2023 ANNUAL CONGRESS

SCHIZOPHRENIA INTERNATIONAL RESEARCH SOCIETY

Overcoming Global Adversity: Mind and Body Matter

11-15 MAY 2023

TORONTO, CANADA

SCHIZOPHRENIARESEARCHSOCIETY.ORG

Concurrent Workshops

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

1. SCHIZOPHRENIA SPECTRUM DISORDERS AND CARDIOVASCULAR COMORBIDITY: PROVIDING REAL-WORLD CARE FOR A METABOLIC CHALLENGE

Margaret Hahn, *Center for Addiction and Mental Health*

Overall Abstract: Patients with severe mental illness (SMI) have a significantly decreased life expectancy by up to 25 years due to cardiovascular (CV) disease. Half of patients with SMI are obese and the prevalence of type 2 diabetes (T2D) is 3 to 5-fold higher compared with the general population. Moreover, these modifiable CV risk factors are undetected and vastly untreated in SMI. The consequences of early cardiometabolic abnormalities in SMI extend beyond CV morbidity and mortality. For example, medication-related weight gain has a negative impact on quality of life and self-view of patients.

This workshop aims to provide an overview of our current understanding of the biology of overweight/obesity, moving to discuss special considerations and best practice management of cardiometabolic risk factors in SMI.

Dr. Donal O'Shea (University College, Dublin, Ireland) will focus on how the body regulates weight, and the challenges of weight reduction in accordance with our current understanding of adipose tissue biology. This will be contextualized within realistic weight management goal setting and importance of decreasing self-stigmatization.

Dr. Sri Mahavir Agarwal (Centre for Addiction and Mental Health (CAMH), Toronto, Canada) will review underlying causes for high cardiometabolic comorbidity in SMI, including contributing effects of psychotropic treatments. He will also review the current disparities in care and their implications, issues around perceived scope of practice in psychiatry to address physical health, as well as monitoring strategies to facilitate early identification and intervention.

Dr. Margaret Hahn (CAMH, Toronto, Canada) will review best practice guidelines to manage obesity tailored to individuals with SMI. This will include a review of evidence for antipsychotic switching strategies, adjunctive pharmacological and/or lifestyle approaches. She will also share the model of metabolic care employed at the CAMH Metabolic Clinic.

Dr. Fiona Gaughran (King's College, London, UK) will review applied informatics to support 'real-world" care for metabolic comorbidity in SMI. This will include emerging innovations from a large London Mental Health Trust in applied informatics, alongside a mixed-methods study exploring the use of digital devices to support physical health by people with SMI.

1.1 UNDERSTANDING ADIPOSE TISSUE REGULATION OF THERMOGENESIS AND BODY WEIGHT

Donal O'Shea, *St Vincents University Hospital, University College Dublin*

Individual Abstract: There is an adult set point for body weight and we know that weight gain is 90% irreversible for 90% of people. The immune system is regulating body weight and medication that cause weight gain do so in part by impacting on the immune system and thermogenesis. Understanding this improves our empathy in dealing with people living with

obesity. The newer agents for treating obesity also act via the immune system and the future. The role of the immune system in regulating weight and the actions of drugs will be discussed. We are finally move towards accepting that "eat less, move more" is not the treatment for obesity and the availability of effective treatments will make this more widely accepted.

1.2 METABOLIC HEALTH IN MENTAL ILLNESS: HISTORICAL LINKS AND CURRENT IMPLICATIONS.

Mahavir Agarwal, *University of Toronto*

Individual Abstract: Patients with schizophrenia (SCZ) have a 15–20-year shorter life expectancy than the average population, a finding directly attributable to their increased rates of obesity, cardiovascular disease, and type 2 diabetes. There are several factors contributing to higher metabolic liability in schizophrenia including biological links, system related factors, lifestyle aspects, and of course, antipsycotics. Antipsychotics remain the cornerstone of treatment in schizophrenia but are associated with serious metabolic adverse effects that are often most pronounced in the first few months after their initiation. As such, there is an urgent need for safe and effective approaches to be implemented at the earliest stages of illness to ameliorate metabolic dysfunction.

My contribution to the workshop will focus on reviewing the underlying causes for high cardiometabolic comorbidity in schizophrenia spectrum disorders, including contributing effects of psychotropic treatments. It will also review the disparities in care that exist in this population, and suggest monitoring strategies to facilitate early identification and intervention.

1.3 BEST PRACTICE APPROACHES TO ADDRESS OVERWEIGHT/OBESITY IN SEVERE MENTAL ILLNESS

Margaret Hahn, *Center for Addiction and Mental Health*

Individual Abstract: Severe mental illness (SMI), including schizophrenia spectrum disorders (SSDs) is associated with premature cardiovascular mortality. Obesity and dysmetabolism caused in part by antipsychotics (APs) and lifestyle comprise modifiable risk factors, which remain undetected, hence undertreated, in psychiatric clinical care. This session will review evidence for different mitigation strategies, including antipsychotic-switching, lifestyle-interventions and add-on of weight-reducing medications. The latter will include an overview of agents approved for chronic management of obesity in the general population, as well as off-indication agents studied specifically in the context of AP-induced weight gain. An overview of an integrated care pathway approach to target metabolic comorbidity, employed at the Mental Health and Metabolic clinic (co-led by Drs. Hahn and Agarwal), will be shared. The aim of this workshop is to provide a pragmatic, best-evidence approach to help clinicians working in the field of mental health to feel comfortable to address metabolic comorbidity in SMI.

1.4 APPLIED INFORMATICS TO SUPPORT 'REAL-WORLD" CARE FIONA GAUGHRAN (PRESENTING), DIPEN PATEL, RICHARD DOBSON, RAY MCGRATH, CATHY GILLIS, JULIE WILLIAMS, GRACIE TREDGET, DAVID CODLING, ROB HARLAND

Fiona Gaughran, *Institute of Psychiatry, Psychology and NeuroScience, King's College London*

Individual Abstract: A smorgasbord of health-related digital tools is available, but there is limited evidence on implementation into real-world practice. The following innovations in applied informatics in a large London Mental Health Trust will be briefly presented, alongside

a mixed-methods study exploring the use of digital devices to support physical health by people with serious mental illness (SMI).

1. The implementation and outcomes of the introduction of "Consultant Connect", an App-based system which allows mental health clinicians to contact nearby general hospital doctors in over 80 specialties for advice on their patients.

2. An ongoing feasibility and acceptability trial, identifying facilitators and barriers to implementation and process outcomes of a real-time electronic clinical decision support system, using the CogStack@Maudsley information retrieval and extraction platform. The system automatically alerts clinicians to guideline-based recommendations for dysglycaemia monitoring and management, tailored to individual HbA1c levels.

3. The impact of 'VIEWER: Visualisation and Interaction With Electronic Records" on offer and uptake of physical health checks. VIEWER, a platform for population health management, provides clinicians and staff with multidimensional clinical knowledge and patient information, filtered and visually presented including geo-locations, allowing care teams to identify gaps and direct resources to improve health care and outcomes.

4. People with SMI using digital health interventions (DHIs) to support their physical health were generally satisfied with their quality. The most used DHIs addressed diet, exercise and weight management. Factors encouraging and hindering their use, along with impacts and preferred place in the health system will be highlighted.

2. OPUS PANEL WORKSHOP

Merete Nordentoft*, Mental Health Centre Copenhagen*

Overall Abstract: In this workshop, four people with lived experience will explain how it is to live with an invisible disorder: They will present how they have used their own experience in dialogue with other service users and their families, and how they contributed to decrease stigma among staff members and in media.

2.1 JEAN MANNEVILLE THEAGENE PEER SUPPORT

Jean Manneville*, CHUM*

Individual Abstract: Jean Manneville Theagene story

2.2 LIVED EXPERIENCE RECOVERY STORY

Ilyas Khamis*, Toronto Metropolitan University*

Individual Abstract: I will speak about my recovery journey after going through psychosis and eventually reaching a diagnosis of schizoaffective disorder. I will tie in themes of early intervention, concurrent substance use, and hope for a better future as research and investment continues to grow in schizophrenia care. I may also touch on the value of peer support and giving back as longer term recovery goals I have reached towards.

2.3 OPUS PANEL WORKSHOP

Kirsten Bruell*, Banedanmark*

Individual Abstract: Together with Sissel Lange, I will present the Opus Panel. The Opus Panel is a panel consisting of former patients and relatives to patients who have been diagnosed with a mental disorder on the psychotic spectrum, including schizotypal disorder or

schizophrenia. All patients have been a part of the OPUS treatment which is a specialized treatment program in Denmark lasting up to two years for young people between 18 and 35 years of age, who have recently been diagnosed with a psychiatric diagnosis on the psychotic spectrum. The Panel's work is based on personal stories with a focus on the individual's recovery process. We tell our personal stories to recently diagnosed patients, relatives and professionals in the field of psychiatry. Further, we participate in different research projects and interviews. Our core focus areas are to contribute to, or create hope for, families who are in the beginning of a treatment, destigmatize mental disorders and inform about a life with a psychiatric diagnosis.
In addition to our presentation of the Opus Panel, I will share my own personal story as a former patient of OPUS, diagnosed with schizotypal disorder.

2.4 OPUS PANEL WORKSHOP
Sissel Juhl*, OPUS*

Individual Abstract: Together with Kirsten Bruell, I will present the Opus Panel. The Opus Panel is a panel consisting of former patients and relatives to patients who have been diagnosed with a mental disorder on the psychotic spectrum, including schizotypal disorder or schizophrenia. All patients have been a part of the OPUS treatment which is a specialized treatment program in Denmark lasting up to two years for young people between 18 and 35 years of age, who have recently been diagnosed with a psychiatric diagnosis on the psychotic spectrum. The Panel's work is based on personal stories with a focus on the individual's recovery process. We tell our personal stories to recently diagnosed patients, relatives and professionals in the field of psychiatry. Further, we participate in different research projects and interviews. Our core focus areas are to contribute to, or create hope for, families who are in the beginning of a treatment, destigmatize mental disorders and inform about a life with a psychiatric diagnosis.

In addition to our presentation of the Opus Panel, I will share my own personal story as a former patient of OPUS, diagnosed with schizophrenia.

2.5 OPUS PANEL WORKSHOP
Amal Abdel-Baki, *Centre hospitalier de l'Université de Montréal*

2.6 OPUS PANEL WORKSHOP
Tina Iversen, *Regional Psychiatric Hospital/RHP*

2.7 OPUS PANEL WORKSHOP
Chris Summerville, *Schizophrenia Society of Canada*

3. EARLY CAREER/EXPERT CLASS WORKSHOP
Dost Ongur*, Mclean Hospital*
Overall Abstract: This workshop will focus on providing support and strategies for success to early career investigators.

3.1 CAN WE REALLY, REALLY PREVENT PSYCHOSIS?

Celso Arango, *Hospital General Universitario Gregorio Marañon*

Individual Abstract: Available treatment methods have shown little effect on the burden associated with mental health disorders. I will review promising universal, selective, and indicated preventive mental health strategies that might reduce the incidence of psychotic disorders, or shift expected trajectories to less debilitating outcomes. Some of these interventions also seem to be cost-effective. In the transition to mental illness, the cumulative lifetime effect of multiple small effect size risk factors progressively increases vulnerability to psychotic disorders. This process might inform different levels and stages of tailored primary interventions to lessen risk, or increase protective factors and resilience, especially during sensitive developmental periods (therapeutic windows). Gaps between knowledge, policy, and practice need to be bridged.

3.2 HOW TO DEVELOP SUCCESSFUL AND ENJOYABLE SCIENTIFIC COLLABORATIONS

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

Individual Abstract: Networking and establishing collaborations with colleagues working in our or a similar field of research is one of the important skills we need to master as academics to increase the reach of our work and advance our own professional development. How to best achieve this is not something we are taught, and we wish we had known early on how to develop a collaboration, with whom, how to maintain it and how to make sure it is successful. We often learn by trial and error. This talk will be an opportunity to share experiences and hear some tips learned over the years that might help early career researchers to get there more quickly and effectively!

3.3 EARLY CAREER/EXPERT CLASS WORKSHOP

Dost Ongur, *Mclean Hospital*

Individual Abstract: In this workshop, we will discuss common challenges facing early career investigators and strategies for addressing them (publishing, promotion, funding, research direction, mentoring etc)

Congress Welcome, Awards and Keynote Lecture

5:45 p.m. - 7:15 p.m.

4. SIX SCHIZOPHRENIC BROTHERS ON HIDDEN VALLEY ROAD: PERSEVERANCE IN THE FACE OF ADVERSITY – THE VALUE OF THERAPY

Merete Nordentoft, *Mental Health Centre Copenhagen*

4.1 SIX SCHIZOPHRENIC BROTHERS ON HIDDEN VALLEY ROAD: PERSEVERANCE IN THE FACE OF ADVERSITY – THE VALUE OF THERAPY

Lindsay Rauch

Individual Abstract: My eldest brother Donald was diagnosed in 1968 with schizophrenia. I was three years old. Over the course of the next thirteen years, five of my older brothers were

diagnosed on the spectrum of Serious Mental Illness. My story is that of a sibling, a victim, a survivor, and now, an advocate and thriver.

My therapeutic journey began at age 18 when I took myself to the local mental health center while in college at University of Colorado in Boulder. Thinking I was delusional, the therapist did not believe my story. Dr. Nancy Gary, a family friend of my parents and a child psychologist, introduced me to Dr. Louise Silvern, a psychology professor specializing in childhood trauma. I spent the next 25 years in her care battling chronic PTSD.

The impact on me, as an unaffected sibling, has required a lifelong unraveling. Therapy taught me to feel safe with negative feelings, to identify past emotion as part of my past. This hard work gave me permission to have joy and gave me the tools to overcome survivor guilt. Experiencing my brothers, one after another, succumb to the terror and confusion of psychosis is traumatizing to a child. It left me with the chronic and overwhelming fear I was next. I spent my youth not expressing anger or sadness as I attributed these emotions to being "mentally ill". I grew a mask of wishful perfection to try and hide any flaws, any cracks in my armor.

Without the guidance, expertise, compassion, and empathy from this remarkably skilled therapist, I would not have found a way out of the darkness, the ruminating, and the effects of trauma.

The resilience I developed to overcome this tremendous adversity was found in a little therapy room at the University of Colorado psychology department.

Plenary Session I: Deidre Anglin

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

5. RACISM AND SOCIAL DETERMINANTS OF PSYCHOSIS RISK

Diane Gooding*, University of Wisconsin-Madison*

Overall Abstract: Our plenary speaker is Dr. Deidre M. Anglin, Professor of Psychology at The City College and Graduate Center, City University of New York. She will provide a critical overview of the relationship between racialized identity, sociocultural factors underlying risk for psychosis, and ethnoracial disparities in schizophrenia. Her lecture will explore how racial discrimination and related social determinants may increase the risk for psychotic experiences. Dr. Anglin examines growing evidence from multiple sources (e.g., nontreatment seeking, nationally representative, clinical high-risk, and first-episode psychosis samples) that demonstrate how social, and environmental factors may increase the risk for psychosis outcomes among ethnoracial minoritized populations. Dr. Anglin uses qualitative examples from a Photovoice study with young people with first-episode psychosis to illustrate how social and cultural isolation in neighborhoods and experiences of racial discrimination can serve as triggers for vulnerable Black youths.

5.1 RACISM AND SOCIAL DETERMINANTS OF PSYCHOSIS RISK

Deidre Anglin*, The City College of New York (CCNY)*

Individual Abstract: While there is a documented history of over- and mis-diagnosis of schizophrenia in Black people in the U.S., there is also increasing evidence that racial discrimination and related social determinants may increase risk for psychotic experiences in

Black and Latinx populations—experiences that may or may not lead to a clinical psychotic disorder, but that contribute to mental morbidity. This lecture will provide a critical overview of the role of structural racism in shaping social determinants of psychosis risk and outcomes and ethnoracial disparities in these outcomes. In addition, this lecture examines accumulating evidence from non-treatment seeking, nationally representative, clinical high risk, and first episode psychosis samples that demonstrates aspects of the social environment are associated with increased vulnerability for psychosis outcomes among ethnoracial minoritized populations. Qualitative examples from a Photovoice study with Black young people with first episode psychosis will be used to illustrate how social and cultural isolation in neighborhoods and racial discriminatory experiences can be triggering for vulnerable youth.

Concurrent Symposia

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

6. EARLY RISK FACTORS FOR ABERRANT NEURODEVELOPMENT UNDERLYING EMERGING PSYCHOPATHOLOGY

Bjorn Ebdrup*, University of Copenhagen*

Overall Symposia Abstract: Converging lines of evidence strongly implicate aberrant neurodevelopment in the etiology of schizophrenia and other neuropsychiatric disorders. Specifically, prenatal and early life insults during critical periods of brain development and maturation are associated with the subsequent emergence of psychopathology, albeit with potentially differential developmental trajectories for males and females. A deeper understanding of the complex neurobiological mechanisms leading to psychopathology and impaired cognition is a prerequisite for individual risk stratification, early intervention, and identification of new treatment strategies. In this symposium we will explore how early risk factors influence neurodevelopment from converging lines of research including epidemiological, clinical and preclinical research.

Dr Cecilie Lemvigh will present findings from a nation-wide danish register study examining how multiple early factors influence disease risk and age of illness onset in males and females with a psychotic disorder. She will relate the register data to data from clinical cohorts of child-, adolescents, and adult patients with first-episode psychosis with detailed psychopathology and cognition.

MD Julie Rosenberg will present clinical data from a large prospective birth cohort of 700 mother-child pairs followed from pregnancy (The COPSYCH Study). The data show that maternal low-grade inflammation in pregnant mothers increase the risk of psychopathology in the child at age 10. Ongoing analyses relate these findings to the children's' white matter integrity.

Dr Vernon will present data from human induced pluripotent stem cell models that provide evidence for cell specific effects of IL-6 and IFN-y on human neurons and microglia that recapitulate cellular and molecular phenotypes associated with neurodevelopmental disorders.

Finally, Dr Elisa Guma will present preclinical data examining the effects of early or late gestational exposure to maternal immune activation on mouse neurodevelopment across the lifespan. These data highlight the differential effects due to gestational timing of exposure on trajectories of brain development for neuroanatomy, behaviour, and transcription.

6.1 THE IMPACT OF EARLY RISK FACTORS ON AGE OF ILLNESS ONSET AND COGNITION IN CHILDREN, ADOLESCENTS AND ADULTS WITH A SCHIZOPHRENIA SPECTRUM DISORDER

Cecilie Lemvigh*[1], Birgitte Fagerlund[2], Merete Osler[3], Jens Richardt Jepsen[2], Mette Nielsen[4], Jacob Rydkjaer[5], Kirsten Borup Bojesen[6], Christos Pantelis[7], Birte Glenthøj[8], Anne Katrine Pagsberg[9], Bjorn Ebdrup[10]

[1]*Center For Neuropsychiatric Schizophrenia Research,* [2]*Center for Neuropsychiatric Schizophrenia Research,* [3]*Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospitals AND Section for Epidemiology, University of Copenhagen,* [4]*Center for Neuropsychiatric Schizophrenia Research CNSR,* [5]*CINS and CNSR, Psychiatric Center Glostrup,* [6]*Psychiatric Center Glostrup,* [7]*Melbourne Neuropsychiatry Centre, The University of Melbourne,* [8]*Center for Neuropsychiatric Schizophrenia Research (CNSR) and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS), Copenhagen University Hospital, Mental Health Center Glostrup,* [9]*Child and Adolescent Mental Health Centre, Mental Health Services Capital Region of Denmark,* [10]*CNSR and CINS*

Background: Schizophrenia is associated with widespread cognitive deficits often preceding psychosis onset by many years. The level of cognitive performance is highly heritable and twin studies have demonstrated genetic overlap between cognition and schizophrenia risk. Additionally, several early risk factors for schizophrenia have been identified and some studies report and association between the early risk factors and impaired cognition. However, only few studies have examined multiple risk factors simultaneously and the cumulative effect on schizophrenia risk and cognition is therefore unclear. Finally, the effects of age of onset and sex on these relationships have not been examined.

Methods: First, we performed a register study of all individuals in Denmark with a schizophrenia spectrum diagnosis from 1973-2018 (N=29149). A healthy control (HC) sample was matched 5:1 to patients on age, sex, and parental socioeconomic status (N=136387). Data on early risk factors was obtained from the Medical Birth Registry. Secondly, these early risk factors were related to cognition in a clinical cohort of children, adolescents and adult patients with first-episode psychosis (FEP) and matched HCs aged 9-45 (N=608).

Results: Parental history of psychiatric illness (OR=2.2), advanced paternal age (OR=1.4), maternal smoking (OR=1.4) and low birth weight (OR=1.2) independently increased the risk of schizophrenia. Subgroup analyses based on sex revealed that advanced paternal age only increased the risk in females. ~20% of patients were early-onset cases (<18 years). Female sex (OR=1.6) and parental history (OR=1.4) were significant predictors of having a child-onset, while winter birth decreased the risk (OR=0.9). We also observed a cumulative effect of early risk factors on age of illness onset with more risk exposures resulting in an earlier age of onset. In the clinical study, FEP patients performed worse than HCs on all cognitive measures (all p's < .001),and had significantly lower birth length (p = .005) and weight (p =.004). Linear regression with IQ as the dependent variable revealed gestational age (p = .006), birth weight (p = .047) and group (FEP vs HC) as significant independent variables, while birth length, Apgar score, paternal age, winter birth and age (child vs adult) did not contribute significantly (adjusted R2 for the model = 0.164). Only birth weight (p = .043), group (p < .001) and age (p = .015) were significant for processing speed (adjusted R2 = 0.162). We observed no interaction effects between the significant early risk factors and group (FEP vs HC) or age (child vs adult). Including sex in the models did not change the findings. The remaining cognitive measures were not significantly influenced by the included early risk factors.

Conclusions: Multiple early factors independently increase the risk of developing a schizophrenia spectrum disorder, and once accumulated result in an earlier illness onset. Only IQ and processing speed were significantly associated with the included early risk factors, although the observed effects were small. Low birth weight and premature birth have previously been associated with impaired cognition in both healthy individuals and patients with schizophrenia, yet the available literature is sparse. These findings provide a basis for future treatment strategies in terms of individual risk stratification and early intervention.

6.2 MATERNAL INFLAMMATION DURING PREGNANCY IS ASSOCIATED WITH RISK OF ADHD IN CHILDREN AT AGE 10. RESULTS FROM THE COPSYCH STUDY.

Julie Rosenberg*[1], Jens Richardt Møllegaard Jepsen[2], Parisa Mohammadzadeh[1], Astrid Sevelsted[3], Rebecca Vinding[3], Mikkel Sørensen[1], Klaus Bønnelykke[3], Bjørn H. Ebdrup[4]

[1]*Center for Neuropsychiatric Schizophrenia Research,* [2]*Mental Health Services – Capital Region of Denmark, Child and Adolescent Mental Health Centre, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Mental Health Services - Capital Region of Denmark, Center for Neuropsychiatric Schizophrenia Research and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research,* [3]*Copenhagen Prospective Studies on Asthma in Childhood,* [4]*Centre for Neuropsychiatric Schizophrenia Research (CNSR), Mental Health Centre Glostrup*

Background: Maternal inflammation during pregnancy may affect early neurodevelopment. However, the evidence for risk of long-term aberrant neurodevelopment is scarce and based on preclinical data and register studies. In the mother-child cohort, COPSAC2010, we investigated potential associations between severity of maternal inflammation during pregnancy, and risk of ADHD and sub-diagnostic ADHD symptomatology in the children at age 10.
Methods: COPSYCH is based on the COPSAC2010 cohort consisting of 700 unselected mother-child pairs, who have been followed prospectively since pregnancy week 24, allowing for deep phenotyping of the cohort. At 10 years of age the children have completed an extensive examination of neurodevelopment reflected in categorical and dimensional psychopathology using Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version (K-SADS-PL) and ADHD-Rating Scale (ADHD-RS). The exposure variable was the inflammatory marker high sensitivity C-Reactive Protein (hs-CRP), and pre- and postnatal covariates were included from the COPSAC2010 database.
Univariate, multivariate logistic and linear regression analyses were used to estimate odds ratios (OR), respectively, estimates for psychopathological outcomes.

Results: Out of the 700 children in the COPSAC2010 cohort, 593 children participated in the COPSYCH visit at age 10 (85% of the cohort). Sixtyfive (11 %) fulfilled a research diagnosis of ADHD (16 girls (25%) and 49 (75%) boys). Maternal hs-CRP in pregnancy week 24 (median 5.1 mg/L) was significantly associated with risk of ADHD, adjusted OR 1.38, 95%CI (1.14-1.67), p=0.001. Additionally, hs-CRP was positively associated with severity of ADHD traits in the complete male-population, reflected by ADHD-RS and the K-SADS ADHD symptom score. Children's own level of hs-CRP at 6 months was not significantly associated with risk of ADHD after adjusting for prenatal maternal level of inflammation.
Conclusions: These results add clinical data to the growing evidence of the importance of prenatal early life exposures including increased maternal inflammation as a risk factor for ADHD in children. The study also adds knowledge to the association between inflammation and severity of ADHD traits in the general population. These findings will provide a potential

prevention target during pregnancy, ultimately reducing the risk of ADHD in children and the severity of ADHD traits in the male general child population.

6.3 USING STEM CELL MODELS TO EXPLORE THE EFFECTS OF EARLY LIFE IMMUNE STIMULATION ON NEURODEVELOPMENT IN NEURONAL AND NON-NEURONAL CELLS

Kate Warre-Cornish[1], Leo Perfect[2], Amalie Couch[1], Deepak Srivastava[1], Anthony Vernon*[3]

[1]*Institute of Psychiatry, King's College,* [2]*Institute of Psychiatry, King's College London,* [3]*Institute of Psychiatry, Psychology and Neuroscience, King's College London*

Background: Converging lines of evidence support a link between elevated levels of specific pro-inflammatory cytokines including interferon-γ (IFN-γ) and interleukin (IL)-6 during pregnancy and increased risk for psychiatric disorders with a neurodevelopmental origin in the offspring. Although animal models provide important evidence for causality and plausible mechanisms, it is critical to evaluate these in human model systems to account for species differences in gene expression, regulatory networks and response to immune stimuli. We therefore tested the hypothesis that exposure to either IFN-γ or IL-6 would contribute to molecular and cellular phenotypes associated with neurodevelopmental disorders in two relevant human cell types, neural progenitor cells (NPCs) and microglia (MGL).

Methods: Human induced pluripotent stem cells (hiPSC) were collected from neurotypical donors matched for age and sex in accordance to the "Patient iPSCs for Neurodevelopmental Disorders (PiNDs) study" (REC no. 13/LO/1218) with informed consent obtained from all subjects participating. Ethical approval for the PiNDs study was provided by the National Health Service (NHS) Research Ethics Committee at the South London and Maudsley NHS R and D Office. From each donor, hiPSC were differentiated to either NPCs or MGL as monocultures using established protocols for each cell type (Adhya et al. Biological Psychiatry, 2021; Haenseler et al. Stem Cell Reports, 2017). Monocultures were then exposed acutely (3-24 hours) to either IFN-γ (25 ng/ml) or IL-6 (100 ng/ml) at D18 or D14 of differentiation respectively. We then performed RNA sequencing and cell-specific assays in parallel, including neurite outgrowth, motility and secretion of cytokines and chemokines. Sample size: hiPSC were generated from N=3 donors. Experiments were performed N=3 independent clones, with each clone acting as a biological replicate to give N=3 per donor line. Each experiment consisted of a minimum of N=3 technical replicates, defined as individual wells in a tissue culture plate.

Results: At the cellular level, transient exposure of NPCs to IFN-γ increased neurite outgrowth (IFN-γ treatment: $F_{1,24} = 17.02$, $P = 0.0004$), which was dependent on up-regulation of major histocompatibility class (MHC)-I and promyelocytic leukemia (PML) nuclear bodies. Transient exposure to IL-6 increased Y705-STAT-3 phosphorylation within 15 minutes in MGLs ($p<0.05$) but not in NPCs ($p<0.05$). In MGLs acute exposure to IL-6 (3 hours) triggered increased cell/process motility ($p<0.01$) and increased the secretion of pro- and anti-inflammatory cytokines. At the molecular level, using RNA sequencing we provide evidence that transient exposure of NPCs to IFN-γ and MGLs to IL-6 disproportionately alter the expression of genes associated with either schizophrenia or autism, suggestive of an interaction between genetic and environmental risk factors (Fishers Exact test $p<0.05$; $q<0.05$).

Conclusions: These data provide evidence that IFN-γ or IL-6 stimulation recapitulates morphological and transcriptomic changes associated with neurodevelopmental disorders in a cell-specific manner. Studies in patient-derived cells are now required.

6.4 EARLY OR LATE GESTATIONAL EXPOSURE TO MATERNAL IMMUNE ACTIVATION DIFFERENTIALLY AFFECTS MOUSE OFFSPRING NEURODEVELOPMENT

Elisa Guma*[1], Pedro do Couto Bordignon[2], Gabriel Devenyi[3], Daniel Gallino[4], Vedrana Cvetkovska[2], Maude Bordeleau[2], Fernando Gonzalez-Ibanez[5], Emily Snook[6], Bratislav Misic[2], Marie-Eve Tremblay[7], Brian Nieman[6], Rosemary Bagot[6], M. Mallar Chakravarty[8]

[1]*National Institute of Mental Health,* [2]*McGill University,* [3]*McGill University, Douglas Mental Health University Institute,* [4]*Douglas Mental Health University Institute,* [5]*Universitaire de Québec–Université Laval,* [6]*University of Toronto,* [7]*University of Victoria,* [8]*Douglas Mental Health University Institute, McGill University*

Background: In utero exposure to maternal immune activation (MIA) is a risk factor for neuropsychiatric disorders. Neurodevelopmental processes and maternal immune responsiveness vary greatly across gestation, which indicates that the gestational timing of MIA-exposure may influence the nature and severity of disruptions to offspring neurodevelopment. The impact of gestational timing of MIA exposure on downstream development remains unclear. Furthermore, although several studies have investigated the effects of MIA-exposure on adolescent and adult offspring neurodevelopment, few have characterized the effects of this risk factor on offspring across the lifespan. Thus, we sought to investigate the differential effects of early or late MIA-exposure on offspring development throughout the lifespan.

Methods: Mice were prenatally exposed to the viral mimetic poly I:C (polyinosinic:polycytidylic acid) on gestational day 9 (early) or 17 (late). Offspring neurodevelopmental trajectories were characterized using longitudinal structural magnetic resonance imaging (MRI) from weaning to adulthood, as well as behavioural phenotyping in adolescence and adulthood. Using multivariate methods, we identified a subset of candidate brain regions associated with behavioural changes to further investigated using RNA sequencing, namely, the dorsal and ventral hippocampus, and the anterior cingulate cortex. In a follow up study, to better understand whether the changes postnatally were already visible prenatally, we performed high-resolution ex vivo MRI on mouse embryos exposed to MIA, again, on either gestational day 9 or 17, and investigated putative neuroanatomical underpinnings of MIA timing using electron microscopy.

Results: Early exposure to MIA was associated with accelerated brain volume increases, as well as anxiety-like, stereotypic, and sensorimotor gating impairments in the adolescent/early-adult period. Both the neuroanatomical and behavioural alterations normalized in adulthood. Transcriptional changes due to early MIA-exposure were most pronounced in the dorsal hippocampus, with enrichment for genes association with fibroblast growth factor regulation, inflammatory pathways, autistic behaviour, and microRNA regulation. MIA-exposure in late gestation had a subtle impact on both neuroanatomy and behaviour. In the follow-up study of the mouse embryo brain, MIA-exposure induced striking neuroanatomical alterations, with differential effects due to early or late exposure. Electron microscopy studies identified increased apoptotic cell density due to early exposure, and increased density of neurons and glia with ultrastructural features associated with increased neuroinflammation and oxidative stress.

Conclusions: Overall, our findings indicate that MIA timing differentially affects offspring development. Postnatally, exposure in late gestation leads to subthreshold deficits, while exposure in early gestation perturbs brain development mechanisms associated with neurodevelopmental disorders. Furthermore, differential effects of MIA were also detected at

the earliest stages of development in utero. These findings may further our understanding of how early life risk factors increase risk for developing neuropsychiatric disorders later in life.

7. PSYCHOSIS AROUND THE GLOBE: NOVEL INSIGHTS FROM THREE RESEARCH PROGRAMMES IN THE GLOBAL SOUTH (INTREPID II, SCOPE, PSYMAP-ZN)

Teshome Kelkile*, Dalhousie University, New Brunswick Horizon Network Zone 3*

Overall Symposia Abstract: There are striking global inequities in our knowledge and treatment of psychotic disorders. Over 80% of the world's population live in the global south, but less than 10% of research on psychotic disorders is done in these settings. This limits our understanding of the epidemiology, aetiology and course of psychosis, and hinders our ability to develop accessible and effective services that are informed by local evidence.

These studies contribute to a new generation of research on psychosis in the global south that is beginning to address this major evidence gap. The symposium brings together findings from three programmes, conducted in India, Nigeria, Trinidad, Ethiopia and South Africa. A great strength of these programmes is that they use comparable methods - including case ascertainment, inclusion criteria, and measures – thus enabling direct comparisons across settings.

INTREPID (International Programme for Research on Psychotic Disorders) is a multi-country programme in three settings in Tamil Nadu (India), Oyo state (Nigeria) and Trinidad. The aims of the programme were to investigate the incidence, aetiology, course and outcome, and treatment of psychotic disorders, using population-based cohorts of cases with an untreated psychotic disorder and controls with no history of psychotic disorder. Over two years, 220 cases were recruited in India, 210 in Nigeria, and 212 in Trinidad, along with equal numbers of controls, who were subsequently followed up for two years. PSYMAP-ZN (PSYchosis MAPping in KwaZulu-Natal) took an equivalent approach in KwaZulu-Natal (South Africa), for which case recruitment is ongoing. SCOPE (Studying the Contexts of recent Onset Psychoses in Ethiopia to develop interventions to improve outcomes) is currently in the formative stages before epidemiological research activities begin, after which the epidemiological findings will be used to inform the development and piloting of interventions to meet the needs of people living with psychosis in Addis Ababa, Gurage, and Oromia in Ethiopia.

This symposium brings together four sets of analyses from these three programmes. In the first, Alem et al present formative research from SCOPE on contexts of help-seeking and care for people with psychosis in Ethiopia, mapping of extensive community resources informed participatory development of a Theory of Change for achieving earlier detection and better care to support recovery for people with psychosis and their families. In the second, Chiliza et al present incidence rates for psychosis in KwaZulu-Natal (South Africa), showing a higher rates (53 per 100,000) in this setting, with a mean age of 27 and a 4:1 ratio of men to women. In the third, Gureje et al compared physical health indicators between INTREPID sites and between cases and controls, finding that hypertension was rare in cases compared to controls in India and Nigeria, while the reverse held in Trinidad, and malnutrition was substantially more common in cases than controls in both India and Nigeria, indicating very different needs. Finally, Donald et al analysed symptom dimensions of psychosis across all INTREPID sites, finding substantial variation in the presentation of psychosis.

These findings point to important differences between contexts (e.g. in physical health, incidence and presentation), with important implications for our understanding of psychoses and development of effective services.

7.1 DEVELOPING INTERVENTIONS FOR EARLIER AND BETTER CARE TO OPTIMISE RECOVERY FOR PEOPLE WITH PSYCHOSIS: STUDYING THE CONTEXT OF PSYCHOSIS IN ETHIOPIA TO IMPROVE OUTCOMES (SCOPE)

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Background: Previous efforts to expand access to mental health care for people with psychosis in Ethiopia have demonstrated beneficial impacts on functioning, human rights, and food security; however, the duration of untreated psychosis is long, premature mortality is high, engagement with care is patchy and families remain impoverished. The aim of the SCOPE project is to develop and evaluate scalable interventions to achieve early detection and optimal recovery of people with psychosis in Ethiopia, grounded in local evidence and context and anchored in the priorities of people with lived experience of psychosis.

Methods: SCOPE is working in Addis Ababa (capital city) and rural districts in Oromia and the Gurage Zone in south-central Ethiopia. In the formative phase we are conducting the following: 1) mapping of community resources and pathways to care, 2) ethnography of family interactions, 3) analysis of in-depth interviews to understand conceptualisations of recovery, 4) participatory theory of change and community engagement workshops with key stakeholders, 5) supporting involvement of people with lived experience in all aspects of the project, 6) developing strategies for proactive community case detection and awareness-raising, and 7) a population-based cohort study of 290 people with recent-onset psychosis and their caregivers to obtain detailed information about unmet mental health, physical health, economic and social needs. An additional cross-sectional assessment of 50 people who are homeless and have psychosis will be conducted.

Results: Theory of change maps outlining the steps to achieving valued outcomes for people with psychosis and their families have been developed for rural and urban settings, including for people who are homeless. Early detection strategies in the capital city will include working with Family Health Teams who provide community outreach from primary health care facilities, including to people who are homeless, alongside establishing registration and notification systems in religious and traditional healing sites, prisons, police stations and health facilities. In rural settings, greater focus will be given to house-to-house approaches to case detection, working with community-based health extension workers, and local radio. Prioritised outcomes include ability to work and contribute, sufficient economic resources to live with dignity, social inclusion and social functioning. Both urban and rural areas have substantial numbers of social organisations, although not currently accessed by people with psychosis. Co-produced social contact interventions will seek to address barriers to help-seeking and access to community resources by increasing awareness and reducing stigma in groups important in the care pathway. Development of additional interventions will be informed by findings from the population-based study.

Conclusions: Through a multi-faceted approach to understanding existing resources, unmet needs, priorities and opportunities in these settings in Ethiopia, the need to adopt community-

based approaches that engage with the social worlds of people with psychosis and their families has become evident. At the heart of efforts will be rights-based approaches to overcoming social exclusion.

7.2 SYMPTOM DIMENSIONS OF PSYCHOTIC DISORDERS IN INDIA, NIGERIA AND TRINIDAD

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Background: The high comorbidity index and substantial symptom overlap among the diagnoses of schizophrenia, schizoaffective, and bipolar and depressive disorders with psychotic features challenge the validity of diagnosis using traditional categorical models. Recent findings using a transdiagnostic model of psychosis suggest a bifactor model encompassing one general and five specific factors, resulting from the variance-covariance of all symptoms and specific subgroups of symptoms, respectively. However, the extent to which these models represent symptom manifestation outside western settings is unclear. Therefore, we examined the symptom dimension structure of psychopathology in three diverse settings of the Global South – India, Nigeria and Trinidad, and the associated sociodemographic characteristics.

Methods: In each site, individuals with an untreated psychotic disorder were identified through a comprehensive case detection system that included professional, folk, and popular sectors. During a two-year period, we recruited and assessed 220 cases in India, 210 in Nigeria, and 212 in Trinidad. Inclusion criteria were age of 18-64, resident in catchment area, presence of a ICD-10 psychotic disorder, and no more than one continuous month of treatment with antipsychotic medication prior to the start of case identification. Diagnoses were confirmed through a Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview, administered by a trained researcher and reviewed by a psychiatrist. Detailed data on demographic details were collected using the MRC Sociodemographic Schedule. SCAN data were converted to the OPerational CRITeria (OPCRIT) system. These symptom ratings were analysed using multidimensional item response modelling in Mplus to estimate five theory-based models of psychosis. We used multiple regression models to examine demographic factors associated with symptom dimensions.

Results: A bifactor model, composed of one general factor and six specific dimensions of hallucinations, delusions, disorganisation, negative, manic and depressive symptoms, best-represented associations among ratings of psychotic symptoms. Across the three sites, we observed variation in all dimensions when comparing participants from Trinidad with those from India and with those from Nigeria. We also found significant variation in the disorganization (B= 0.345, 95% CI 0.21–0.47) and manic (B= 0.53, 95% CI 0.40–0.65) dimensions when comparing Indian and Nigerian participants. While in Nigeria, there was no

variation in any dimension between males and females, in India, we found a moderate variation between genders in the disorganisation symptom domain (B= -0.12, 95% CI -0.24–0.00). In Trinidad there was significant variation between males and females in the delusion (B= -0.42, 95% CI -0.61 to -0.24), disorganisation (B= -0.312, 95% CI -0.51 to -0.12), negative (B= -0.33, 95% CI -0.57 to -0.11) manic (B= 0.003, 95% CI -0.22 to 0.23) and depression (B= -0.59, 95% CI 0.39 – 0.80) dimensions and moderate variation in the hallucination dimension (B= 0.19, 95% CI -0.01– 0.40). Also, in Trinidad Indo versus Afro Trinidadians were more likely to exhibit depressive symptoms (B= 0.344, 95% CI 0.07–0.61)

Conclusions: We confirmed that a bifactor model with one general and six specific factors was the best fit for our sample. This result somewhat fits in with previous studies done in the West where the bifactor model proved to also be the best fit for psychotic symptomatology. The variation in specific dimensions across and within sites suggests that symptom manifestation may be context driven and has implications for locally-relevant treatment interventions, tailored to the dominant presentations in each setting.

7.3 PSYCHOSIS MAPPING IN KWAZULU-NATAL

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Background: PSYchosis MAPping in kwaZulu-Natal (PSYMAP-ZN) is an epidemiological study of psychosis in South Africa and a collaboration between the Universities of KwaZulu-Natal and Exeter. Building on our successful INCET pilot study in the same region, we aim to identify all incident cases of psychosis within Msunduzi Municipality in KwaZulu-Natal Province, South Africa over a 2-year period. In our pilot study we developed an effective strategy to collaborate with traditional health practitioners in case identification and we will further develop this approach.

Methods: We utilized innovative spatial epidemiological (GIS) methods to map the formal and informal health care practitioners that are likely to see clients with first episode psychosis. We are also using GIS to characterize the socioeconomic and physical environment and map the distribution of incident cases across varying neighborhoods within the catchment area (e.g. varying by urban/rural, population density, socioeconomic status, levels of crime, and amount of green space).

Results: We have started to recruit 240 cases and 240 age and gender matched controls into a case-control study and evaluate psychopathology, individual and neighborhood level factors associated with psychosis risk and presentation. We will explore the help-seeking behaviors and pathways to care of people with psychosis and their carers using quantitative, spatial and qualitative methods.

Conclusions: Our findings will contribute substantially to the very limited evidence-base on psychosis epidemiology in the Global South, the impact of the environment on psychosis, and help-seeking behaviors and pathways to care of people with psychosis in LMIC settings. In particular our findings will inform the development of appropriate and effective services for this vulnerable population and produce a model for successful collaboration between formal and informal providers.

7.4 PHYSICAL COMORBIDITY AMONG PEOPLE WITH UNTREATED PSYCHOSIS IN INDIA, NIGERIA, AND TRINIDAD

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Background: The high comorbidity of chronic physical conditions among persons with psychotic disorders is partly responsible for the substantial premature mortality observed them. However, even though the main causes of disability and mortality vary considerably between contexts, the vast majority of current evidence on physical health of people with psychosis originates from North America, Western Europe and Australasia. Given the limited health care available in low- and middle- income countries, the impact of comorbid physical health conditions for such persons may be even higher than in high-income countries. In this paper, we present an analysis of data from three diverse catchment areas in Tamil Nadu (India), Oyo state (Nigeria), and northern Trinidad, on physical health among individuals with an incident/untreated psychotic disorder and matched population controls.

Methods: In each site, individuals with psychotic disorder were identified through a comprehensive case detection system that included professional, folk, and popular sectors. During a two-year period, we recruited and assessed 220 cases in India, 210 in Nigeria, and 212 in Trinidad. Inclusion criteria were age of 18-64, resident in catchment area, presence of an ICD-10 psychotic disorder, and no more than one continuous month lifetime treatment with antipsychotic medication. Diagnoses were confirmed through a Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview, administered by trained researchers and reviewed by apsychiatrists. Controls individually matched for age, sex and neighbourhood were also recruited in each site. Detailed data were collected on a range of socio-demographic and indices of physical health through a combination of self-report and clinical measures. Data were analysed using cross-tabulation to compare prevalence of comorbidities between sites and conditional logistic regression models to compare the physical health of cases versus controls.

Results: Individuals with psychosis in Trinidad had a higher prevalence of cardiometabolic conditions than those in either India or Nigeria, and were ~4 times more likely to report a history of head injury than those in Nigeria. Conversely, anaemia and malnutrition were more prevalent among cases in India, and Nigeria than in Trinidad. Infections were most prevalent among the Nigerian sample.

Controls were twice more likely to have hypertension than cases in Nigeria and India but the reverse was observed in Trinidad. Both in India and Nigeria, there was a 3-fold elevated prevalence of malnutrition among cases relative to controls. Also in Nigeria, cases were more likely than controls to have elevated level of inflammatory protein (O.R=2.7, 95% C.I=1.4-5.4) and of infection (O.R=3.2, 95% C.I=1.7-6.0).

Conclusions: This study provides rare data on comorbid health conditions among people with psychosis in three socially, culturally and economically diverse settings in the global south. Our observation that hypertension was more common in controls than in people with psychosis in the Indian and Nigerian settings was unexpected, but has been reported in some previous

studies. The ~3-fold elevated odds of malnutrition may reflect the social and economic disadvantage of this group. These findings can inform service planning to reduce disability and mortality among this highly marginalised population.

8. THE IMPACT OF DURATION OF UNTREATED PSYCHOSIS ON OUTCOME: REAL WORLD EFFECT OR PHANTOM? LEARNING FROM LANDMARK OBSERVATIONAL STUDIES

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Overall Symposia Abstract: It has been more than 30 years since Richard Wyatt published his influential paper 'Neuroleptics and the Natural Course of Schizophrenia'. In this paper, he argued that patients who received delayed treatment of neuroleptics had worse outcome than those who were promptly treated, due to a neurotoxic effect of the psychosis. The correlation between duration of untreated psychosis (DUP) and later outcome has since been reproduced in several meta-analyses. These data have provided the rationale for developing and funding specialized Early Intervention in Psychosis services internationally. Detecting and reducing DUP, as well as developing comprehensive treatment programs for first episode psychosis, are core aims of these services.

However, the explanatory processes underpinning this relationship have never been adequately clarified. Aside from the neurotoxicity hypothesis, DUP has been proposed as an illness marker, associated with an insidious onset, more pronounced negative symptoms, and functional decline. It has also been argued that that further investigation of a biopsychosocial model – with consideration given to dopaminergic hyperfunction, salience attribution, individual meaning making, and lifestyle-related factors – may aid our understanding of the relationship. Recently, Jonas et al., in a paper in the American Journal of Psychiatry in 2020, posited that the correlation could be due to lead-time bias, explaining the association by patients with a long DUP being farther along the illness trajectory than those with a short DUP.

Understanding the nature and progression of early psychosis is of major importance for designing service models and developing targeted and appropriate methods to support recovery. In this symposium, we include four presentations using different approaches to examining DUP and its relationship to outcome. Firstly, Dr. Jonas will present data from the Suffolk County Mental Health Project (New York, United States of America), showing the correlation between DUP and functional outcome to be due to lead-time bias. Secondly Dr. Albert will present results from the OPUS study (Copenhagen and Aarhus, Denmark), using slightly different statistical models, not finding lead-time bias to be an explanatory factor. Thirdly, Dr. O'Keeffe will present data from the iHOPE cohort (Dublin, Ireland) that illuminate heterogeneity in associations between DUP and different outcome domains, showing that these effects endure across a 20-year period following first admission, and therefore appear inconsistent with lead-time bias. Fourthly, Prof. Waddington will present results from the Cavan-Monaghan First Episode Psychosis Study (Cavan and Monaghan, Ireland) that show how long-term outcome is predicted by both DUP and duration of untreated illness. The progressive diminution in associations between DUP and outcome, that would be predicted by lead-time bias, was not found.

Studying the DUP in a randomized design is challenging, and it would be considered unethical to randomize patients to prolonged DUP. A few studies have successfully conducted trials with

a quasi-experimental design and more of these trials are needed, but in this symposium, we explore what knowledge can be gained by using data from some of the larger landmark long-term observational studies recently published. Further, the co-chair Dr. Hegelstad and the discussant Dr. Srihari have, in Norway and the United States of America respectively, administered two of the quasi-experimental trials and successfully reduced DUP. This provides the opportunity for discussing what questions can be answered in observational studies, what questions need different designs, and how we should design future DUP studies.

8.1 LEAD-TIME BIAS EXPLAINS THE ASSOCIATION BETWEEN DUP AND LONG-TERM OUTCOMES

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Background: At first hospitalization, a long duration of untreated psychosis (DUP) predicts illness severity and worse treatment outcomes. The mechanism of this association, however, remains unclear. It has been hypothesized that lengthy untreated psychosis is toxic, or reflects a more severe form of schizophrenia. Alternatively, the association may be an artifact of lead-time bias. These hypotheses are tested in a longitudinal study of schizophrenia with 2,137 observations spanning from childhood to 20 years after first admission.
Methods: Data are from the Suffolk County Mental Health Project. The cohort included 287 individuals with schizophrenia or schizoaffective disorder. DUP was defined as days from first psychotic symptom to first psychiatric hospitalization. Psychosocial function was assessed using the Premorbid Adjustment Scale (PAS) and Global Assessment of Functioning (GAF) scale. Psychosocial function trajectories were estimated using multilevel spline regression models adjusted for gender, occupational status, race, and antipsychotic medication.
Results: Both long and short DUP patients experienced similar declines in psychosocial function, but declines occurred at different times relative to first admission. Long DUP patients experienced most of these declines prior to first admission, while short DUP patients experienced declines after first admission. When psychosocial function was analyzed relative to psychosis onset, DUP did not predict illness course.
Conclusions: The association between DUP and psychosocial function may be an artifact of early detection, creating the illusion that early intervention is associated with improved outcomes. In other words, DUP may be better understood as an indicator of illness stage than a predictor of course. These results will be discussed in the context of continued efforts to replicate our findings.

8.2 DOES LEAD TIME BIAS CONFOUND THE ASSOCIATION BETWEEN DURATION OF UNTREATED PSYCHOSIS AND OUTCOME IN SCHIZOPHRENIA? A REPLICATION STUDY

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Background: The association between duration of untreated psychosis (DUP) and later outcome is not fully understood. Jonas et. al. (Jonas KG, Fochtmann LJ, Perlman G, et al.: Lead-Time Bias Confounds Association between Duration of Untreated Psychosis and Illness Course in Schizophrenia. Am J Psychiatry 2020) found that the association could be explained be lead-time bias. In this study we aimed to analyse the relationship between DUP, time since onset of psychosis and functional outcome using a similar statistical approach as in the Jonas et. al. study.
Methods: Using data from 496 participants with first episode schizophrenia, DUP was assessed using the IRAOS and functioning were at the baseline assessment and the subsequent follow-ups (1, 2, 5 and 10 years) assessed using the GAF-F. For premorbid functioning the Premorbid Assessment of Functioning Scale was used and rescaled to correspond to the GAF.
Results: The model with the best fit of data to model change in function was placing the inflection point at the time of first treatment and including not just a slope change but a level change in the model. This model indicated a slow decline per year until first treatment, at which point there was a sharp decrease in functioning, and after which functioning gradually improved again. Both in this model and in models accounting for potential lead-time bias, however, longer DUP was associated with a decrease in function for each additional week of DUP. This is in contrast with the Jonas et al. study.
Conclusions: In this study, we did not find evidence of a lead-time bias, but rather found that onset of treatment occurs at the time when participants level of functioning was most impaired, and consequently was not at random.

8.3 HETEROGENEITY IN ASSOCIATIONS OF DURATION OF UNTREATED PSYCHOSIS WITH SYMPTOMS, FUNCTIONING, AND QUALITY OF LIFE AT 6 MONTHS AND 4, 8, 12, AND 20 YEARS POST FIRST-EPISODE PSYCHOSIS

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Background: Clarifying the extent that associations between duration of untreated psychosis (DUP) and outcome endure over time necessitates prospective, systematic studies of epidemiologically representative incidence cohorts across decades. There is a need to investigate transience, persistence, or heterogeneity in associations between DUP and distinct outcome domains over the very long term.
Methods: We conducted prospective, sequential follow-up studies of an epidemiologically representative first-episode psychosis incidence cohort (iHOPE) in Dublin, Ireland (N=171). We ran linear mixed-model analyses to determine if prospective associations of DUP with symptoms, functioning, and quality of life were consistent or varied across over a 20-year period post first-episode psychosis. We evaluated time, DUP quartile, and DUP quartile-by-time interaction effects.
Results: Results showed positive and negative symptoms, functioning, and quality of life to display four different trajectories of improvement in relation to shorter DUP. Regardless of heterogeneity in course and relationship to premorbid features, relationships between shorter DUP and greater improvement were still evident 20 years after a person's first episode of psychosis. While associations between DUP and long-term outcome varied according to outcome domain, they were sustained across decades in a way that could not be accounted for by premorbid features or lead-time bias.
Conclusions: Further investigation of a biopsychosocial model may help explain the heterogeneity in associations between DUP and different domains of symptomatic and functional outcome that we found. Although our study was not a controlled evaluation of the

effectiveness of Early Intervention in Psychosis services, results nonetheless imply that efforts to reduce DUP may have clinical benefits that could last for at least 20 years post first-episode psychosis.

8.4 DUP: RECALIBRATING THE PROSPECTIVE, LONG-TERM RELATIONSHIP TO OUTCOME AND ELABORATION TO DURATION OF UNTREATED ILLNESS (DUI)

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Background: In a prescient and heuristic study of first episode psychosis (FEP), Crow and colleagues (1986) noted "persistence of symptoms untreated by neuroleptic drugs leads to abnormality, which cannot be completely reversed by subsequent treatment" and "medication instituted early and continued during and perhaps after an acute episode of illness will have enduring beneficial effects on the course of the condition". While recent meta-analysis across subsequent studies confirms the statistical robustness of these relationships, debate endures as to how they should be interpreted: (i) Is DUP not a direct predictor of outcome but, rather, confounded with premorbid features and, most recently, lead-time bias? (ii) Do associations between DUP and impairment at FEP extend to long-term outcome? (iii) Do they involve particular domains of outcome? (iv) Are they distributed uniformly across the range of DUP encountered or vary with particular gradations of DUP? (v) Do they relate primarily to schizophrenia spectrum psychosis or generalise to affective psychosis? (vi) If DUP is a direct predictor of outcome, what bio-psychosocial processes might underlie these relationships? (vii) Critically, does duration of untreated illness (DUI), which adds length of the psychosis prodrome to DUP, conflate two distinct processes or reflect a unitary process dichotomised into two moieties at an arbitrary threshold along a continuum?

Methods: The Cavan-Monaghan First Episode Psychosis Study (CAMFEPS) is embedded within Irish public mental health services to identify and assess an epidemiologically representative population of incident FEP. We have recently conducted, for the first time: (a) systematic epidemiological and clinical comparison between all 12 DSM-IV psychotic diagnoses in terms of psychopathology, neuropsychology, neurology, premorbid intellectual function, premorbid adjustment, quality of life and insight; (b) systematic comparisons of DUP vs DUI in terms of their associations with assessments at FEP and 7-year follow-up. We here outline our findings and ongoing analyses as they relate to challenges (i) to (vii) above.

Results: Longer DUI but not DUP predicted more severe positive and general symptoms, while longer DUP and particularly DUI predicted more severe negative symptoms; neither longer DUP nor DUI predicted more severe cognitive impairment or more neurological soft signs; longer DUP and DUI predicted reduced quality of life; longer DUI but not DUP predicted reduced insight. Prediction by longer DUP and DUI of greater psychopathology, particularly negative symptoms, and lower quality of life remained stable between FEP and 7-year follow-up; longer DUP and DUI also predicted lower functionality and service engagement at follow-up. While most associations were confined to the longest DUP-DUI quartile, only those between DUP-DUI and negative symptoms and quality of life were distributed in a graded manner across DUP-DUI quartiles.

Conclusions: Across these studies there was little confounding with premorbid features and findings were generally similar with or without inclusion of affective psychoses. That prediction of outcome by DUP appeared both constant across seven years and independent of inclusion/exclusion of affective psychoses is inconsistent with two proffered tenets of lead-time bias. DUP and DUI may differ only in the numerical sense that DUI accumulates longer

expression of an untreated bio-psychosocial process than DUP by inclusion of length of prodrome; thus, instances where DUI is more reliably associated with a given outcome than DUP may reflect DUI capturing the earlier start and longer duration of that process.

9. FUTURE DIRECTIONS FOR PSYCHOTIC EXPERIENCES RESEARCH: A GLOBAL PERSPECTIVE

Sinan Guloksuz*, Maastricht University*

Overall Symposia Abstract: Psychotic experiences are observed in the general population with prevalences of around 17% in children, decreasing to 5–7% in later life. Although subthreshold psychotic experiences lie on the less severe end of the psychosis spectrum, they predict later mental ill-health and functional impairment. Evidence suggests etiological continuity between subclinical expression and clinical manifestation of psychosis. Therefore, a better understanding of the etiopathology of psychotic experiences is essential to guide prevention and intervention strategies along the psychosis spectrum. This symposium provides an overview of recent important studies investigating psychotic experiences, covering forefront research on risk factors, trajectories, and outcomes in children, adolescents, and adults.

Prof. Cannon will provide results from a recent systematic review and meta-analysis of lifetime incidence and persistence rates of psychotic experiences, including 35 papers. The pooled Incidence rate was 0.025 per-person year, with 34% showing persisting psychotic experiences. Both the incidence and persistence rates were the highest in adolescence. Findings provide important insights into the development of psychotic experiences across the lifespan and highlight adolescence as an important transitional stage for intervention.

Dr. Calkins will discuss long-term trajectories of psychotic experiences and associated environmental factors, presenting unpublished findings from a large youth cohort covering the age-range of 8 to 21 years, the Philadelphia Neurodevelopmental Cohort. They found only those with recurrent psychosis expression displayed a nonlinear developmental trajectory of positive symptoms, with declining functioning and increasing disorganized and general symptoms. These findings highlight the great opportunity for early identification and intervention throughout this sensitive developmental period and encourage investigating risk and protective factors underlying trajectories toward the psychosis spectrum.

Dr. Lin will discuss recent findings from the first exposome-wide association study of psychotic experiences in the UK Biobank. This study investigated the association of psychotic experiences with 247 environmental, lifestyle, behavioral, and economic factors through exposome-wide analyses to identify 36 factors independently associated with psychotic experiences. By applying subsequent Mendelian Randomization analyses, they showed that experiencing sexual assault might be a causal risk factor for psychotic experiences, but experiencing physically violent crime and cannabis use rather appeared to be possible aftereffects of having psychotic experiences.

Dr. Pries will discuss unpublished findings from a general population twin cohort collected in Belgium. This study investigated the gender-specific associations of exposure to childhood adversities with psychosis expression across psychopathology domains. They found gender-specific patterns of susceptibility to childhood abuse (particularly sexual and emotional) for women and childhood neglect (particularly physical) for men. Their findings underscore the urgent need to investigate gender-specific patterns underlying the environmental etiopathology of early psychosis.

Prof. Kelleher will summarize and discuss the key findings and implications of these findings for future studies on psychosis spectrum and intervention opportunities in the general population.

9.1 INCIDENCE AND PERSISTENCE OF PSYCHOTIC EXPERIENCES IN THE GENERAL POPULATION: SYSTEMATIC REVIEW AND META-ANALYSIS.

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Background: Psychotic experiences (PE) are associated with increased risk for psychotic disorders, mental disorders, suicidal behaviour and poor functioning. Persistent or recurrent PE are thought to be associated with greater psychiatric risk than transient PE. We wished to systematically review and meta-analyse the incidence and persistence of PE in the general population.

Methods: Two independent reviewers conducted a double blind search of databases (Embase, Pubmed PMC, Psychinfo, Medline, Web of Science) from inception to January 2021, and data extraction. Study quality was assessed using the NIH assessment tool. Incidence rate per-person-year and persistent PE rate per-year were calculated. Random effects models were conducted to calculate pooled incidence rate per-person year, and proportion of persistent PE. Age, publication year, and study design were all examined using subgroup analyses.

Results: Using a double blind screening method for abstract (k=5763) and full text (k=198) were screened. In total 39 samples from 35 studies were included, of which 31 were included in a meta-analysis (incidence k=15, n=46,554; persistence k=16,n=83870). Pooled Incidence rate (IR) was 0.025 per-person year (95%CI[0.0147;0.0351]). That is, for every 100 people, 2.5 reported first onset PE in a year. This was highest in adolescence (13–17 years; IR=0.05) and declined in older samples. The pooled persistence rate for PE was 33.95% (95%CI[0.2922, 0.3867]) This was highest in adolescence (42.78%;95%CI[34.02, 51.53]).

Conclusions: This systematic review and meta-analysis investigated the incidence rate per year of PE in the general population, as well as the persistence rate of PE. Two key findings emerged: the incidence rate of PE per year was 0.025 per person years i.e. for every 100 individuals, 2.5 will report new onset PE in a given year. This was highest in adolescents and lowest in older adults.

This is the largest systematic review to date to examine incidence, and the first with sufficient data to analyse to calculate the incidence rate per-person year. This is an important measure for research as knowledge of expected numbers of PE allows for the study of the causes of PE. The systematic review also found that almost all studies which measured PE at multiple time points found a subsample reporting persistent PE, suggesting that recurrence is a relatively common feature of PE. The meta-analysis conducted showed that about one third of those who experience PE will have persistent PE - the pooled proportion of persistent PE was 33.9%. Stratification analysis found that incidence and persistence or PE were both highest in adolescence which has implications for interventions to prevent or reduce recurrence of psychotic experiences.

9.2 LONGITUDINAL TRAJECTORIES OF CLINICAL FEATURES IN COMMUNITY YOUTH WITH RECURRENT PSYCHOSIS SPECTRUMS: FINDINGS FROM THE PHILADELPHIA NEURODEVELOPMENTAL COHORT (PNC)

Monica Calkins*[1], Ellyn Butler[2], Tyler Moore[1], Jerome Taylor[3], Ran Barzilay[3], Kosha Ruparel[1], Bart Larsen[1], Daniel Wolf[1], Theodore Satterthwaite[1], Ruben Gur[1], Raquel Gur[1]

[1]*University of Pennsylvania,* [2]*Northwestern University,* [3]*University of Pennsylvania and Children's Hospital of Philadelphia*

Background: Subthreshold psychosis spectrum (PS) experiences are relatively common in the general youth population, progressing to psychotic disorders in a minority. Prior work indicates community youth with PS symptoms exhibit neurobehavioral, neurocognitive, and functional impairments consistent with those observed in individuals with threshold psychotic disorders. General population studies suggest that more severe, recurrent subthreshold psychosis symptoms are associated with heightened risk of progression to threshold psychosis. Increasing efforts aim to understand and characterize features and predictors of varying PS trajectories. Such understanding may apprise methods to both identify youth at highest risk of deleterious outcomes and target preventative interventions. In the current investigation, we thus sought to expand and temporally extend our prior two-year follow-up of youth with recurrent psychosis spectrum symptoms in the Philadelphia Neurodevelopmental Cohort (PNC) through examining and comparing long term trajectories of PS related symptoms and function.
Methods: The PNC is a collaboration between the Children's Hospital of Philadelphia and the University of Pennsylvania through which 9,498 community youth (age 8-21) were recruited from a pediatric healthcare network at Time 1. A subsample of participants (n=752) was invited for follow-up based on Time 1 screening indicating presence or absence of PS symptoms. Youth participated in repeated prospective evaluations, with the interval between the first and last assessment ranging from 0.2 to 9.3 years (mean = 4.52 years). On average, participants completed 2.75 visits (age range first visit = 8.1-21.9; age range final visit = 9.5-29.9). Youth were classified into 9 groups according to longitudinal combinations of PS symptoms, other psychopathology, and/or no psychopathology, at the first and last visits. Longitudinal trajectories of PS symptoms (positive, negative, disorganized, general) and global functioning were modeled using generalized additive mixed models (GAMMs). Baseline traumatic exposures and neighborhood environment were evaluated as predictors of final PS status.
Results: Only the group with recurrent PS displayed a nonlinear developmental trajectory of positive psychosis symptoms such that severity increased slowly until the early 20's, at which point the symptoms briefly plateaued before increasing significantly in the late 20's. They also exhibited significant increases over time in disorganized ($p<0.05$) and general symptoms ($p<0.005$), which were lower in severity and relatively stable over time in the other groups. Compared to the other groups, in whom global functioning impairment consistently ranged from mild to absent, global functioning in the recurrent PS group was moderately impaired, declining to serious over time. Both number of trauma types and neighborhood poverty were associated with increased likelihood of final PS status.
Conclusions: Results underscore the existence of a wide developmental window of opportunity to not only investigate risk and protective factors associated with varying clinical outcomes, but also improve early identification and intervention.

9.3 EXPOSOME-WIDE ANALYSIS AND MENDELIAN RANDOMIZATION FOR THE SYSTEMATIC IDENTIFICATION OF NONGENETIC CORRELATES OF PSYCHOTIC EXPERIENCES IN THE UK BIOBANK

Bochao Lin*[1], Lotta-Katrin Pries[2], Halil S. Sarac[3], Jim van Os[4], Bart P. F. Rutten[3], Jurjen Luykx[5], Sinan Guloksuz[6]

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Background: Although hypothesis-driven ("candidate exposure") approaches identified several non-genetic factors associated with psychotic experiences, these approaches overlook the multiplicity of exposures and have several limitations such as preconception biases and selective reporting. Systematic hypothesis-free exposome-wide approaches are needed to detect strong, consistent, and novel correlates of psychosis. Therefore, we analyzed the correlates of psychotic experiences through data-driven agnostic analyses and genetically informed approaches to probe causality.

Methods: For the current study, we analyzed data from the UK Biobank (UKB project number: 55392) Mental Health Survey. The binary endorsement of psychotic experiences was defined by the report of any of the following four lifetime experiences: visual hallucination, auditory hallucination, reference delusion, and persecutory delusion. Furthermore, 247 non-genetic variables were included in the analyses after quality control. The analyses comprised three sequential main analytical steps. First, an exposome-wide association study was conducted in two equal-sized split discovery and replication data sets. Second, variables associated with psychotic experiences in the exposome-wide analysis were tested in a multivariable model. Third, for the variables associated with psychotic experiences in the final multivariable model, the SNP-based heritability and genetic overlap with psychotic experiences using linkage disequilibrium score regression were estimated, and Mendelian Randomization (MR) approaches were applied to test potential causality. The significant associations observed in one-sample MR analyses were further tested in multiple sensitivity tests, including collider-correction MR, two-sample MR, and multivariable MR analyses.

Results: The study included 155.247 participants (87.896 [57%] female; mean [SD] age, 55.94 [7.74] years). In the discovery data set, 162 variables (66%) were associated with psychotic experiences. Of these, 148 (91%) were replicated in the replication data set. The multivariable analysis of the 148 replicated variables revealed that 36 (24%) were associated with psychotic experiences. Of these, 28 had significant genetic overlap with psychotic experiences. Compared to the exposome-wide analyses, the associations of 5 variables with psychotic experiences were in the opposite direction (i.e. the so-called Janus effect) in the multivariable analysis. One-sample MR analyses revealed potential forward causal effects with 3 variables and reverse causal effects for 3 variables. The sensitivity tests confirmed the forward associations with ever having experienced sexual assault and pleiotropy of risk-taking behavior. Furthermore, reverse associations without pleiotropy of experiencing a physically violent crime as well as cannabis use and the reverse association with pleiotropy of worrying too long after embarrassment were confirmed.

Conclusions: Our systematic investigation revealed associations of psychotic experiences with both well-studied and unexplored variables. Several variables showed Janus effects: the direction of the association was reversed in the final multivariable and MR analyses. Forward MR analyses showed an association with having experienced sexual assault and pleiotropy of risk-taking behavior. Reverse MR analyses showed an association with having experienced

physically violent crime, cannabis use, and worrying too long after embarrassment. The findings of this study underline the need for systematic approaches and triangulation of evidence to extract reliable knowledge from "big data" that will help to develop population-based prevention strategies.

9.4 GENDER DIFFERENCES IN THE ASSOCIATIONS BETWEEN CHILDHOOD ADVERSITY AND PSYCHOPATHOLOGY IN THE GENERAL POPULATION

Lotta-Katrin Pries*[1], Thanavadee Prachason[2], Irem Mutlu[3], Laura Fusar-Poli[4], Claudia Menne-Lothmann[5], Jeroen Decoster[6], Ruud van Winkel[7], Dina Collip[5], Philippe Delespaul[5], Marc De Hert[8], Catherine Derom[9], Evert Thiery[10], Nele Jacobs[11], Marieke Wichers[12], Jim van Os[13], Bart Rutten[5], Sinan Guloksuz[14]

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Background: Research suggests differential susceptibility to childhood adversity (CA) in men and women. However, there has been little research on gender-specific associations of the exposure to CA subtypes on population-based psychopathology (including psychosis phenotypes). Therefore, the current study aimed to explore gender-stratified associations of CA subtypes and psychopathology in the general population.
Methods: Data was retrieved for 791 twins and their siblings from the general population TwinssCan project. The Symptom Checklist-90 Revised (SCL-90) was used to assess total psychopathology and nine subdomains: total SCL-90, psychoticism, paranoid ideation, anxiety, depression, somatization, obsessive-compulsive, interpersonal sensitivity, hostility, and phobic anxiety. The Childhood Trauma Questionnaire (CTQ) was used to measure total CA and five CA subtypes: total CTQ, physical abuse, emotional abuse, sexual abuse, physical neglect, and emotional neglect. Linear regression analyses were applied to test the associations between the CTQ and SCL-90 scores for men and women separately. All analyses were adjusted for age and clustering of family membership. The associations between the five CA

subtypes and the total SCL-90 score were tested in a mutually adjusted model accounting for the co-occurrence of the other CA subtypes. As explorative analyses, the associations between the five CA subtypes and the nine SCL-90 subdomain scores were tested in nine mutually subtype-adjusted models.
Results: Total CTQ explained 15.4% of the variance of total SCL-90 in men (B = 0.013, SE = 0.003, P < .001) and 12.9% in women (B = 0.011, SE = 0.002, P < .001). Furthermore, total CTQ was significantly associated with all symptom domains in men and women (all P < .001). For men, the top three hits with the highest explained variance included psychoticism (15.7%), phobic anxiety (15.7%), and depression (12.7%). For women, the top three hits with the highest explained variance included psychoticism (13.7%), paranoid ideation (11.7%), and somatization (8.6%). The CA subtype analyses showed gender-specific patterns. The associations of emotional neglect (B = 0.57, SE = 0.26, P = .026) and physical neglect (B = 0.167, SE = 0.043, P < .001) with total SCL-90 were only significant in men. The association of sexual abuse with total SCL-90 was only significant in women (B = 0.217, SE = 0.053, P < .001). Emotional abuse was associated with total SCL-90 in women (B = 0.173, SE = 0.030, P < .001) and men (B = 0.080, SE = 0.035, P = .023). Furthermore, the explorative analyses of the symptom domains showed that emotional abuse was significantly associated with all symptom domains and sexual abuse was associated with six symptom domains in women. In men, physical neglect was significantly associated with six symptom domains and emotional neglect was associated with depression. No other significant associations between CA subtypes and the SCL-90 scores were observed in men or women.
Conclusions: The study confirmed the non-specific influence of CA across all symptom domains in men and women. However, early childhood adversities might be specifically relevant to the development of severe mental health problems including psychosis phenotypes. Psychoticism was among the top three hits with the highest explained variance by CA in men and women. Additionally, paranoid ideation was among the top three hits for women. The CA subtype analyses suggested gender-specific patters of susceptibility to abuse (especially sexual and emotional) for women and neglect (especially physical) for men. This finding underscores the need to take gender-specific patterns into account when evaluating the effects of CA subtypes on psychopathology.

10. COMPLEMENT C4 GENE AND SCHIZOPHRENIA

James Kennedy, *CAMH*

Overall Symposia Abstract: Immune disturbances have long been associated with the development of SCZ. Advances in large-scale genetic studies and immunology have increased our understanding of the immune system's potential involvement in SCZ. A recent genome-wide association study (GWAS) identified 287 loci associated with SCZ. The Major Histocompatibility Complex (MHC), which is located on chromosome 6, showed the strongest association with SCZ. MHC encodes hundreds of genes, of which many have important roles in the immune system. Due to the complex linkage disequilibrium structure of the MHC region, identifying the functional alleles responsible for its association with SCZ has been challenging. Sekar et al. (2016) showed the complement component C4 gene located in the MHC, to be associated with SCZ risk. The C4 protein is an important component of the complement system, in the innate immune system, and has two structurally and functionally distinct isotypes, C4A and C4B. Moreover, C4 can segregate in long (C4AL and C4BL) or short (C4AS and C4BS) forms depending on presence or absence of a human endogenous retroviral (HERV) insertion. Studies showed increased C4A expression to be associated with higher SCZ risk and the underlying mechanism of this association is suggested to be due to excessive synaptic pruning. Furthermore, studies have shown C4 to have a major role in sex dimorphism

in SCZ and other diseases such as Sjogren's syndrome and systemic lupus erythematosus. The association of the complement component C4 gene with SCZ and potentially other psychiatric diseases is still poorly understood. Thus, exploring the role of C4 in the etiology of SCZ may influence our understanding of this illness and potentially guide us towards development of C4 as a novel drug target and accelerate treatment advances.
Dr. Alex Hatzimanolis will present on the C4 gene and peripheral expression in first-episode psychosis and links to cognitive ability.

Dr. Clare Beasley will present data on complement component C4 in animal models and human postmortem studies.

Ms. Kowsar Teymouri will present on the association of complement component C4 (N > 400) with SCZ phenotypes, such as age of onset, general assessment of functioning (GAF score), sex differences, and treatment resistance.

Dr. Romain Rey will present data on C4 genotypes in the OPTIMISE SCZ study, as well as C4 gene expression in postmortem brain regions.

Dr. Robert Yolken, as discussant, will add overall commentary from a senior researcher point of view, and including gene environment interaction of C4 with the microbiome.

10.1 THE EFFECT OF COMPLEMENT COMPONENT 4 (C4) IN CLINICAL CHARACTERISTICS OF SCHIZOPHRENIA AND TREATMENT RESISTANCE

Kosar Teymouri*[1], Cheng Cheng Chen[2], Mahbod Ebrahimi[2], Clement Zai[2], James Kennedy[2]

[1]*Center for Addiction and Mental Health,* [2]*Centre for Addiction and Mental Health, University of Toronto*

Background: Recent advances in immunology and large-scale genetic studies have strongly supported a role of the complement system in schizophrenia. One of the roles of the complement proteins is their involvement in clearing waste and cellular debris in the brain and other tissues. The most recent genome-wide association studies (GWAS) identified 287 loci to be associated with schizophrenia, in which the complement component C4 gene remains as the strongest genetic site for schizophrenia risk. The human C4 gene codes for two structurally and functionally different isotypes, C4A and C4B and it also has long or short forms (C4L and C4S) depending on the presence of a human endogenous retroviral (HERV) insertion. Sekar et al. (2016) showed that brain expression levels of C4A and C4B depend on the structural forms of the C4 gene. Previous studies have associated C4L with higher C4A brain expression and observed the C4 gene to differentially affect risk for men versus women. In this study, we aimed to investigate the association between the C4 structural forms as well as predicted brain expression with treatment resistant schizophrenia, sex and clinical characteristics of schizophrenia including age of onset, global assessment of functioning (GAF), and symptom severity.
Methods: The total of 434 subjects, age 18 to 80 were diagnosed research SCID interviews. Patients prescribed with clozapine were considered treatment resistant.
Results: Our preliminary study of a subset of subjects (N=163) did not show significant association between C4 copy number and treatment resistant schizophrenia. However, the results for the total of 434 subjects will be presented at the symposium. Our results showed significant associations between C4 structural forms and C4 expression with age of onset, GAF score and symptom severity. Age of onset and C4AS showed marginal association ($t = 1.964$, $p = 0.050$). Also, significant association was observed between symptom severity and C4B copy number ($t = 2.587$, $p = 0.010$) and C4B expression ($t = 2.566$, $p = 0.011$). C4A ($t = 2.442$,

p = 0.015) and C4A expression (t =2.524, p = 0.012) were significantly associated with GAF score. Moreover, C4AL (p = 0.006) and C4AS (p=0.036) were significantly overrepresented in males, while C4BS (p = 0.013) was observed to exert higher risk in females.
Conclusions: Overall, our study provides further support for a role of the C4 gene as a genetic biomarker for schizophrenia risk and provides a scan of major subphenotypes in schizophrenia. More detailed genetic investigations of C4 across the subtypes of schizophrenia are warranted.

10.2 ALTERED PERIPHERAL EXPRESSION OF SCHIZOPHRENIA-IMPLICATED COMPLEMENT COMPONENTS C4A AND CSMD1 IN FIRST-EPISODE PSYCHOSIS AND ASSOCIATION WITH COGNITIVE FUNCTION

Alex Hatzimanolis*[1], Stefania Foteli[2], Angeliki Ntigrintaki[2], Maria Gazouli[2], Nikos Stefanis[3]

[1]*National and Kapodistrian University of Athens Medical School,* [2]*National and Kapodistrian University of Athens,* [3]*National and Kapodistrian University of Athens, Greece*

Background: Overexpression of the complement component 4A (C4A) in the brain has been suggested to promote excessive synaptic pruning and increase susceptibility to schizophrenia (SZ) development. Higher gene expression levels of C4A has been observed in SZ postmortem brain tissue, and the gene encoding for a protein inhibitor of C4A activity, CUB and Sushi multiple domains 1 (CSMD1) gene, has been implicated in SZ risk and cognitive ability, though genetic investigations.
Methods: C4A and CSMD1 mRNA expression levels were examined in peripheral blood mononuclear cells from antipsychotic-naive individuals with first-episode psychosis (FEP; n = 73) and healthy volunteers with no history of mental illness (n = 48). Serum protein levels of C4A were also determined using standard immunoassays. Genotype impution of C4 locus structural alleles was performesd and genetically-determined C4A expression was explored. Associations with symptom severity and cognitive performance indices were investigated.
Results: CSMD1 gene expression was significantly decreased among FEP patients compared to healthy volunteers, while a positive correlation between C4A and CSMD1 mRNA levels in healthy volunteers but not in FEP cases. In addition, genetically-determined C4 copy number variants previously associated with elevated SZ risk correlated with higher C4A mRNA levels within FEP cases, which confirms the previously observed regulatory effect of C4 structural variants on gene expression. Evidence also emerged for markedly elevated C4A serum concentrations in FEP cases. Within the FEP patient group, higher C4A mRNA levels associated with more severe general psychopathology symptoms and lower CSMD1 mRNA levels predicted worse working memory performance.
Conclusions: Our findings provide evidence for aberrant C4A complement pathway expression in individuals with FEP and imply differences in

psychopathology symptom severity. Further, the results corroborate the involvement of CSMD1 component in prefrontal-mediated working memory ability.

10.3 COMPLEMENT C4 EXPRESSION IN POSTMORTEM FRONTAL CORTEX IN SCHIZOPHRENIA: ASSOCIATION WITH SYNAPTIC DENSITY

Clare Beasley*[1], Li Shao[1]

[1]*University of British Columbia*

Background: Genome-wide association studies have revealed an association between schizophrenia (SCZ) and structural variants in the complement component 4 (C4) gene. The complement system is a key effector of innate immunity in the brain, mediating elimination of pathogens and debris. It is now known that the complement system also participates in synaptic pruning and plasticity, with C4 involved in opsonization of synapses for elimination via microglial phagocytosis, both during development and in adulthood. While it has been proposed that complement C4 may confer SCZ risk via effects on synaptic refinement, the role of the complement system in SCZ pathogenesis is not yet fully understood, and the impact of complement levels and C4 genetic diversity on synaptic density in this disorder remains to be elucidated.

Methods: Protein and mRNA expression of complement C4 was quantified in postmortem frontal cortex from individuals with SCZ (n = 35), bipolar disorder (n = 34), and matched controls (n = 35) by immunoblotting and quantitative PCR. C4 protein levels were also determined in serum in the same individuals. C4 haplotypes were recorded for each subject. The relationship between complement C4 and levels of the pre-synaptic protein SNAP-25, quantified via enzyme-linked immunosorbent assay, was examined. Effects of antipsychotic medications on C4 protein levels were explored in a rodent model.

Results: In frontal cortex, gene expression of C4A differed between groups, with contrast analysis indicating that expression was significantly greater in the SCZ group relative to the control group. While C4 protein levels did not differ between groups, both C4A expression and C4 protein levels were higher in subjects with greater C4A allele frequency. Correlational analyses revealed inverse associations between brain C4 protein and C4A gene expression and levels of pre-synaptic protein. Serum C4 protein levels were elevated in rats administered clozapine, but not haloperidol.

Conclusions: Our results corroborate previous findings of increased C4A gene expression in postmortem brain tissue in SCZ. We extend this line of research to reveal that individuals with high C4A expression have lower synaptic density, potentially indicative of excess synaptic pruning. Our data highlight a relationship between complement C4 and synaptic density in SCZ, furthering understanding of the etiopathophysiology of this disorder, and potentially providing clues to novel treatment strategies. Additional research is needed to explore the temporal course of complement dysregulation in SCZ and downstream impacts on brain circuits.

10.4 FURTHER EVIDENCE OF AN ALTERED COMPLEMENT SYSTEM ACTIVITY IN SCHIZOPHRENIA: ABNORMAL EXPRESSION OF C4, COMPLEMENT CONTROL PROTEINS AND MICROGLIA SPECIFIC GENES IN BRAIN AND BLOOD OF SCHIZOPHRENIC INDIVIDUALS

Romain Rey*[1], Anna Fiorito[2], Ibrahim El Cherif[3], Thierry D'AMATO[4], Eric Fakra[2], Guillaume Sescousse[2], Ryad Tamouza[5], Marion leboyer[5]

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Background: The synaptic pruning process is based on the joint action of the complement system and microglia. In schizophrenia (SZ), accumulating evidence support that abnormal synaptic pruning during adolescence may be due to an altered Complement system activity. While this hypothesis is supported by C4 overexpression in various brain regions of SZ individuals, such alterations should be replicated and extended to other brain regions. Moreover, transcriptional studies of genes encoding regulators of the complement system activity (complement control proteins, CCP) and microglia-specific genes are lacking. Furthermore, it remains unknown whether brain and peripheral expression of such genes are related.

Methods: We explored expression of C4 as well as 4 CCP encoding genes and 10 microglia-specific genes at the brain and peripheral levels. We analyzed candidate gene expression from 9 Gene Expression Omnibus datasets obtained from 333 SZ individuals and 306 healthy controls (HC). We first compared expression of the candidate genes between SZ individuals and HC in postmortem brain samples from 7 different brain regions. Then, the same comparison was made in 4 different peripheral tissues.

Results: Regarding the complement system, we observed C4 overexpression in the DLPFC, parietal, temporal cortex and associative striatum of SZ individuals. Furthermore, we report distinct altered expression patterns of CCP genes in the DLPFC, hippocampus and cerebellum of SZ individuals. At the peripheral level, only CD46 expression was altered in the blood of SZ individuals. Regarding microglia, we report an underexpression of several microglia-specific genes in the cerebellum, associative striatum, hippocampus and parietal cortex of SZ individuals vs. HC. At the peripheral level, we observed a mixed altered expression pattern in the whole blood of SZ individuals.

Conclusions: Firstly, our results suggest that the CCP-mediated regulatory mechanisms of the Complement system are impaired in the DLPFC of SZ individuals, potentially contributing to an excessive Complement system activity (CSA). Our findings expand this increased CSA in the associative striatum, the parietal and temporal cortices of SZ individuals. Eventually, hippocampus and cerebellum of SZ subjects exhibit altered CSA. Overall, our results support the hypothesis of an altered CSA in various brain regions of SZ individuals which may disrupt the synaptic pruning during adolescence.

Secondly, our results support the hypothesis of a widespread underexpression of microglia-specific genes in brain tissues of SZ individuals. Functionally, two alternative hypotheses can be drawn regarding these latter results. As a first hypothesis, the observed transcriptional alterations may be related to the synaptic pruning impairment. Since most of the candidate genes are involved in microglia key functions, their underexpression may disrupt microglia's critical role in the synaptic pruning. Alternatively, the identified transcriptional alterations may translate a compensatory mechanism for neuroinflammation in the brain of SZ individuals.

In the whole blood, the identified altered transcriptional pattern may represent a potential peripheral signature of SZ.

Plenary Session II: Soumitra Pathare

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

11. RIGHTS OF PERSONS WITH SEVERE MENTAL ILLNESS

Celso Arango*, Hospital General Universitario Gregorio Marañon*

11.1 RIGHTS OF PERSONS WITH MENTAL ILLNESS

Soumitra Pathare*, Centre for Mental Health Law and Policy, Indian Law Society India*

Individual Abstract: In almost all societies, persons with enduring severe mental health problems are particularly subject to discrimination and social exclusion. The adoption of the United Nations Convention on Rights of Persons with Disabilities (CRPD) in 2006 has created a paradigm shift in our approach to addressing this problem from seeing such persons as objects of charity to holders of rights, as passive recipients of care to active partners in managing their lives. While the CRPD ensrhines a number of existing rights into international law, the challenge is to ensure the realization of these rights for persons with enduring and severe mental illness in almost all countries. These barriers are at the societal level but also at the level of health services and attitudes of health professionals. In particular, the realization of these rights requires a fundamental paradigm shift in the way services are funded and provided for persons with enduring and severe mental illness. All too often, societal attitudes are shaped by the way services are designed (for example a reliance on institutional and coercive care) and attitudes of mental health professionals (eg. attitudes towards risk and dangerousness). Communities also use these service organization and health professional attitudes to justify their social exclusion.

These ideas and possible solutions that can be applied even in resource poor settings will be discussed in my talk.

Concurrent Symposia

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

12. SCHIZOPHRENIA: REVISITING CURRENT STRATEGIES FOR DIAGNOSIS AND TREATMENT

Gary Remington*, University of Toronto*

Overall Symposia Abstract: Advances in our understanding of schizophrenia have highlighted its complexity across diagnosis, treatment, and outcome. The notion that it is a unitary diagnostic entity mediated by a single mechanism has been set aside. It has been suggested that schizophrenia may better be conceptualized as a syndrome and, as such, differs one individual to the next. Numerous shifts in research capture these changes in thinking e.g., trans-diagnosis, clinical staging and subtyping, novel research targets.

This symposium examines these shifts from various perspectives. For example, the complexity of schizophrenia's clinical presentation is now mirrored by the complexity of proposed underlying pathophysiological mechanisms, calling for strategies that can assist in establishing groups that are biologically and pharmacologically meaningful. At the same time, new lines of research are identifying risk factors that warrant further research and possible inclusion as we strive to isolate those that influence risk, course, and outcome. A focus on early intervention has been embraced as part of schizophrenia research for the better part of 4 decades now, and research on this topic has grown exponentially. What have we learned and what are the

challenges going forward? In a similar fashion, antipsychotic treatment resistance was identified soon after the introduction of chlorpromazine but as a diagnostic entity it really emerged in the 1980's in the form of 'treatment resistant schizophrenia', paralleling clozapine's reintroduction. Once again, what have we learned what issues stand out as relevant to work in this area?

Summarizing, the symposium and each of its presentations seek to provide an update on topics relevant to clinical diagnosis and treatment, as well as strategies to advance the field going forward.

12.1 USING BIOMARKERS IN PSYCHOSIS

Carol Tamminga*[1], Brett Clementz[2], Jennifer E. McDowell[3], Elliot S. Gershon[4], Sarah S. Keedy[4], Godfrey Pearlson[5], Matcheri Keshavan[6], Elena Ivleva[7]

[1]*University of Texas Southwestern Medical Center,* [2]*University of Georgia,* [3]*University of Georgia,* [4]*University of Chicago,* [5]*Olin Neuropsychiatry Research Center,* [6]*Beth Israel Deaconess Med. Ctr. and Harvard Medical School and Harvard Medical School,* [7]*UT Southwestern Medical Center*

Background: The BSNIP Consortium collected a broad and extensive biomarker battery from a large number of individuals across the spectrum of psychosis, including schizophrenia (SZ), schizoaffective disorder (SAD) and psychotic bipolar disorder (PBD), as well as healthy controls (HC). This has provided a basis for biomarker characterization of Biotypes of psychosis as well as other psychosis disease characteristics. It provides a complementary approach to categorization, in contrast to phenomenological approaches like DSM, and, furthermore, demands a demonstration of which parts of this biomarker approach are clinically useful, in application.

Methods: The BSNIP consortium has been studying (i) whether a rationally selected biomarker can identify clozapine-responsive psychotic individuals for treatment trials; (ii) whether biomarkers can predict the outcome of the standard Coordinated Specialty Care (CSC) treatment in Early Psychosis; and (iii) whether we can use predictive biomarkers for kynurenic acid (KYNA) levels in brain to segregate study recruits into potentially responsive vs unresponsive to an anti-KYNA cognitive enhancing agent.

Results: The guiding principles for constructing these projects include how to use biological measures to gain clinical advantage in research will be articulated and discussed. These are projects in progress and preliminary study progress will be presented. Idealized outcomes will be presented.

Conclusions: These are all potential examples of how psychiatry could incorporate the usefulness of biomarkers into clinical care, in addition to their use as classifiers, eg Biotypes 1-3. Psychiatry will have to learn not only how to use biomarkers in practice and which strategies are useful where, but also which biomarkers are informative and what things they inform.

12.2 PARENTAL AGE AND SCHIZOPHRENIA: FROM EPIDEMIOLOGY TO GENETICS AND THE CLINIC

Dolores Malaspina*[1]

[1]*Icahn School of Medicine at Mount Sinai*

Background: Introduction: In accounting for the complex genetics of schizophrenia we proposed that advancing paternal age (APA) could be a source of influential de novo rare gene variants, then showing robust associations between APA and increasing risk for schizophrenia in the Jerusalem Birth Cohort (Malaspina et al, 2001;2019), now replicated in a dozen cohorts. Next we conducted nested exome sequencing of healthy parents and sporadic cases from the cohort and identified a handful of de novo variants (Kranz et al 2015). A replication study in NYC identified other novel and rare variants in these genes (Kranz et al , 2015) for which we presented detailed multilevel phenotypes (Kranz et al, 2016), as were plentiful rare variants in neurotrophic pathways (Kranz et al 2015). When the heritability of SZ was unexplained by common variants it became clear that de novo and rare variants are key components of its genetic architecture. However information on the biology and phenotypes associated with these is sparse beyond diagnosis. Information needs to also include longitudinal information on phenotypes and comorbidities.
Methods: We report on an enigmatic case referred to our center for a diagnosis who had a late onset of psychosis. She had first presented as a childhood developmental disorder, with dramatically shifting presentations. With special schooling she achieved good function in a sheltered workshop, but deteriorated in her 30's, presenting as anxiety and depression, then in a psychotic and catatonic state, and then to dementia. Comorbid with her decline was early menopause, numerous autoimmune conditions, including thyroid and Type 1 diabetes, and intermittent deafness.
Results: On genetic analysis compared to family members she showed a de novo mutation in DLG4 (disks large homolog 4), located on 17p13.1, which codes for the DLG4 protein known as PSD-95 (postsynaptic density protein 95). It is a scaffolding protein in the postsynaptic density (PSD), present on the post-synaptic membrane of excitatory synapses and contains glutamate receptors. The PSD-95 protein stabilizes NMDA (N-methyl-D-aspartic acid) receptors and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors on the membrane surface. It is a target of the neurotrophin receptor pathway and is transported to dendrites after NMDA receptor activation (Yoshii et al., 2007). All major downstream pathways of the BDNF receptor TRKB (NTRK2) regulate DLG4 localization on the postsynaptic membrane. Higher amounts of PSD-95 are needed for increased synaptic strength and are a key element of synaptic plasticity. This abnormal gene is pertinent to her wealth of pathologies.
Conclusions: These findings points to the many different phenotypic presentation that can accompany a single influential rare variant with effects on fundamental neuronal processes. Moreover, the clinical picture unfolds developmentally and over the life course so cross sectional diagnostic classifications are insufficient for phenotyping many SNV, as we have earlier shown for a different group of genes with de novo and novel/rare variants. This gene, like many other rare variants linked to psychosis, particularly impacted glutamatergic neurons and neurotrophin function with post synaptic locations. Developmental and other medical comorbidities may identify groups of genes with specific actions for precision treatment.

12.3 EARLY INTERVENTION IN PSYCHOSIS: FACING CHALLENGES TO MAKE IT COUNT

Ashok Malla*[1]

[1]*McGill University*

Background: The development and implementation of Early Intervention Services (EIS) for first episode psychosis (FEP), arguably the biggest improvement in delivery of mental health services in the past many decades, has been supported by evidence through controlled trials,

mostly limited to the first two years. To continue and improve the benefits of EIS, several emerging challenges need to be addressed.
Methods: The presentation is based on a review of a number of relevant studies, including those conducted by the author/presenter.
Results: The following emerging findings will be elaborated:

1. EIS benefits on clinical outcome (remission and relapse), substance use, overall functioning and costs are confirmed for the first two years and in some cases over an extended period of 5 years of EIS.

2. Only a proportion (less than 50% of referred incidence cases) might receive EIS in a defined catchment area. Not receiving EIS is associated with 4 times greater mortality over a two-year period (NNT1:40).

3. Despite overwhelming evidence of the causal role of DUP in determining clinical and functional recovery and demonstration of the positive impact of reducing DUP on short and long term outcome, there is little evidence of EIS, in different jurisdictions, having reduced DUP. A more comprehensive understanding of components and determinants of DUP will be presented to promote DUP reduction in individual EIS.

4. While two years of EIS is beneficial to most patients with a FEP, extended EIS over an additional 3 years may benefit or be necessary for only a proportion of patients. These include those with a DUP of 12 weeks or less and those with characteristics known to portend poor outcome e.g. lack of sustained remission at two years.

5. Gaps between rates of remission (higher in EIS) and rates of functional recovery (not achieved in EIS) continue despite EIS. There is no evidence currently of improved functional outcome with or without extending EIS beyond 2 years. Medication discontinuation for a proportion of patients may be associated with better functional outcome.

6. Family involvement and support have been demonstrated in multiple studies to be associated with better clinical outcomes, further supported by new data from a cross-cultural study of EIS, but this asset is poorly utilized in EIS in high income countries (HIC).

In addition, clinical high-risk (CHR) knowledge is not utilized in EIS due to lack of integration with EIS for FEP. EIS development and implementation are confined to HIC.

Conclusions: A population based approach to EIS is needed to increase access to all incidence cases of FEP; a deeper understanding of determinants of components of DUP is likely to better inform locally effective interventions to reduce DUP; further research is needed to identify appropriate length of EIS for subgroups of patients; interventions specifically designed to improve functional outcome introduced early in the course of EIS and continued for longer periods is likely to improve outcome; active interventions to improve family involvement in treatment are likely to improve outcome in EIS. Integrating knowledge from CHR research into EIS may improve early detection of cases thus reducing DUP. New EIS models need to be developed that are more appropriate for low-middle income countries (LMIC).

12.4 TREATMENT-RESISTANT SCHIZOPHRENIA: CONCEPTUALIZATION AND UPDATE

Gary Remington*[1]

[1]*University of Toronto*

Background: Refractory schizophrenia in the context of antipsychotic response dates back to the 1950's, within years of chlorpromazine's introduction i.e., "drug-resistant schizophrenia" (Allen VS, 1959). However, it would be the late 1980's when Treatment Resistant Schizophrenia (TRS) firmly established itself with the publication of specific criteria and evidence that clozapine offers superior efficacy in this population (Kane J et al. 1988). Subsequently, other criteria have been published, including those that distinguish clozapine non-responders or "ultra-resistant schizophrenia" (URS) (Lee J et al., 2015).
This line of investigation aligns with the popular strategy of clinical subtyping, in this case supporting the position that at least 3 forms of schizophrenia exist: (i) responsive to non-clozapine antipsychotics, (ii) responsive to clozapine, (iii) not responsive to existing antipsychotics, clozapine included (Farooq S et al. 2013). It is a strategy that has considerable appeal, although on closer examination there a number of issues and lines of investigation supporting a more nuanced approach.

Methods: The focus here is the concept of TRS itself. While modifications in criteria have been suggested e.g., number of antipsychotic trials, trial duration, it has remained essentially unchanged.
Results: Since the 1990's,TRS has been a fixture in schizophrenia research. More recently, considerable research has been carried out using the aforementioned subtyping (3 categories), with the goal of distinguishing these populations both biologically and clinically. A closer examination, though, identifies various factors that can potentially influence categorization e.g., diagnostic criteria, onset, illness course, clozapine use, co-morbid diagnoses.
Conclusions: Different lines of evidence suggest that clinically subtyping schizophrenia based on treatment response fails to address a number of variables that can influence this. Further, existing criteria do not align with current evidence regarding the scope of antipsychotics' action(s).

13. ETHICAL ISSUES SURROUNDING PREDICTIVE MODELING IN SCHIZOPHRENIA

Clement Zai*, University of Toronto and CAMH*

Overall Symposia Abstract: Predictive modeling is an burgeoning field with the potential to transform mental health care. While medical knowledge and technologies continue to grow, there is a need to address ethical issues that emerge with these advancements. Our ethics symposium will present complementary topics in predictive modeling in schizophrenia, involving latest predictive modeling methods and ethical challenges pertaining to diagnostics, screening, and precision medicine.
Dr. Gwyneth Zai will introduce ethical principles and how they apply to predictive modeling in schizophrenia. She will discuss examples including genetic prediction of antipsychotic treatment response and side effects.

Dr. Nikolaos Koutsouleris will introduce the latest risk stratification models for predicting early psychotic and mood disorders. He will discuss the current challenges of study design, heterogeneity of outcome phenotypes, and lack of prospective studies. He will further propose solutions to these challenges, including the use of interpretable methods

Dr. Todd Lencz will provide an overview of current methods in polygenic risk scoring and discuss the ethical considerations regarding the clinical applications of polygenic risk scores in predicting schizophrenia in prodromal adolescents and pre-implantation embryo screening.

Dr. Stephanie Hare will discuss autonomy, privacy, and how biases (e.g., racial, gender) can be introduced into seemingly objective predictive algorithms. She will use a thought experiment using an example scenario to illustrate how some of these biases can be coded into various stages of a predictive model.

Potential solutions to the ethical challenges mentioned above as well as applications of predictive modeling will be discussed.

13.1 POTENTIAL ETHICAL, LEGAL, AND SOCIAL ISSUES CONCERNING PREDICTIVE MODELING

Gwyneth Zai*[1]

[1]*Centre for Addiction and Mental Health; University of Toronto*

Background: The use of precision medicine has grown over this past decade with the goal of providing individualized treatment and management by incorporating variations in genetics, lifestyle, and environment factors. Pharmacogenomics in psychiatry with the most significant advancement in pharmacogenetic testing has the potential to direct medication prescribing to improve effectiveness and reduce side effects, in addition to predicting illness risk. Several of these tests have been introduced into clinical practice while others are primarily for research purposes. There are significant implementation challenges and ethical considerations including the limited evidence-base available to guide clinical use for most genetic testing and the lack of data from diverse populations, reducing the generalizability of these genetic testing. With advancement in genomic technologies and computational biostatistics approaches, predictive modeling has become increasingly discussed with the caveat of raising considerable ethical, legal, and social concerns that can potentially lead to harm in these often unexplored territories.
Methods: This presentation will discuss the potential ethical, legal, and social issues regarding predictive modeling with the use of individual characteristics, clinical data, genomic data, and stress/environmental data, etc., to predict illness risk, treatment response, and/or tolerability.
Results: Ongoing research should prioritize standardizing procedures in order to enhance the reproducibility/replicability of such precision modeling and how to incorporate predictive modeling into clinical practice.
Conclusions: Ethical, legal, and social issues should be explored and discussed while balancing a need to provide decision support tools for clinicians and patients in order to address their needs and accommodate flexibility in their treatment plans.

13.2 ETHICAL CHALLENGES OF PRECISION PSYCHIATRY FROM DATA ACQUISITION TO MODEL IMPLEMENTATION

Nikolaos Koutsouleris*[1]

[1]*Ludwig-Maximilian-University*

Background: The main driving force of the forthcoming transition from traditional to precision psychiatry are (differential) diagnostic, prognostic and theranostic models that employ artificial intelligence algorithms. To date, the psychiatric data field field has largely focused on technical feasibility while neglecting the clinical, ethical, societal and regulatory implications of individualized risk stratification methods
Methods: My talk will provide a synopsis of the current technological state-of-the-art of precision psychiatry with a focus on risk stratification methods in the early recognition of

psychotic and affective disorders. I will then review and discuss key ethical challenges of precision medicine in psychiatry fueled by (1) the shortcomings of current study designs and downstream patient recruitment protocols, (2) the heterogeneity of phenotypes selected for prediction (3) the lack of generalizability of machine learning methods and (4) lack of prospective clinical studies and implementation science in the field of psychiatric data science.
Results: I will proceed with discussing possible solutions to these ethical challenges that integrate implementation aspects ranging from the study conception to the implementation phases, such as unbiased patient enrolment, debiasing strategies, model analysis methods and ethical AI designs. A specific focus of the talk will lie on the use of interpretable AI methods instead of the currently ubiquitous black-box technologies.
Conclusions: Ethical challenges specific to the peculiarities of mental disorders and the current mental healthcare system exist that must be addressed before these methods can be implemented at scale at the point-of-care.

13.3 ETHICAL ISSUES IN THE CLINICAL USE OF POLYGENIC RISK SCORES FOR SCHIZOPHRENIA

Todd Lencz*[1]

[1]*Zucker School of Medicine at Hofstra/Northwell*

Background: Most complex phenotypes, including psychiatric disorders such as schizophrenia and traits such as cognitive ability, are highly polygenic in nature; they are influenced by many hundreds or thousands of common variants throughout the genome, each with tiny effect sizes. These small allelic effects, can be summated into a single number, called a polygenic risk score (PRS), for any given individual using a variety of computational approaches. Notably, the concept of PRS was developed in the context of early genomewide association studies (GWAS) for schizophrenia, which is amongst the most highly polygenic phenotypes in biomedicine. This talk will explore the interplay of statistical and ethical issues in two potential clinical applications of PRS: 1) prediction of schizophrenia in prodromal adolescents; and 2) pre-implantation screening of IVF embryos for schizophrenia risk.
Methods: This talk will briefly review the methods involved in calculation of PRS from GWAS data, with specific application to the most recent schizophrenia data derived from the PGC. We will review existing data on clinical prediction of schizophrenia using PRS in both adolescents with prodromal symptoms, and present our own recent data on potential usage of PRS for schizophrenia in the context of IVF-derived embryos.
Results: In patients with prodromal symptoms, a schizophrenia PRS provides statistically significant prediction of future schizophrenia (within two years), but effect sizes are too small for clinical utility. Clinical utility is even further diminished when considering other predictive risk factors (i.e., clinical and cognitive signs and symptoms) derived from prodromal calculators.
In pre-implantation embryo screening, PRS may provide numerically large reductions in relative risk of schizophrenia in offspring, depending on the "selection strategy" that is employed. However, absolute risk reduction would necessarily be very low for disorders with low base rates such as schizophrenia.

Critical empirical considerations that will be discussed include:

1) Socio-economic status appears to be a significant potential confound for PRS, particularly for behavioral and neurocognitive traits of interest to psychiatry.

2) PRS for behavioral and neurocognitive traits are also especially sensitive to confounding effects of "genetic nurture" – the fact that the genes of parents also shape the environment in which the offspring grow up.

3) Accuracy and applicability of PRSs are dependent upon clarity of phenotypic definitions, which can be vague or ambiguous for psychiatric traits as compared to other biomedical traits.

Conclusions: After providing the necessary empirical and statistical background of PRS for schizophrenia, this talk will focus on the ethical issues that are raised. In particular, the use of PRS raises issues of equity, insofar as GWAS have been primarily performed in individuals of European ancestry and made not be applicable to patients of other ancestries. Additionally, clinical use of PRS, especially in the embryo context, may increase stigma of disorders that are subject to selection, and stigma is already a significant problem in the context of psychiatric disorders. Moreover, such considerations may hinder future psychiatric genetics research, if research participants feel their data might be used in a manner that enhances stigmatization.
Any discussion of embryo screening with PRS must begin with concern over the possible encouragement of eugenicist beliefs. These concerns are accentuated in the context of genetic screening for mental health conditions, insofar as these were the primary initial focus of coercive eugenics programs. A more subtle concern is that the promulgation of PRS may promote genetic essentialism, the belief that one's identity is reducible to genes, and the related concept of genetic fatalism. Genetic fatalism could lead to 1) a lack of perceived agency or internal locus of control of the individual, 2) relatedly, an increase in deterministic thinking about the self (either that the individual should not or cannot have mental health concerns), or 3) the over-medicalization of mental health symptoms, in which psychosocial interventions are discounted or even avoided by patients and their parents.

13.4 SOURCES OF BIAS AT THE INTERSECTION OF AI, NEUROIMAGING AND PSYCHIATRY

Stephanie Hare*[1]

[1]*Maryland Psychiatric Research Center*

Background: The fields of biological psychiatry and schizophrenia research have seen a surge in publications using biological variables to group individuals into existing diagnostic categories, or new, latent categories (e.g. "biotypes") using artificial intelligence (AI) and machine learning. This raises several ethical challenges to autonomy/agency, privacy, and the risk of bias and discrimination that may be introduced by these seemingly "objective" AI algorithms. With respect to the latter topic, a racial bias already exists in which black individuals are more likely than white individuals to be diagnosed with schizophrenia. To date, ethical analyses on the topic of "biodiscrimination" have focused on how racial bias may be introduced early in the process with uneven representation of ethnic groups in the training dataset. While this is an important consideration, I perform an ethical analysis to advance the conversation by introducing a thought experiment, and three novel ways in which existing biases may get (re)coded into AI algorithms.
Methods: I perform an ethical analysis of existing literature on the topics of AI and discrimination (and/or racial bias) relevant to the field of schizophrenia research. This includes a thought experiment and an applied ethical analysis of the book, Race After Technology (R. Benjamin, 2019). Rather than providing a mere overview of these topics, this analysis advances the conversation by discussing three novel ways in which biases (racial, gender, etc.) may

become coded into seemingly objective AI algorithms at nearly all stages of data interpretation (see Results).

Results: First, through use of a thought experiment, I show how interpretations of data such as "dysfunctional control of an emotion-regulation network" can become a new code for stereotypes tied to certain behaviors such as impulsivity or aggression. Next, I use this same example (e.g. "dysfunctional control of an emotion-regulation network") to show how biases may get re-coded at nearly every stage of data interpretation. Finally, I discuss how bias may get introduced by the inclusion of sociodemographic factors that are included to increase the model's predictive power.

Conclusions: The conclusions of this ethical analysis suggest that psychiatric research teams must be vigilant and aware that AI algorithms used to predict mental health diagnoses and outcomes are not "purely objective" and free of bias. Potential "solutions" to the three ethical challenges above are discussed. This discussion is intended to open up a conversation around these ethical issues, rather than providing absolute principles that will stomp out racism or gender biases in the field of schizophrenia research (or psychiatric research more broadly).

14. VIDEOGAMES and PSYCHOSIS: CAUSE FOR CONCERN OR OPPORTUNITY FOR EARLY INTERVENTION AND RECOVERY?

Manuela Ferrari, *McGill Universuty and Douglas Mental Health Institute*

Overall Symposia Abstract: More than 13.32 billion people worldwide play videogames, and 70% of gamers are 18 years of age or older. Teens describe video gaming as a daily activity. Videogames are also one of the preferred and most heavily used technologies among youth who access mental health services, including early intervention services for psychosis. Contrary to popular belief that playing videogames is a solitary activity, around 75% of youth play video games with others. Because of the amount of time spent by youth on videogames, researchers, clinicians, and the general population have expressed concerns their addictive potential, as well as their impact on sleep and functioning — factors that may subsequently influence mental health and psychosis.

Given the popularity of videogames, researchers have been studying the role of this technology in promoting both prosocial and antisocial behavior among young players. The vast majority of research has focused on the negative impacts of videogames, describing their potential to lead to aggression, addiction and depression. However, emerging literature has also identified many benefits of playing videogames, such as promoting better attention span, strengthening memory and problem-solving skills, and enhancing the ability to cope with failure, manage emotions, and socialize. Moreover, innovative research has focused on the impact of using videogames as mental health interventions for psychotherapy or for teaching social skills. While many commercial video games have perpetuated well-known stereotypes and prejudices, associating mental illness (e.g., violence, fear, insanity, hopelessness), some game developers have taken advantage of game interactivity to tell engaging, real-life stories about psychosis. The award-winning videogame Hellblade: Senua's Sacrifice follows the story of Senua, a traumatised Celtic warrior who is on a quest to save her lover's soul from the underworld. During her journey, Senua experiences frequent hallucinations and delusions. The developers of Hellblade consulted with psychiatrists and people living with psychosis to create an in-game experience that depicts psychosis realistically. Hellblade has received recognition from the Wellcome Trust.

Can videogames exacerbate psychosis and paranoia? How do videogames portray psychosis? Could video games be beneficial for people with psychosis? This symposium will bring to light current evidence on this topic, unpacking the concerns but also underlining the achievements and opportunities for research and improved clinical practice. Therapeutic game-based interventions now exist for most psychiatric disorders, including psychotic conditions, with research suggesting that young people respond well to technology-assisted treatment. The symposium thus aims to arrive at a balanced assessment about the potential of video games for mental health treatment from many disparate perspectives.

14.1 ASSOCIATION BETWEEN VIDEO GAMING AND PSYCHOTIC EXPERIENCES IN THE COMMUNITY: A LONGITUDINAL COHORT STUDY

Vincent Paquin*[1], Frederick L. Philippe[2], Holly Shannon[3], Synthia Guimond[4], Isabelle Ouellet-Morin[5], Marie-Claude Geoffroy[1]

[1]*McGill University,* [2]*University of Quebec in Montreal,* [3]*Carleton University,* [4]*University of Quebec in Outaouais,* [5]*University of Montreal*

Background: Video gaming is popular among young people. Through its impacts on lifestyle and other determinants of mental health, it may be a risk factor for psychotic experiences. However, the direction of association between video gaming and psychotic experiences remains unclear. In this prospective cohort of youth, we aimed to examine between- and within-person associations of video gaming with psychotic experiences, and the potential influence of confounding factors.

Methods: Adults aged 18-25 years from the general population of the province of Québec, Canada were recruited online. Participants completed questionnaires on three occasions: in June-July 2021, September-October 2021, and December-January 2022. At each time point, video gaming was measured as the average time spent playing video games daily in the past 3 months. The frequency of psychotic experiences in the past 3 months was measured with the 15-item Community Assessment of Psychic Experiences. Covariables included age, sex, cannabis use, chronotype (i.e., sleep schedule), physical activity, time spent in green spaces, depression levels, and anxiety levels. To explore conditional associations between all measures, we generated a Gaussian graphical network model of the baseline data. Then, we examined between- and within-person associations of video gaming and psychotic experiences over follow-up using a random-intercept, cross-lagged panel model.

Results: The baseline sample included 425 participants (82.5% female), of whom 61.9% completed at least 2 of the 3 time points. In the network model, psychotic experiences were directly connected with depression, anxiety, and video gaming, but not with other lifestyle and behavioral measures. The connection (edge) between psychotic experiences and video gaming was stable in bootstrapped analyses. Video gaming was also connected with time spent in green spaces and sleep schedule, but not with other measures, including depression and anxiety. The random-intercept cross-lagged panel model, which yielded indices of good fit, supported an association between video gaming and psychotic experiences at the between-person level: individuals with a tendency for higher amount of video gaming also had a tendency for more frequent psychotic experiences: r=0.23 (95% CI: 0.07, 0.38). However, at the within-person level, a person's fluctuation in video gaming at one time point was not associated with fluctuations in psychotic experiences at the next point: β=0.11 (95% CI: -0.06, 0.27); the reverse association, from psychotic experiences to video gaming, was likewise not significant: β=0.05 (95% CI: -0.28, 0.38). Results were similar when adjusting for covariables (age, sex, educational attainment, cannabis use, physical activity, sleep schedule, time spent in green

spaces, depression, and anxiety), and when restricting the sample to participants who completed at least 2 time points.
Conclusions: These findings show that youth from the community who spend more time playing video games endorse more psychotic experiences. However, individuals' momentary increase or decrease in video gaming does not seem to predict variations in their subsequent levels of psychosis expression. The absence of within-person associations suggests that video gaming is not a causal risk factor for psychotic experiences, at least for the time scale examined here (3-month intervals). Other factors, such as personality traits or social capital, could explain the shared propensity for video gaming and psychotic experiences. Understanding why youth with psychotic experiences are drawn to video games could inform counselling and use of video games in mental health care.

14.2 MENTALHEALTHCRAFT: CURRENT STATUS AND EMERGING TRENDS - FROM COMMERCIAL VIDEO GAMES TO THERAPEUTIC (OR SERIOUS) GAMES

Manuela Ferrari*[1], Sarah V McIlwaine[2], Gerald Jordan[3], Sahar Fazeli[2], Judith Sabetti[4], Suzanne Archie[5], Jai Shah[2], Srividya Iyer[6]

[1]*McGill Universuty and Douglas Mental Health Institute,* [2]*McGill University,* [3]*University of Birmingham,* [4]*Douglas Research Centre,* [5]*McMaster University,* [6]*Douglas Research Centre, McGill University*

Background: Nearly all young people use the internet daily. Many youth with mental health concerns are using this route to seek help especially since the Covid-19 pandemic, whether through digital mental health treatment, illness prevention tools, or supports for mental wellbeing. Video games have wide appeal among young people, including those who receive early intervention services for psychosis. A growing body of literature explores the advantages of playing digital games for improving attention span and memory, managing emotions, promoting behavior change, and supporting treatment for mental illness (e.g., anxiety, depression, or posttraumatic stress disorder). The research field has also focused on the negative impact of video games, describing potential harms related to aggression, addiction, and depression.
Methods: To promote clarity on this matter we examine the findings from two systematic scoping reviews aimed at assessing the impact of commercial video games (games designed for entertainment purposes) and serous videogame (games designed primarily for purposes of education or health care rather than pure entertainment). The first review identified how mental illness, especially psychosis, is portrayed in commercial video games. Based on keyword searches among games made available on Steam (a popular personal computer gaming platform), a total of 789 games were identified and reviewed to assess whether their game content was related to mental illness. The screening phase resulted in the retention of 100 games for review. The second review aimed to identify and assess video game interventions for young people (ages 12-29), focusing on evidence for the capacity of games to support treatment and recovery. A search of multiple databases identified a total of 8,733 articles. They were screened, and 49 studies testing 32 digital games retained.
Results: The review of commercial videogames indicated that nearly all of the games (97%, 97/100) portrayed mental illness and psychosis in particular, in negative, misleading, and problematic ways, associating these conditions with violence, fear, insanity, hopelessness, and the like. These games portrayed mental illness as a mystery, both obscure and unpredictable, and its treatment fraught with uncertainty as game characters had to undergo experimental treatments to get better. Unfortunately, the identified video games offered little or no hope for

recovery, instead presenting mental illness as an ongoing struggle if not an endless battle between the mind and the self. By contrast, the second review of 32 serous video games supports the potential to integrate digital games into mental health services, offering continuity of care (from mental health promotion/prevention and early access, to treatment for mild to moderate mental conditions, to treatment for severe and complex mental conditions). Studies showed high levels of user satisfaction, and relatively high program retention rates.
Conclusions: Building on evidence from both reviews, we will discuss how to bring the commercial and therapeutic game worlds together to prevent harm, promote well-being and create opportunities for recovery from psychosis.

14.3 ONTRACK>AN ONLINE ROLE-PLAYING GAME

Franco Mascayano*[1], Lisa Dixon[2]

[1]*Columbia University/NYSPI/NYPH,* [2]*NYSPI/Columbia University Medical Center*

Background: Coordinated Specialty Care (CSC) programs for people experiencing early psychosis can reduce hospitalization, decrease psychiatric symptoms, improve quality of life, and result in better social and occupational functioning. However, few tools have been developed to promote engagement and participation in care. In response to this need, Columbia University and University of Maryland have partnered with the Center for Social Innovation, to develop and test OnTrack>An Online Role-Playing Game (OTG). OTG offers players the opportunity to immerse in a fictional neighborhood that centers around four domains for supportive recovery as defined by SAMHSA: health, home, purpose, and community. The player interacts with other game characters including new acquaintances, friends/peers, a family member, and a treatment team, allowing the player to practice social and communication skills, while fostering personal relationships and building a support network. Additionally, the game provides players with helpful resources including psychoeducation materials and videos of real people who have experienced a first episode of psychosis, sharing their stories of hope and recovery.
Methods: The objectives were to 1) evaluate the effectiveness of OTG compared to the control condition (Recovery Videos, or RV) on empowerment, stigma, and engagement, and 2) understand clients and providers' experiences with the game or videos, including technical difficulties, what was helpful and what could be improved.
This study involved a mixed-methods randomized controlled trial in which 159 young people from first-episode CSC programs were recruited throughout the U.S. and U.S. territories. Participants were randomized into 1 of 2 conditions: (1) OTG or (2) RV, a website that includes information and videos about first episode psychosis. Follow-up assessments were conducted at 2 and 5 months. Engagement was measured by the Signh O'Brien Level of Engagement Scale and a self-reported engagement with CSC program scale. Empowerment was measured by the Herth Hope Index, the Recovery Attitude Questionnaire, and the Roger's Empowerment Scale. Stigma was measured by the Questionnaire on Anticipated Stigma and the Rüsch Stigma Stress. Additionally, qualitative interviews were conducted to gather participants' perceptions about the game and videos. Intention-to-treat analysis was used to compared groups on trial primary outcomes. Interviews were analyzed using the rapid identification of themes from audio recordings method.

Results: No significant differences were detected on any outcomes when comparing OTG vs RV at 5 months. Though qualitative findings indicated increased sense of hope, empowerment, and the possibility of recovery in the OTG group. Moreover, providers suggested providing

access to computers or tablets for clients and hosting a demonstration of OTG and RVs on the OnTrackNY website to increase accessibility and usage.
Conclusions: Although trial's results were not positive, qualitative findings were encouraging. Potential strategies to promote OTG implementation and dissemination are discussed.

14.4 USING BACK TO REALITY SERIES VIDEO GAMES TO EDUCATE BLACK YOUTH ABOUT CANNABIS AND PSYCHOSIS RISK

Suzanne Archie*[1]

[1]*McMaster University*

Background: Cannabis use is built on a history of criminalization, negative stereotypes, and stigma for people with serious mental illness and youth from Black communities. Safer spaces to discuss lived experiences with cannabis use and to learn credible scientific knowledge about underage cannabis use are needed to provide better options for youth experiencing a first episode of psychosis, particularly those from Black communities.
Online video game technology offers engrossing platforms for youth to receive and integrate mental health information. The Back to Reality Series Video Games are designed to translate research knowledge about cannabis use and early signs of psychosis. The Series constructs a lived experience of a Black youth with psychosis and cannabis use issues while exploring his attempts to access care from the mental health system. There are three modules: Harry's Journey, Harry's Journal, and Harry's Pathways to Care.

Methods: A group of ten McMaster undergraduate students participated in a research-based thesis course where the students learned about the research relevant to the association between youth cannabis use and psychosis, using the Back to Reality Series as the inspiration for the learning objectives. The students were also taught how to facilitate tutorial sessions and create the content for the tutorial sessions. The student researchers conducted two facilitated tutorials with Black youth recruited from Free For All Foundation, a charitable organization serving Black youth. Participants were 16 to 19 years of age and of Black African or Caribbean descent. Participants were administered the Psychosis and Cannabis Test quiz (DOI: 10.2196/33693) about cannabis and psychosis to evaluate their knowledge. Their perceptions were explored using thematic analysis of tutorial transcripts. Undergraduate students and research staff conducted Individual interviews with young people experiencing a first episode of psychosis from racialized background (DOI:10.2196/36758). The undergraduate students explored their perceptions about the Back to Reality Series and insights into their cannabis use.
Results: Nine Black youths completed the tutorials involving undergraduate students. There was a significant increase ($P<.05$) in scores on the knowledge test before (mean scores 5.67+ 1.7) and after (mean scores 7.78 + 1.8) the knowledge translation program of tutorials and video game play. Nine young people experiencing a first episode of psychosis completed the individual interviews to date about their video game play experiences. Young people experiencing their first episode of psychosis felt the Video games resonated with their own experiences of psychosis. The Black youth thought they learned about psychosis and pathways to care from the video game series.
Conclusions: Nine Black youths completed the tutorials involving undergraduate students. There was a significant increase ($P<.05$) in scores on the knowledge test before (mean scores 5.67+ 1.7) and after (mean scores 7.78 + 1.8) the knowledge translation program of tutorials and video game play. Nine young people experiencing a first episode of psychosis completed the individual interviews to date about their video game play experiences. Young people experiencing their first episode of psychosis felt the Video games resonated with their own

experiences of psychosis. The Black youth thought they learned about psychosis and pathways to care from the video game series.

15. VALIDITY AND UTILITY OF A DIMENSIONAL MODEL OF PSYCHOSIS OVER THE LIFESPAN

Diego Quattrone*, Institute of Psychiatry, King's College London*

Overall Symposia Abstract: Accumulated evidence established a large heterogeneity in risk factors, phenomenology, course and outcome of non-affective and affective psychotic disorders, even when using a narrow diagnostic construct. The categorical classification of psychotic disorders, as operationalised in the DSM and ICD, is therefore regarded as useful but not valid for research and clinical practice. For example, genome-wide studies failed to separate psychotic disorders based on genetic risk variants, showing an 80% genetic correlation between schizophrenia and bipolar disorder instead. Thus, it has been proposed and is now widely accepted that transdiagnostic symptom dimensions can more adequately illustrate the complexity of psychotic phenomena. Recently, transdiagnostic models encompassing general and specific latent factors have proven to be good constructs for examing the shared and not-shared characteristics among diagnostic categories. However, some uncertainty remains on the type and number of dimensions, their longitudinal validity, as well as biological validation. This symposium addresses these questions bringing together young and expert researchers into the phenomenology, course and outcome of psychosis.

First, Roman Kotov will present novel findings from a 25-year follow-up of the Suffolk County Mental Health Project, examining the longitudinal stability and prognostic validity of five dimensions identified by the Hierarchical Taxonomy Of Psychopathology (HiTOP). Results show that such dimensions remain stable and distinct over time, outperforming traditional diagnostic categories in predicting symptom and functional outcomes.

Second, Julia Schulte-Strathaus will present novel data using multidimensional item-response modelling to examine whether a bifactor model of psychopathology holds in an ultra-high-risk sample. Results confirm the validity and utility of such a construct.

Third, Diego Quattrone will present data from a first episode of psychosis (FEP)- control sample to provide a biological validation of the bifactor model of psychopathology. Results show that genetic, environmental, and epigenetic factors map into psychosis dimensions in both cases and controls.

Forth, Fabiana Corsi-Zuelli will present data from a FEP - unaffected sibling - control sample to examine the associations between low-grade inflammation and symptom dimensions across the psychosis continuum. Results show that cytokine dysregulation map into transdiagnostic dimensions in subgroups of patients.

Uli Reinhingaus will co-chair the symposium providing insight into the challenges of transdiagnostic approaches versus diagnostic categories in psychosis. Paola Dazzan will discuss the present findings and provide directions for future research, leading an interactive discussion between the panel and the audience.

15.1 PSYCHOSIS DIMENSIONS AND THEIR TRAJECTORIES OVER 25 YEARS FOLLOWING FIRST ADMISSION

Roman Kotov*[1]

[1]*Stony Brook University*

Background: Hierarchical Taxonomy Of Psychopathology (HiTOP) consortium has identified five dimensions of psychosis symptomatology: reality distortion, disorganization, inexpressivity, avolition, and mania. Other dimensions that are not core to psychosis but are important to consider include depression, cognitive functioning, and real-world functioning. The present talk will examine temporal stability and prognostic validity of this dimensional model.
Methods: We investigated these questions in the first U.S. study to follow an epidemiological cohort (N = 628) with psychotic disorders for 25 years after first hospitalization. Participants were assessed in-person 7 times across the follow-up, with the retention rate of 68% among survivors.
Results: The five core dimensions were internally consistent, showed moderate temporal stability (r = .20 - .38), and remained distinct from each other over the 25 years. This model substantially outperformed traditional diagnoses in predicting long-term outcomes such as remission, social functioning, unemployment, diabetes onset, etc. The core dimensions were distinct from the three auxiliary dimensions, except for substantial correlations between avolition, real-world functioning, and cognition over time. All constructs improved following the first hospitalization, but with time reality distortion, disorganization, avolition, real-world functioning, and cognition worsened substantially. In particular, in participants with schizophrenia, functioning declined to GAF score of 35 and IQ score of 80. In contrast, inexpressivity, mania, and depression remained stable.
Conclusions: These findings reaffirm the value of distinguishing dimensions that underpin psychotic disorders. The resulting constructs are internally consistent, can be measured reliably, and show high prognostic validity. Importantly, they follow different trajectories, and the singular concept of remission does not capture these complex patterns. Trajectory analyses revealed a substantial burden of symptoms and impairments across psychotic disorders that increased with time. Additional research is needed, but previous studies suggest that different care models may preempt this decline.

15.2 TRANSDIAGNOSTIC SYMPTOM DIMENSIONS IN INDIVIDUALS AT ULTRA-HIGH RISK FOR PSYCHOSIS

Julia Schulte-Strathaus*[1], Christian Rauschenberg[1], Isabell Paetzold[1], Jessica Hartmann[1], Paul Amminger[2], Hok Pan Yuen[2], Patrick McGorry[2], Barnaby Nelson[2], Ulrich Reininghaus[1]

[1]*Central Institute of Mental Health, University of Heidelberg,* [2]*Orygen Research Centre, University of Melbourne*

Background: Research has increasingly shifted its focus from categorical to dimensional conceptualizations of mental disorders. This is supported by the high amount of overlap among disorders, particularly psychosis spectrum disorders, which cut across traditional diagnostic boundaries. The growing body of evidence on transdiagnostic symptom dimensions has stimulated debates about aetiology and symptom trajectories. While there is evidence for a general factor of psychopathology in service users with schizophrenia, schizoaffective disorder, and psychotic bipolar I disorder, transdiagnostic dimensions of psychopathology have not been replicated in young individuals at ultra-high risk (UHR) for psychosis. The aims of the proposed analyses are to investigate: 1) whether transdiagnostic dimensions of psychopathology can be replicated in UHR individuals; 2) the diagnostic utility for classifying UHR individuals correctly into criteria of a) UHR (trait vulnerability, attenuated psychotic

symptoms, BLIPS) and b) comorbid DSM diagnoses; and 3) associations between demographic, clinical, and social variables and transdiagnostic dimensions at baseline.
Methods: Multidimensional item-response modelling was conducted on symptom ratings of the brief psychiatric rating scale (BPRS) at baseline in the staged treatment in early psychosis (STEP) trial, which aims to determine the most effective type, timing, and sequence of interventions in the UHR population.
Results: In total, 342 help-seeking young people enrolled in the trial. A bifactor model with one general symptom dimension and four specific factors of positive symptoms, negative symptoms, affect, and activation provided the best model fit. This lends support to the notion of a shared general construct across the risk syndrome, pointing at a pluripotent risk state, while simultaneously recognizing the contribution of single, domain-specific factors.
Conclusions: These findings shed light on the dimensionality of symptoms in youth at UHR for psychosis and highlight the importance of further investigating transdiagnostic phenotypes at developmentally early stages of psychopathology.

15.3 BIOLOGICAL VALIDATION OF TRANSDIAGNOSTIC SYMPTOM DIMENSIONS AT FIRST EPISODE PSYCHOSIS

Diego Quattrone*[1], Marta Di Forti[2], Ulrich Reininghaus[3], Robin Murray[4]

[1]*Institute of Psychiatry, King's College London,* [2]*SGDP, Institute of Psychiatry, KCL,* [3]*Central Institute of Mental Health, University of Heidelberg,* [4]*Institute of Psychiatry, King's College, London*

Background: Epidemiological and biological evidence shows no boundaries between diagnostic categories of non-affective and affective psychoses, thus challenging the current nosological model developed from Kraepelin's paradigm. This study aims to 1) identify the transdiagnostic dimensional structure of i) psychotic symptoms in first-episode psychosis (FEP) patients and ii) psychotic experiences in the general population; 2) investigate the relationship between these dimensions with genetic, environmental, and epigenetic factors.
Methods: We conducted a multisite incidence and case-control study across six countries [i.e. the 'EU-GEI' study]. To examine the latent structure of psychopathology, we analysed ratings of psychotic symptoms and experiences using multidimensional item response modelling in Mplus, to estimate a bifactor model of psychopathology, including a common general factor and five specific dimensions of positive, negative, disorganization, manic, and depressive symptoms.
The sample was genotyped using Illumina HumanCoreExome-24 BeadChip array (GWAS) and Illumina Infinium HumanMethylation850 Genome-wide DNA methylomic (EWAS) profiling in human peripheral blood tissue.

To examine the common variant liability to psychosis, we built a schizophrenia (SZ) polygenic risk score (PRS) weighting the common risk alleles by the log(odds) ratio from the summary statistic of SZ Psychiatric Genomic Consortium, wave 3.

We used adjusted multiple linear regression to examine the relationship between the latent structure of psychopathology and SZ-PRS, demographic and context determinants, and detailed patterns of cannabis consumption, accounting for ancestry-derived principal components for population stratification.

Finally, an adjusted linear model was used to compare across the genome DNA methylomic profiling of general and specific symptom dimensions, covarying for sociodemographics, tobacco smoking score, cell type proportions and medication.

Results: The associations among ratings of psychotic symptoms in FEP patients and psychotic experiences in population-based controls fit well with a bifactor model. In FEP patients, the examination of general and specific dimensions with external factors showed that 1) higher scores on the negative symptom dimension were associated with being a male and having never used cannabis; 2) higher scores on the positive symptom dimension were associated with exposure to socioenvironmental risk factors in psychosis, such as being part of an ethnic minority and having had exposure to cannabis in a dose-response fashion, with those having used high potency varieties daily having the highest score; 3) both higher scores on the positive and negative symptom dimensions were associated with a higher SZ-PRS.
In population-based controls, the examination of general and specific dimensions with external factors showed that 1) higher scores on the positive psychotic experience dimension were associated with the current use of cannabis but not with the extent of lifetime exposure to cannabis; 2) higher scores on the general and all the specific psychotic experience dimensions were associated with a high SZ-PRS.

Finally, EWAS analysis showed that Differentially Methylated probes were more represented for negative symptoms in FEP patients, with the strongest association with the flavonoid metabolic process pathway (p=5.94E-101).

Conclusions: Symptom dimensions emerged as useful psychosis phenotypes validated by psychometric data and socioenvironmental and genetic factors. Specifically, the bifactor model of psychopathology holds across diagnostic categories of non-affective and affective psychosis at FEP and in the general
population. Furthermore, use of cannabis is associated with more positive and less negative symptoms at FEP, consistently with the hypothesis that cannabis users who develop psychosis have less early neurodevelopmental impairment than their non-user counterparts. Overall, these findings indicate that it is appropriate to conduct research using symptom dimensions, and they have translational relevance.

15.4 TRANSDIAGNOSTIC DIMENSIONS OF PSYCHOTIC SYMPTOMS AND EXPERIENCES IN FIRS-EPISODE PSYCHOSIS, UNAFFECTED SIBLINGS, AND COMMUNITY-BASED CONTROLS: ASSOCIATIONS WITH STATE AND TRAIT CYTOKINES

Fabiana Corsi-Zuelli*[1], Diego Quattrone[2], Taciana Ragazzi[1], Camila Marcelino Loureiro[1], Rosana Shuhama[1], Jim Van Os[3], Menezes Paulo Rossi[4], Paulo Louzada-Junior[1], Cristina Marta Del-Ben[1]

[1]*University of São Paulo - Ribeirão Preto Medical School - FMRP USP,* [2]*Institute of Psychiatry, King's College London,* [3]*Maastricht University Medical Centre,* [4]*Faculty of Medicine, University of São Paulo*

Background: Attenuated psychotic symptoms (psychotic experiences; PEs) exist in the general population and pose longitudinal risks for the development of psychosis and other common mental disorders. Low-grade inflammation may be related to the pathogenesis of transdiagnostic symptoms and experiences. Nevertheless, there is significant heterogeneity in investigations of psychosis symptom domains and inflammation as related to illness stage, antipsychotic exposure, and adjustment for confounding. In addition, previous investigations on PEs and inflammation were centered on one or two immune markers (IL-6 or CRP) and no study has ever tested the role of familial liability. The psychosis continuum model is an attractive strategy to study potential biological mechanisms of psychosis while overcoming

illness-related confounding by disease duration, prolonged exposure to antipsychotics, metabolic changes, and poor lifestyle factors. The investigation of biological correlates of PEs could help to understand the pathophysiology of psychosis and identification of promising targets for early intervention.

Methods: We included first-episode psychosis patients (FEP), their unaffected siblings, and community controls to investigate associations between low-grade inflammation and the psychosis continuum model. Data were retrieved from a cross-sectional study conducted in Ribeirão Preto/SP Brazil (STREAM), which integrates the EU-GEI consortium. Samples included 134 FEP patients, 66 unaffected siblings, and 235 community controls. Dimensions of psychopathology (positive, negative, depressive, manic, disorganisation) in patients were generated using the Operational Criteria Checklist for Psychotic Illness and Affective Illness (OPCRIT). PEs (positive, negative, depressive) in siblings and controls were assessed using the Community Assessment of Psychic Experience (CAPE). Previously described trait (IFN-γ, TNF-α) and state (IL-1β, IL-6, TGF-β) cytokine markers, as well as anti-inflammatory cytokines (IL-10, IL-4) and the acute phase protein hsCRP, were evaluated in plasma (multiplex). Analyses were adjusted for sex, age, body mass index, and tobacco smoking and corrected for multiple testing (Benjamini-Hochberg, 5%). We also explored if associations differed between subgroups of patients, siblings, and controls with high or low CRP levels (i.e., CRP>3mg/L but <10mg/L).

Results: After multiple corrections, significant associations were only found in subgroups of FEP patients and their unaffected siblings with signs of high hsCRP (hsCRP>3mg/L). In FEP patients with high hsCRP (31.3%), TNF-α was positively correlated with disorganisation (b = 0.37, p = 0.01); IL-4 and TGF-β were negatively correlated with depressive symptoms (b = -0.47, p = 0.001; b= -0.31, p = 0.003). In siblings with high hsCRP (28.8%), IFN-γ and IL-10 were related to positive (b=0.96; p=0.002; b=1.02, p=0.002) and negative PEs (b=0.85, p=0.02; b=0.80, p=0.01), respectively. Furthermore, positive and negative PLEs were negatively related to IL-6 (b = -0.43, p = 0.01; b = -0.68, p = 0.01) and TGF-β (b=-0.68, p=0.002; b=-0.70, p=0.004). TNF-α was negatively correlated with the positive dimension (b=-1.03, p=0.02).

Conclusions: The results indicate that cytokine dysregulation may contribute to the pathogenesis of transdiagnostic symptoms and experiences but only in subgroups of patients and siblings with high hsCRP. However, directions of associations between state and trait markers may differ across the psychosis continuum. Negative correlations between PEs and cytokines in the sibling group could indicate that some markers (e.g., IL-6, TNF-α) fluctuate along the continuum or even the presence of still unknown protective factors in this group.

16. BIAS IN REPORTING OF RESEARCH IN PSYCHIATRY

Marcus Munafò, *University of Bristol*

Overall Symposia Abstract: Challenges in transparent reporting of the results of RCTs in schizophrenia are widespread and can be extremely damaging to the field. It is extremely important both for researchers, and funders and journal editors to be aware of this and to search for potential solutions to prevent non-publication of negative findings and outcome reporting bias. This symposium will present evidence from senior journal editors and researchers in the field, describing the magnitude of the phenomenon and potential solutions.

Dr. Ongur will present a study comparing reporting practices of major medical and psychiatric journals in presenting the results of intervention studies. One hundred twenty-seven papers were assessed. Psychiatric journals were less likely to report confidence intervals (93% vs 83%), methods for choosing sample size (93% vs 69%), adverse events (94% vs 80%), and were more likely to report race and ethnicity by randomization group (51% medical vs 73%

psychiatric). Confidence intervals were included less often in the abstract and reported less often for efficacy results in psychiatric than medical journals ($p<0.005$, $p=0.04$, after multiple testing correction).

Dr. Weiser will present data on rates of publications of 280 RCTs funded by the Stanley Medical Research Institute. Eighty six percent of those with positive findings were published, in contrast to 53% of those with negative findings ($P < .001$). In 70% of the manuscripts published, there were major discrepancies between the published manuscript and the original RCT protocol (change in the primary outcome measure or statistics, change in number of patient groups, 25% or more reduction in sample size.

Dr. Marsh will discuss the importance of publishing negative findings, with a distinction between a true negative showing that an intervention does not work and a failed study from which conclusions cannot be drawn because of methodological flaws. She will discuss the importance of complete clinical trial reporting as opposed to salami publication, and will discuss reducing bias in the peer-review process.

Dr. Munafo will present new approaches to research, funding and publication that are being developed which may serve to improve the transparency and robustness of scientific findings, and ultimately allow us to advance knowledge more rapidly. This includes collaborative approaches to open research practices, and partnerships between funders and journals to promote uptake of novel publishing formats such as Registered Reports, as well as entirely new approaches to scholarly communication.

16.1 REPORTING OF CLINICAL RESEARCH STUDIES IN PSYCHIATRY

Caitlin Ravichandran[1], Suzann Babb[1], Dost Ongur*[2], Peter Harris[1], Bruce Cohen[1]

[1]*McLean Hospital,* [2]*Mclean Hospital*

Background: We assessed how well articles in major medical and psychiatric journals follow best reporting practices in presenting the results of intervention studies.
Methods: A standardized custom data collection tool was used to review studies published in three major medical and four major psychiatric journals over a 12-month period. Two team members independently reviewed each article.
The primary outcome measure was proportion of papers clearly reporting consensus elements required to understand and evaluate the results of the intervention used in each trial. The secondary outcome measure was the comparison of complete and accessible reporting in the major medical versus the major psychiatric journals.

Results: One hundred twenty-seven articles were identified for inclusion. Elements reported by at least 90% of articles in both medical and psychiatric journals included sample size, statistical significance, randomization method, elements of study flow, and age, sex, and illness severity by randomization group. Selected elements less frequently reported in the abstract by either medical or psychiatric journals were confidence intervals (93%, 95% CI: 68%, 83% medical; 58%, 95% CI: 45%, 69% psychiatric) and In the main text, methods for choosing sample size (93%, 95% CI: 84%, 97% medical; 69%, 95% CI: 57%, 80% psychiatric), adverse events (94%; 95% CI: 86%, 98% medical; 80%, 95% CI: 68%, 88%), and race and ethnicity by randomization group (51%, 95% CI: 40%, 63% medical; 73%, 95% CI: 60%, 83% psychiatric). Confidence intervals were included less often in the abstract and reported less

often for efficacy results in psychiatric than medical journals ($p<0.005$, $p=0.04$, after multiple testing correction).
Conclusions: Recommendations include the standard inclusion, in all manuscripts, of a table specifying the outcome(s) designated as primary, the sample size, effect size(s), confidence interval(s), and p-value(s) corresponding to the primary test(s) for efficacy.

16.2 MISREPORTING OF RESULTS OF RESEARCH IN PSYCHIATRY

Jana Bowcut[1], Linda Levi[2], Ortal Livnah[2], Joseph S. Ross[3], Michael Knable[4], MIchael Davidson[5], John M. Davis[6], Mark Weiser*[7]

[1]*Stanley Medical Research Institute,* [2]*Sheba Medical Center at Tel Hashomer,* [3]*Yale University School of Medicine*[4]*Sylvan C. Herman Foundation,* [5]*University of Nicosia Medical School,* [6]*University of Illinois in Chicago,* [7]*Sheba Medical Center at Tel Hashomer*

Background: Few studies address publication and outcome reporting biases of randomized controlled trials (RCTs) in psychiatry. The objective of this study was to determine publication and outcome reporting bias in RCTs funded by the Stanley Medical Research Institute (SMRI), a U.S. based, non-profit organization funding RCTs in schizophrenia and bipolar disorder.
Methods: We identified all RCTs (n=280) funded by SMRI between 2000 and 2011, and using non-public, final study reports and published manuscripts, we classified the results as positive or negative in terms of drug compared to placebo. Design, outcome measures and statistical methods specified in the original protocol were compared to the published manuscript.
Results: Of 280 RCTs funded by SMRI between 2000 and 2011, at the time of this writing, 3 RCTs were ongoing and 39 were not performed. Among the 238 completed RCTs, 86 (36.1%) reported positive and 152 (63.9%) reported negative results 86% (74/86) of those with positive findings were published in contrast to 53% (80/152) of those with negative findings ($p<0.001$). In 70% of the manuscripts published, there were major discrepancies between the published manuscript and the original RCT protocol (change in the primary outcome measure or statistics, change in number of patient groups, 25% or more reduction in sample size).
Conclusions: We conclude that publication bias and outcome reporting bias is common in papers reporting RCTs in schizophrenia and bipolar disorder. These data have major implications regarding the validity of the reports of clinical trials published in the literature.

16.3 WAYS JOURNALS CAN REDUCE REPORTING BIAS

Joan Marsh*[1]

[1]*The Lancet Psychiatry*

Background: Journal editors have been working to reduce reporting bias in clinical trials for many years. The CONSORT (Consolidated Standards of Reporting Trials) Statement was published in 2010 and is endorsed by most leading medical journals, including the Lancet group. However, other sources of bias exist, which journal editors can help to address.
Methods: N/A
Results: Topics to be discussed include the importance of publishing negative findings, with a distinction between a true negative showing that an intervention does not work and a failed study from which conclusions cannot be drawn because of methodological flaws; the importance of complete clinical trial reporting as opposed to salami publication, and reducing bias in the peer-review process.
Conclusions: Editors should work with authors and peer reviewers to reduce reporting bias in clinical trial publications.

16.4 NOVEL APPROACHES TO SCIENTIFIC FUNDING AND PUBLISHING TO IMPROVE RESEARCH QUALITY

Marcus Munafò*[1]

[1]*University of Bristol*

Background: Concerns regarding the robustness of published research are leading to novel collaborations between funders and publishers to address these. This presentation will discuss these innovative approaches, including collaborative approaches to open research practices, and partnerships between funders and journals to promote uptake of novel publishing formats such as Registered Reports, as well as entirely new approaches to scholarly communication.
Methods: Not applicable.
Results: Not applicable.
Conclusions: New approaches to research, funding and publication may serve to improve the transparency and robustness of scientific findings, and ultimately allow us to advance knowledge more rapidly.

17. RESILIENCE AND THE PSYCHOSIS SPECTRUM

Amanda Mccleery*, The University of Iowa*

Overall Symposia Abstract: Psychosis research has traditionally focused on risk. Comparatively little work has explored those factors that confer resilience—averting serious mental illness among those at-risk and promoting positive outcomes among those with psychosis. However, the study of resilience is critical to better understand the etiology, outcomes heterogeneity, and for therapeutic innovation for psychotic illness. In this symposium, we present data demonstrating significant resilience among adults with psychosis and the modifiable psychological factors that contributed to resilient trajectories. In addition, we describe psychosocial interventions that shore up the capacity for resilience, and present promising results: of two intervention studies conducted with young people at-risk for psychosis. Data presented here span illness and developmental stages: from at-risk adolescents to older adults with psychosis.

The first two talks will describe resilient trajectories in individuals diagnosed with psychotic disorders and the factors that predict positive adaptations in the context of adversity. Ellen Lee will present data on the longitudinal relationships between stress-coping ability with physical well-being and clinical outcomes over four-year follow-up in 174 adults with psychotic illness and 158 non-psychiatric comparison subjects. Contrary to expectations, stress-coping ability significantly improved in the psychosis group. Stress-coping was associated with physical well-being across the entire sample, and clinical symptom trajectories among the psychosis group. Jonathan Wynn will present data on clinical and functional trajectories in 81 Veterans with psychosis and 74 control Veterans over the first 15 months of the COVID-19 pandemic. While mental health symptoms worsened for both groups in the early stages of the pandemic, the psychosis group recovered more quickly than controls. Several modifiable psychological factors supported resilient trajectories, buffering the negative impact of the pandemic on mental health outcomes. These psychological factors may serve as therapeutic targets to foster resilience.

The last two talks present data on resilience-promoting interventions in young people at risk for psychosis. Daphne Holt will discuss the development of a brief resilience training intervention and findings from a recent trial of remote delivery of the intervention in 103 young adults with psychotic-like experiences (PLEs). The intervention, which includes skills training to support emotion regulation and decentering, was highly acceptable and feasible. Significant reductions in PLEs, anxiety, and depression were observed, along with increases in mindfulness and self-compassion, and these clinical changes were associated with changes in frontohippocampal connectivity. This work provides a blueprint for widespread dissemination of a resilience-promoting intervention for young adults at-risk for psychosis. Finally, Lorna Staines will discuss ProfScreen, a school-based prevention and early intervention program that includes mental health screening and an integrated referral system. Data from a randomized controlled trial with 1096 adolescents demonstrated that ProfScreen was associated with significantly reduced PLEs, depression, and anxiety. The effects suggest that widespread screening may foster resilience at a population level.

These data contribute to a shifting narrative of psychosis outcomes and highlight the abilities and assets that can promote resilience. A greater understanding of resilience has the potential to inform psychosis intervention and prevention efforts at multiple levels, including individuals, institutions, and policy.

17.1 TRAJECTORIES OF RESILIENCE AND THE IMPACT ON HEALTH OUTCOMES IN SCHIZOPHRENIA: RESULTS FROM A 4 YEAR LONGITUDINAL STUDY

Ellen Lee*[1], David Adamowicz[1], Lisa Eyler[1]

[1]*University of California - San Diego*

Background: Psychological resilience, the "positive adaptation, or the ability to maintain or regain mental health, despite experiencing adversity," has been associated with better health outcomes (e.g., less depression, less pain, better social functioning, and better physical health.) For the rapidly growing population of middle-aged and older people with schizophrenia (PwS), understanding how resilience may be associated with mental and physical health outcomes could guide innovative psychosocial interventions. Age has not been associated with resilience in cross-sectional studies. Longitudinal data on changes in resilience over time and their impact on outcomes is limited. This study assesses resilience trajectories in PwS and a non-psychiatric comparison group (NCs). We hypothesized that trajectories of resilience would worsen over time among PwS and NCs, and lower resilience levels would be associated with worse depression (in both groups) and with worse positive and negative symptoms among PwS. We explored longitudinal changes of resilience with baseline age and longitudinal relationships of resilience with physical well-being.

Methods: This sample included 174 PwS and 158 NCs, mean age 51 years, age range 26-68 years, and 52% women, with 4.1 year mean follow-up time and average of 2.9 follow-up visits. The two groups were comparable in age, sex, and follow-up time. Standardized assessments were administered to evaluate resilience (Connor-Davidson Resilience scale), depression (Patient Health Questionnaire – 9 item), positive and negative symptoms (Scale for the Assessment of Positive Symptoms, Scale for the Assessment of Negative Symptoms), and physical well-being (Medical Outcomes Survey – short form 36). Independent sample t-tests were used to assess differences between PwS and NCs. Linear mixed effects models were conducted to examine the trajectories of resilience over time (dependent variable resilience), study the relationships of age to resilience trajectories (dependent variable resilience), and

examine the relationships of baseline resilience to trajectories of other variables (dependent variables: depression, positive and negative symptoms, and physical well-being) over time. All models included covariates of sex, time, and time interactions with the covariates and resilience.
Results: PwS had lower baseline resilience compared to NCs (M=23.0, SD=8.5 and M=32.5, SD=6.0, respectively; t(330)=11.7, p<.001, d =1.28). PwS had significant improvement in resilience over time, compared to NCs (Diagnostic group x time interaction, p=.005). Sex and age did not significantly influence the resilience trajectories in either group.
Lower baseline resilience levels (B= -1.78, SE =.21, p <.001) and having schizophrenia (B= -3.8, SE =.53, p <.001) were significant predictors of worse severity of depressive symptoms over time.

Among PwS, higher resilience at baseline predicted greater declines in the severity of positive and fewer negative symptoms over time (B= -.59, SE =.21, p =.005 and B= -.72, SE =.23, p =.002, respectively).

In the entire sample, the model of physical well-being found a main effect of resilience (B= 2.46, SE =.38, p <.001), age, male sex, and diagnosis of schizophrenia as well as a significant resilience x time interaction. People with greater improvement in resilience over time showed greater increase in physical well-being over time.

Conclusions: These findings highlight the importance of resilience and its link to mental and physical health over time. Resilience may be a key protective factor in aging among PwS, and the potential to improve resilience is an important and understudied approach for improving outcomes for older PwS.

17.2 THE ROLE OF RESILIENCE IN MITIGATING NEGATIVE IMPACTS OF THE COVID-19 PANDEMIC ON MENTAL HEALTH AND FUNCTIONAL OUTCOMES IN VETERANS WITH PSYCHOSIS

Jonathan Wynn*[1], Amanda Mccleery[2], Eric Reavis[3], Derek Novacek[1], Damla Senturk[4], Catherine Sugar[4], Alyssa Marquez[5], Gillian Ozawa[5], Michael Green[4]

[1]*VA Greater Los Angeles Healthcare System/UCLA,* [2]*The University of Iowa,* [3]*Semel Institute for Neuroscience and Human Behavior at UCLA,* [4]*University of California, Los Angeles,* [5]*VA Greater Los Angeles Healthcare System*

Background: The COVID-19 pandemic has had unprecedented changes to our daily lives that ultimately negatively impacted people's functioning and mental health. Vulnerable populations, including Veterans with a psychotic disorder, may have been more susceptible due to their already tenuous functioning and poorer mental health. However, as the pandemic wore on it became increasingly clear that some people were not as negatively impacted as expected. In this study, we explored how people's positive or negative strategies (hereafter broadly defined as "resilience") mitigated the impacts of the pandemic on mental health and functioning.
Methods: We assessed 81 Veterans with a psychotic disorder (PSY) and 74 community control Veterans without a psychotic disorder (CTL) at five different time points, longitudinally over a 15-month period (between May 2020 – July 2021). All studies were conducted remotely over the phone. We recruited participants using U.S. Department of Veterans Affairs (VA) administrative databases and a repository of participants in our pre-pandemic lab studies. Resilience was measured with five different measures assessing: intolerance of uncertainty, defeatist attitudes, adaptive coping, maladaptive coping, and perceived stress. We computed a

composite score by norming each measure and averaging across the five normed scores; a higher score indicated better resilience. For mental health, we assessed for depression, anxiety, loneliness, and obsessive-compulsive behaviors. For functioning, we assessed family and social functioning, work/school productivity, and independent living. All assessments were administered at each of the 5 time points. In addition, we asked participants to retrospectively provide ratings for how they believed they were in January 2020, which served as a pre-COVID baseline. We examined fixed and time-varying effects using generalized additive models (GAM) conducted in R, separately for each outcome using resilience as a time-varying covariate.

Results: Both groups showed increases relative to the pre-COVID assessment in anxiety, depression, loneliness, and obsessive-compulsive behaviors, particularly in the first several months of the study. Surprisingly, measures of functioning were relatively stable in both groups. Importantly, the GAM analyses revealed that resilience had a significant positive impact on trajectories for each mental health outcome (all ps < 0.05), with greater resilience related to smaller changes. These impacts were different for the two groups for different mental health measures. Resilience significantly impacted obsessive-compulsive ratings for both PSY and CTL, was marginally significant in PSY ($p < 0.06$) and significant for CTL for depression, and significantly impacted loneliness ratings for CTL (ps < 0.05).

Conclusions: Resilience mitigated exacerbations in clinical symptoms in both Veterans with psychosis and Veteran control participants. However, these effects varied in both the timing of the effect for different mental health outcomes and the magnitude varied between the two groups. While we expected that vulnerable Veterans with psychosis would be more negatively impacted by the pandemic, we found the opposite pattern. This could potentially be explained the many wrap-around mental health and social services offered by the Veterans Administration. However, we found that both vulnerable and non-vulnerable Veterans with greater resilience showed even fewer negative impacts. These findings point to the potential of intervention targeting measures of resilience to mitigate continuing effects of the continuing COVID pandemic and any potential future pandemics.

17.3 A RESILIENCE-ENHANCING BEHAVIORAL INTERVENTION FOR AT-RISK YOUNG ADULTS: EVIDENCE FOR IMPROVEMENTS IN EMOTION REGULATION AND FRONTOHIPPOCAMPAL CONNECTIVITY

Daphne Holt[1], Nicole DeTore[1], Anne Burke[1], Lauren Utter[1], Jordan Zimmerman[1], Rachel Sussman[1], Louis Vinke[1], Nicole DeTore*[2]

[1]*Massachusetts General Hospital,* [2]*Harvard Medical School, Massachusetts General Hospital*

Background: Subclinical psychotic symptoms, or psychotic experiences (PEs), are associated with an elevated risk for the development of a range of psychiatric conditions including psychotic disorders. However, despite this evidence, there has been little research to date on interventions that may reduce the incidence or severity of PEs. Thus recently we have developed and tested a brief (4 session) group-based behavioral intervention called Resilience Training (RT), which is focused on teaching skills that can improve emotion regulation and social functioning. A previous randomized controlled trial demonstrated that RT was associated with improvements in mindfulness and self-compassion and reductions in PEs, anxiety and depression (DeTore, Luther et al, 2022). During the COVID-19 pandemic, we adapted RT for delivery via videoconferencing; in a single arm feasibility study, we tested whether this adaptation of RT was feasible and acceptable and demonstrated efficacy similar to that observed with the original, in-person version. We also collected fMRI data in order to

investigate the mechanisms of action of RT, assessing the hypothesized role of a frontohippocampal pathway thought to play a role in emotion regulation.
Methods: 103 college students were enrolled in the study. Eligibility criteria included having a mildly elevated score on a measure of PEs and/or depression (Peters Delusion Inventory score > 3 and/or Beck Depression Inventory score > 5) and no current psychological or psychiatric treatment. The feasibility and acceptability of the program were measured, and self-report measures of resilience-related capacities and symptoms, as well as resting-state fMRI scans, were collected before and after the intervention. The fMRI data were analyzed with FreeSurfer using a hypothesis-driven, region-of-interest approach.
Results: 81% of the enrolled participants completed all four sessions. 93% of participants rated the program as beneficial, 94% said they would recommend it to a friend and 95% found the concepts useful. Significant reductions in PEs, anxiety and depression, and significant increases in mindfulness, self-compassion and emotion regulation abilities were observed (all $p < .02$), as well as a significant increase in frontohippocampal connectivity ($p < .008$), following RT. Lastly, a significant association between the increase in frontohippocampal connectivity and decrease in PEs was fully mediated by the improvement in emotion regulation.
Conclusions: A remotely delivered resilience-enhancing intervention may reduce PEs by improving emotion regulation capacity via its effects on the function of a frontohippocampal circuit; further controlled studies are needed to confirm this model. Taken together, RT could serve as one validated approach for disseminating resilience-enhancing emotion regulation skills to young people with PEs who have limited access to in-person mental health services.

17.4 INVESTIGATING THE EFFECTIVENESS OF THREE SCHOOL BASED INTERVENTIONS TO PREVENT PSYCHOTIC EXPERIENCES OVER A YEAR PERIOD – A SECONDARY DATA ANALYSIS STUDY.

Lorna Staines*[1], Colm Healy[1], Paul Corcoran[2], Helen Keeley[3], Helen Coughlan[1], Elaine McMahon[2], Padraig Cotter[4], David Cotter[1], Ian Kelleher[5], Camilla Wasserman[6], Romuald Brunner[7], Michael Kaess[8], Marco Sarchiapone[9], Christina W. Hoven[10], Vladimir Carli[11], Danuta Wasserman[11], Mary Cannon[1]

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Background: Lorna Staines, PhD Candidate, will present on 3 school based interventions aimed at preventing psychotic experiences.
Prevention is a key step to improving public mental health, by identifying and addressing symptoms prior to onset of a mental disorder, and by sustaining the mental wellbeing in those who are currently healthy. Psychotic experiences are relatively common in the general population. They are also significantly associated with high psychopathology, and a substantial increased risk of developing a mental disorder. Therefore, psychotic experiences are well placed to be used as a “marker” for prevention studies to test efficacy.

Current knowledge on prevention of psychotic experiences is extremely limited, with only one previous study. Similarly, few studies have examined intervention, with all previous studies utilizing some form of cognitive behavioural therapy. With such limited information, but such potential benefits, we opted to conduct a secondary data analysis to test 3 types of school based intervention on psychotic experiences.

Methods: This study used the Saving and Empowering Lives in Europe (SEYLE) study, Irish site (n=1096). Three intervention arms were included in SEYLE; a universal teacher training course (QPR), a universal educational tool (YAM), and a universal mental health screener and integrated referral system (ProfScreen). The design also included a minimal intervention arm to act as a control. Schools were randomly assigned to one of the 4 arms, and the students were followed over a year period. Psychotic experiences were measured at baseline, 3-month and 12-month follow up.

Results: The universal mental health screener and integrated referral intervention (ProfScreen), showed a 12 month reduction in point prevalence in psychotic experiences i.e. students in those schools, regardless of if they were referred or attended clinical services, showed a decrease in psychotic experiences. This intervention arm was also associated with a reduction in depression and anxiety scores in those who reported psychotic experiences. The teacher training and educational intervention approaches did not show a reduction in psychotic experiences.

Conclusions: This is the first study to look at school based interventions for psychotic experiences, and examine prevention interventions for psychotic experiences in school students. The results offer promising evidence for the value of universal screening and selective referral strategies for improving psychotic experience rates, and depression and anxiety symptoms. Notably, the ProfScreen intervention showed improvements for all students in that sample, not just those who attended the clinical referral. This suggests that universal monitoring may in itself support better mental health and may be an important integrative component to improving resilience at a population level.

Plenary Session III: Nina Kraguljac

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

18. MOVING TOWARDS NEUROIMAGING-INFORMED PRECISION MEDICINE IN SCHIZOPHRENIA

Dost Ongur*, Mclean Hospital*

Overall Abstract: Dr. Kraguljac will deliver a plenary talk on the promise and pitfalls of a personalized approach to neuroimaging research in schizophrenia. She will review "growth charting" techniques which can provide novel insights into changes in brain biology in this condition.

18.1 MOVING TOWARDS NEUROIMAGING INFORMED PRECISION MEDICINE IN SCHIZOPHRENIA

Nina Kraguljac*, University of Alabama at Birmingham*

Individual Abstract: Psychosis spectrum disorders are characterized by significant clinical and neurobiological heterogeneity. Current diagnostic criteria and psychopharmacological strategies do not take this heterogeneity into account, instead clinicians are relegated to make

'one size fits all' diagnoses and provide treatments based on trial-and-error. There is an urgent need to develop clinically relevant biomarkers that aid in dissecting clinical heterogeneity and treatment decisions with the ultimate goal to improve patient care and clinical outcomes for patients how suffer from this complex neuropsychiatric syndrome.
Here we show that neuroimaging data captured using different imaging modalities (structural, functional, neurometabolic) contain clinically relevant information, both in the context of predicting treatment response and in dissecting clinical heterogeneity, albeit at the group-level. To make further progress towards precision medicine, it is important to move beyond the group-level, where interindividual differences are considered noise, and instead capture this variability in context of the normal range.

We use normative modeling ("brain growth charting"), a statistical technique that allows characterization of neurobiological disease signatures at the individual level. Data our team has collected in a large group of antipsychotic medication-naive first-episode patients shows that normative modeling allows to capture inter-individual heterogeneity in neurobiological disease signatures in psychosis spectrum disorder patients. We also demonstrate, for the first time, that region level structural brain volume deviations from the reference range in key dopaminergic brain regions are better predictors of subsequent clinical response to antipsychotic treatment compared to raw volume measures.

This holds great promise for progress in precision medicine in psychiatry, where group-level studies have failed to derive definitive maps of brain pathology in psychosis spectrum disorders.

Concurrent Symposia

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

19. THE MECHANISMS UNDERLYING EARLY AND LATE LACK OF RESPONSE TO ANTIPSYCHOTICS: FROM BRAIN MORPHOLOGY AND PHYSIOLOGY, TO IMMUNE, MITOCHONDRIAL AND OXIDATIVE STRESS MARKERS

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

Overall Symposia Abstract: Antipsychotic drugs remain the first-line pharmacological treatment for schizophrenia and other psychoses. However, approximately 30% of people do not respond to two (or more) trials of these drugs, and another 30% of those who initially responded subsequently experience symptom relapse even during assured maintenance treatment with long-acting antipsychotics. This second group has been particularly neglected by research so far, although antipsychotic loss of effectiveness over time has emerged as a key issue for people with lived experience of psychosis taking long-term treatment.
We urgently need to characterise the mechanisms underlying both early and late lack of response to antipsychotics. Characterizing these mechanisms can inform the etiopathogenesis of schizophrenia, and provide a basis for personalized treatments, stratification in clinical trials and pharmacological testing.

Chaired by P. Dazzan (London, UK) and A. Vernon (London, UK) this symposium will present clinical and pre-clinical evidence on neuromorphological, physiological and cellular biomarkers of early and late lack of response to antipsychotic drugs. P. Dazzan will discuss the relationship between brain morphology and response to antipsychotics. R. Upthegrove (Birmingham, UK) will introduce evidence on novel approaches to investigating the relevance

of peripheral inflammatory markers, brain structure and targeted treatments. This will be extended by I. Khadimallah (Lausanne, Switzerland), with new data on mechanistic response biomarkers reflecting oxidative stress and mitochondrial dysfunction in treatment-resistant patients in early phase of psychosis (TRS). She will highlight the critical role of NMDAR co-agonists pathways in TRS patients and their interaction with mitochondrial deficits, which together may represent potential biomarkers based on central mechanisms of cognitive impairment in these patients. In the fourth presentation, D. Amato (Cincinnati, USA) will offer a reverse-translational perspective, showing preclinical data demonstrating cellular and molecular mechanisms of primary and acquired antipsychotic treatment resistance. Finally, J. Kane (New York, USA) will lead the discussion on how these findings can inform future research to advance our understanding of early and late response to antipsychotic medications.

19.1 NEUROMORPHOLOGICAL CORRELATES OF EARLY AND LATE LACK OF ANTIPSYCHOTIC RESPONSE FOLLOWING THE FIRST EPISODE OF PSYCHOSIS

Paola Dazzan*[1]

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

Background: The identification of biomarkers associated with response to treatment with antipsychotics may improve our understanding of the basis of therapeutic response, and facilitate the stratification of patients to different types of intervention. Magnetic Resonance Imaging (MRI) is a useful tool to study the brain morphological correlates of early and later symptom remission following the first episode of psychosis.
Methods: We present a body of work that includes multiple, unique datasets of individuals evaluated at the time of their first episode of psychosis (n=650) aged 18–40 years and followed up for periods ranging from 12 weeks to 6 years. MRI scans were acquired when patients were either antipsychotic-naive or minimally medicated. Regional volumes, cortical thickness, surface area and local gyrification and gyrification-based network connectivity were estimated at baseline. The relationship between these brain morphological measures at onset, and symptomatic response to antipsychotics at 4 and 12 weeks, and at 1 and 6 years was evaluated with a variety of methodological approaches.
Results: Early lack of response was associated with reduced frontal and cingulate gyrification, and a reduced structural connectivity with, differences in node centrality across anterior cingulate, frontal and temporal regions which became more apparent when lack of response became established. Similarly, the analysis of regional volumes at illness onset showed that widespread cortical volume reductions were associated with late lack of response to antipsychotics at 1 and 6 years.
Conclusions: Neuromorphological alterations at psychosis onset are differentially associated with response to antipsychotics and can identify subgroups of individuals with psychosis that go on to follow distinct illness trajectories. These alterations can help disentangle the heterogeneity underlying the neurobiology of psychosis and help identify individuals who could benefit from targeted future treatment trials.

19.2 INFLAMMATION AND OXIDATIVE STRESS IN EARLY PSYCHOSIS: WHEN AND HOW BEST TO TARGET TREATMENT?

Rachel Upthegrove*[1], Alexander Murray[1], Jack Rogers[1]

[1]*University of Birmingham*

Background: Immune dysfunction and/or deficient oxidative defence is implicated in the aetiology of schizophrenia with elevation of peripherally measured cytokines prior to the onset of disorder and causality suggested in genomic studies. However, there is considerable heterogeneity in the potential clinical profile of immune active psychosis and challenge in identifying the stage of illness and symptom profile to stratify for potential candidates of novel treatments.
Methods: Data presented from the Psychosis Immune Mechanism Stratified Medicine study, a MRC funded collaboration identifying immune active subgroups of psychosis and novel treatment targets. This presentation will include recent systematic reviews of studies measuring inflammatory markers in the periphery of patients at early staged of psychosis who are medication naive, together with data on the relevance of oxidative stress and how these are best measured.
Results: Evidence to date suggests inflammation is elevated prior to the onset of illness, with risk of psychosis related to affective dysfunction and persistent anxiety. In early stages of psychosis, there is normal or elevated glutathione, as measured by H1-MRS, which is reduced in chronic samples. Preclinical and mechanistic interpretation will include potential relevance to oxidative stress and potential novel targeted treatments.
Conclusions: It is possible that an appropriate antioxidant response is present in early stages of psychosis, which becomes exhausted in chronicity, potentially related to ongoing low- level non resolving inflammation. Appropriate targeting of anti-inflammatory adjuncts and treatments aimed at bolstering oxidative defence may need to focus on early stages of illness and in defined subgroups with evidence of immune activation in future trials.

19.3 MECHANISTIC RESPONSE BIOMARKERS REFLECTING NMDAR HYPOFUNCTION AND MITOCHONDRIAL DYSREGULATION IN TREATMENT-RESISTANT EARLY PSYCHOSIS PATIENTS

Ines Khadimallah*[1], Sara Camporesi[1], Margot Fournier[1], Philippe Golay[2], Lijing Xin[3], Philippe S Baumann[4], Martine Cleusix[1], Raoul Jenni[1], Romeo Restellini[1], Kenji Hashimoto[5], Kim Do[1], Philippe Conus[2]

[1]*Center for Psychiatric Neuroscience, Lausanne University Hospital,* [2]*Service of General Psychiatry, Lausanne University Hospital,* [3]*Laboratory of Functional and Metabolic Imaging, Ecole Polytechnique Fédérale de Lausanne, Switzerland,* [4]*Lausanne University,* [5]*Chiba University, Clinical Neuroscience*

Background: Treatment resistant schizophrenia (TRS) is characterized by long-term impaired social functioning and cognition. The early impact of cognitive symptoms and the mechanisms underlying TRS remain unclear. Moreover, NMDAR hypofunction, which has been linked to psychotic diseases, has also been linked to cognition deficits in human and animal model studies. In this work, we showed the critical role of NMDAR co-agonists pathways in TRS patients and their interaction with mitochondrial deficits. Together, these alterations may represent potential biomarkers based on central mechanisms of cognitive impairment in TRS patients.
Methods: From a total of 697 EPP aged 18 to 35, included in the Treatment and Intervention in early Psychosis Patients cohort in Lausanne, we identified 183 RESP and 51 TRS patients. For this, we generated an automated algorithm to apply the strict Treatment Response and Resistance in Psychosis (TRRIP) criteria, with compliance ascertained by antipsychotic plasma levels. No patient was taking clozapine at baseline. We assessed and compared in TRS, RESP and in HC (n=114) at baseline and prospectively over 3 years: a) Neurocognitive profile (MATRICS); b) Clinical profile: PANSS, GAF, number of hospitalized days (NHD); c) D-

Serine pathway: D-Serine, L-Serine, Glycine, Serine Racemase (SRR) and Serine Hydroxymethyltransferase (SHMT1) plasma levels and d) Glutamate pathway: glutamate and glutamine plasma and prefrontal cortex levels (MRS); EAAT3 (glutamate transporter) plasma levels; e) Combined exosomal levels of miR-137 and COX6A2 were used as stratification tools to identify individuals with (Psy-D) and without (Psy-ND) mitochondrial dysfunction (Khadimallah et al, 2021).
Results: Compared to RESP, TRS patients display lower scores in processing speed, attention/vigilance and visual learning, lower GAF, higher negative symptoms and a consistently higher NHD. No difference was found in positive symptoms between the two patients groups. At plasma levels, SHMT1 protein level was higher in RESP compared to both TRS and HC. SRR level was higher in RESP compared to HC. Levels of D-serine and L-serine and of L-serine and glycine were positively correlated in TRS but not RESP. Moreover, SRR and SHMT1 were positively correlated only in RESP. Regarding glutamate pathway; we found that plasma and brain levels of glutamate were negatively correlated in all patients but not in HC subjects. Plasma glutamate was increased in TRS compared to RESP. EAAT3 and glutamate plasma levels were negatively correlated only in RESP patients. The TRS and RESP subgroups showed different correlation patterns between miR-137 and COX6A2 levels. Interestingly, the majority of TRS individuals, in contrast to RESP patients, exhibited high level of mitochondrial dysfunction, classifying them as Psy-D group.
Conclusions: Our findings revealed that TRS display lower cognitive scores and poorer functioning than RESP already in the early phases of psychosis. Moreover, our results highlight the critical role of NMDAR co-agonists pathways in TRS patients and their interaction with mitochondrial deficits. Together, these alterations may represent potential biomarkers based on central mechanisms of cognitive impairment in TRS patients.

19.4 CELLULAR AND MOLECULAR MECHANISMS OF PRIMARY AND ACQUIRED ANTIPSYCHOTIC TREATMENT RESISTANCE

Anna Kruyer[1], Ariana Angelis[2], Davide Amato*[3]

[1]*Division of Pharmaceutical Sciences, University of Cincinnati,* [2]*College of Charleston, USA,* [3]*Division of Pharmaceutical Sciences, University of Cincinnati*

Background: A significant proportion of patients with schizophrenia show a poor response to antipsychotics during both acute and chronic treatment protocols. Understanding the biological mechanisms of this poor treatment outcome will help in design of improved therapies for schizophrenia and may offer insight into the mechanisms of schizophrenia symptoms and into response trajectories to various treatments. Using positron emission tomography in animal models we have shown that reduced antipsychotic efficacy occurs despite substantial D2 receptor blockade. Our results instead showed the crucial role of the dopamine transporter (DAT) in regulating antipsychotic response, in that increased DAT binding potential predicted acquired antipsychotic treatment resistance. In addition to this presynaptic mechanism, we find post- and peri-synaptic cellular adaptations in rodents developing acquired antipsychotic resistance using in vivo and ex vivo single cell imaging approaches. Finally, we are currently evaluating the impact of reduced DAT levels as causative of the primary response failure to antipsychotics.
Methods: We combined single cell in vivo calcium imaging, slice electrophysiology and biochemical approaches to describe the neural basis of antipsychotic-elicited effects on post- and peri-synaptic cells of the nucleus accumbens core (NAcore), a brain structure mediating antipsychotic effects in rodents, in transgenic mice to examine markers for acquired treatment resistance. In a separate set of studies, we have developed a model of primary antipsychotic

failure through molecular- or pharmacological reductions in DAT and the glutamatergic transporter (GLT1) levels in the striatum of rodents.
Results: Acquired treatment resistance: While we did not find clear alterations in D1 receptor-expressing medium spiny neuron (D1-MSN) activity, D2-MSNs were hyperactive during antipsychotic treatment resistance and related side effects ($p = 0.0174$). This was associated with increased expression of the calcium-permeable AMPA receptor in D2-MSNs with stronger rectification than control conditions ($p < 0.0055$) and with attenuated D2 receptor-mediated IPSCs ($p < 0.0001$). Furthermore, while synapsin I immunoreactivity ($p < 0.0001$) and GLT-1 expression ($p = 0.0078$) in the NAcore were elevated during antipsychotic treatment resistance, synaptic proximity of astroglia was reduced ($p = 0.0065$). Primary treatment resistance: Antipsychotics were effective in reducing locomotion in the tail-pinch and in ketamine models in control animals, but were their efficacy was significantly reduced in animals that had self-administered cocaine prior to testing ($p = 0.001$ and $p < 0.05$). Since chronic use of addictive drugs decreases DAT and GLT-1 expression in ventral striatum, we tested whether either of these adaptations were causative of the antipsychotic resistant phenotype by delivering DAT- or GLT-1-targeted morpholino oligomers the nucleus accumbens to reduce their expression. We found that either manipulation recapitulated primary antipsychotic resistance ($p < 0.05$).
Conclusions: Here I present data describing mechanisms of high relevance to understanding the biology of primary and acquired antipsychotic treatment failure using animal models. Our data points to the role of specific proteins that regulate levels of dopamine and glutamate in the ventral striatum in the first animal model of primary antipsychotic treatment resistant. Our data also highlight for the first time the role of post- and peri-synaptic striatal cell plasticity in contributing to the behavioral responses of antipsychotic medications during acquired treatment resistance.

20. SOCIAL COGNITION, SYMPTOMS, AND NEUROBIOLOGY ACROSS SCHIZOPHRENIA AND AUTISM SPECTRUM DISORDERS: HETEROGENEITY AND TRANSDIAGNOSTIC IMPLICATIONS

Stephanie Ameis, *University of Toronto*

Overall Symposia Abstract: Overlapping symptoms in SSDs and ASD have long been recognized. In particular, social cognitive impairments contribute to disability and lack effective treatment options across disorders. Limited research has examined the neural basis of social cognition across these disorders in an effort to inform targeted treatment innovation. Highly heterogeneous clinical presentation and co-occurrence are also characteristic across SSDs and ASD. In the current symposium, we present findings characterizing social cognitive deficits, symptoms, and underlying neurobiological mechanisms in SSDs and ASD, to enhance understanding of shared and divergent pathways contributing to key functional and symptom domains across disorders. Dr. Stephanie Ameis (Clinician Scientist, Centre for Addiction and Mental Health (CAMH); Associate Professor, University of Toronto) will introduce the topic of our symposium, providing a historical context, insights from her ongoing cross-disorder multimodal research, and incorporating her clinical perspective on the utility of SSD-ASD research. Dr. Lindsay Oliver (Project Scientist, CAMH, Toronto) will present results from a meta-analysis of studies comparing social cognitive performance in participants with SSDs compared to ASD, showing similar levels of social cognitive impairment across disorders. Dr. Tim Ziermans (Assistant Professor, University of Amsterdam) will discuss findings from an 8-year follow-up study examining the relationship between positive psychosis symptoms, social cognition, and executive functioning during childhood and positive symptoms at follow-up in

young adults with ASD. Dr. Iska Moxon-Emre (Postdoctoral Fellow, CAMH, Toronto) will share results comparing the functional neural correlates of social cognition across SSDs, ASD, and typically developing (TD) individuals during a social mirroring task and the Empathic Accuracy task. Dr. Michal Assaf (Director of the Autism and Functional Mapping Lab, the Olin Neuropsychiatry Research Center, Hartford) will present task-related brain activation and dynamic functional connectivity findings from two social processing tasks, and associations with social cognitive abilities across SSDs, ASD, and TD individuals. The panel will conclude with a discussion and question period led by Dr. Amy Pinkham (Professor, University of Texas at Dallas), an expert in social cognitive processing in psychiatric populations. The results of this symposium will highlight both overlapping and distinct patterns of social cognitive abilities, symptoms, and underlying neurobiology in SSDs and ASD. Taken together, the presented studies confirm the need to move beyond diagnosis-based analyses and suggest that transdiagnostic research will be essential to identify subgroups within and across disorders that may be more homogeneous in underlying etiology and targeted treatment response.

20.1 SOCIAL COGNITIVE PERFORMANCE IN SCHIZOPHRENIA SPECTRUM COMPARED TO AUTISM SPECTRUM DISORDERS: A SYSTEMATIC REVIEW, META-ANALYSIS, AND META-REGRESSION

Lindsay Oliver*[1], Iska Moxon-Emre[1], Meng-Chuan Lai[1], Laura Grennan[1], Aristotle Voineskos[2], Stephanie Ameis[2]

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

Background: Schizophrenia spectrum disorders (SSDs) and autism spectrum disorder (ASD) both feature deficits in social cognition, including emotion processing and theory of mind, which are associated with poor functional outcome. Overlapping symptoms in SSDs and ASD, and social impairments in particular, have long been recognized. However, these disorders have historically been examined separately using a range of tests and subdomain focus, and at different time points in the lifespan. Despite some evidence for similar levels of social cognitive impairment across SSDs and ASD, results are mixed. Thus, our objective was to determine how deficits in social cognitive domains diverge or overlap between SSDs and ASD by conducting a systematic review and meta-analysis of studies directly comparing social cognitive performance in people with SSDs and ASD.

Methods: Literature searches were conducted in MEDLINE, Embase, PsycINFO, and Web of Science to identify articles that utilized performance-based measures of social cognition in both SSDs and ASD samples. Quality and risk of bias were assessed for included articles. Random-effects meta-analyses were performed for measures of emotion processing, theory of mind, and the Reading the Mind in the Eyes test (RMET) in SSDs compared to ASD. Effect sizes were estimated using Hedges' g (SSDs-ASD). Heterogeneity of effects and publication bias were assessed for each meta-analysis. Meta-regressions were performed for age, publication year, quality assessment scores, and antipsychotic medication use.

Results: Of the 4175 screened articles, 36 were included in the qualitative analysis (SSDs N=1212, ASD N=1109), and 33 were included in the quantitative analyses (SSDs N=1113, ASD N=1015). Included studies highlighted the prevalence of small, male-predominant samples, and a paucity of cross-disorder clinical measures. The meta-analyses showed that there were no significant differences between SSDs and ASD on emotion processing measures (k=15, g=0.12, 95% CI [-0.07, 0.30], p=.21, I2=51.0%; one outlier excluded), theory of mind measures (k=17, g=-0.01, 95% CI [-0.21, 0.19], p=.92, I2=56.5%; one outlier excluded), or the RMET (k=13, g=0.25, CI [-0.04, 0.53], p=.095, I2=75.3%). There was no evidence of

publication bias. Sensitivity analyses confirmed robustness of findings. However, SSDs-ASD performance differences between studies were significantly heterogeneous (all $p<.05$), which was only minimally explained by explored moderators.
Conclusions: Similar levels of social cognitive impairment may be present in people with SSDs and ASD, across emotion processing and theory of mind. However, cross-disorder studies of social cognition including larger samples, consensus batteries, consistent reporting of measures, and data across multiple levels of analysis are needed to substantiate these findings, clarify underlying mechanisms, and parse heterogeneity.

20.2 CAN POSITIVE SYMPTOMS AND COGNITIVE MARKERS IN CHILDHOOD PREDICT PSYCHOSIS VULNERABILITY IN YOUNG ADULTS WITH AUTISM? RESULTS: FROM AN 8-YEAR FOLLOW-UP STUDY

Tim Ziermans*[1], Britt Kok[2], Sophie van Rijn[3]

[1]*University of Amsterdam,* [2]*University of Amsterdam,* [3]*Leiden University*

Background: Attenuated positive symptoms are the best-validated vulnerability markers for psychosis and are commonly associated with cognitive impairments in youth at-risk for psychosis. However, it is currently unknown to what extent such risk markers translate to young individuals with an autism spectrum condition (ASC).
Methods: ASC individuals (N = 30; M = 20.3 y, 82% male) filled out the Schizotypal Personality Questionnaire – Brief Revised (SPQ-BR) at 8-year follow-up and were compared to a normative dataset (N = 5546). Next, it was tested whether positive symptoms in adulthood were associated with positive symptoms and cognitive markers (executive functions and social cognition) assessed in childhood. Baseline questionnaire and cognitive data was available for this purpose. Bayesian comparisons, correlations and linear regressions were used to analyze the data.
Results: There was moderate evidence that positive symptoms in ASD differed (BF10 = 3.9), with a lower median than in the normative sample. Furthermore, within the autism sample there was no evidence for positive symptom stability over time, nor for a (linear) relation between cognitive markers assessed in childhood and positive symptoms at follow-up.
Conclusions: These results: suggest that self-reported positive symptoms in young autistic individuals are transitory over time and not elevated during young adulthood. Furthermore, positive symptoms and traditional cognitive markers in childhood appear to have limited predictive capacity. There is dire need for more sensitive psychosis vulnerability markers in autism.

20.3 NEURAL CORRELATES OF SOCIAL COGNITION IN AUTISM-SPECTRUM AND SCHIZOPHRENIA-SPECTRUM DISORDERS

Iska Moxon-Emre*[1], Lindsay Oliver[1], Colin Hawco[1], Erin W. Dickie[1], Rachael E. Lyon[1], Peter Szatmari[1], John D. Haltigan[1], Anna Goldenberg[2], Pushpal Desarkar[1], Robert W. Buchanan[3], Anil K. Malhotra[4], Meng-Chuan Lai[1], Aristotle N. Voineskos[1], Stephanie H. Ameis[1]

[1]*Centre for Addiction and Mental Health,* [2]*Hospital for Sick Children,* [3]*Maryland Psychiatric Research Center,* [4]*Zucker Hillside Hospital*

Background: Social cognitive deficits are central features of autism spectrum disorder (ASD) and schizophrenia spectrum disorders (SSDs). Impairment levels are comparable across diagnoses, yet limited research has examined the neural basis of social cognition across ASD

and SSDs. We sampled individuals with ASD or SSDs, and typically developing controls (TDC), from the Social Processes Initiative in Neurobiology of Autism-spectrum and Schizophrenia-spectrum Disorders (SPIN-ASD) (1R01 MH114879-01A1) and SPINS (R01 MH102324) studies. Our goal was to compare the neural correlates of social cognition across ASD, SSDs and TDC groups, using two functional magnetic resonance imaging (fMRI) tasks; a social mirroring imitate/observe (ImObs) task to probe lower-level social cognition (e.g., emotion recognition), and the empathic accuracy (EA) task to probe both lower-level and higher-level (e.g., theory of mind) social processes.

Methods: fMRI data analyzed were from participants, aged 16-34y, with: 1) useable EA task data: n=174 (ASD: n=59, 21.2[3.97]y, 23-female; SSDs: n=56, 25.3[4.54]y, 19-female; TDC n=59, 25.8[3.93]y, 32-female), and 2) useable ImObs task data: n=164 (ASD: n=56, 20.9[3.92]y, 22-female; SSDs: n=50, 24.7[4.44]y, 17-female; TDC: n=58, 25.8[3.96]y, 32-female). During fMRI scanning, participants performed the: 1) EA task, where they watched 9 videos of individuals detailing autobiographical events, and provided continuous ratings of how positive/negative they thought the individual felt, and the 2) ImObs task, where they were shown photographs of 80 individuals expressing emotions, and were instructed to either imitate or observe (without imitating) the facial expression. Data were acquired on 3T Prisma scanners across the Centre for Addiction and Mental Health (CAMH), Zucker Hillside Hospital (ZHH) and Maryland Psychiatric Research Center (MPRC), preprocessed using fMRIPrep, then transformed onto the cortical surface using Ciftify (6mm smoothing applied). Subject-level data for both tasks were analyzed using GLMs, with: 1) EA scores as parametric modulators (activation maps therefore reflect brain activity that varies with EA score), and 2) a linear contrast for imitate vs. observe. Group-level comparisons were conducted with FSL's PALM, covarying for age and sex, and using 1000 permutations (thresholded at $p<0.05$ FWE-corrected).

Results: EA task performance differed across groups ($F(2,171)=7.31$, $p<0.01$); the SSDs group scored lower than the ASD and TDC groups (all $p<0.01$). EA performance did not differ between ASD and TDC groups ($p>0.05$). There were no group-level differences in neural correlates for either the EA or ImObs tasks. Across all groups, widespread activity in the right hemisphere, including regions implicated in social cognition (e.g., superior temporal sulcus, temporal pole, inferior parietal lobule, temporo-parietal junction), were positively related to EA. During the ImObs task, bilateral activity within the fronto-parietal mirror neuron system (MNS) network (e.g., inferior frontal gyrus, premotor cortex, inferior parietal lobule) was observed across all groups.

Conclusions: Our data suggest that EA performance recruits brain regions implicated in social cognition, largely from the right hemisphere. Though the SSDs group had poorer EA task performance than the ASD and TDC groups, there were no group differences in correlational patterns between neural activity and EA, nor in activity during the ImObs task. Our findings emphasize the need to move beyond the case-control approach to identify transdiagnostic subgroups featuring more homogeneous brain-behavior profiles related to social cognition.

20.4 AUTISM SPECTRUM DISORDER AND SCHIZOPHRENIA: A CASE OF SIMILAR SOCIAL-EMOTIONAL PHENOTYPE WITH DIVERGING UNDERLYING NEURAL MECHANISMS

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Background: Schizophrenia (SZ) and autism spectrum disorder (ASD) are considered separate clinical entities, yet recent evidence suggests overlap in social-emotional symptoms and underlying neural impairments. We compared ASD, SZ and typically developed (TD) samples and their associated social cognitive abilities to investigate differential neural architecture related to these processes within and between diagnoses. To do so, we assessed the neural correlates of mentalizing processes during an intersocial competitive task and of social-emotional processes during an emotional simulation task.
Methods: We recruited adults ages 18-35 (IQ>80) diagnosed with ASD (n=42), SZ (n=41), or TD (n=55). Participants underwent assessment of social cognitive functions, including mentalizing, alexithymia and emotion recognition, and social-communication behaviors, as well as fMRI scans while (1) performing a competitive Domino task, and (2) watching social-emotional 3.5 minutes video clips of actors telling either happy, sad or neutral stories. Independent component analysis (ICA) was used in the analyses of both tasks to identify task-related functional regions. For Domino we calculated mentalizing task-related activity (MTR) in the brain regions comprising the mentalizing network, including the medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), Precuneus (PrC) and bilateral temporo-parietal junction (TPJ). In the social-emotional task, we applied k-means clustering to windowed functional network connectivity (FNC) matrices, to identify four unique whole-brain dynamic FNC (dFNC) states. Fraction and dwell times (FT and DT), assessing states' engagement, were used as dependent variables in mixed-models with group as between-subject factor, and emotion and social-cognitive measures as within-subject factors.
Results: ASD and SZ groups showed significant differences from TD in social-communication behaviors ($F>21.8$, $p<.001$). In the Domino fMRI task, both SZ and ASD groups showed MTR activity deficits in PCC and TPJ compared to TD ($F>6.3$, $p<0.014$). In TPJ and MPFC, MTR activity modulation was associated with social communication impairments only in ASD ($p<0.01$), while in the PrC, MTR activity was associated with increased self-reported fantasizing only in SZ ($p=0.009$). In the social-emotional fMRI task, during happy videos , both patient groups spent less time in a happy-associated state and more time in a weakly connected state, compared to TD (main effect of DT: $F=7.4$, $p=0.001$; FT: $F=3.1$, $p=0.049$). During sad videos, while both patient groups spent more time in a sad-associated state (FT: $F=3.3$,$p=0.04$), it was significant only in ASD ($t=2.5$, $p=0.014$). Differences between ASD and SZ were not significant ($p>0.1$). Additionally, ASD showed a significant relationship between dFNC measures and a) alexithymia scores during the sad videos (group-by-alexithymia interaction: $F=4.244$, $p=0.017$; significant slope in ASD only, $p=0.003$), and b) emotion recognition during happy videos ($F=3.836$, $p=0.024$; significant slop in ASD only, $p=0.006$).
Conclusions: While SZ and ASD showed overlap in social-communication deficits compared to TD, as well as abnormal MTR and dFNC patterns during social tasks, the associations between neural patterns and social-cognitive measures diverged between the groups. These results potentially point to underlying disorder-specific neural mechanisms of social-emotional deficits that can be uniquely targeted with behavioral, pharmacological, or neuromodulation interventions.

21. ORIGINS AND MODULATION OF EXCITATION/INHIBITION IMBALANCE IN THE PATHOPHYSIOLOGY OF SCHIZOPHRENIA

Gemma Modinos*, King's College London*

Overall Symposia Abstract: Normal brain function relies on a balanced interplay between glutamatergic excitatory neurons and GABAergic inhibitory interneurons. Several lines of evidence suggest that an imbalance in this excitation/inhibition (E/I) ratio due to parvalbumin-positive (PV+) inhibitory interneuron dysfunction is a core feature of psychosis. This interdisciplinary symposium will take a translational approach across preclinical and clinical research to examine factors leading to altered E/I balance and the emergence of schizophrenia. This will be achieved through four inter-related talks, bridging complementary knowledge across scales in schizophrenia neuroscience, from genes to molecules to cells to large-scale networks to environment, behaviour and outcomes. Kim Do (Switzerland) will begin by presenting recent work on how the predictive accuracy of schizophrenia polygenic risk scores (PRS) could be improved by inclusion of pathway-specific PRS and expression quantitative trait loci, centered on pathways highlighted in the oxidative stress hub (glutamate, oxidative stress/redox, GABA interneurons, neuroimmune/neuroinflammation and myelin). This genetic approach will be complemented by Felipe Gomes (Brazil), who will describe how adolescent stress increases vulnerability via disruption of immature PV+ interneurons and perineuronal net loss in the ventral hippocampus. Importantly, he will show that that this vulnerability can be reinstated in the adult by digestion of perineuronal nets prior to stress exposure. Next, delving deeper into this critical period, Anthony Grace (USA) will show how the period of vulnerability differs between male and female rats, with male rats showing prepubertal vulnerability driven by PV+ loss in the amygdala, whereas female vulnerability is dependent on postpubertal stress leading to loss of PV+ function in the nucleus reticularis-nucleus reuniens pathway. In both cases, the result is PV+ loss in the limbic hippocampus and a hyperdopaminergic state. The disruption appears to be driven by a precocious maturation of the amygdala-prefrontal pathway due to early stress, which disrupts the normal maturation of E/I balance. Finally, Gemma Modinos (UK) will present electronic health records data from 758 individuals at clinical high-risk (CHR) for psychosis suggesting that prescription of GABA-enhancing drugs may be associated with an increased risk of developing psychosis. Since decoding the cellular and neurochemical pathways involved in neuroimaging biomarkers of psychosis risk may be key to identify biological mechanisms that might be amenable to intervention, she will also show that neural activity alterations in CHR individuals are associated with the expression of genes broadly involved in immune function, oligodendrocyte differentiation and necrotic cell death, and track the distribution of NMDA receptor densities. The symposium will conclude with a discussion led by world-leading expert Oscar Marin (UK), who will integrate this set of complementary findings from interrelated disciplines to facilitate a stimulating discussion with the audience. In view of the increasing attention devoted to the research of brain complexity at multiple scales, this timely interdisciplinary symposium will offer new insights and tools to better our understanding of the mechanisms underlying schizophrenia, toward the development of novel strategies for treatment and prevention.

21.1 GENE SET ENRICHMENT ANALYSIS OF PATHOPHYSIOLOGICAL PATHWAYS HIGHLIGHTS OXIDATIVE STRESS IN PSYCHOSIS

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Background: Converging evidence from clinical and preclinical data highlights the crucial role of either redox dysregulation, glutamate/NMDAR hypofunction, neuroinflammation or mitochondria bioenergetics dysfunction, initiating "vicious circles" centred on oxidative stress during neurodevelopment. These processes would lead to impairments of parvalbumin-GABAergic neurons microcircuits and myelinated fibers of long-range macrocircuitry known to be at the basis of neural synchronization abnormalities and cognitive deficits characteristic of schizophrenia. Currently, the predictive power of schizophrenia polygenic risk scores (PRSs) is not large enough to allow high-accuracy discrimination between cases and controls and thus not adequate for clinical integration. Since PRSs are rarely used to reveal biological functions or to validate candidate pathways, to fill this gap, we investigated whether their predictive ability could be improved by building genome-wide (GW-PRSs) and pathway-specific PRSs using single nucleotide polymorphisms (SNPs) and distance- or expression quantitative trait loci (eQTLs)- based mapping between genetic variants and genes in two first-episode psychosis case-control samples.

Methods: Analyses were first performed in the Lausanne Treatment and Early Intervention in Psychosis Program (TIPP) study (n = 340, cases/controls: 208/132), a sample of first episode of psychosis patients and matched controls, and then validated in an independent study, the epidemiological and longitudinal intervention program of First Episode Psychosis in Cantabria (PAFIP) (n = 352, 224/128). GW genotyping using the Infinium OmniExpress-24 v1.3 SNP array for the TIPP and the Illumina Infinium PsychArray for PAFIP cohort. We derived 18 PRSs: 3 GW-PRSs and 15 pathway-PRSs, focused on five pathways (glutamate, oxidative stress, GABA/interneurons, neuroimmune/neuroinflammation and myelin). Functional variants used to derive GW-PRSeQTLs and pathway-PRSeQTLs were identified through (1) Genotype-Tissue Expression v8 (GTEx) and (2) MetaBrain databases. Case-control status (dependent variable) was regressed on GW-PRSs and pathway-PRSs using logistic regressions and the first five ancestry-informative genetic principal components were included as covariates.

Results: A total of 692 participants from 2 separate studies were included in the analysis; 259 were women (37.4%) and the mean (SD) age at study interview was 29.5 (9.15) years. We investigate the ability of both genome-wide (GW-PRSs) and pathways (pathway-PRSs) schizophrenia polygenic risk scores to discriminate early psychosis case-control status. In addition, we compared PRS derived using SNPs and brain cortex eQTLs. We found that GW-PRSs were significantly associated with the early psychosis status regardless of whether SNPs or eQTLs were used. Pathway-PRSSNPs did not show any significant enrichment in either the TIPP or the PAFIP samples. In the TIPP sample, pathway-PRSeQTLs based on GTEx showed an enrichment for the oxidative stress, interneurons and neuroinflammation pathways. In the PAFIP sample, pathway-PRSeQTLs based on both GTEx and MetaBrain showed an enrichment for the oxidative stress pathway. Thus, the only pathway based PRS that showed a replicated association with early psychosis status was the oxidative stress pathway derived using eQTLs. Notably, in the TIPP study, the predictive power of oxidative stress pathway-PRSeQTLs on the case-control status, accounted for up to 100% of the predictive power of the

respective GW-PRSeQTLs, whereas in the PAFIP study, the predictive power, accounted up to 97% of the predictive power of the respective GW-PRSeQTLs.
Conclusions: Our results highlight the critical role of cis-regulatory elements eQTLs, both genome-wide and within the oxidative stress pathway, which are potentially driven by gene-environment interactions. They suggest that the predictive accuracy of polygenic risk scores could be improved with the inclusion of information from functional annotations, and through a focus on specific pathways, emphasizing the need to build and study functionally informed risk scores.
They also support the hypothesis that that redox dysregulation/oxidative stress plays a critical role in pathophysiology of schizophrenia.

21.2 PERINEURONAL NETS SURROUNDING PARVALBUMIN INTERNEURONS ACT AS A PROTECTIVE FACTOR AGAINST THE LASTING DELETERIOUS CHANGES CAUSED BY STRESS

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Background: Perineuronal nets (PNNs) are unique extracellular matrix structure that aggregates around parvalbumin-containing GABAergic interneurons (PVI). These PNNs attenuate plasticity by stabilizing glutamatergic inputs onto PVI and protects these interneurons from oxidative and metabolic damage. However, the formation of PNNs around PVI is not complete until early adulthood. Studies show that PVI are more susceptible to damage in periods with immature PNNs, such as adolescence that can lead to the development of psychiatric disorders. Our hypothesis is that exposure to stress during adolescence, which is a sensitive period in which the PVI interneurons are not completely protected by the PNNs, results in PV loss in the vHipp. Similar changes would not be found after the exposure of adult animals to stress given that during adulthood PVI are protected by the PNNs. Also, if the differential developmental vulnerability of PVI driven by the formation of PNNs is a causative factor, we further predict that the degradation of PNNs in the vHipp of adult animals could recreate an adolescent phenotype of stress susceptibility.
Methods: Male Sprague-Dawley rats were exposed to a combination of stressors, consisting of daily footshock (1.0 mA, 2 s, randomized every 60±20 s) for 10 days during adolescence (PND 31-40) or adulthood (PND 61-70), and three 1-hour restraint stress sessions (days 1, 2 and 10), right after the footshock session. Three weeks after the stress, the animals were submitted to behavioral tests to evaluate anxiety [elevated plus-maze (EPM) and light-dark box], sociability (social interaction test), cognitive function [novel object recognition (NOR) test], and increased locomotor response to the NMDAr antagonist MK-801. Since a PVI loss in the vHipp is proposed to cause an increase in the activity of vHipp pyramidal neurons and dopamine system overdrive, we also evaluated the impact of stress on in vivo electrophysiological activity of vHipp pyramidal neuron and dopamine neurons in the ventral tegmental area (VTA). Only males were used in this study since we have previously found that female rats were resistant to present behavioral and electrophysiological changes after exposure to the same stress protocol. In a second set of experiments, adult animals received intra-vHipp infusion of chondroitinase ABC (0.05U/microL, 700 nL), which degrades PNNs, or penicillinase (control given that it is inert in mammals). One week later, animals were submitted to stress and tested 2-3 weeks post-stress.
Results: Adolescent stress exposure produced in adult rats anxiety responses in the light-dark box (decreased the time in the light compartment), decreased social interaction, impaired cognitive function in the NOR test, and increased locomotor response to MK-801. Furthermore,

adolescent stress increased the firing rate of vHipp pyramidal neurons and the number of spontaneously active VTA dopamine neurons, along with a decrease in the number of PV+, PNN+, PV+/PNN+ cells in the vHipp. These findings are similar to those found in animal models for schizophrenia. Correlation matrix analysis indicated that increased VTA dopamine system activity was highly correlated with anxiety behaviors, impairments in social interaction and cognitive function induced by adolescent stress. In contrast, adult stress did not induce long-lasting changes in behavior, electrophysiology and the number of PV+, PNN+, PV+/PNN+ cells in the vHipp. However, the infusion of ChABC into the vHipp causes the adult stress to produce cognitive deficits in the NOR test and increase VTA DA neuron population activity similar to that induced by the adolescent stress. The degradation of PNNs in naïve animals did not produce any change.

Conclusions: Our findings indicate that stress during adolescence, a period when PVI are not completely protected by the PNNs, caused long-lasting behavioral deficits that was correlated with a schizophrenia-like hyperdopaminergic state. These findings are in accordance to epidemiological studies indicating that stress during adolescence acts as a major risk factor for schizophrenia. In addition, degradation of perineuronal nets degradation in the vHipp of adult rats recreates an adolescent-like phenotype of stress susceptibility, suggesting that PNNs act as a protective factor against the lasting deleterious changes caused by stress.

21.3 JUVENILE VS ADOLESCENT STRESS LEADS TO HIPPOCAMPAL PARVALBUMIN NEURON LOSS AND DOPAMINE SYSTEM ALTERATION, BUT IS MEDIATED VIA DIFFERENT PARVALBUMIN-REGULATED PATHWAYS IN MALE VS FEMALE RATS.

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Anthony Grace*, University of Pittsburgh*

Background: There is increasing evidence that childhood stress or trauma is a significant risk factor for the development of major psychiatric disorders in adults, including schizophrenia, depression, and anxiety. Using rodent models, we have been exploring how prepubertal or postpubertal stressors increases vulnerability to disorders in adulthood. We have found that the pathological consequences depend on the timing and intensity of the stressors, with parvalbumin (PV) neuron loss a driver of the pathology. This would result in an excitation/inhibition imbalance driving a hyperdopaminergic state observed in schizophrenia.

Methods: Male and female rats were subjected to either daily handling or daily footshock + 3 restraint sessions over 10 days from PD21-30 (prepubertal) or from PD41-50 (postpubertal) and tested as adults (>PD65). Dopamine (DA) neurons were recorded in the VTA in a cells/track protocol, and recordings were made from ventral hippocampal (vHip) and basolateral amygdala (BLA) neurons. Behavioral tests include elevated plus maze (EPM) and novel object recognition (NOR).

Results: Male rats that received combined stressors pre or peripubertally exhibited hyperdopaminergic state (increased number of DA neurons firing ($F(1,31)=9.852$, $p<0.01$) as well as anxiety (elevated plus maze $F(1,38)=6.228$, $p<0.05$) and deficits in NOR $F(1,37)=6.884$, $p<0.01$) in the adult; however female rats were resilient to the long-term effects of stressors. In contrast, exposure to stress postpubertally caused female rats to exhibit increased DA population activity ($F(1,31)=11.47$; $p<0.01$), primarily in the affect-related medial VTA; in this case the males were resilient. In both sexes, vHip activation impacted DA neuron activity (male-selective increase by PreP-S ($p<0.05$; Dunn's test) and female-selective increase by PostP-S ($p<0.01$)) and in both cases was driven by significant vHip PV neuron loss.

However, in males vHip activity is correlated with loss of PV neurons in the BLA leading to BLA activation with prepubertal stress (Kruskal–Wallis test, $H=24.69$, $p<0.0001$; Dunn's test, PreP-S:Males, $p<0.0001$). In contrast, in the female preliminary results show that postpubertal stress caused elevated vHip firing rate via possible PV loss in nucleus reticularis leading to nucleus reuniens activation, presumably via the nucleus reuniens-vHip pathway.
Conclusions: These results show that male rats are vulnerable to prepubertal stress-induced disruption of DA neuron activity and deficits in anxiety and cognition as adults due to vHip PV neuron loss, whereas females are resilient. In contrast, female rats were susceptible only to stress administered postpubertally and vHip PV loss leading to alterations only in the affect-related medial VTA, consistent with anxiety and susceptibility to depression. Furthermore, these alterations produced pathway-specific changes in males vs females. This is consistent with a resilience of females to severe schizophrenia pathology compared to males, and is driven by an excitation/inhibition imbalance throughout the circuit.

21.4 EXCITATION/INHIBITION BALANCE AND VULNERABILITY FOR PSYCHOSIS: FROM NEURAL MECHANISMS TO REAL-WORLD CLINICAL OUTCOMES

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[1]*King's College London*

Background: Multiple lines of evidence suggest that an imbalance in neuronal excitatory-inhibitory activity due to inhibitory interneuron dysfunction is central to the development of psychotic disorders such as schizophrenia. Furthermore, while research in experimental animals has shown that enhancing GABAergic signalling during the premorbid stage can prevent the emergence of psychosis-relevant phenotypes, the relationship between GABA-enhancing drugs and real-world outcomes in individuals at clinical high-risk (CHR) for psychosis has not been examined. Our previous neuroimaging work showed that cortical GABA levels were related to the increase in resting activity that is seen in CHR individuals who subsequently transitioned to psychosis. However, the lack of specificity of most MRI-based markers to the underlying molecular and cellular properties has limited their potential to inform mechanisms that may be amenable to treatment.
Methods: Our first experiment was a naturalistic, retrospective, observational cohort study using electronic health records from 758 CHR individuals accessing a secondary mental health care service in London (UK) from 2001-2021. Cox proportional-hazards regression models assessed whether benzodiazepine exposure +/-3 months of accessing the service modulated the risk of developing a psychotic disorder or event indicative of clinical crisis >3 months after first contact. Individual models were run on each outcome variable using both the whole database and a subset of the database following propensity score matching (PSM) to overcome confounding-by-indication.
Our second experiment applied state-of-the-art (1) imaging transcriptomics and (2) neuroreceptor mapping approaches to investigate the transcriptional, cellular and neurochemical pathways linked to a non-invasive quantitative MRI marker of neuronal activity (regional cerebral blood flow, rCBF) in 129 CHR individuals and 58 healthy controls. The main goal was to identify (1) genes and (2) neuroreceptor densities with spatial profiles that track rCBF abnormalities in the CHR state.

Results: Our first experiment included a total of 436 individuals: n=61 with early benzodiazepine exposure and n=369 benzodiazepine naïve. Unmatched analyses showed that CHR individuals with early benzodiazepine exposure had an increased risk of developing

psychosis (HR=2.77; 95% CI: 1.48-5.17; p=0.002), receiving a home visit (HR=1.91; 95% CI: 1.24-2.95; p=0.004), attending A and E (HR=1.89; 95% CI: 1.17-3.04; p=0.009), or receiving a hospital admission (HR=4.42; 95% CI 2.04-9.58; p<0.001). In the PSM sample (n=61 in both groups), early benzodiazepine exposure did not significantly increase the risk of developing psychosis or event indicative of clinical crisis.
Our second experiment revealed that distribution of rCBF differences between CHR and HC significantly tracks the expression of oligodendrocyte genes (pFDR<0.05). Gene ontology enrichment analyses showed that this case-control rCBF pattern was associated with molecular processes involved in immune function, oligodendrocyte differentiation and necrotic cell death (all pFDR<0.05). Furthermore, the case-control rCBF map tracked the distribution of NMDA receptor densities as measured with [18F]GE179 PET (pFDR<0.05).

Conclusions: These results show that benzodiazepine use may be associated with an increased risk of developing psychosis and worse clinical outcomes in CHR individuals. However, based on the PSM results this may be due to benzodiazepines being prescribed to CHR individuals who are clinically more unwell. Decoding the cellular and neurochemical pathways involved in neuroimaging biomarkers of psychosis risk may have important implications to understand biological mechanisms behind vulnerability to pathological changes, and which might be amenable to pharmacological intervention.

22. THE ASSOCIATION BETWEEN CANNABIS AND PSYCHOSIS: EVEN IF GENES ARE IMPORTANT SHOULD WE FORGET ABOUT MODIFYING THE ENVIRONMENT?

Marta Di Forti*, SGDP, Institute of Psychiatry*

Overall Symposia Abstract: Consistent epidemiological evidence supports the association between cannabis use and risk of psychosis. General population studies report that cannabis users are more likely to report psychotic like experiences (PLEs) compared to non-users. Daily use cannabis has been associated with a 3-fold increase in risk of psychotic disorders. A genetic overlap between both lifetime cannabis use and Cannabis Use Disorder (CUD) with schizophrenia (SCZ), has been consistently reported. Some Mendelian randomization studies suggest a direction of causality from schizophrenia genes to cannabis use, others support the direction from cannabis use to psychosis phonotypes. Other evidence indicates that genetic predisposition to schizophrenia further increases risk of psychosis among cannabis users.
In this symposium we shall present data that explore the role of genetics but also affective states to better understand the association between cannabis use and psychosis phenotypes.

Emma Johnson will open the symposium presenting a cross disorder analysis aimed to identify genome-wide significant loci that are pleiotropic (i.e., genetic variants exerting an effect on both phenotypes) for CUD and SCZ, using the largest to date GWAS datasets. Among the 121 independent genome-wide significant loci identified, two showed a particularly strong signal for both CUD and SCZ , suggesting shared genetic vulnerability between the two phenotypes.

Isabelle Austin-Zimmerman will show results exploring the genome-wide genetic correlation between cannabis use and the psychosis phenotype. Isabelle run localised genetic correlation analysis using LAVA to fine map the specific regions that contribute to the overall genetic correlation. The MAGMA analysis of these regions reveals enrichment of gene sets in the brain, including the frontal cortex, basal ganglia and hippocampus. These preliminary analyses begin to explore the differing genetic architecture underlying cannabis-related psychotic disorders, as well as psychosis in the absence of cannabis use.

Mike Wainberg will present his findings from 109,308 UK Biobank participants. His data suggest that cannabis users, especially frequent users are more likely to report four PLEs and at a younger age than never users. Indeed, cannabis ever-use is associated with 67% greater adjusted odds of delusions of reference among individuals in the top fifth of polygenic risk, but only 7% greater adjusted odds among the bottom fifth; hence individuals genetically predisposed to schizophrenia seem more vulnerable to psychotic experiences when using cannabis.

Finally, Sinan Guloksuz will address the lack of longitudinal research investigating the temporal association of psychotic experiences (PE) with cannabis use, anxiety, and depressive symptoms. In particular, he will present data that investigate the reciprocal mediation roles of cannabis use, anxiety, and depressive symptoms in the onset of PE may provide insight into understanding this complex relationship. His findings from the second longitudinal Netherlands Mental Health Survey and Incidence Study (NEMESIS-2), support for an "affective pathway" to psychosis expression.

Therefore, at time when the debate on the association between cannabis use and risk of psychosis is at its pick, it is important to clarify if genes explain it all and if affective states can identify those more likely to develop psychosis when using cannabis. Cannabis continues to be the most widely used recreational drug as well as increasingly used for medicinal reasons, hence the data we present provide a rare opportunity to psychiatry for primary as well as secondary prevention.

22.1 THE ASSOCIATION BETWEEN CANNABIS USE, GENETIC RISK FOR SCHIZOPHRENIA, AND PSYCHOTIC-LIKE EXPERIENCES IN THE UK BIOBANK

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Background: Cannabis is known to produce acute, transient psychotic-like experiences. However, it is unclear whether cannabis disproportionately increases the risk of specific types of psychotic experiences and whether genetic predisposition influences the relationship between cannabis use and psychotic experiences.
Methods: In this cross-sectional study of 109,308 UK Biobank participants, we examined how schizophrenia polygenic risk modulates the association between self-reported cannabis use and four types of psychotic experiences: auditory hallucinations, visual hallucinations, persecutory delusions, and delusions of reference.
Results: Frequent cannabis use was associated with all four types of psychotic experiences, especially persecutory delusions. Cannabis users' psychotic experiences tended to be earlier-onset and cause greater distress than non-users', but were not more likely to lead to help-seeking. Cannabis ever-use was associated with 67% greater adjusted odds of delusions of reference among individuals in the top fifth of polygenic risk, but only 7% greater adjusted odds among the bottom fifth.
Conclusions: Our results suggest that cannabis use is a predictive risk factor for psychotic experiences, including early-onset and distressing experiences. Individuals genetically predisposed to schizophrenia may be especially vulnerable to psychotic experiences as a result of using cannabis.

22.2 UNDERSTANDING THE GENETIC RELATIONSHIP BETWEEN CANNABIS USE AND PSYCHOSIS

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Background: Previous GWAS have identified multiple genetic risk variants for both psychosis and cannabis use, and there is evidence of share genetic liability for these traits. However, the causal direction of this common genetic liability and the specific regions of shared genetic risk remain unclear. We build on the previous work in this field by conducting localised genetic correlation and pathway analyses, to identify the shared pathways and pleiotropic variants that contribute to the observed correlation between psychosis and cannabis use, as well as elucidate those biological pathways that are specific to each phenotype.
Methods: We first conducted a meta-analysis of the PGC GWAS results for schizophrenia and bipolar disorder to establish a broad psychosis phenotype. We these summary statistics and published results for cannabis use disorder to define the SNP-based heritability of these two traits and establish the genome-wide genetic correlation between the traits, both within and across ancestry. In addition, we investigate the genome-wide genetic correlation for various other traits previously found to be associated with cannabis use and psychosis, such as educational attainment. We conduct localised genetic correlation analysis using LAVA to fine map the specific regions that contribute to the overall genetic correlation. Where we observe regions of significant association, we will calculate genetic pathway scores for the relevant gene sets. We will calculate two sets of genetic pathways scores for both psychosis and cannabis use disorder, including and excluding those SNPs associated with both traits. Pending additional data, we will also conduct the first GWAS of psychosis among cannabis naive participants only and repeat the above analyses to establish pathways specific to psychosis in the presence and absence of cannabis use.
Results: A meta-analysis of schizophrenia and bipolar disorder GWAS results identified 413 independent genomic risk loci, and 1,479 mapped genes. The genetic correlation between the primary studies (PGC schizophrenia and PGC bipolar) was r2=0.7. The cross-trait meta-analysis reveals more genome-wide significant risk loci than either primary GWAS. MAGMA analysis reveals enrichment of gene sets in the brain, including the frontal cortex, basal ganglia, and hippocampus, as well as the pituitary. SNP-based heritability (h2) for our broad psychosis phenotype is estimated to be 0.14±0.004, p=6.3x10-25. SNP-based h2 = CUD is 0.12±0.01, p=3.6x10-33.
Conclusions: This research furthers the understanding of the differing genetic architecture underlying cannabis-related psychotic disorders, as well as psychosis in the absence of cannabis use.

22.3 INVESTIGATING THE NATURE OF GENETIC OVERLAP BETWEEN CANNABIS USE DISORDER AND SCHIZOPHRENIA

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Background: Recent genome-wide association studies (GWAS) have found modest but significant genetic correlations between schizophrenia (SCZ) and cannabis ever-use, and between SCZ and cannabis use disorder (CUD). Furthermore, we recently found that genetic liability to CUD was significantly associated with SCZ even when accounting for cannabis ever-use, ever-smoked tobacco regularly, and nicotine dependence as simultaneous predictors in a genomic structural equation model. However, no study has yet examined the specific genetic loci associated with both CUD and SCZ liability.
Methods: First, we applied ASSET, a cross-disorder method, to identify genome-wide significant loci that are pleiotropic for CUD (N = 357,806) and SCZ (N = 161,405). We also examined bivariate and local genetic correlations between CUD and SCZ after conditioning on tobacco smoking (N = 632,802), as smoking is correlated with both cannabis use and SCZ. We are planning to update these analyses with a larger GWAS of CUD that is forthcoming, as well as extending our analyses to include individuals of non-European ancestries.
Results: We found >100 independent genome-wide significant ($p < 5e-8$) loci pleiotropic for CUD and SCZ (i.e., genetic variants exerting an effect on both CUD and SCZ), with 54 loci showing convergent effects (i.e., same direction of effect on both disorders) and 51 loci demonstrating divergent effects (i.e., risk-increasing for one disorder and protective for the other). A chromosome 8 locus that contains the genes EPHX2 and CHRNA2 showed a particularly strong signal for both CUD and SCZ (lead SNP rs11783093 meta-analysis p = 8.1e-19; SCZ GWAS p = 7.6e-12; CUD GWAS p = 2.7e-9), suggesting that this may be a point of shared genetic vulnerability. Using a local genetic correlations approach, we identified one region (chr10: 79952997-81190573) that showed significant partial genetic correlation between CUD and SCZ after conditioning on tobacco smoking (partial rg = 0.54, p = 0.003).
Conclusions: Genetic liability for CUD is uniquely, positively correlated with SCZ risk, even after accounting for the genetic component of tobacco use. This shared genetic vulnerability may partially account for the frequent comorbidity of SCZ and heavy cannabis use.

22.4 ANXIETY AND DEPRESSIVE SYMPTOMS MEDIATE THE ASSOCIATION BETWEEN CANNABIS USE AND PSYCHOTIC EXPERIENCES: A BIDIRECTIONAL MEDIATION ANALYSIS

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Background: Although survey findings show that people use cannabis to relieve anxiety and depression, it is well-established that cannabis use also dramatically exacerbates psychosis and affective psychopathology. There is a lack of longitudinal research investigating the temporal association of psychotic experiences (PE) with cannabis use, anxiety, and depressive symptoms. Examining the reciprocal mediation roles of cannabis use, anxiety, and depressive symptoms in the onset of PE may provide insight into understanding this complex relationship. Our hypothesis was that cannabis use mediates the association between anxiety/depressive symptoms and PE. We also investigated whether the association between cannabis use and PE was mediated by preceding anxiety/depressive symptoms.

Methods: Data from the second longitudinal Netherlands Mental Health Survey and Incidence Study (NEMESIS-2) were analyzed. The NEMESIS-2 collected data from the general population (n = 6646 at baseline) at four time points every three years over a 9-year follow-up period. A 20-item questionnaire based on CIDI 1.1 was used to evaluate PE. The CIDI 3.0 core symptoms at each time point were used to assess anxiety and depressive symptoms. Cannabis use was defined as once per week or more in the previous year. We performed a mediation analysis using the Karlson–Holm–Breen method (KHB logit in STATA) adjusted for age, sex, and educational attainment to examine the link between cannabis use, anxiety/depressive symptoms, and PE.
Results: Cannabis use mediated the association between preceding anxiety, depressive symptoms, and later PE incidence. However, the indirect contribution of cannabis use was small (for anxiety: % of total effect attributable to cannabis use = 1.00%; for depression: % of total effect attributable to cannabis use = 1.4%). In the subsequent analysis that estimated the mediation effect of the presence of affective dysregulation (any anxiety symptom and any depressive symptom, separately), we found that anxiety and depressive symptoms mediated the association between previous cannabis use and later PE incidence to a much larger degree (% of total effect attributable to anxiety = 17%; % of total effect attributable to depression = 37%).
Conclusions: Our findings from the first longitudinal analysis of the mediational association between cannabis use, anxiety/depressive symptoms, and PE reveal bidirectional associations between cannabis use, anxiety/depressive symptoms, and PE in the general population. However, anxiety/depressive symptoms as a mediator contributed more than that of cannabis. This study provides additional support for an "affective pathway" to psychosis expression. It is yet to be determined if interventions for treating affective dysregulation in cannabis users can lower the risk of PE incidence.

23. DOES FAULTY ENERGY METABOLISM UNDERLIE SCHIZOPHRENIA? FROM MOLECULES TO CIRCUITS AND SYMPTOMS

Oliver Howes*, MRC LMS and KCL*

Overall Symposia Abstract: The recent development of novel tools and new samples from a number of sources provide the potential for significant advances in understanding of energy metabolism in schizophrenia. This makes it timely to bring these new data together in one symposium to consider how the new findings advance understanding of the mechanisms underlying schizophrenia, and how to treat it better. This symposium brings together basic and clinical researchers, and a range of different measures, from genetic and cellular, through animal models, to living patients, to interrogate the nature of metabolic dysfunction in schizophrenia, focusing on mitochondrial proteins.

Dr Glausier will present novel data from frontal cortical brain post-mortem samples from people with schizophrenia, showing down-regulation of mitochondrial gene expression but no alteration in markers of oxidative stress, indicating reduced mitochondrial function is not a consequence of oxidative stress.

Dr Anderson will present new cellular data derived from people who carry the single largest genetic risk factor for schizophrenia, a deletion of DNA at 22q11.2. A key strength of this sample is that it includes carriers with and without schizophrenia to show that deficits in mitochondrial complex 1 protein is specific to carriers with schizophrenia, and replicating this finding in a prospective study of carriers prior to the development of schizophrenia. They also

showed that a medication that enhances mitochondrial function reverses deficits in energy production in the cellular models, and improves cognitive function in a mouse 22q model.

Until recently it has not been possible to measure mitochondrial proteins in vivo. However, the recent development of a PET tracer specific for these enables it for the first time. Dr Howes will present the first data in schizophrenia using a tracer to measure levels of mitochondrial complex 1 in cortical brain regions. Showing that levels are lower both in patients with chronic schizophrenia and first episode schizophrenia, and that lower levels are associated with greater symptoms and circuit alterations measured using fMRI.

Dr Du will present the first data in schizophrenia and bipolar disorder using 31P MRS imaging to measure creatine kinase reaction, a marker of energy flux, to show lower levels in schizophrenia, and that these are associated with altered brain function in key circuits implicated in schizophrenia, but not brain structural measures.

Finally, Dr McCullumsmith will lead the discussion of the findings and place them in a wider context. He has led research on energy metabolism in schizophrenia using molecular, cellular and human techniques. He also has a clinical background. This expertise makes them well placed to consider how the new data advance understanding of schizophrenia, and identify new avenues for research.

23.1 MEASURES OF OXIDATIVE PHOSPHORYLATION AND OXIDATIVE STRESS IN PREFRONTAL CORTEX OF SCHIZOPHRENIA SUBJECTS

Jill Glausier*[1]

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Background: Mitochondrial dysfunction has been associated with some of the functional, morphological and molecular alterations present in dorsolateral prefrontal cortex (DLPFC) in schizophrenia (SZ). Mitochondria are responsible for multiple essential processes, including ATP production via oxidative phosphorylation (OXPHOS), free radical generation, Ca2+ buffering and apoptosis. Determining the specific mitochondria functional pathways affected in SZ can provide key insight into pathologic processes underlying cortical dysfunction. Thus, we analyzed transcriptomic data that index the diversity of mitochondria functions in DLPFC gray matter of SZ subjects.

One proposed upstream contributor to mitochondrial alterations in SZ is the presence of oxidative stress and damage. Excessive oxidant production that overwhelms the glutathione (GSH) antioxidant defense system and/or direct impairments to GSH availability can damage mitochondria, including OXPHOS complexes. If oxidative stress and damage contributes to mitochondrial transcriptomic alterations, then their markers should be present in DLPFC of SZ subjects. Thus, we used mass spectrometry (MS) to quantify markers of the GSH system and oxidative damage in DLPFC of SZ subjects.

Methods: DLPFC grey matter RNASeq data were analyzed from the CommonMind Consortium in SZ (N=57, 44M/13F) and unaffected comparison (UC; N=82, 59M/23F) subjects. Gene Ontology ‘mitochondria’ (GOMito) pathway genes were included for analysis (n=1,033). Analyses of differentially-expressed genes (DEGs), DEG functional pathway enrichment, and higher-order gene co-expression features via weighted gene co-expression analysis (WGCNA), were performed.

Targeted liquid chromatography tandem MS (LC-MS/MS) was utilized to quantify free GSH and oxidized glutathione (GSSG) in DLPFC grey matter from a separate cohort of 25 pairs of SZ and UC subjects. LC-MS was utilized to also quantify malondialdehyde (MDA), a product of lipid oxidative damage. ANCOVA models were performed that included the dependent measure, independent variable of diagnostic group and any significant covariate.

Results: In DLPFC grey matter, 41% of GOMito were DEGs in SZ (all $q<0.05$), and 83% of these DEGs were downregulated. DEGs were significantly ($p<7.7x10-6$) enriched for energy production pathways such as 'OXPHOS', and 100% of the 'OXPHOS' genes were lower in SZ. WGCNA identified five co-expression modules. This module structure was preserved in SZ, despite the abundance of DEGs, including the module that was significantly enriched for energy production pathways (all $p<7.7x10-6$). Together these data demonstrate a selective and coordinated downregulation of energy production genes in DLPFC in SZ.
SZ and UC subjects did not differ in the mean abundance of free GSH, GSSG, GSSG:GSH or MDA in DLPFC (all $F47<1.0$, all $p>0.3$). Together, these data suggest that DLPFC oxidative stress and damage are not greater in SZ relative to UC subjects.

Conclusions: The selective and coordinated downregulation of energy production genes suggests that SZ is associated with less ATP synthesis via OXPHOS in DLPFC. The metabolomic findings suggest that 1) downregulation of OXPHOS transcripts is likely not due to oxidative damage to mitochondria, and 2) oxidative stress and damage may not represent common pathogenic mechanisms in SZ. Together, these findings are most consistent with the coordinated transcriptional adjustments neurons normally make to meet reduced ATP demand due to persistent reductions in neuronal firing and synaptic signaling. This interpretation is also consistent with the existing genetic, anatomic and in vivo molecular imaging studies implicating impaired cortical synaptic processes in SZ.

23.2 THE FRONTAL HYPOFUNCTION HYPOTHESIS OF SCHIZOPHRENIA: AN IN VIVO TEST USING PET IMAGING OF BRAIN MITOCHONDRIAL PROTEINS IN FIRST EPISODE AND CHRONIC SCHIZOPHRENIA

Oliver Howes*[1], Tom Whitehurst[2], Ekaterina Shatalina[2], Ellis Onwordi[2], Ilan Rabiner[3], Sridhar Natesan[2]

[1]*MRC LMS and KCL,* [2]*MRC LMS,* [3]*Invicro*

Background: It is hypothesised that frontal hypofunction underlies cognitive and negative symptoms in schizophrenia. Multiple imaging studies indicate there is lower frontal function and glucose metabolism in schizophrenia, whilst genetic and post-mortem indicate this could be due to lower mitochondrial complex I protein. However, this has not yet been directly tested in vivo. The development of 18F-BCPP-EF, the first PET tracer that specifically binds to mitochondrial complex one (MCI) enables this to be tested.
Methods: We used 18F-BCPP-EF positron emission tomography to investigate levels of MCI in the anterior cingulate cortex, frontal cortex and hippocampus in 66 subjects (25 controls and 41 people with schizophrenia (21 untreated first episode patients)) and measured negative symptoms and cognitive function. In addition, we used fMRI to measure frontal neural response during a cognitive task.
Results: We found significant a significant main effect of group on 18F-BCPP-EF volume of distribution [$F1, 61=12.52$, $p<.001$], with significantly lower levels in patients relative to controls in the frontal cortex [mean (SD) ml*cm3: patients=21.70 (3.9); controls=24.45 (3.62); $t62 = -2.97$, $p=.007$, Cohen's $d=-0.72$], including the anterior cingulate cortex [patients=21.50 (3.4); controls 24.88.08 (4.1); $t61 = -3.55$, $p<.001$, $d=-0.9$]. Unmedicated first episode patients

had significantly lower 18F-BCPP-EF distribution volume compared to controls in the anterior cingulate cortex [unmedicated patients 22.31 (3.13); controls 24.87 (4.05); t42 = -2.32, p=.026, d= -.70]. In first episode untreated patients, we found an inverse correlation between negative symptoms and 18F-BCPP-EF distribution volume in the frontal cortex (-0.6, p = .007). [18F]BCPP-EF DVR in fronto-parietal regions was significantly correlated with IQ (Z>2.3, cluster threshold p<0.05) and associated with altered frontal connectivity in controls, but not in patients.

Conclusions: These data indicate MC1 protein levels are lower in schizophrenia, and linked to symptoms and brain functional alterations, particularly in frontal cortex. These suggest lower MC1 levels could underlie frontal hypofunction and identify MC1 as a potential therapeutic target.

23.3 PREDICTION OF SCHIZOPHRENIA RISK AND THE IDENTIFICATION OF A POTENTIAL PREVENTATIVE PHARMACOTHERAPY FOR SCHIZOPHRENIA IN THE CONTEXT OF THE 22Q11.2 DELETION SYNDROME.

Stewart Anderson*[1]

[1]*University of Pennsylvania*

Background: Since schizophrenia in 22q11.2 deletion syndrome (22qDS) aligns with non-syndromic Sz, the 25% rate of Sz in 22qDS provides an opportunity for longitudinal studies that identify cognitive and physiological changes that predict Sz risk and may lead to preventative interventions. Studies have suggested that aspects of the 22qDS neural phenotypes involves mitochondrial dysfunction. These results raise the possibility that variable penetrance for Sz in 22qDS may be influenced by an individual's capacity for mitochondrial compensation, a common feature of mitochondrial disease. Consistent with this concept, a previous study of monocytes from 22qDS children found mitochondrial alterations consistent with compensation occurring in around 70% of the group (Napoli et al., 2015).

Methods: This study involves transgenic 22q11DS model mice (22qMc), human subjects-derived induced pluripotent stem cells (IPSCs), and human subjects-derived lymphoblastoid cell lines (LCLs).

IPSCs derived glutamatergic neurons were generated from young adults from 3 groups, typically developing (TD) controls, 22qDS with Sz, and 22q DS NO Sz. Studies have been completed on 4 lines from each group, and data from another 3 lines of each group is being added. Both sexes were studied. All lines were generated by Sergiu Pasca's group at Stanford University. Assays include ATP levels, Complex I and Complex IV activity, mRNA expression for nuclear and mitochondrial DNA-derived transcripts, and the influence of mitochondrial-biogenesis enhancing agents on these measures.

Data will be also presented from the study of LCLs from teenagers with 22qDS who were not psychotic when lines were generated, but who subsequently either did or did not develop psychosis over the following 5-10 years. Currently 5 lines of each group have been analyzed, and similar numbers of additional lines are in process. Multiple metabolic measures are conducted in the laboratory of Cecilia Giulivi (UC Davis) (i.e. lactate/pyruvate, OXPHOS pathway activities, and BHI (State 3 X State3u)/State 4). These are evaluated via Orthogonal Projections to Latent Structures Discriminant Analysis (OPLS-DA).

Finally, data will be presented on the effect of the PPARa agonist Bezafibrate, provided via chow to 22qMc and controls from 4-8 weeks of age. The mice were then tested for hippocampal

dependent cognitive tasks including social learning and fear conditioning. This experiment involves chow-treated and untreated 22q model and control mice of both sexes, 80 mice total.

Results: In IPSC derived glutamatergic neurons, ATP levels were reduced in the 22q+Sz group, relative to the 22q NO Sz group by 30% ($p<.02$), which was unchanged relative to the typically developing group. The same pattern was present for Complex 1 activity (20% reduced in the 22q+Sz; $p<.01$) and for multiple OXPHOS-related genes of encoded by nuclear and mitochondrial DNA.
Similar findings were made using lymphoblastoid cell lines (LCLs) from different adult individuals with 22q+Sz (n=8) and 22q NO Sz (n=10). Bezafibrate, a medication that enhances mitochondrial biogenesis, normalized OXPHOS-related gene expression and ATP production by IPSC derived neurons from the 22q+Sz group (ATP level enhanced in 22q+Sz group by 60%, $p<.001$).

Using the LCLs from 22qDS teenagers who were not psychotic when LCLs were generated, and either did or did not develop psychosis by there 20s, we found by OPLS-DA analysis that the mitochondrial deficits found in LCLs from 22q individuals who had already developed Sz, appears to be present prior to its development.

In 22q model mice, we found that bezafibrate treatment during adolescence improves social memory at young adulthood (comparison of N=20 mice, split by sex).

Conclusions: Variable penetrance for schizophrenia in the 22qDS context appears to be influenced by an individual's capacity to compensate for a deficiency in mitochondrial ATP production via enhancing mitochondrial biogenesis and turnover. The practicality of combining blood-based mitochondria risk measures and prodromal psychosis scores to identify a "super"-risk group of 22qDS older teenagers for a trial of bezafibrate or similar PPARa activator for the prevention of schizophrenia will be discussed. Ongoing efforts to uncover how OXPHOS deficits could contribute mechanistically to psychosis in the context of 22q11.2 deletion syndrome, via analyses of synaptic energetics in human IPSC derived neurons in vitro, will also be discussed.

23.4 ABNORMAL BIOENERGETICS ASSOCIATED WITH DISRUPTED BRAIN CIRCUITS IN PSYCHOTIC DISORDERS

Fei Du[1], Dost Ongur*[1]

[1]*McLean Hospital/Harvard Medical School*

Background: Cognitive function is served not only by discrete brain regions, but also by brain networks. When these anatomically remote brain regions work together as a network, they need to coordinate with each other by synchronizing their neural activities, or in other words building up "functional connectivity (FC)". Coordinated activity within and differential activity between large scale neuronal networks such as default mode network (DMN) and task-positive networks (TPN) is a critical feature of brain organization. Impaired FC is associated with the abnormal cognitive function seen in numerous neuropsychiatric disorders, for instance, schizophrenia (SZ) and bipolar disorder (BD). These are characterized by abnormal FC within neural networks such as DMN, the attenuated functional segregation (FS), and compromised anticorrelation between DMN and TPN. However, the cellular and molecular mechanisms underlying this phenomenon are poorly understood. On the other hand, bioenergetic processes are critical for brain spontaneous activity, synaptic connectivity and are also abnormal in psychotic disorders. Therefore, we examined the association between brain energy metabolism and FC in psychotic disorders.

Methods: 31P magnetization transfer spectroscopy from medial prefrontal cortex (MPFC), whole-brain fMRI and structural imaging DTI data were collected from demographically matched groups of SZ (n=27), BD (N=39), and healthy control (HC, N=29) subjects. The creatine kinase (CK) reaction flux calculated from 31P spectroscopy was used as an index of regional energy production rate. FC maps were generated with MPFC as the seed region, and negative degree centrality (NDC) method was applied to quantify FS using fMRI data, i.e. the magnitude of anticorrelation between a given voxel and all other brain grey matter voxels.
Results: We found that CK Flux was significantly lower in SZ compared to HC ($F_{1,52}=5.59$, $p=0.022$, $\eta p2=0.10$) and BD ($F_{1,62}=4.27$, $p=0.043$, $\eta p2=0.064$), but not significantly different between HC and BD. While both BD and SZ patients showed significantly decreased FS and anticorrelation between MPFC and TPN. CK flux was significantly correlated with FS and FC between MPFC and other DMN nodes in HC ($r=0.72$, $p<0.001$). This correlation was reduced modestly but still significant in BD ($r=0.47$, $p=0.0032$), and further diminished in SZ ($r=0.34$, $p=0.079$). CK flux was also correlated with the anticorrelation between MPFC and TPN in HC ($r=-0.68$, $p<0.001$), but this relationship was not observed in BD. ANCOVA showed that the correlation coefficients between CK flux and FC were significantly different among the three groups. Post-hoc analyses showed all these correlations were significantly higher in HC than in SZ and BD. TBSS analyses from DTI data showed no statistically significant difference in FA among the three groups. Furthermore, including FA values as covariates did not change the results of correlation analyses, which suggested that the FS and FC abnormalities in our data cannot be explained by white matter abnormalities but instead are associated with bioenergetic processes.
Conclusions: Taken together, these results indicate that energy metabolism rates are associated with stronger FC within networks and stronger anticorrelation between networks in HC. However, this association is compromised in SZ and BD, where bioenergetic and FC abnormalities are evident. This pattern may suggest that impairment in energy metabolism in SZ and BD underlies the impaired neural connectivity. Our study reveals the general principle of brain energy-activity organization and suggests that the metabolism-neural synchrony pathway could be a new potential treatment target for neuropsychiatric disorders.

24. IMPROVING RECOVERY OF DAILY AND COMMUNITY FUNCTIONING IN PSYCHOSIS - INNOVATIONS IN ASSESSMENT, INTERVENTION AND IMPLEMENTATION.

Lisette Van der Meer, *University of Groningen*

Overall Symposia Abstract: Social and functional recovery in psychosis are important treatment goals that received more and more attention the past decades. Researchers and clinicians around the globe are continuously searching for new interventions, updating treatment guidelines and searching for tools to prevent relapse and as such improve social and daily functioning in individuals with psychosis. This symposium aims to highlight three topics related to improving daily and community functioning: (1) assessing improvements in daily and community functioning, given its personal nature, (2) using technological advances of this time in promoting daily and community functioning, and (3) innovative treatments to improve daily and community functioning.
Anika Poppe will present data from a large cohort study (> 1000 people with psychosis) on predictors of transitioning from dependent to independent living after three and six years. Results show that cognition, particularly executive functioning, predicts whether people move from dependent to independent living. results from a pilot study combining cognitive remediation and transcranial direct current stimulation suggest this is feasible and acceptable

for people with psychosis in sheltered living to improve cognitive and daily functioning and support transitioning to independent living.

Alice Medalia will present data on a large implementation RCT around a new cognitive health toolkit in programs for people with first episode psychosis (FEP) and examine feasibility and clinical utility of the toolkit. Currently treatment programs do not routinely assess cognitive health in FEP. Preliminary feasibility data of integrating the cognitive health toolkit into a network of Coordinated Specialty Care programs for people with FEP seems encouraging. Cognitive health was not only assessed, but people were referred to and received cognitive remediation which led to cognitive and functional improvement.

John Torous will discuss the use of new smartphone based applications that can assess risk in prodromal and FEP by two example cases. The first case is the AMP-Schizophrenia study which is currently recruiting participants from around the world at clinical high risk for psychosis. The second case focusses on detecting relapse in younger patients at risk for relapse across sites in India and Boston. Results suggest that methods like this are feasible are and acceptable to people at risk for or with FEP, but that ensuring digital signal quality is important to ensure the detection of valid and reliable behavioral markers.

Joseph Ventura will talk about different ways in which we can measure functional outcomes. The recognition that many individuals with schizophrenia can manage to function without full resolution of their positive symptoms or even their negative symptoms suggest the need to carefully select how we measure community functioning. He will give an overview of various "objective" vs "subject" functional outcome measures, and initiate a discussion about general guidelines for how to select the most relevant measure of community functioning for a given clinical or research question.

Til Wykes is an expert in research on treatment innovations, including cognitive remediation and digital technology solutions to mental health treatment, and has ample experience in the measurement of functional outcomes. She will lead the discussion of this session.

24.1 IDENTIFYING AND TARGETING BARRIERS OF INDEPENDENT LIVING IN PEOPLE WITH PSYCHOSIS

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Background: An important goal in the process of functional recovery and a common wish of individuals with psychosis is to live independently; yet the transition towards living independently can be challenging. The identification of individuals that are at-risk for staying in supported housing or living with parents, and offering extra support, e.g., tailored treatments, could increase the rate of individuals living independently.
Methods: This session will focus on the results from two studies that show the identification of risk-factors for not moving towards independent housing, and how these factors could be

targeted by the use of innovative treatments. In the first study, the housing state of 1119 individuals with non-affective psychosis from the Genetic Risk and Outcome of Psychosis study was assessed at baseline, at three- and six-year follow-ups as either dependent (sheltered housing or with parents) or independent (single or with partner/family). We estimated the probabilities of transitioning between housing states and investigated the influence of demographic characteristics, symptomatology, cognition, social support, and premorbid social adjustment on transition using Markov chain modelling. The second study focused on the feasibility and acceptability of combining cognitive remediation and transcranial direct current stimulation (tDCS) in clinical practice to target these cognitive impairments and enhance functional recovery (including independence of living) in individuals with severe mental illness. Feasibility was defined a priori as 60% of the participants completing at least 20 of 32 sessions of the intervention (16 weeks, twice weekly). We invited participants to participate in interviews to assess the acceptability of the intervention.
Results: The results of the first study showed that most participants (~60%) living in a dependent housing state remained there during the six-year follow-up period. Regression analyses showed that the likelihood of transitioning from dependent to independent housing was higher for women (HR 3.24; 95% CI 1.20-8.73), individuals with better overall cognition (HR 1.73; 95 CI 1.03-2.91), and better executive functioning (HR 1.58; 95 CI (1.03-2.42), and for those with a course of low positive symptoms (HR 0.14; 95% CI 0.03-0.06). In the second study, 62.5% of the participants completed at least 20 sessions of cognitive remediation combined with either sham tDCS or active tDCS. In the interviews, participants reported that they liked the cognitive remediation program, were not bothered by the tDCS, they observed improvements in their cognitive functioning and everyday life (e.g., fewer problems with doing groceries, being more organized and less dependent on others), and they would recommend the intervention to others.
Conclusions: Our findings highlight that a large group of individuals with psychosis in dependent housing is unlikely to transition to independent living. Older men with cognitive impairments who show continuous severe positive symptoms are the least likely to transition to living independently. The combination of cognitive remediation and tDCS is feasible and acceptable, and could be offered to individuals in dependent housing situations.

24.2 ADDRESSING COGNITIVE HEALTH TO ENHANCE FUNCTIONING IN PEOPLE WITH FIRST EPISODE PSYCHOSIS

Alice Medalia[1], Alice Saperstein[1], Lisa Dixon[1], Melanie Wall[1], Iruma Bello[1], Cale Basaraba[1], Alice Saperstein*[2]

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Background: Most people with schizophrenia have cognitive impairments that already significantly contribute to poor functioning at the time of the first episode of psychosis (FEP). Early intervention to reduce cognitive deficits has the potential to impact recovery and quality of life; however, early intervention services (EIS) do not routinely address cognitive health. Methods to identify and harness individual cognitive strengths while addressing relative weaknesses have the potential to complement EIS but systematic implementation methods for large systems of care are needed. We developed a cognitive health toolkit, trained teams from OnTrackNY, a network of EIS programs for people with FEP and examined toolkit and cognitive remediation (CR) feasibility and clinical utility.
Methods: The toolkit includes a clinician manual, assessment and decision-making tools, and a menu of cognitive health service options inclusive of cognitive remediation. Assessment uses objective, subjective and clinician rated measures of cognitive functioning which, together,

determine participant- and clinician-perceived cognitive health need. Referral to cognitive remediation results when participant and clinician agree that a 24-hour program of restorative cognitive exercise and strategy coaching would facilitate recovery goal attainment. Using a cluster randomized controlled trial design, clinics were randomized to deliver A) TAU or B) 12 once-weekly clinician-led sessions combined with an additional 12 hours of independent cognitive practice or C) 24 twice-weekly clinician-led sessions. System wide supports of the cognitive health initiative included a standardized training program, site supervision and learning collaboratives which brought together sites to discuss implementation successes and barriers. Program-level data were analyzed for rates of cognitive health assessment, identification of needs, cognitive health service provision and impact on functional outcome.
Results: Following initial implementation of the cognitive health toolkit across 18 OnTrackNY teams including data from 933 participants, cognitive health need was identified by self-report (57.6%) and clinician-report (69.9%) and led to provision of specific services, including psychoeducation, compensatory and restorative cognitive skills training. Tracking of cognitive remediation referrals occurred during the pandemic at 6 clinics from 2020 to 2021 and 11 clinics in 2022. Over 24 months, 93 people were referred, 86 went on to receive a brief neurocognitive assessment, 75 commenced a cognitive remediation program- with bias for once-weekly clinician-led sessions, and 27 completed all 24 hrs CR. Across all CR sites, CR program completers expressed satisfaction with the service and made gains on the Neurocognitive Composite of the MCCB ($p<.01$) and on measures of functioning: MIRECC GAF Symptom Score ($p<.004$); MIRECC GAF Occupational Score ($p<.08$) MIRECC GAF Social functioning ($p<.03$). Further analyses consider comparisons of outcomes between randomized groups, inclusive of noncompleters.
Conclusions: Preliminary feasibility data are encouraging. Brief measures to identify cognitive health need identified participants at rates generally consistent with reported rates of cognitive impairment in the FEP population. Even with the challenges posed by the pandemic, people were referred to and received cognitive remediation which was associated with cognitive and functional improvement most noticeable in symptom and social domains, while gains in occupational functioning approached significance. Given the challenge of completing 24 hours CR, dosing schedules require further consideration.

24.3 REMOTE SMARTPHONE SCREENING IN PRODROMAL PSYCHOSIS AND RELAPSE IN FIRST EPISODE PSYCHOSIS

John Torous*[1]

[1]*BIDMC / Harvard Medical School*

John Torous*, BIDMC / Harvard Medical School*

Background: The additional stress experienced by youth around COVID-19 may be a novel risk factor development of mental illnesses including schizophrenia. Smartphones offer a new method to screen for the risk of psychosis or relapse in those with psychosis and gather new functional data around related behaviors.
Methods: This session will explore two unique use cases of smartphone sensing to assess risk in prodromal and first episode psychosis. The first use case is the AMP-Schizophrenia study which is ongoing and recruiting participants from around the world at clinical high risk for psychosis. The second study uses the same methods but towards detecting relapse in younger patients at risk for relapse across two sites in India and a third in Boston. In the context of these studies, we will discuss ethics, digital phenotyping, methodology considerations, and early results.

Results: Final and emerging results at the date of the presentation will be shared. Preliminary results suggest these digital markers can high correlated with classical clinical markers related to mood, anxiety, and psychosis if there is high data quality (coverage) with the sensors is high.
Conclusions: Smartphone sensing offers tremendous potential to offer more phenotypically dense and longitudinal outcomes that can bring new insights into risk. Our results suggest the importance of ensuring digital signal data quality remains high to ensure any resulting behavioral markers are valid and reliable. Our results also suggest that methods like this are feasible are and acceptable to people at risk for or with first-episode psychosis, which sets the bar for the next stage of research findings.

24.4 FUNCTIONAL OUTCOME ASSESSMENT -- "OBJECTIVE" VS "SUBJECTIVE" RATING SCALES: ONE SIZE DOES NOT FIT ALL SO WHICH ONE SHOULD YOU CHOOSE AND WHY?

Joseph Ventura*[1], Kenneth Subotnik[2], Keith Nuechterlein[2]

[1]*UCLA Semel Institute for Neuroscience and Human Behavior,* [2]*University of California, Los Angeles*

Background: The recognition that many individuals with schizophrenia can manage to function without full resolution of their positive symptoms or even their negative symptoms suggests the need to carefully select how we measure community functioning.
Methods: At UCLA a RCT evaluating a cognitive training program included a Bridging Group. The primary function of this group was for patients to learn how to implement their newly learned neurocognitive and social cognitive skills and abilities in their daily living. We found that the patients identified six primary domains of functioning during goal setting, which included but went beyond work and school to include physical exercise and other healthy living habits. Thus, patients identify many different domains of community functioning.
Results: This presentation will focus on rater-administered functional outcome measures and address questions such as when to use "objective" vs "subjective" assessment scales. For example, the Heinrichs-Carpenter Quality of Life Scale includes items reflecting objective aspects of functioning, (e.g., work functioning) as well as subjective components (e.g., work satisfaction, sense of purpose). In addition, there are several logistical decisions needed regarding choice of assessment such as ease of training and use, administration time, desired frequency of use, target group, e.g., clinical high risk (CHR) or first episode (youth) vs multi-episode individuals, and a relevant comparison reference group. Careful thought is required for the selection of the most relevant functional outcome rating scale. The Role Functioning Scale (RFS) allows for the separate evaluation of four domains of functioning: Work Productivity, Independent Living, Family Network Relationships, and Immediate Social Relationships, while the Global Functioning Scale separates Role (independent living, work/school) and Social (family/friends) into only two domains. In some forms of Group CBTp or Motivational Interviewing the individual can select his/her own set of personal goals using the Goal Attainment Scale (GAS). Further, the domain of Work/School functioning can be evaluated in binary ways or on a continuum of the amount of time spent or quality of activity. Modifications of the Social Attainment Survey (SAS) allow for a rating within one's role responsibilities of "Cognitive Complexity," or "Impaired Performance" vs. "Distress."
Conclusions: This presentation is meant to stimulate a lively discussion and general guidelines for how to select the most relevant measure of community functioning for a given clinical or research question.

Plenary Session IV: Charlene Sunkel

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

25. EXPERTS BY EXPERIENCE - KEY PARTNERS IN RESEARCH

Til Wykes, *Institute of Psychiatry, Psychology and Neuroscience*

Overall Abstract: This is an important topic on enabling people with lived experience of psychosis and other mental health conditions to become our research partners to deliver meaningful and useful results. This means having lived experience authors on our papers who feel their views have been considered throughout the project. This means more than just consulting them and our speaker, Charlene, will provide us with the strategies that work the best.

25.1 EXPERTS BY EXPERIENCE - KEY PARTNERS IN RESEARCH

Charlene Sunkel, *Global Mental Health Peer Network*

Individual Abstract: Global recognition for the crucial role of meaningful and authentic involvement of people with lived experience in the mental health and social development sectors has gained momentum. People with lived experience are being acknowledged as integral partners in the fields of research, policy reform, service development and delivery, project implementation and monitoring and evaluation. In research, people with lived experience, both academic and non-academic, are able to contribute lived experience expertise throughout all project phases, not merely be seen as subjects of research. In my presentation I will speak about the benefits of including people with lived experience in research, the existing obstacles and the principles and key strategic elements to meaningfully and authentically involve academic/ non-academic lived experience partners.

Plenary Session V: Raymond Chan

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

26. THE WEAKEST LINK: ANHEDONIA ACROSS AND BEYOND THE SCHIZOPHRENIA SPECTRUM DISORDERS

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

Overall Abstract: Negative symptoms remain some of the more difficult to treat and incapacitating symptoms of schizophrenia. Among these, anhedonia, which involves a reduced capacity for pleasure, is also found in other psychiatric and neurological disorders. Interestingly however, its severity and extent vary across these disorders, affecting from few to many pleasurable activities that life offers. This makes it crucial that we understand more about the different components of anhedonia, as well as about its possible underlying neural mechanisms and measure that can assess it, in order to move towards more appropriate interventions.

26.1 THE WEAKEST LINK: ANHEDONIA ACROSS AND BEYOND THE SCHIZOPHRENIA SPECTRUM DISORDERS

Raymond Chan, *Institute of Psychology, Chinese Academy of Sciences*

Individual Abstract: Schizophrenia is associated with a wide range of cognitive and emotional impairments including the reduced ability to experience pleasure and happiness,

namely anhedonia. Anhedonia is one of the key negative symptoms affecting the ultimate functional outcome and has an adverse impact on quality of life for patients with schizophrenia. Recent findings suggest that anhedonia is shared by other psychiatric disorders such as major depressive disorder and bipolar disorder. Moreover, individuals with subclinical features may also exhibit anhedonia. However, it is still not clear the underlying behavioural and neural mechanisms associating with anhedonia in these subclinical populations. With the guidance of the advanced theoretical framework of anhedonia, I will first address the issue of the latent factor structure of negative symptoms in schizophrenia patients and illustrate specifically the important role of Motivation and Pleasure factor but not Expression factor contributing to social functioning in these patients. I will then highlight the recent findings of anhedonia across and beyond the schizophrenia spectrum disorders. These findings help to validate and establish a set of measures to characterize the evaluation of anhedonia and highlight potential development of intervention platform for anhedonia across clinical and subclinical populations.

Concurrent Symposia

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

27. THE MANY FACES OF SCHIZOPHRENIA RESILIENCE RESEARCH

Robert Bittner*, University Hospital Frankfurt, Goethe University*

Overall Symposia Abstract: The many faces of schizophrenia resilience research

Elucidating the neurobiological and psychological mechanisms, which promote resilience against schizophrenia, promises to provide novel pathways toward improved treatment and prevention strategies. Resilience is a dynamic process facilitating adjustments to potentially disabling stressors. Nevertheless, there is clear evidence that resilience factors, which increase resilience capacity, can be genetically determined. Resilience and resilience factors are orthogonal to illness vulnerability and risk factors respectively. Thus, the resilience paradigm constitutes a complementary approach to traditional risk-centered strategies by aiming to induce or enhance these protective mechanisms, which can buffer against central pathophysiological processes underlying schizophrenia. To this end current research focuses on high-risk individuals who do not develop schizophrenia. In addition to people at clinical high risk (CHR) risk this includes cohorts at elevated genetic risk. The former group can illuminate factors protecting against a conversion to full blown illness. The latter group can help identify genetic resilience factors, which can facilitate the search for resilience mechanisms that have evolved naturally in the general population.

This symposium will highlight current finding based on these approaches including data from genetics, neuroimaging, psychopathology, and psychotherapeutic interventions.

Dr. J. Hess will discuss successful attempts at elucidating the genetic architecture of schizophrenia resilience, which have discovered common genetic variants that offset the inherited risk for schizophrenia among resilient unaffected individuals. These findings resulted in the derivation and subsequent refinement of a multivariate measure of genetic resilience in the form of a polygenic resilience score.

Dr. R. Bittner will present neuroimaging data, which indicate that heritable mediators of resilience to schizophrenia exert their protective effect partly through cortical neuroplastic alterations with the strongest impact in the fusiform gyrus. This indicates that schizophrenia resilience emerges partly from the strengthening of neural circuits crucial for the

disambiguation of social and non-social visual information. These findings also imply an important role for neuroplasticity in promoting schizophrenia resilience.

Dr. K. Cadenhead will present data from the NAPLS 3 study of CHR individuals demonstrating that prosocial involvement and resilient personality traits comprising empathy, psychological maturity and self-directedness are more common in people who did not convert to psychosis. Enhancing these resilience factors through targeted psychotherapeutic interventions might therefore not only have a positive impact on symptom severity and functional outcome but also reduce the rate of conversion to psychosis.

Dr. D. Holt will present data demonstrating the beneficial effects of a brief resilience-enhancing behavioral intervention in college students. This intervention led to significant reductions in subclinical psychopathology including depression, anxiety, and psychotic experiences as well as improvements in resilience-related factors including emotion regulation. Furthermore, fMRI data revealed a significance increase in fronto-hippocampal connectivity, which was associated with a comparable decrease in PEs. This effect was fully mediated by improvements in emotion regulations.

Together, these findings illustrate how findings from resilience research can be leveraged to develop novel strategies for improved risk prediction, illness prevention as well as treatment.

27.1 DERIVATION OF A NOVEL POLYGENIC RESILIENCE SCORE THAT MODULATES RISK FOR SCHIZOPHRENIA

Jonathan Hess*[1], Manuel Mattheisen[2], Tiffany Greenwood[3], Ming Tsuang[3], Howard Edenberg[4], Peter Holmans[5], Stephen Faraone[1], Stephen Glatt[1]

[1]*SUNY Upstate Medical University,* [2]*Aarhus University, Aarhus C,* [3]*University of California, San Diego,* [4]*Indiana University,* [5]*MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University*

Background: Over the past decade, scientists have accelerated efforts to understand schizophrenia by studying genetic variation from hundreds of thousands of individuals to identify genes associated with risk. Much has been learned about the genetics of schizophrenia from the perspective of risk states, but it is virtually unknown which genes help to mitigate predisposition to schizophrenia, thereby shielding a person from mental illness. We posit that some individuals at relatively high genetic risk for schizophrenia remain unaffected due to having an inherited signature of genetic resilience, dampening effects of risk-conferring variants. To improve our understanding of genetic resilience, we developed a novel pipeline to mine genome-wide association data for common genetic variants that offset the inherited risk for schizophrenia among "resilient" unaffected individuals.

Methods: Genome-wide association data collated by the Psychiatric Genomics Consortium (PGC) was used as a discovery sample to identify resilience genes for schizophrenia. Subjects were ranked by polygenic risk scores (PRS) for schizophrenia and a percentile-based threshold was used to identify the highest-risk controls, i.e., "resilient" controls, along with cases with similarly high PRS. We performed a genome-wide association study (GWAS) testing for allele frequency differences between the high-PRS "resilient" controls and matched-PRS cases. Risk genes for schizophrenia and their linked loci were discarded to ensure that any polygenic resilience score derived from our analysis was independent of the polygenic risk score used to stratify the samples. We generated a polygenic resilience scoring formulae from the resulting

GWAS summary statistics, and evaluated the association of the resilience score in independent cohorts.
Results: We derived the first-known multivariate measure of genetic resilience for schizophrenia called the polygenic resilience score, which shows a significant protective effect against schizophrenia among high-PRS controls in three independent cohorts comprised of 7,653 high-PRS controls and 1,903 matched-PRS cases (OR = 1.12 per standardized unit increase in resilience score, SE = 0.041, two-tailed p = 0.0044). We replicated this finding using newly released GWAS data from the PGC-Schizophrenia Working Group comprising 2,812 high-PRS controls and 4,579 matched-PRS cases (OR=1.1, SE=0.023, p=1.7×10-5). In addition to replicating our existing polygenic resilience score, we tested how varying the LD-filtering criteria for pruning SNPs impacted the performance of the resilience score, yielding an optimal resilience scoring formulae that optimizes performance while maintaining orthogonality with PRS (as originally postulated) among high PRS cases.
Conclusions: In order to operationalize resilience, we studied individuals in the highest decile of PRS for SCZ whose risk for SCZ is similar to someone who has an affected first-degree relative (when compared to individuals in the lowest decile of PRS). We have validated that polygenic resilience scores moderate against elevated genetic risk for SCZ among unaffected individuals, and provide data on the performance of various criteria for deriving them. We hypothesized the resilience genes instill a general capacity that buffers the brain against vulnerabilities posed by genetic risk, though resilience processes may unfold over time providing adaptive protection to vulnerabilities instilled by risk factors. Our conceptualization of genetic resilience may benefit from future studies determining the timing and mechanism by which resilience genes promote protection against risk factors.

27.2 IMAGING GENETICS IMPLICATES VISUAL COGNITION AND NEUROPLASTICITY IN SCHIZOPHRENIA RESILIENCE MECHANISMS

Robert Bittner*[1], Tom Lancaster[2], David E. J. Linden[3], Andreas Reif[4], Meike Hettwer[5]

[1]*University Hospital Frankfurt, Goethe University,* [2]*Cardiff University School of Medicine,* [3]*School for Mental Health and Neuroscience, Maastricht University,* [4]*Goethe University Hospital Frankfurt Germany,* [5]*Max Planck School of Cognition, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig*

Background: Recently the first common genetic resilience variants for schizophrenia, which reduce caseness in people with an elevated genetic risk, have been identified. Elucidating neurobiological mechanisms underlying their protective effect is crucial for more effective prevention efforts. Current models implicate adaptive neuroplastic changes in the visual system and their pro-cognitive effects as a potential schizophrenia resilience mechanism. We investigated whether common genetic resilience variants might affect brain structure in similar neural circuits.
Methods: Using structural magnetic resonance imaging, we measured the impact of an established schizophrenia polygenic resilience score (PRSResilience) on cortical volume, thickness, and surface area in 101 healthy subjects in a vertex-wise whole-brain analysis (cluster-wise $p < .05$, adjusted for testing both hemispheres separately, i.e. $p < .025$; CFT = $p < .001$; Monte Carlo simulations (10,000 iterations)). We also carried out a confirmatory analysis in a replication sample of 33,224 healthy subjects (UK Biobank) using a ROI-based approach (Desikan-Killiany parcels).
Results: We observed a significant positive whole-brain correlation between PRSResilience and cortical volume in the right fusiform gyrus (FFG) (r=0.35; p=.0004). Post-hoc analyses in this cluster revealed an impact of PRSResilience on cortical surface area. The replication

sample showed a positive correlation between PRSResilience and global cortical volume and surface area in the left FFG. Averaged across hemispheres, FFG effects of PRSResilience on surface area ($z = 2.5$, $p = .012$) and cortical volume ($z = 2.09$, $p = .036$) were significantly higher than for all other ROIs in the replication sample.
Conclusions: Our findings represent the first evidence of a neurobiological correlate of a genetic resilience factor for schizophrenia. The particularly pronounced effect in the FFG in comparison with all other cortical areas indicates that the FFG plays a central role in promoting resilience to schizophrenia. They support the view that schizophrenia resilience emerges from a strengthening of neural circuits in the ventral visual pathway and an increased capacity for the disambiguation of social and non-social visual information. This may aid psychosocial functioning, ameliorate the detrimental effects of subtle perceptual and cognitive disturbances in at-risk individuals, and facilitate coping with the cognitive and psychosocial consequences of stressors. Importantly, this also raises the possibility that similar protective neuroplastic adaptations might be inducible through well-timed, targeted interventions. Our results thus provide a crucial link between visual cognition, the vulnerability-stress concept and schizophrenia resilience models. They demonstrate the potential of the resilience paradigm for the discovery of novel pathways toward improved treatment and prevention strategies for schizophrenia.

27.3 PROTECTIVE FACTORS IN CLINICAL HIGH RISK YOUTH PREDICT BETTER OUTCOMES

Kristin Cadenhead*[1], Jean Addington[2], Carrie Bearden[3], Tyrone Cannon[4], Barbara Cornblatt[5], Matcheri Keshavan[6], Daniel Mathalon[7], Diana Perkins[8], William Stone[9], Elaine Walker[10], Scott Woods[4]

[1]*University of California, San Diego,* [2]*University of Calgary,* [3]*University of California, Los Angeles,* [4]*Yale University,* [5]*The Zucker Hillside Hospital,* [6]*Harvard Medical School,* [7]*University of California, San Francisco,* [8]*University of North Carolina At Chapel Hill,* [9]*Harvard Medical School / Beth Israel Deaconess Medical Center,* [10]*Emory University*

Background: The study of the putative prodrome of psychosis provides an opportunity to examine risk factors as well as protective factors that predict clinical and functional outcome of individuals at Clinical High Risk (CHR) for psychosis. Protective factors and resilience are described as modifiers that reduce risk from a known risk factor (Morgan et al., 2013). In the North American Prodrome Longitudinal Studies (NAPLS) Consortium, as well as studies in the CARE (Cognitive Assessment and Risk Evaluation) program at UCSD, we have identified multiple protective factors and biomarkers associated with better outcomes, symptom remission and failure to convert to psychosis.
Methods: Participants in this study were recruited as part of the nine-site consortium study, NAPLS-3, a five-year study that included two years of follow-up clinical and biomarker assessments. The sample includes N=684 CHR participants, 372 were male and 312 were female, with a mean age of 18.21 (SD 4.08). Those included in the CHR category met the criteria for a psychosis risk syndrome according to the Criteria of Psychosis-Risk Syndromes (COPS) based on the Structured Interview for Psychosis Risk Syndromes (SIPS) (McGlashan et al., 2010). The Structured Assessment of Violence Risk in Youth (SAVRY) (Borum et al., 2010) was used to assess multiple risk factors as well one Protective Factor Index. The Protective Factor Index is made up of several subcategories including Prosocial Involvement, Strong Social Support, Strong Attachment and Bonds, Positive Attitude Toward Intervention/Authority, Strong Commitment to School and Resilient Personality Traits.

Results: The Protective Factor Index was negatively associated with severity of symptoms and also differentiated those N=68 CHR participants who later converted to psychosis and N=380 who were followed for 1 year and did not convert to psychosis. Investigation of the subcategories that comprised the SAVRY Protective Factor index reveals that, more specifically, prosocial involvement and resilient personality traits are more common in the CHR sample who did not convert to psychosis within 2 years. Resilient personality traits included factors such as empathy, psychological maturity and self-directedness.
Conclusions: In terms of clinical and public health implications, the SAVRY risk scores could be used to identify the level of intervention needed and guide decisions regarding focus of individual and group psychotherapy, family therapy and case management in the CHR population. Focusing on the enhancement of protective factors within individuals who meet criteria for CHR may help to not only reduce violence risk but symptom severity, poor functional outcome, and conversion to psychosis. Strong social support is a protective factor for both psychosis in adolescents and risk for violence (Borum et al., 2010; Riches et al., 2019). Although many of the risk factors for violence are non-modifiable, protective factors are potential targets for psychosocial intervention. Facilitation of involvement in community activities, social resources, and teaching strategies for promoting resilience could improve functional outcome and decrease risk of violence. Further research is warranted into community, psychotherapeutic, and home-based interventions that foster social support and promote resiliency in the population meeting criteria for CHR.

27.4 RESILIENCE AND PSYCHOPATHOLOGY -RELATED PREDICTORS OF CLINICAL AND ACADEMIC OUTCOMES IN YOUNG ADULTS AND POTENTIAL BRAIN MECHANISMS

Daphne Holt*[1], Rachel Sussman[1], Jordan Zimmerman[1], Nicole DeTore[1], Anne Burke[1], Louis Vinke[1]

[1]*Massachusetts General Hospital*

Background: It has been shown that subclinical psychotic symptoms in young people represent a transdiagnostic risk factor for the later development of a range of psychiatric disorders and poor functional outcomes. What has been less well-studied are the relationships between potentially protective capacities known to promote positive mental health and resilience and such outcomes, as well as the brain mechanisms linked with these protective factors. Here psychopathology and resilience -related predictors of objective functional and clinical outcomes, such as academic performance and utilization of clinical services, were measured in a cohort of U.S. college students. In addition, the effects of a brief behavioral intervention on those predictors and on the functioning of implicated brain circuitry were evaluated.
Methods: College students were assessed at baseline and followed every 6 months using online self-report questionnaires. In addition, academic and counseling center records were obtained annually from the students' undergraduate institutions. Symptoms and resilience factors predicting one-year outcomes (including credits earned, academic standing, use of psychiatric crisis services and psychiatric hospitalizations) were entered into multiple regression models. In an independent cohort, 103 college students with subclinical symptoms of depression and/or psychosis participated in a brief (4-week) resilience-enhancing behavioral intervention (Resilience Training, RT; DeTore, Luther et al, 2022); self-report symptom and resilience measures and resting-state fMRI data were collected before and after the intervention.
Results: In the first (longitudinal) cohort, a total of 3079 students completed baseline assessments. Controlling for demographic factors related to the outcomes, baseline subclinical

psychotic symptoms (i.e., psychotic experiences, PEs) were found to predict, at one year follow-up, the percentage of credits attempted that were earned, overall academic standing, and number of psychiatric hospitalizations (all $p < .04$). Also, levels of baseline resilience predicted usage of psychiatric crisis services at one year ($p < .02$). In the intervention study, significant reductions in symptoms (depression, anxiety and PEs, all $p<.006$) and significant improvements in resilience-related capacities such as mindfulness, self-compassion and emotion regulation (all $p<.020$) were observed following RT, as well as a significance increase ($p<.008$) in frontohippocampal connectivity. In addition, a significant association between the increase in frontohippocampal connectivity and decrease in PEs was found to be fully mediated by the improvement in emotion regulation.
Conclusions: Both baseline psychopathology and resilience-promoting capacities were related to functional and clinical outcomes in a cohort of U.S. college students. Improvements in resilience may be linked to changes in brain circuitry that may lead to sustained benefits in terms of psychopathology and functioning; future studies using a randomized controlled design can fully assess this possibility.

28. TARGETING ANTIPSYCHOTIC SIDE EFFECTS IN THE DIGITAL ERA: UNDERSTANDING AND IMPLEMENTING THE EVIDENCE

Rob McCutcheon, *University of Oxford*

Overall Symposia Abstract: Side-effects of antipsychotics impair quality of life, contribute to morbidity/mortality rates, increase stigma, and result in poor medication concordance and thus psychiatric relapse. Optimising psychopharmacological treatment can greatly ameliorate this burden and is a key priority for people with schizophrenia; however, this is a highly complex process given the multifactorial decisions involved. Novel approaches to both investigating moderating factors and synthesising available evidence are required to provide optimal care. The current symposium facilitates this by providing a state-of-the-art update on the clinical science of antipsychotic side effects.

Both side effect burden and antipsychotic effectiveness varies between patients, and understanding this is crucial to providing personalised care. Professor Iris Sommer will present data from recent cohort studies and randomised controlled trials that highlight the need to consider sex differences when considering antipsychotic treatment. Her findings will demonstrate that dosing, side effect burden, and efficacy are moderated by age and sex and will explore the implications for clinical practice.

Metabolic side effects of antipsychotics can be ameliorated by the prescription of adjunctive medications. Dr Margaret Hahn will present a new Cochrane meta-analysis examining over 50 studies to identify the most effective adjunctive medications for treating antipsychotic induced weight gain.

In addition to adjunctive treatment, switching antipsychotics may be an effective option for reducing antipsychotic related cardiometabolic burden, but a clear synthesis of the evidence is needed. Professor Dan Siskind will present a meta-analysis of over 50 studies identifying the best switching strategies to optimise cardiometabolic outcomes.

Most treatment guidelines state that antipsychotic side effects should be weighed up based on patient preferences when choosing a treatment. However, considering all side-effects of all available antipsychotics is a complex multidimensional process, complicated further by the need to tailor discussions to the individual. Dr Rob McCutcheon will present results of a novel data-driven approach to classifying antipsychotics based on receptor affinities, and the results

of an umbrella review that provides the most comprehensive database of antipsychotic side effects to date (comparative data on 13 different side effects for 32 antipsychotics). He will also demonstrate a novel digital tool that combines the umbrella review-derived side effect database with patient preference (i.e., relative concern for one side effect over another) to provide personalised treatment options.

As discussant, Dr Toby Pillinger will aim to explore further with delegates the rationale for side effect-minded prescribing in the treatment of people with psychotic disorders, and global barriers to this practice. He will aim to reflect on key action points from two pertinent documents he has contributed to, the recently published Lancet Commission for Physical Health Conditions in Psychiatry, and The Maudsley Practice Guidelines for Physical Health Conditions in Psychiatry.

28.1 NOVEL METHODS TO ENHANCE PERSONALIZED PRESCRIBING

Rob McCutcheon*[1], Oliver Howes[2], Allan Young[3], David Taylor[4], Toby Pillinger[5]

[1]*University of Oxford,* [2]*MRC LMS and KCL,* [3]*Institute of Psychiatry, King's College,* [4]*Maudsley Hospital, Denmark Hill, London and Institute of Pharmaceutical Science, King's College London,* [5]*Institute of Psychiatry, King's College London*

Background: Antipsychotics exert their effects on psychotic symptoms via dopamine D2 receptor blockade. Despite a common mechanism, there exist over 25 licensed antipsychotics, with diverse pharmacological and side effect profiles. The most used classification to date, the 'typical/atypical' dichotomy, does not accurately reflect pharmacological profiles

There is a need for (A) a classification scheme suitable for clinicians and researchers which maps onto both pharmacological and clinical effects, and (B) a method to identify the optimal antipsychotic for a given patient based on a multidimensional assessment of multiple side-effects. The current presentation describes the solutions: (A) a data-driven classification system based systematically upon compound pharmacology, and (B) a digital tool to facilitate comprehensive, evidence-based, and personalised antipsychotic prescribing decisions.

Methods: To address (A) we analysed affinities of 27 antipsychotics for 42 receptors from 3,325 receptor binding studies. We used a clustering algorithm to group antipsychotics based on patterns of receptor affinity. Using partial least squares regression, we examined the ability of this grouping to predict 13 common antipsychotic-induced side effects.

To address (B) we first created a database of antipsychotic side-effects via an umbrella review. We searched Pubmed for meta-analyses that rank antipsychotics based on side-effects. Effect size magnitude data were extracted from the largest meta-analyses, or ordinal rankings from guidelines where insufficient data existed. Second, we constructed an interface to allow users to select multiple side-effects and assign each a degree of relative concern. This user input data is then integrated with the database of side-effect magnitudes.

Results: Our receptor based clustering analysis identified 4 groups of antipsychotic. Group 1 - antagonism at the muscarinic receptors (associated with high cholinergic, adrenergic, and metabolic side effects); group 2 - lack of muscarinic or serotonergic antagonism but adrenergic antagonism and dopamine D2 partial agonism (associated with globally low side effect burden); group 3 - serotonergic and dopaminergic antagonism (associated with globally moderate side effect burden); group 4 - relatively pure dopaminergic antagonism (associated

with dopaminergic side effects). In addition to reflecting pharmacological profiles this grouping was also superior in predicting side effect profiles.
From our umbrella review of 2060 citations, 11 meta-analyses met inclusion criteria. Data were extracted for 32 antipsychotics and 13 side-effects. An online side effect balancer was developed in which the user selects which side-effects the degree of relative concern. User weighting and effect size data are synthesised using the TOPSIS multi-criteria decision-making method.

Conclusions: We present a data-driven drug classification approach with the potential to benefit both patients and researchers, guiding appropriate treatment and future drug development. We also have developed a digital application that supports patients and prescribers to make evidence-based, personalised, and comprehensive antipsychotic prescribing decisions based on drug side-effect profiles.

28.2 PHARMACOLOGICAL INTERVENTIONS FOR WEIGHT GAIN IN SCHIZOPHRENIA SPECTRUM DISORDERS: A COCHRANE SYSTEMATIC REVIEW AND META-ANALYSIS, AND CONTEXTUALIZATION WITHIN CURRENT OBESITY GUIDELINES

Sri Mahavir Agarwal[1], Nicolette Stogios[2], Margaret Hahn*[3], Zohra Ahsan[4], Jonathan Lockwood[4], Markus Duncan[5], Hiroyoshi Takeuchi[6], Taylor Valerie[7], Gary Remington[8], Guy Faulkner[9], Margaret Hahn[10]

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Background: Weight gain and obesity are common problems encountered by patients with schizophrenia spectrum disorders (SSDs). This is partially attributable to use antipsychotic (AP)s that are associated with weight gain and other metabolic disturbances. The significance of this prevalence and its impact on quality of life, treatment adherence, and premature cardiovascular morbidity requires better consensus on its management. The objective of this systematic review and meta-analysis was to determine the effects of adjunctive pharmacological interventions aimed at reducing weight gain in schizophrenia. Further, we place results of the review in context the of the recently updated Canadian Obesity Guidelines, providing an overview of best practice management strategies to manage obesity and AP-included weight gain in this population.
Methods: We searched the Cochrane Schizophrenia Group's Trials Register for all randomized controlled trials examining any adjunctive pharmacological intervention for weight loss in patients with SSDs receiving treatment with APs. The primary outcome of each study had to be body weight or a weight related measure. As endpoint and change data was combined in the analysis, mean differences (MD) of the change from baseline were calculated using Review Manager 5.3.
Results: Fifty-nine randomized controlled trials met inclusion criteria for this review (pooled n = 3273). Metformin is effective in bringing about modest weight loss (Weight: MD -3.23 kg, 95% CI -4.63 to -2.06; participants = 731; studies = 12; BMI: MD -1.31, 95% CI -1.86 to -0.77; participants = 879; studies = 13). Heterogeneity was reduced by dividing populations into first episode psychosis (FEP) and chronic populations, where FEP patients appeared to benefit

most from early metformin intervention (Weight: MD -5.18 kg, 95% CI -6.22 to -4.14; BMI: MD -1.87 kg/m2, 95% CI -2.19 to -1.56; participants = 214; studies = 3). Metformin as a treatment for weight gain may be associated with additional adaptive changes in fasting insulin levels and insulin resistance. The frequency of adverse effects did not differ between metformin and placebo groups. Moreover, glucagon-like peptide agonists (GLP-1RAs), such as liraglutide and exenatide, were also effective in reducing weight (Weight: MD -3.95 kg, 95% CI -7.08 to -0.83; participants = 165; studies = 3; BMI -1.26 kg/m2, 95% CI -2.21 to -0.30; participants = 165; studies = 3; waist circumference: MD -3.25, 95% CI -5.93 to -0.57; participants = 165, studies = 3). The frequency of adverse effects did not differ between GLP-1RA and placebo groups. Topiramate 200 mg was also effective for weight reduction as well (Weight: MD=-6.61 kg, 95% CI -9.62 to -3.61; BMI: MD=-2.72, 95% CI -3.25 to -2.20; participants = 181, studies = 3). The effects of 100 mg topiramate were not as prominent.
Conclusions: Of the drugs studied, metformin has the most evidence and was most effective in bringing about modest weight loss, and this is now reflected in recent Canadian Obesity Guideline practice recommendations. GLP-1RAs, a class of medications approved for chronic management of obesity in the general population, have accumulating evidence supporting efficacy in reducing weight in the context of schizophrenia and AP use. However, guideline recommendations supporting routine use of GLP-1RAs in SSDs and AP-induced weight gain have not been made to date. Interpretation for other agents is limited by the small number of studies, sample size, short study duration, and in the case of topiramate, assessment of potential negative cognitive adverse effects.

28.3 A SYSTEMATIC REVIEW AND META-ANALYSIS OF THE IMPACT OF SWITCHING ANTIPSYCHOTIC MEDICATIONS TO AMELIORATE WEIGHT GAIN IN PATIENTS WITH SCHIZOPHRENIA.

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Background: People with schizophrenia die 16-20 years earlier than the general population. This mortality gap is driven largely by avertable cardio-metabolic disease. Antipsychotic medications, notably clozapine, quetiapine and olanzapine drive glucose dysregulation, increase appetite and lead to weight gain. While adding additional pharmacological agents can help reduce obesity and adverse metabolic outcomes, switching to less metabolically problematic antipsychotic agents may also have a role. We aimed to review the evidence for switching antipsychotics to reduce cardiometabolic burden.
Methods: We searched PubMED, Embase, PsycINFO and Cochrane for articles reporting weight and metabolic changes. We included studies that had data on metabolic outcomes for antipsychotic switching versus staying on the previous antipsychotic. Meta-analyses were conducted both across and within groups.
Results: Sixty-one studies met inclusion criteria. Fifty-nine had data that could be included in the meta-analyses. Only aripiprazole significantly reduced weight (-5.52kg, 95%CI -10.63, -0.42, p=0.03) in pair-wise meta-analysis of switch-versus-stay. Olanzapine led to significantly increased weight (2.46kg, 95%CI 0.34, 4.57, p=0.02). There were significant improvements in fasting glucose (-3.99mg/dl, 95%CI-7.34, -0.64, p=0.02) and triglycerides (-31.03mg/dl, 95%CI -48.73, -13.34, p=0.0001) with switching to aripiprazole. There was no difference in rates of dropouts nor changes psychosis scale scores between switch and stay groups for either aripiprazole and olanzapine. When before-to-after switch meta-analyses were conducted, both

aripiprazole (-1.96kg, 95%CI -3.07, -0.85, p<0.001) and ziprasidone (-2.22kg, 95%CI=-3.84, -0.60, p=0.007) were associated with weight loss. Weight gain was seen with olanzapine (2.71kg, 95%CI 1.87, 3.55, p<0.001), and clozapine (2.80kg, 95%CI 0.26, 5.34, p=0.03). For switching to amisulpride, quetiapine, lurasidone or paliperidone/risperidone, no significant weight or other cardiometabolic changes were observed.
Conclusions: Improvements in weight profile and other cardiometabolic outcomes were seen with switching to antipsychotics agents with lower weight gain potential such as aripiprazole and ziprasidone. The weight gain potential of the pre- and post-switch antipsychotic medications should be considered when contemplating a switch in agents. A balance must be struck between the risk of increased psychotic symptoms versus any potential improvement in metabolic outcomes when considering a switch in in psychiatrically stable patients.

28.4 SEX INFLUENCES ON ANTIPSYCHOTIC SIDE EFFECTS AND EFFICACY

Iris Sommer[1], Bodyl Brand*[2], Shiral Gangadin[1], Antti Tanskanen[3], Jari Tiihonen[3], Heidi Taipale[4]

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Background: Throughout the life of women with psychotic disorders, lower estrogen levels are associated with a more severe disease course. At perimenopause in the mid-40s, estrogen levels decline to remain persistently low. This period is hypothesized to increase relapse risk and reduce antipsychotic effectiveness. Furthermore, female patients may on average show differences compared to males in terms antipsychotic metabolism and side effect burden. However, current guidelines for patients with psychotic disorders do not take sex differences into account.
Methods: In the first study a cohort of persons with schizophrenia/schizoaffective disorder was identified from Finnish nationwide registers (N = 61 889) and stratified by sex and age. Hospitalizations for psychosis were defined per 5-year age group during the follow-up 1996–2017. Risk of psychosis hospitalization (Adjusted Hazard Ratio, aHR) was assessed using within-individual design, by comparing antipsychotic monotherapy use to nonuse periods in the same individuals for seven dose categories in defined daily doses (DDDs).
In our second study, 144 patients (93 men, 51 women) with a schizophrenia spectrum diagnosis and ongoing psychosis were included and randomized to amisulpride, aripiprazole, or olanzapine in flexible dose (registered with ClinicalTrials.gov NCT01446328). Primary outcomes were sex differences in dose, dose-corrected serum levels, efficacy, and tolerability.

Results: In the cohort study we found that starting at age 45–50, women were consistently more often hospitalized for psychosis than their male peers. Women ≥45 had significantly higher aHRs than women <45 at antipsychotic monotherapy >0.6 DDDs, and than men at >1.1 DDDs/ day. This female-specific age-dependent decrease in effectiveness was present for clozapine doses >0.6 DDDs, olanzapine doses >1.4 DDDs, and for specific doses of quetiapine (0.9–1.1 DDDs) and risperidone (0.6–0.9 DDDs).
In the randomised trial, we found dosing was higher for men in the aripiprazole group (p = 0.025) and, at trend level, in the olanzapine group (p = 0.056). Dose-corrected serum levels were 71.9% higher in women for amisulpride (p = 0.019) and 55.8% higher in women for aripiprazole (p = 0.049). In the amisulpride group, men had a faster decrease in psychotic symptoms than women (p = 0.003). Moreover, amisulpride was more effective than the other medications in men but not in women. Prolactin levels were higher in women than men,

especially for amisulpride ($p < 0.001$). Women had higher BMI increase on amisulpride compared to the two other antipsychotics ($p < 0.001$).

Conclusions: In both studies we found clear influences of sex on disease course and medication response. Our cohort study demonstrates that while younger women have a lower risk of relapse than men, starting in mid-forties older women with psychotic disorders should be regarded as a vulnerable group that deserve special attention. Our randomised trial highlights that clinicians should be aware of the risks of overdosing in women, especially for amisulpride and aripiprazole. Amisulpride is highly effective in men, but in women, amisulpride showed more severe side effects and may thus not be the drug of first choice.

29. PARTICIPATORY RESEARCH, CO-DESIGN AND PATIENT-REPORTED MEASURES: MANY ROADS TO ENHANCING PATIENT INVOLVEMENT IN LEARNING HEALTH SYSTEMS AND MEASUREMENT IN EARLY PSYCHOSIS?

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Overall Symposia Abstract: Early intervention services for psychosis, proven superior to usual care, are being widely implemented. They have catalysed substantial research on multiple topics ranging from neurobiology to policy and culture. While this research has advanced our understanding of course, outcomes, and treatments, it is only relatively recently that various innovative research models and strategies (e.g., learning health systems) are emerging to address evidence-practice and implementation gaps, and create continuous loops from practice to data, data to knowledge, and knowledge to practice. It is essential that these innovative services research models/strategies be grounded in patient and family voices and perspectives, an ongoing challenge in the field.

Pagdon (USA), an early career researcher with lived experience of psychosis, will present how a participatory mixed methods project was embedded within a large 24-site early psychosis learning health system to understand salient questions around peer support (roles, impacts, mechanisms). Thara (India), a senior clinician-scientist, will discuss various patient and family reported outcome and experience measures that were created, adapted, tested and used as part of a large comparative study of outcomes and family factors in early psychosis in Chennai, India and Montreal, Canada. These measures were created to address the paucity of relevant patient and family reported measures that are deployable across contexts. Her presentation will outline how literature, qualitative data and patient, family and clinician inputs from both sites were used to create/adapt 16 patient and family reported measures, and how these have yielded insights about how contexts shape psychosis outcomes. Jones (USA), an early career researcher with disabilities (psychosis), will describe the design, implementation and findings of a multi-phase participatory and service user co-led mixed methods project that leveraged the national learning health system infrastructure. The project sought to understand barriers to career mobility and development in early psychosis, using both qualitative interview data and quantitative data. Findings challenge dominant approaches to measurement of vocational outcomes and vocational interventions in early psychosis and illustrate the value of service user co-led research in early psychosis. Abdel-Baki (clinician-scientist) and Come, a lived experience expert (Canada) will describe Quebec's rapid learning health system of 11 early psychosis programs. Their presentation will focus on the involvement of patients and families with lived experience at all stages of conceiving and implementing this learning health system, from choosing indicators and measures; providing feedback on data visualization; co-producing and co-facilitating training and capacity-building activities, etc. Quantitative and qualitative findings on the processes involved in and the impacts of this multi-stakeholder

engaged learning health system will be discussed, along with innovative approaches to elicit patient and family perspectives in real-time, such as the use of a smiley button experience survey.

29.1 PATIENT AND FAMILY REPORTED OUTCOME AND EXPERIENCE MEASURES AS AN AVENUE TO ATTEND TO PATIENT AND FAMILY PERSPECTIVES: INSIGHTS FROM CHENNAI, INDIA

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Background: Recently, there has been growing support for the use of patient-reported outcome measures (PROMs), patient-reported experience measures (PREMs), family-reported outcome measures (FROMs) and family-reported experience measures (FREMs) in health research, including psychiatry. Various arguments have been made in favour of these measures, including that these types of measures are one of many avenues to prioritize patient and family voices. Such measures can also support shared decision-making, measurement-based care and learning health systems. Despite this, patient and family reported measures are infrequently used in early psychosis. Moreover, few such measures have been developed and deployed in non-WEIRD countries. This presentation focuses on how these gaps were addressed in a comparative study of outcomes and family factors in first-episode psychosis in Chennai, India and Montreal, Canada.

Methods: We created or adapted, tested and used PROMs, PREMs and FREMs in Tamil and English in Chennai, India and in French and English in Montreal, Canada (168 and 165 patients in Chennai and Montreal, respectively and their families). The choice of constructs assessed by these measures and their design were informed by literature; pilot quantitative and qualitative work; and inputs from patients, families, clinicians and/or researchers at both sites. Reliability, validity and ease of use were assessed. The measures were also deployed in separate, larger samples at both sites.

Results: Our protocol included 16 PROMs, PREMs and FREMs, including measures of the same construct assessed from patient, family and clinician perspectives. While measures were generally found to have acceptable psychometric properties (test-retest reliability, internal consistency, criterion validity, etc.) and were rated as easy to understand and complete, these characteristics varied based on site and language of testing. The use of these measures revealed interesting site (Chennai vs. Montreal) and stakeholder (families vs. patients) differences on critical dimensions (e.g., trust, care experiences).

Conclusions: Having been co-designed and developed in three languages and tested in a low-and-middle-income and a high-income context, our measures show potential for deployment across wider geographies. The collaborative, multi-step process we followed also fostered creativity, e.g., we created a visual disk that requires minimum literacy and assesses the novel construct of stakeholder views on how responsibility for recovery should be distributed between patients, families and treatment providers. Our presentation will highlight various lessons learned and insights gleaned in this process that can advance our understanding about and use of patient and family reported measures in varied geo-sociocultural contexts.

29.2 SARPEP: A RAPID LEARNING HEALTHCARE SYSTEM FOR EARLY INTERVENTION FOR PSYCHOSIS SERVICES– INTEGRATION OF PERSONS

WITH LIVED EXPERIENCE IN ALL IMPLEMENTATION STEPS AND SYSTEM COMPONENT

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Background: Rapid learning health systems (RLHS) use technology to collect data and provide feedback to the RLHS users on quality of care and patient outcomes indicators and involves an Integrated Knowledge Translation. By actively involving knowledge users and persons with lived experience (PLE) throughout the design and implementation of the entire system, it can improve the uptake of clinical guidelines in clinical settings and improve quality of care. Integrating PLE throughout the RLHS implementation requires planning and efforts to maximise their input.
Methods: The SARPEP project deployed a RLHS in 11 EIS (Quebec province (Canada)), integrated PLE (patients and family members) during all implementation phases from the selection of indicators and technology tools, feedback creation and knowledge exchange activities of the community of practice gathering all stakeholders. The RE-AIM (Reach, Effectiveness, Adoption, Implementation, Maintenance) framework was used to inform both the questions and the data analysis of 5 focus groups on the RLHS implementation (including 11 clinicians, 6 managers, 5 service users, 2 family members involved in different capacities in the SAR PEP project). Data on PLE integration will be discussed.
Results: Challenges, facilitators and advantages of engaging PLE are identified. Their specific roles in every component of the RLHS, how it was implemented, and their contribution to the RLHS regarding the RE-AIM framework dimensions will be discussed.
Conclusions: PLE input can contribute to motivation and engagement of PLE in the RLHS and help improve practices in the most relevant areas so that patient-centered care can be improved.

29.3 UNDERSTANDING AND IMPROVING IMPLEMENTATION OF PEER SUPPORT ROLES IN A LARGE EARLY PSYCHOSIS LEARNING HEALTHCARE SYSTEM

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Background: Although a widely implemented component of early psychosis services, there are huge gaps in the literature on peer support roles in EP settings, leaving myriad questions about role optimization and effective implementation unanswered. Our goal with the project described here was to investigate how peer specialists understand their roles, barriers and challenges, and perceived impact and mechanisms of impact on early psychosis clients and then feed knowledge generated by the project back into the learning health care system.
Methods: Along with lead state-level peer specialist trainers, we co-developed a participatory mixed methods research project beginning with a survey of current peer specialists (N = 22), followed by in-depth interviews (N = 16). The project was embedded within a large multi-state early psychosis learning healthcare system spanning 25 EP sites. Individual peer specialists were consulted on design and numerous changes made to the protocol based on peer specialist and peer trainer feedback. Following transcription, all participants had the opportunity to review and amend transcripts. Coding and analyses were carried out in direct collaboration with peer specialist trainers for the LHS, and the collaborating peer specialist

trainers have subseuqently used project learning to develop and/or modify LHS training and technical assistance.
Results: Thematic findings highlight the often unique and intersectional nature of the "experiential knowledge" peer specialists bring to their roles, including race, gender, and heterogenous personal service trajectories and diagnoses, as well as challenges of navigating these roles in the context of site-varying supervisors and team dynamics. Specific areas we will highlight include concerns about wages and career mobility, and the impact of heterogeneous supervisory relationships on the integration of peer specialists within the larger treatment team. Overall, findings point to multiple ways in which peer support implementation, including sustainment, supervision and team integration, can be strengthened.
Conclusions: Particularly in under-researched and under-resourced areas such as peer support, it is critical to engage deeply with the on-the-ground experiences of direct stakeholders (peer specialists in our project). Our work highlights numerous concrete and specific ways in which a collaborative approach strengthened and transformed study design, study protocols, ethical deliberation and interpretation of findings, ultimately helping ensure real-world impact.

29.4 DIGGING DEEP: PARTICIPATORY AND MIXED METHODS RESEARCH FOCUSED ON UNDERSTANDING AND PREVENTING LONG-TERM POVERTY AMONG INDIVIDUALS WITH PSYCHOSIS

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Background: While rates of recovery in schizophrenia have incrementally improved in the past decades (cf Huxley at al., 2021), outcomes remain poor for many, particularly those who experience multi-episode psychosis. The majority of adults with schizophrenia across high income settings are un- or underemployed and live below national poverty lines. Early intervention (EI) programs offer the possibility of preventing deepening poverty and disability benefit dependence. However, in the US RAISE trial, rates of disability benefit receipt did not differ between RAISE recipients and controls, in turn raising important questions about the extent to which current EI models in fact support decision making regarding disability benefit enrollment and alternative pathways to a living wage and socioeconomic security. Given the importance of financial well-being, and troubling RAISE findings, we report on an in-process, large-scale multi-site and multi-phase investigation of vocational, socioeconomic and disability-benefit trajectories in early psychosis, funded by the National Institutes of Mental Health and embedded with the NIMH Early Psychosis Intervention Network (EPINET) Learning Healthcare System (LHS).
Methods: This presentation will briefly describe our larger service user co-produced and co-designed multi-phase study (estimated N = 5000), while otherwise focusing on already analyzed preliminary qualitative (N = 38) and quantitative (N = 1458) data. Analyses presented will synthesize both qualitative and quantitative findings.
Results: Preliminary quantitative findings underscore the strength of social and structural influences on vocational and socioeconomic outcomes, while qualitative work suggests that the underdevelopment of an explicit career development focus in dominant US EP models often leads to a focus on short-term low-wage work placements rather than long-term career development, particularly among clients from low SES backgrounds. Meanwhile, college-bound service users are better positioned to tap into career development resources outside of clinical systems. When we turn to disability benefit decision-making, marked differences

emerge in the perceived tradeoffs on the part of college-bound or -educated service users who aspire to a living wage career, versus those whose exposure to work has primarily centered on low-wage, often part-time and/or seasonal, blue-collar work.

Conclusions: Both our preliminary findings and ongoing research underscore the importance of integrating service user experiences, spanning direct involvement as project leadership, consultation and qualitative research, into psychosis LHS studies. By digging deep into the complexities of what young people actually experience, and the social and structural contexts of these experiences, we are pushed to ask new and different questions, measure "good" or "poor" outcomes in different ways, and grapple with how we can support clinical programs to reorient to what, from service user perspectives, may actually matter most.

30. THE PROMISE OF INTERVENTIONS TARGETING THE MOTOR SYSTEM IN PSYCHOSIS

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Overall Symposia Abstract: Motor abnormalities such as psychomotor slowing, deficits in movement coordination and sequencing, or catatonia are frequent in schizophrenia spectrum disorders across all stages. Motor abnormalities may arise long before the onset of core psychotic symptoms and in the absence of antipsychotic treatment. Specifically, hypokinetic motor abnormalities such as psychomotor slowing and catatonia are associated with increased negative symptoms and impaired cognition. Similarly, motor abnormalities predict poor outcomes and low social functioning. Neuroimaging studies have offered some insight into aberrant structure and function in the motor system in psychosis. However, the association between brain alterations and motor abnormalities is still poorly understood. Understanding the pathobiology of the cortico-cerebellar-thalamo-cortical circuitry would offer critical information for brain stimulation. The cerebral motor system could be targeted with non-invasive brain stimulation at multiple entry points that promise direct effects on key cortical motor areas but also distant effects on basal ganglia due to intense connectivity. Furthermore, these interventions may exert positive effects on symptoms and course at different stages of the disorder, i.e. in subjects at risk, at first episode, or in chronic illness. This symposium will first offer insight on how symptom dimensions of schizophrenia are related to connectivity in the motor system, and second provide first evidence for interventions targeting key areas such as the cerebellum or the supplementary motor area (SMA). One talk will discuss how connectivity from the cerebellum to basal ganglia or cortical motor areas is linked to symptoms and motor behavior in schizophrenia and subjects at risk for psychosis. Another talk will elucidate how cerebellar-SMA functional connectivity is linked to deficits in processing speed. Furthermore, cerebellar transcranial magnetic stimulation (TMS) of this circuit improved processing speed in psychosis. In addition, one talk will present the effect of cerebellar transcranial direct current stimulation on working memory in subjects at clinical high risk for psychosis. Finally, one presentation will introduce the results of a double blind, randomized, placebo-controlled trial of repetitive TMS on the supplementary motor area to treat psychomotor slowing in schizophrenia. Results of this trial indicate superior effects of 15 sessions of 1 Hz inhibitory stimulation of the SMA compared to facilitatory stimulation, sham stimulation or waiting group. Collectively, these studies provide first evidence for beneficial effects of brain stimulation interventions on the motor system in psychosis. In addition, the side effects and barriers will be evaluated. We will discuss whether brain stimulation of the motor system in psychosis may focus on ameliorating motor abnormalities or whether these interventions have potential to modulate other symptom domains beyond aberrant motor

behavior. In sum, this symposium will facilitate the implementation of novel, neurobiologically informed interventions in this exciting field of psychosis research.

30.1 CEREBELLO-BASAL GANGLIA NETWORKS IN PSYCHOSIS

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Background: Psychotic disorders are conceptualized as brain-network diseases and both the cerebellum (CB) and basal ganglia (BG) are implicated in psychosis-related dysfunction. The CB and BG are functionally and anatomically connected to each other and to cortical networks via domain-specific, topographically organized loops and may be nodes in larger, brain-wide and domain-spanning networks. We have previously differentiated cognitive and motor CB-BG networks (CCBN, MCBN) and showed CB-BG network global efficiency (GE), a measure of network integration, is related to both cortical network GE in healthy young adults and to depression and hyperactivity symptoms in a community sample. It is currently unknown whether CB-BG GE relates to psychotic symptoms or diagnoses.
Methods: Here, we combined data from three sources to construct groups of clinically high-risk (CHR; n=91), early course psychosis (ECP; n=104), and chronic psychosis (CP; n=49) participants, as well as healthy controls (HC; n=204). We computed GE for the CB-BG networks and investigated group differences therein. Furthermore, we investigated relationships between CB-BG GE measures and symptom severity and cognition to determine the degree to which these factors are related. Finally, we explored the degree to which CB-BG networks predicted cortical network GE across groups. For all analyses we controlled for age, alcohol and marijuana usage, and CPZ equivalency.
Results: CCBN GE was lower in CHR individuals, compared to HC and CP. We also found associations between CCBN and cognitive dysfunction and between MCBN and negative symptoms of psychosis. This association with cognition was present in the ECP group, while the MCBN associations with negative symptoms were seen in the CHR group alone, and when combining the HC, ECP, and CP groups. Together, this highlights a possible link between motor networks and symptomatology in psychosis. Last, we detail CB-BG associations with sensory, motor, default mode, and salience networks across groups, with group effects demonstrating differences in ECP.
Conclusions: In this study, we show that CB-BG GE predicts cognitive dysfunction and negative symptom scores. We also detailed relationships between CB-BG GE and cortical GE across groups and found both networks contribute to sensory, attentional, and motor networks, particularly within the ECP group. We propose CB-BG network GE may be a potential contributor to psychosis symptoms and further studies may determine it as a potential biomarker of a variety of psychiatric and neurological disorders.

30.2 A CORTICO-CEREBELLAR CIRCUIT IS DYNAMICALLY LINKED TO INFORMATION PROCESSING SPEED IN BOTH THE PRODROME AND IN PSYCHOSIS

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Background: Cognitive deficits in psychosis are among the strongest predictors of disability. Impaired processing speed is consistently reported, severely impaired, and strongly linked to poor functional outcomes. This deficit is already present in the prodrome to psychosis. Identifying the circuit basis of this deficit and demonstrating that these brain targets can be engaged therapeutically is a critical unmet need.
Methods: We analyzed three datasets: Adults diagnosed with psychosis (n=103) underwent fMRI imaging and cognitive testing. We used fully data-driven analysis to identify circuit correlates of processing speed. This analysis was repeated in individuals at clinical high risk (CHR) for psychosis (n=137 including n=21 future converters). Finally, in a cohort of adults with schizophrenia (n=11), we measured the impact of repeated sessions of transcranial magnetic stimulation (TMS) directed at one node of a putative cognitive circuit.
Results: In participants with psychosis, the strongest (r=.396, p< .001) correlate of processing speed was a cerebellar-frontal circuit. This link was stronger in antipsychotic-free individuals (n=40, r=.52, p<.001). Independent analysis in the CHR cohort replicated this result (r=.392, p< .001) and this connectivity-cognition relationship was strongest in future converters (r=.558 p=.012). In the TMS cohort, within-subject change in processing speed was strongly linked to change in circuit connectivity (r=.888, p<.001).
Conclusions: Cognitive impairment in psychosis is linked to cerebellar-frontal circuit connectivity. As predicted, this relationship is present in the prodrome. Within-subject variation in cognitive performance is strongly linked to circuit connectivity. These results are consistent with a causal relationship between cerebellar connectivity and cognitive impairment in psychosis.

30.3 CEREBELLAR STIMULATION SHOWS PROMISE FOR COGNITIVE REMEDIATION IN ALONG THE PSYCHOSIS CONTINUUM

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Background: Cognitive deficits in early psychosis periods contribute to functional impairment but at the present time there are limited treatment options for these pernicious symptoms. A growing body of work indicates that the cerebellum plays an important role in modulating cognitive function. A number of well-designed studies have also indicated that dysfunction in the cerebellar circuit contributes to more localized as well as higher order cognitive dysfunction in psychosis. This circuit dysfunction presents an opportunity for novel remediation efforts, as the cerebellum is an ideal target for non-invasive brain stimulation.
Methods: An analog study was designed to determine if cerebellar stimulation could in fact impact cognitive function in those with psychosis vulnerability. A total of 24 community participants exhibiting symptoms of non-clinical psychosis (NCP) and 18 healthy control (HC) individuals participated in a randomized double-blind cross-over study. In this cross-over

design, participants received 25 minutes of anodal or 25 minutes of sham cerebellar transcranial direct-current stimulation (tDCS) (separated by one week; those randomized to receive the sham or active stimulation condition during visit 1 received the other condition during visit 2) and completed a procedural learning (pursuit rotor task, consisting of 4 sessions, separated by 15 minutes each). In a follow-up study, a total of 13 early course-psychosis (ECP; onset of psychotic disorder within 5 years) and 37 HC individuals participated in a randomized double-blind cross-over study. The ECP group received 25 minutes of anodal or 25 minutes of sham cerebellar tDCS (separated by one week; those randomized to receive the sham or active stimulation condition during visit 1 received the other condition during visit 2) while the HC group received only 25 minutes of sham cerebellar stimulation. Participants in this study completed a Sternberg verbal working-memory task which included easy, medium, and difficult conditions.

Results: Results from the analog study indicated that in the sham condition, the HC group showed a significantly greater increase in motor learning over the course of the 4 trials when compared to the NCP participants [$F(3,234)=4.31$, $p=.006$], but in the active simulation group, performance in the clinical group improved such that two groups were comparable in their learning. Results from the 2nd study indicated that among the ECP group there was significant heterogeneity, with a clear group of responders (n=5) and a second group of non-responders (n=8). While the study was not powered to test the interaction, main effects for stimulation [$t=2.83$, $p=.005$], group [$t=2.12$, $p=.04$] and condition[$t=2.63$, $p=.009$] indicated a pattern suggesting that across task difficulty conditions, the sham ECP condition performance was uniformly poorer but that active stimulation condition produced a normalization effect where accuracy performance in responders approximated that of the HC sham group.

Conclusions: Taken together, these results suggest that cerebellar stimulation has exciting potential to impact both more proximal (motor learning) along with higher-order (verbal working memory) cognitive deficits along the psychosis continuum. Further, the results indicate that early psychosis heterogeneity may play an important role for study design and treatment development. Implications for precision medicine as well as updates from ongoing supporting functional imaging analyses (indicating increased cerebellar to whole-brain connectivity on active vs sham visits in study 2), will be discussed.

30.4 INHIBITORY REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION ON THE SUPPLEMENTARY MOTOR AREA AMELIORATES PSYCHOMOTOR SLOWING IN PSYCHOSIS – A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

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Background: Psychomotor slowing is a core symptom domain in psychosis and impairs gross and fine motor behaviors. It affects approximately 50% of the patients with schizophrenia and is associated with poor functioning and poor outcomes. A pilot study of our team suggested that 15 sessions of inhibitory repetitive transcranial magnetic stimulation (rTMS) may ameliorate psychomotor slowing in a transdiagnostic cohort. This study aimed at testing the

effects of rTMS on the supplementary motor area (SMA) in patients with schizophrenia and psychomotor slowing.
Methods: This was a single-site, randomized, double-blind, placebo-controlled trial of 15 sessions rTMS on the SMA in three weeks. Patients with schizophrenia spectrum disorders with severe psychomotor slowing (Salpetriere Retardation Rating Scale (SRRS) >= 15) were randomized to one of four treatment arms: inhibitory 1 Hz stimulation with 1000 pulses at 110% resting motor threshold (RMT), facilitatory intermittend theta burst stimulation (iTBS) at 50 Hz with 1200 pulses at 80% RMT, sham stimulation with a placebo coil identical sound and duration to 1 Hz, and waiting group. The waiting group completed baseline assessments twice in 3 weeks and was afterwards started on 15 sessions of 1 Hz stimulation. Assessments included side effects and SRRS scores weekly, and clinical rating scales at baseline, week 3 and week 6 (waiting group only) assessing total symptoms (PANSS), negative symptoms (BNSS), catatonia (BFCRS), and functioning (GAF). The primary outcome was response at week 3 (> 30% improvement in SRRS score from baseline). Last observation carried forward method was applied. We calculated Chi2 tests across four groups, as well as raw and adjusted odds ratios testing 1 Hz against other arms. Secondary outcomes were course of SRRS total scores, course of PANSS, BNSS, BFCRS, and GAF.
Results: 103 patients were enrolled, of whom 15 dropped out before the first stimulation. Thus, 88 patients were in the intention-to-treat population. The ITT patients were 36.8 years old, 51% male, with a PANSS total score of 80.2 and a BMI of 25.1. Patients in the four treatment arms differed in sex distribution and antipsychotic medication. Number of Drop outs during the first 3 weeks were not different between groups. There were no serious adverse effects. At week 3, groups differed in the proportion of responders (1Hz: 64%, iTBS: 24%, Placebo: 36%, waiting: 18%; Chi2 = 10.6, df = 3, p = .014). Odds ratios for 1 Hz vs. placebo were at .33 p = .054 (raw) and .34 p = .129 (adjusted for sex and olanzapine equivalents). Time by protocol interactions were seen for BNSS anhedonia and catatonia ratings. No interactions for GAF or PANSS total. In the waiting group SRRS scores steadily declined after 1 Hz treatment (F = 9.5, df = 5, p < .001) with 63% responders at week 6. Combining all subjects on 1 Hz, the odds ratio of 1 Hz vs. placebo is .33 p = .051 (raw) and .30 p = .033 (adjusted).
Conclusions: 15 sessions of inhibitory rTMS on the SMA were clinically effective in reducing psychomotor slowing in psychosis. Facilitatory stimulation or waiting group had no effect compared to placebo. rTMS was well-tolerated as add-on treatment. Secondary outcomes indicated beneficial effects on catatonia and negative symptoms. Effects were slightly lower compared to the pilot study, rendering this trial slightly underpowered. Future multicenter studies should establish whether inhibitory rTMS should be included in the psychiatrist's toolbox.

31. COMPUTATIONAL ANALYSES OF REWARD LEARNING IN PSYCHIATRIC ILLNESS: EFFECTS OF DIAGNOSIS, EARLY-LIFE ADVERSITY, AND REINFORCER TYPE

Junghee Lee, *The University of Alabama at Birmingham*

Overall Symposia Abstract: During the past decade, aberrant reward processing has emerged as a key feature of psychosis. Impaired reward processing is prevalent and is thought to play a key role in amotivation and social dysfunction in psychosis. However, our poor mechanistic understanding of reward processing in psychosis, as well as the factors that might contribute to impairment, presents a significant obstacle for developing and evaluating interventions for these impairments. Specifically, it is unclear whether different types of reward are associated with different levels of impairment in psychosis. Furthermore, while aberrant reward

processing is implicated in several psychiatric disorders, it remains unclear whether the patterns of aberrant reward processing are similar across the disorders. To address these critical questions, Junghee Lee (Chair, University of Alabama at Birmingham, USA) and James Waltz (Co-Chair, University of Maryland, USA) have assembled a diverse team of scientists.
Jaisal Merchant (Washington University, USA) will present her work on the relative levels of impairment on reward learning in psychosis. She has found that schizophrenia (SZ) patients show greater impairment on social reward learning than nonsocial reward learning on a behavioral level, but not on a neural level. She has also found that impaired social reward learning is related to facial affect recognition, but unrelated to subjective experience of social pleasure. James Waltz (University of Maryland, USA) will present his work on the impact of stress and trauma on reward processing in psychosis. He has found that lifetime stress is related to impaired reward learning at both behavioral and neural levels. He has also found that acute stress affects reward learning in individuals with SZ, with this relationship being moderated by the severity of paranoia. Ling-ling Wang (Chinese Academy of Sciences, China) will present her work on adaptation of value representations (representing value relative to other stimuli and actions, rather than as an absolute) in SZ and major depressive disorder (MDD). She has found a differential pattern of reward value representation between SZ and major depressive disorder, such that individuals with SZ show over-adaptation to rewarding stimuli, whereas individuals with MDD show under-adaptation to rewarding stimuli. Over-adaptation in SZ is also related to reduced anhedonia. Teresa Katthagen (Charité-Universitätsmedizin Berlin, Germany) will present her work on the relationship between dopaminergic function and reward processing in psychosis spectrum disorders. She has found that positive and negative symptoms are related to differential neurocomputational mechanisms of reward processing in SZ. She will also show that the overestimation of volatility is related to impaired reward learning in psychosis and alcohol use disorder, but not in obsessive-compulsive disorder or eating disorder. Daphne Holt (Massachusetts General Hospital, USA) will serve as discussant to place individual presentations in the context of key issues of reward processing in psychosis and other psychiatric disorders, such as mechanistic underpinnings and clinical manifestations. Thus, this symposium will be able to provide valuable insights into behavioral and neural mechanisms of impaired reward learning in psychosis, relationships with clinical symptoms, and transdiagnostic versus illness-specific reward learning processes.

31.1 TRANSDIAGNOSTIC INVESTIGATION OF RANGE ADAPTATION TO VALUE IN PATIENTS WITH SCHIZOPHRENIA AND MAJOR DEPRESSION

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Background: Anhedonia, a diminished ability to experience pleasure, is thought to stem from a deficit in reward processing and is commonly observed in patients with schizophrenia (SZ) and major depressive disorder (MDD). Specifically, alterations in the representation of value during reinforcement learning and decision making may serve as mechanisms of anhedonia and amotivation. Range adaptation underlies the building and contrasting the representation of expected value and outcome value of a given stimulus. It allows for a value's representation to depend on its relative position in the distribution of values that an individual has previously encountered and thereby promotes maximal discrimination of different stimuli, and optimizes coding efficiency. The extant literature only focuses on range adaptation with regard to outcome value but not expected value in SZ patients, and it is not clear whether MDD patients would also exhibit similar outcome value and expected value impairments. This study was designed to examine the range adaptation performance (the degree to which previous experience influences current behavior) and its relationship with clinical symptoms and subjective and objective anhedonia and amotivation manifestations in SZ and MDD patients.
Methods: We administered the Effort-based Pleasure Experience task to 50 SZ patients, 46 MDD patients, and 56 controls, to examine their range adaptation behavior. Range adaptation performance for expected value and outcome value were measured during the decision-making and consummatory rating phases separately, by measuring the influence of previous experience on current decision-making or pleasure experience rating. Clinical interview, self-report questionnaires, and the experimental task was used to evaluate the clinical symptom and the subjective and objective aspects of anhedonia and amotivation behavior.
Results: We observed different patterns of range adaptation impairment in SZ and MDD patients. In SZ patients, we observed abnormal adaptation for both expected value and outcome value; that is, previous experience had an excessive impact of on current behavior. Furthermore, impaired adaptation effects negatively correlated with clinician-rated anhedonia and amotivation symptoms and levels of readiness to expend high-effort for small rewards. By contrast, MDD patients exhibited diminished range adaptation for outcome value (reduced influence of previous experience) but intact range adaptation for expected value. In MDD patients, we observed negative correlation between range adaptation performance for expected value and both self-reported anhedonia and patients' levels of readiness to expend high-effort for small reward.
Conclusions: We found that impairments in range adaptation are shared by SZ and MDD patients, and that there are differences in patterns of range adaptation for expected value and outcome value performance between SZ and MDD patients. Altered adaptation is associated with amotivation in both SZ and MDD patients, but with different roles. Range adaptation may be a core underlying mechanisms and plausible intervention target for anhedonia and amotivation in patients with SZ and MDD.

31.2 FROM BLUNTED PREDICTION ERRORS TO TOO MUCH VOLATILITY: COMPUTATIONAL LEARNING MECHANISMS UNDERLYING SCHIZOPHRENIA SYMPTOMS AND THEIR TRANSDIAGNOSTIC RELEVANCE

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[1]*Charité-Universitätsmedizin*

Background: Heightened dopaminergic tone has been hypothesized to affect positive and negative symptoms in patients with schizophrenia (PSZ), via dysfunctional prediction error signals. However, PSZ also show deficits in reinforcement learning that go beyond prediction error signals. More complex learning models allow for dynamic belief updating in accordance with environmental volatility, and the estimation of the latter seems to be altered in PSZ. Though computational psychiatry aims for a more fine-grained explanation of symptoms via mechanisms, correlations between computational mechanisms and schizophrenia symptoms vary and often point towards broader cognitive deficits. Furthermore, whether these neurocomputational learning deficits are specific to schizophrenia requires transdiagnostic comparisons.
Methods: In order to test the relationship between striatal dopamine synthesis and reward prediction error signaling, unmedicated PSZ underwent multimodal imaging (PET and fMRI, Study 1). The computational and neural signatures of volatility beliefs were assessed across the psychosis continuum (delusion-prone healthy controls and schizophrenia patients) using a hierarchical learning model (Study 2). Findings were embedded in a literature review on dynamic belief updating in psychosis (Study 3). Lastly, we modeled volatility-based reversal learning in a transdiagnostic dataset comprising samples of patients with SZ (n=56), alcohol use disorder (n=37), obsessive-compulsive disorder (n=29), and binge eating disorder (n=21; Study 4).
Results: Striatal dopamine levels were only increased in PSZ without comorbid alcohol abuse ($U=101.0$, $p=.033$) and correlated with higher positive symptoms ($r=.52$, $p=.023$). The striatal prediction error signal was decreased in PSZ (limbic striatum [−10/12/−8], $t=7.11$, $p=.001$) and related to negative symptoms ([12/8/−10], $t = 3.23$, $p=.039$). Striatal dopamine related to stronger prediction error coding in controls, but not in PSZ ($r=.608$, $p=.02$; Study 1). Differentiating between the effects of disorder vs. current delusions in hierarchical learning, patients showed increased volatility levels ($F(1, 62)=8.54$, $p=.005$) that were accompanied by weaker prefrontal activation ([4/30/40], $t=5.52$, $p=.001$). In contrast, controls and patients with delusional ideation showed stronger anterior cingulate ([-6, 38, -6], $t=4.41$, $p=.017$) and accumbens ([8/10/-8], $t=3.88$, $p=.033$) activation for precision weighted prediction errors (Study 2). In line with that, the review of computational psychosis studies revealed an overestimation of volatility in relation to psychosis though no clear association with positive or negative symptoms (Study 3). Comparing psychiatric patient groups using a novel computational model revealed higher choice stochasticity in PSZ as well as in patients with alcohol use disorder ($F=8.266$, $p<.001$). Across patients, depression levels (BDI-II) correlated with decreased learning about volatility ($r=-.24$, $p=0.006$; Study 4).
Conclusions: Taken together, these studies reveal dysfunctional neurocomputational mechanisms at different hierarchy levels of learning relating to different symptoms domains in schizophrenia. Subcortical decreases in reward prediction errors related to negative symptoms, whereas stronger signalling of precision weighted PEs in cortical regions related to delusions. An overestimation of volatility explained learning deficits across various psychosis studies. In contrast, decreased learning about volatility related to depression levels in a transdiagostic sample. Further, increased stochasticity does not seem to be specific to schizophrenia but was also found in patients with alcohol use disorder.

31.3 NEURAL AND BEHAVIORAL CORRELATES OF SOCIAL REINFORCEMENT LEARNING IN SCHIZOPHRENIA

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Background: Individuals with schizophrenia (SZ) have few social relationships and lack social support despite evidence of an intact desire for both. As social connection is closely linked to an array of clinical outcomes, it is critical to examine factors that inhibit the formation of social relationships in SZ. There are well-documented deficits in the ability to modify behavior based on feedback (reinforcement learning) in SZ. However, the majority of studies have examined reinforcement learning using monetary feedback, and the ability to learn from social feedback in SZ is not well understood. Impairments in social reinforcement learning could stem from difficulty recognizing social cues, placing decreased value on social feedback, and/or an impaired ability to update behavior in accordance with this feedback. Understanding the neural and behavioral patterns of social reinforcement learning in SZ, including whether it differs from monetary reinforcement learning, may help us understand the basis of reduced social functioning in SZ.
Methods: Thirty-one individuals with SZ and 31 controls (HC) engaged in two (social and monetary) probabilistic reinforcement learning tasks (PRL) during functional magnetic resonance imaging. The PRL task assessed participants' ability to learn to select stimuli associated with reward (smiling faces or monetary gain) and avoid those associated with punishment (angry faces or monetary loss). We assessed BOLD activation in reward-related brain regions during stimulus selection (choice) and feedback receipt (outcome). Participants also completed tasks that assessed ability to recognize facial expressions (facial affect recognition) and rated the degree of pleasure from seeing the facial feedback (social valuation).
Results: Patients with SZ exhibited impaired reinforcement learning on both the social ($F(1,60) = 15.90$, $p < .001$) and monetary ($F(1,60) = 4.94$, $p = .03$) tasks compared to HC. However, SZs were more impaired in their ability to learn from social than monetary feedback (Group X Task: $F(1,60) = 5.99$; $p = 0.02$). Groups did not differ in the extent to which they valued social feedback (Happy: $t(1,59) = 1.11$, $p = 0.27$); Angry: $t(1,60) = 0.543$, $p = 0.59$), and controlling for social valuation did not account for the differentially worse social reinforcement learning in SZ (Group X Task- Happy: $F(1,58) = 9.23$, $p = .004$; Angry: $F(1,59) = 5.99$, $p = 0.02$). However, SZ had poorer facial affect recognition than HC (ER40: $t(1,56) = 3.08$, $p = 0.003$), and controlling for this accounted for the differential social reinforcement learning impairment (Group x Task: $F(1,55) = 1.69$, $p = .20$). Group differences in BOLD activation, on the other hand, did not vary based on the social versus monetary nature of the trial. Instead, there were distinctions related to trial phase such that SZ had less caudate activation than HC at the time of stimulus choice (social: ts $(1,59) \geq 2.85$, ps ≤ 0.006; monetary: ts $(1,59) \geq 3.37$, ps $= 0.001$), but this activation did not differ between groups at the time of feedback (ps > 0.05).
Conclusions: These results indicate that SZ patients may have more behavioral difficulty with social than monetary reinforcement learning, which could stem from difficulty identifying the social cues in the feedback rather than from decreased social valuation. In fact, SZ and HC reported similar levels of pleasure from social feedback and did not differ in their reward-related neural activation upon receiving social or monetary reinforcement. At the same time, SZ demonstrated reduced reward-related neural activation when making behavioral decisions for both monetary and social feedback. Thus, SZ may struggle to utilize representations of expected reward to inform their choices for both social and non-social reinforcement learning.

31.4 IMPACT OF STRESS AND TRAUMA ON LEARNING AND DECISION-MAKING IN PSYCHOSIS

James Waltz*[1]

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Background: Affective reactions to acute stressors often evoke exacerbations of psychotic symptoms. Across the lifespan, affective reactions to acute stressors are enhanced by successive adverse childhood experiences (ACEs), in a process called "behavioral sensitization". The net effects of behavioral sensitization of acute stress responses are to alter responsivity to positive and negative feedback and to unexpected events, regardless of valence, leading to the maladaptive assignment of salience to stimuli and events. The assignment of "aberrant" salience to stimuli and events has profound consequences for learning and decision-making, which can influence both the positive and negative symptoms of psychosis. In a series of studies, we have investigated how ACEs impacted brain signals and behavior in people with psychotic illness.

Methods: We administered probabilistic reinforcement learning (RL) tasks to two sample of patients with schizophrenia (PSZ), in conjunction with functional MRI scanning. One sample included 27 PSZ (mean age: 38.1+11.9) and 27 healthy volunteers (HVs; mean age: 38.3+12.6), and the other sample included 47 PSZ (mean age: 39.8+10.1) and 24 healthy volunteers (HVs; mean age: 42.4+13.5). In the first study, participants performed a probabilistic RL task, with no reversal, in which they needed to learn to choose the more-frequently-reinforced stimulus from each of 3 pairs. In the second study, participants performed a 3-choice probabilistic reversal learning task twice, once after being administered an acute stressor (the Socially-evaluated Cold Pressor Task), and once after not being stressed. In both data sets, we examined effects of ACEs on behavioral and brain measures. In the second data set, we were able to investigate whether the experience of ACEs modulated effects of acute stress on behavioral measures. The frequency and severity of adverse childhood experiences were assessed using the 28-item Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003). Trial-wise reward prediction errors (RPEs) and subject-wise learning rates were estimated using computational models.

Results: In the first study, we observed no effects of ACEs on behavioral measures, but we found that RPE signals in left limbic (ventromedial; $r=0.448$, $p=0.032$) and right associative (ventrolateral; $r=0.525$, $p=0.010$) subregions of the striatum correlated with CTQ scores. In the second study, we observed effects of both lifetime and acute stressors on behavioral measures. Specifically, PSZ who were physically abused showed worse RL performance, in terms of stages achieved ($t=3.124$, $p=0.002$) and the percentage of optimal choices ($t=3.547$, $p=0.002$) than PSZ who reported no physical abuse. Furthermore, we found that paranoia and acute stress interacted in modulating RL performance. That is, the acute stressor had a more detrimental effect on performance, in terms of both stages achieved ($t=2.500$, $p=0.016$) and the percentage of optimal choices ($t=1.997$, $p=0.052$), in subjects exhibiting suspicious thoughts, when compared with subjects not exhibiting suspicious thoughts. Additional clinical and neural correlates of these effects will be discussed.

Conclusions: In short, our results show how acute and lifetime stress affect performance on a reinforcement learning task, including how clinical symptoms and environmental stressors interact in influencing RL performance. Further, our results show how alterations in the function of the reward and salience networks of the brain figure centrally in stress-psychopathology relationships. A more detailed understanding of these alterations would help us describe the pathways by which childhood trauma and acute stress interact in exacerbating psychopathology, and the processes by which ACEs sensitize susceptible individuals to the noxious effect of future stressors. The reward and salience networks of the brain are likely to serve as important target for intervention, in the development of psychosocial and pharmacological treatments for psychosis.

32. ALTERATIONS IN LEARNING AND DECISION MAKING AS CANDIDATE BIOMARKERS FOR PSYCHOSIS: INVESTIGATING TRANSDIAGNOSTIC SAMPLES TO IDENTIFY PSYCHOSIS-SPECIFIC ALTERATIONS

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Overall Symposia Abstract: Alterations in learning and decision-making (LDM) are proposed to underlie psychotic illnesses, but have also been associated with affective, anxiety and personality disorders. During learning, individuals integrate information about future outcomes such as their probability, reward and effort value. This process is facilitated by discrepancies between expectations and outcomes via the generation of prediction errors. People with psychosis display aberrant prediction error signalling which is thought to bias inferences toward unlikely outcomes such as hallucinations and delusions. Moreover, altered decision-making has been linked to negative psychotic symptoms including motivational impairment. Thus, together, these processes provide promising candidate markers of psychotic symptoms. Importantly, LDM can be measured at scale with limited costs as it can be assessed behaviourally.

To determine the potential of these markers, it is crucial to disentangle alterations in LDM that are unique to psychotic disorders, from those that occur across diagnostic boundaries. Recent developments in computational modelling have enabled a mechanistic deconstruction of LDM processes, facilitating the identification of psychosis-specific alterations. This symposium will bring together recent work investigating LDM in conjunction with computational modelling in transdiagnostic samples, including psychotic disorders.

Franziska Knolle (Technical University Munchen) will present work disentangling model-free and model-based prediction error learning in schizophrenia, obsessive-compulsive disorder (OCD) and major depressive disorder (MDD). Hierarchical Bayesian modelling revealed that schizophrenia patients show decreased model-based learning compared to OCD and MDD, which is associated with psychotic symptomatology. Adam Culbreth (University of Maryland) will show novel data on physical effort-cost decision-making in schizophrenia, schizoaffective disorder, bipolar affective disorder and MDD. He finds that people with schizophrenia exhibit decreased willingness to expend effort compared to healthy controls and that this reduction is associated with the severity of motivational impairment. This effect showed diagnostic specificity as people with MDD and bipolar disorder did not present with differences in effort-cost decision-making. Using a novel, gamified, online task in a large general population sample, Kelly Diederen (King's College London) will show that subclinical delusions, in particular paranoid delusional ideation, is associated with impaired learning in noisy and volatile environments, whereas symptoms of depression and anxiety are associated with improved task performance, an effect that is most pronounced when outcomes include both gains and losses. Andra Geana (Brown University) will present data on several probabilistic reinforcement learning tasks in schizophrenia, bipolar disorder, and healthy controls, and show that computational modelling, in conjunction with machine learning tools, can identify schizophrenia-specific learning patterns, for instance, an overreliance on basal-ganglia-driven prediction error updating, as well as task-independent links between learning processes and clinical symptoms.

This symposium provides support for (1) unique LDM-alterations in psychosis and (2) specific associations between symptoms and aspects of LDM, which (3) are crucial steps in determining the potential of LDM as candidate markers of psychosis. Future work should use longitudinal studies in conjunction with machine learning to determine whether psychosis-specific LDM-parameters can accurately predict clinical outcomes.

32.1 INVESTIGATING MODEL-FREE AND MODEL-BASED DECISION-MAKING IN SCHIZOPHRENIA, OBSESSIVE COMPULSIVE DISORDER AND MAJOR DEPRESSIVE DISORDER

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Background: Decision-making, a hallmark of adaptive human behaviour, is influenced by two distinct strategies: habitual and goal-directed decision-making. While habitual decision-making is focussed on performing routines under consistent circumstances in which choices rewarded in the past are more likely to be chosen in the future; goal-directed behaviours are based on the simulation of our environment which allows flexible tracking of outcomes, states and transitions between states. In many psychiatric disorders such as schizophrenia, obsessive compulsive disorder, major depressive disorder or autism, these two decision-making systems are found to be disbalanced with an over-reliance on the habitual system or an under-reliance on the goal-directed system, which are thought to relate to specific symptoms in each disorder. To understand how alterations in decision-making related to disease specific symptoms as well as symptoms that occur across a range of psychiatric disorders (e.g. Anhedonia), we conducted a transdiagnostic study comparing schizophrenia, obsessive compulsive disorder and major depressive disorder.

Methods: In this study, three patients' groups, schizophrenia (n=25), obsessive compulsive disorder (n=25), and major depressive disorder (n=23), and matched healthy controls (n=40) completed a behavioural two-step task, a reinforcement learning task allowing the discrimination between habitual (i.e., model-free) and goal-directed (i.e., model-based) decision-making. We used four differently complex hierarchical Bayesian models exploring different parameters underlying model-free and model-based belief updating. The winning model, explaining the data best based on the lowest leave-one-out information criterion, contained seven parameters allowing us to investigate the learning rate and inverse temperature (i.e., decision-noise) at both stages, the perseverance (i.e., repetitiveness), model-based weight (i.e., model-based relative to model-free behaviour), and the reinforcement eligibility (i.e., first stage reinforcement based on second stage prediction error). We compared parameters across groups using robust analysis of variance and symptom associations using regression analysis.

Results: Our results showed distinct differences between the patient groups, with schizophrenia patients revealing significantly decreased model-based belief updating and learning rates compared to obsessive compulsive disorder and major depressive disorder. Analysing disease-specific symptom associations, in the schizophrenia group, we found a link between alterations in model-weights and psychotic symptoms. Additionally, we found that anhedonia is associated with reduced model-free learning across all three disorders.

Conclusions: This study revealed disease-specific alterations and symptom-associations in model-free and model-based decision making with strongest deficits in schizophrenia. The results provide first evidence that impaired model-based/goal-directed behaviour related to psychotic symptoms. Interestingly, however, this study furthermore showed that deficits in model-free/habitual learning were linked to increased anhedonia across all groups. This suggests that while there are similar alterations across various psychiatric diseases, potentially indicating shared underlying mechanisms, deficits in model-based/goal-directed learning are specifically linked to psychotic symptoms in schizophrenia. Taken together, this shows the potential of transdiagnostic studies to identify markers specific to psychotic symptoms.

32.2 EXAMINING EFFORT-COST DECISION-MAKING ACROSS DISORDERS CHARACTERIZED BY MOTIVATIONAL IMPAIRMENT

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Background: Recent research suggests that aberrant effort-cost decision-making, the estimation of work required to obtain a reward, may contribute to motivational impairment in individuals with psychotic and mood pathology. Specifically, research has suggested that people with psychotic and mood pathology may experience effort as more costly than comparison controls, and thus are less likely to pursue effortful goals. However, few studies have taken a transdiagnostic approach to studying effort-cost decision-making. This study aimed to determine whether effort-cost decision-making is similar across psychiatric conditions characterized by motivational impairment.

Methods: People with schizophrenia (N=24), schizoaffective disorder (N=22), bipolar disorder (N=32), major depressive disorder (N=29), and controls (N=53) completed an effort-cost-decision-making task. Specifically, on each trial, participants made decisions between completing an easy task (20 button presses) for a small reward (1 point), or completing a harder task (50, 100, or 200 presses) for a larger reward (3-7 points). Clinical interviews were also conducted in order to determine severity of negative and depressive symptoms.

Results: There was a significant effect of diagnostic group on choice ($F=2.54$, $p<0.05$), driven by reduced hard task choice in those with schizophrenia. Moreover, hard task choice was associated with motivational impairment in schizophrenia ($r=-0.56$, $p<0.05$). However, individuals with major depressive disorder and bipolar disorder did not differ from controls in their willingness to expend effort for rewards on our experimental task.

Conclusions: Our results provide support for ECDM as a contributor to motivational impairment in schizophrenia. Additionally, differences between diagnostic groups in ECDM suggest that a seemingly similar behavioral phenotype, reduced motivation, could arise from disparate mechanisms in different psychiatric conditions. We will discuss these implications at the meeting.

32.3 USING GAMIFIED ONLINE ASSESSMENT TO DISENTANGLE ALTERATIONS IN ERROR-DRIVEN LEARNING SPECIFIC TO PSYCHOTIC-LIKE SYMPTOMS FROM THOSE THAT OCCUR IN RELATION TO SYMPTOMS OF DEPRESSION AND ANXIETY

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Background: The identification of objective markers of psychosis is important to improve early diagnosis and treatment. People experiencing psychotic symptoms display aberrant prediction error signalling, leading to an increase of salience towards neutral events or unlikely observations as reflected in hallucinations and delusions. Altered error-driven learning may be a promising marker of psychosis as it is a behavioural process that is underpinned by dopamine, the main neurotransmitter implicated in psychosis. Experimentally, error-driven learning can be assessed at scale with limited costs, through online testing. In order to determine the potential of altered error-driven learning as a marker of psychosis, it is crucial to ensure that the observed alterations are unique to psychotic symptoms, rather than occurring across psychiatric symptoms and illnesses. As aberrant error-driven learning has also been observed

in people with symptoms of depression and anxiety, we set out to disentangle psychosis-specific symptoms, from those occurring in relation to depression and anxiety.
Methods: To facilitate engagement, a novel interactive game was developed as a measure of error-driven learning in a general population sample (N = 595) recruited and tested online. Psychotic-like symptoms were assessed using the schizotypal personality questionnaire, the peters delusion inventory and the green paranoid thoughts scale. Symptoms of depression and anxiety were assessed with the mood and anxiety symptom questionnaire. In the learning task, participants were required to catch pieces of space junk to repair their spacecraft so that they could return to planet Earth. Participants could learn the locations of future space junk through trial-and-error. However, successful performance also required them to arbitrate whether trial-wise variation in the space junk location was the result of noise, or whether there had been an unexpected change in the task's outcome contingencies. The task involved five levels, where each level increased the extent of outcome uncertainty. In addition, in the final level, the stakes were upped by doubling the points won for correct trials and introducing losses for incorrect trials.
Results: Participants were able to learn the outcome contingencies of the task, and their performance decreased as task difficulty increased, suggesting that the novel online task was fit for purpose. Higher scores on delusional ideation, especially paranoid delusions, were associated with decreased learning and performance across all levels. There was a significant interaction with task level, revealing that decreases in learning and performance associated with delusions were most pronounced at the level that contained gains and losses. Depressive symptoms and anxious arousal on the other hand were associated with improved learning and performance across all trials, and an attenuated decrease in task performance at the level that contained gains and losses.
Conclusions: The results indicate a clear dissociation between alterations in error-driven learning that are linked to psychotic-like symptoms versus those that relate to symptoms of depression and anxiety, thus stressing the potential of altered error-driven learning as a marker of psychosis. Our ongoing work in people with early psychosis, who often present with co-morbid symptoms of depression and anxiety, will help determine whether similar effects can be observed in clinical samples. This will provide the logical next step in validating altered error-driven learning as a marker of psychosis.

32.4 A COMPUTATIONAL APPROACH TO ALTERED LEARNING IN SCHIZOPHRENIA

Andra Geana*[1]

[1]*Brown University*

Background: A central goal of computational psychiatry is to develop mechanistic models based on theoretical and functional principles, to complement, expand, and improve the historical symptom-based approach to psychiatric diagnosis and treatment. Recent efforts, for instance, have illuminated the extent to which different underlying circuitry can produce phenotypically similar symptomatology (e.g. psychosis in bipolar disorder vs schizophrenia). This emphasizes the importance of identifying underlying symptom-producing mechanisms and to explore how aberrations in such mechanisms can lead to mental illness. Most studies in this domain, however, employ computational modeling to clinical samples who have been tested on a single task. A more comprehensive approach is needed to expose clusters of symptom-producing mechanisms that could then be targeted for treatment development.
Methods: In two studies, we used well-established probabilistic-reinforcement-learning (RL) tasks, as well as a battery of neuropsychological tests (including IQ, MATRICS) in individuals

with schizophrenia (N1 = 164, N2 = 112) both on (N=120) and off anti-psychotic medications. Both studies included a control group of healthy volunteers (N1 = 72, N2 = 32). Study 1 also included a patient comparison group of bipolar patients with psychosis (N=60). We applied computational models to capture hidden learning patterns in all groups, and we used cross-validation to test whether mechanistic tasks and computational modeling aid patient classification.
Results: Both medicated and unmediated individuals with SZ, but not healthy volunteers or bipolar patients, demonstrated less dependence on learning explicit value representations, as well as greater learning decay between training and test phases. We also found that task-based classifiers matched or outperformed those based on neuropsychological assessments, but only when computational model parameters were used. Finally, canonical correlation analysis revealed that model parameters related to uncertainty and exploration across tasks were predictive of negative symptoms.
Conclusions: Taken together, these findings indicate that mechanistic tasks and computational modeling can complement neuropsychological tests to aid patient classification and mechanism discovery.

Plenary Session VI: Richard Holt

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

33. THE DOUBLE BURDEN OF DIABETES AND SEVERE MENTAL ILLNESS

Margaret Hahn, *Center for Addiction and Mental Health*

Overall Abstract: Individuals with schizophrenia die 15-20 years earlier than the general population, with the leading cause of mortality attributable to cardiovascular disease. The prevalence of type 2 diabetes (T2D) is increased 2-5 fold in schizophrenia and other severe mental illness (SMI). Unfortunately, the consequences of T2D in this group are more severe with higher rates of microvascular and macrovascular complications, acute metabolic dysregulation and diabetes-related deaths. This plenary talk will discuss principles of diabetes management in SMI, including an overview of current treatment algorithms, encompassing lifestyle interventions and pharmacotherapy.

33.1 THE DOUBLE BURDEN OF DIABETES AND SEVERE MENTAL ILLNESS

Richard Holt, *University of Southampton*

Individual Abstract: The prevalence of diabetes is increased 2-3 fold in people with severe mental illness (schizophrenia and bipolar disorder). Diabetes affects approximately 12% of people receiving antipsychotics. The consequences of diabetes in someone with severe mental illness are more severe with higher rates of microvascular and macrovascular complications, acute metabolic dysregulation and diabetes-related deaths.
The reasons why people with severe mental illness are at higher risk of diabetes are complex and include genetic, environmental and disease and treatment specific factors. Although antipsychotics are the mainstay of treatment in severe mental illness, their use is associated with an increased risk of diabetes, albeit of uncertain magnitude.

The principles of diabetes management in people with severe mental illness are similar to the general population and should follow currently established treatment algorithms. Avoidance of drugs that promote weight gain is advised given the high prevalence of obesity in this population. Lifestyle interventions are needed to reduce the incidence of diabetes while better

uptake of opportunities to screen for diabetes will reduce the prevalence of undiagnosed diabetes. There is a responsibility on healthcare professionals, both in primary care and in mental health teams, to ensure that people with severe mental illness are not disadvantaged.

Concurrent Symposia

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

34. THE HEART OF THE MATTER: CARDIAC HEALTH IN PEOPLE WITH PSYCHOSIS

Fiona Gaughran*, Institute of Psychiatry, Psychology and NeuroScience, King's College London*

Overall Symposia Abstract: People living with serious mental illnesses (SMI) have high rates of cardiovascular morbidity and associated premature mortality. In recent years there has been considerable focus on cardiometabolic risk factors such as obesity, dysglycaemia and dyslipidaemia. However, less evidence exists on the relationships between a diagnosis of SMI and specific cardiac conditions, and on how having a psychotic illness may influence the management and outcomes of such conditions. Our session focuses on heart health and care in people with schizophrenia and psychotic disorders.

Dr Christoffer Polcwiartek will present two retrospective cohort studies. One uses data from the Duke University Health System and he has replicated this in the Danish nationwide registries. The studies examine the characteristics, temporal trends, and clinical outlook of heart failure in people with serious mental illnesses, including all-cause mortality and trends for its management, including the use of medical therapies, implantable devices and surgical procedures. His work shows that heart failure affects people with SMI about seven years earlier than their peers, with equal access to advanced procedures. There is an increased risk of associated mortality in men with SMI than without (hazard ratio, 1.36 [95% CI, 1.17– 1.59]).

Dina Farran will present her systematic review on the prevalence, management and outcomes of atrial fibrillation (AF) in people with SMI, which reports low rates of AF in people with SMI. She will present findings from two retrospective cohort studies examining anticoagulation (OAC) prescription trends in people with AF and co-morbid SMI. The first is in a general hospital, where people with SMI were less likely to receive OAC than their peers until 2019, when the difference was no longer significant. The second, in a mental health setting, saw that 61.5% of people with SMI and AF are not anti-coagulated. Substance dependency, and Activity of Daily Living scores on the Health of the Nation Outcome Scale were associated with the likelihood of OAC prescription. She will also describe the development and planned evaluation of our electronic Clinical Decision Support System to guide screening for OAC in mental health settings.

Dr Kevin O'Gallagher will present findings from a new systematic review on the 'treatment gap' in coronary and cardiovascular disease (CVD) in patients with SMI. Importantly, he will summarise the work to date on the interactions between race, ethnicity, SMI and CVD which raises important points for research into intersectional vulnerabilities. He will also present early data from current work on pathways to care in London ,UK for people with a diagnosis of SMI within highly protocolised primary angioplasty pathways.

Prof Dan Siskind will present his new research on the relationship between clozapine and heartrate (HR). This shows a higher pulse rate in inpatients prescribed clozapine than those on other anti-psychotics ($p<0.001$); 30.2% of those on clozapine had a HR >100BPM, although

there was no relationship with prolonged QT intervals. Among outpatients on clozapine, 61.1% had a HR >100BPM, while nearly 10% had rates of over 120BPM.

Our discussant, Prof Margaret Hahn is an expert in cardiometabolic risk and its management in people with psychosis and will bring the panel and attendees together to discuss and summarise the science presented.

Overall, the presenters will provide evidence of the need for better detection and management of clozapine-related tachycardia, AF, coronary artery disease and heart failure in people with psychosis.

34.1 TACHYCARDIA AMONG PEOPLE ON CLOZAPINE

Dan Siskind*[1], Tim Tanzer[2], Teodora Andric[3]

[1]*Metro South Addiction and Mental Health Service,* [2]*PAH Pharmacy,* [3]*Griffith University*

Background: Clozapine is the most effective antipsychotic for reducing positive symptoms, hospitalisations and all-cause mortality among people with treatment refractory schizophrenia. Less than one in four people with treatment refractory schizophrenia are provided with clozapine in most high-income jurisdictions, with concerns about adverse drug reactions being one of the major barriers. Over and above the high-risk adverse drug reactions such as neutropenia, myocarditis and ileus, clozapine is associated with tachycardia. To date, clozapine tachycardia has not been adequately explored.

Methods: Two databases were examined to explore clozapine tachycardia. The first was a database of 861 consecutive admissions to a psychiatric inpatient unit, with heart rate (HR), QTc and use of clozapine at time of admission recorded. Mean HR, and frequency of HR>100 and prolonged QTc was compared between people using or not using clozapine. The second was a cross sectional database of 360 people attending an outpatient clozapine clinic. Heart rate and clozapine dose was recorded, and correlations between these variables explored. Frequency of HR>100 and HR>120 were calculated.

Results: Mean HR among inpatients on clozapine was 93.7 beats per minute (BPM) versus 82.8 BPM for people on other antipsychotics ($p<0.001$). 30.2% of people on clozapine had a HR >100BPM while only 15.2% of people on other antipsychotic had a HR >100BPM. Clozapine was not associated with higher rates of prolonged QTc intervals. Among outpatients on clozapine, the mean HR was 102.1 (SD 14.8), with 61.1% having a HR >100BPM, and 9.3% having a HR>120BPM. Higher clozapine levels were not significantly correlated with HR.

Conclusions: Clozapine is associated with higher rates of tachycardia than with other antipsychotics, but is not associated with higher rates of QTc prolongation. Rates of severe tachycardia (HR>120) approach one in ten, indicating the need for improved guidelines for detection and treatment of clozapine-associated tachycardia, particularly in outpatient clinics.

34.2 CORONARY ARTERY DISEASE IN PATIENTS WITH SEVERE MENTAL ILLNESS

Kevin O'Gallagher*[1]

[1]*King's College London*

Background: Severe mental illnesses affect approximately 1% of the population and account for up to 20 years of decreased life expectancy compared to the general population. The leading cause of death in patients with SMI is cardiovascular disease (CVD), particularly myocardial infarction.
This part of the symposium will discuss the patient factors; disease factors; and system factors that are responsible for the increased risk of CVD in patients with SMI. The interaction between race, ethnicity, SMI and CVD will also be covered.

Methods: We have recently performed a narrative review on ivtersectionalities between race, ethnicity, SMI and CVD. A systematic review of the current literature is underway on care for SMI patients with acute CVD (MI, heart failure). We will also discuss current projects using linkage of Electronic Health Record data between psychiatry and cardiac centres to explore the care of patients with SMI in acute cardiac care pathways e.g. primary angioplasty pathways for MI.
Results: n/a
Conclusions: We will provide an overview of existing data demonstrating the concerning 'treatment gap' in management of CVD in patients with SMI compared to the general population. This includes not only acute presentations such as ST Elevation Myocardial Infarction, but also non-emergency management such as primary and secondary prevention therapies.
We will also present emergent observational data from our ongoing work linking psychiatry and cardiac centres in London, UK on the management of patients with SMI presenting with STEMI within a highly protocolised primary angioplasty pathway.

Finally, future avenues of research and strategies to mitigate the treatment gap for patients with SMI presenting with CVD will be proposed.

34.3 STROKE PREVENTION IN PATIENTS WITH ATRIAL FIBRILLATION AND CO-MORBID PHYSICAL AND MENTAL HEALTH PROBLEMS

Dina Farran*[1], Fiona Gaughran[2], Mark Ashworth[2], Daniel Bean[2], Paul Andrew Scott[2], Richard Dobson[2], James Teo[2], Tao Wang[2], Yamiko Msosa[2], Olwyn Feely[3], Cecilia Casetta[2]

[1]*King's College London, Institute of Psychiatry, Psychology and Neuroscience,* [2]*King's College London,* [3]*Trinity College Dublin*

Background: Atrial fibrillation (AF), the most prevalent cardiac arrhythmia, is associated with fivefold increased risk of stroke. Despite clear evidence that oral anticoagulation (OAC) therapy reduces AF-related stroke risk, underuse has been reported particularly in those with co-morbid serious mental illness (SMI).
Methods: A. We will present our systematic review (SR) on prevalence, management, and outcomes of AF in people with SMI versus the general population (GP).
B. We will also present findings from two retrospective cohort studies (RCS); the first examining anticoagulation prescription trends in people with AF and co-morbid SMI who met criteria for anticoagulation treatment over the past 10 years in a general hospital setting. The second describes patterns of OAC prescriptions in people with AF and co-morbid SMI in a mental healthcare setting.

C. The development of our electronic Clinical Decision Support System to guide screening for OAC will be outlined. The eCDSS compromises a real-time computerised alerting for AF management in a secondary mental healthcare setting, alerting clinician to the need to conduct

a clinical anticoagulation assessment using the CHAD2AD2-VASc (stroke risk assessment tool) and ORBIT tools (bleeding risk assessment tool).

Results: A. SR: Low rates of AF were reported among people with SMI compared to non-SMI. People with AF and co-morbid SMI were less likely to receive OAC therapy compared to the GP. Pooled analysis of risk estimates showed that in patients with AF, SMI was not significantly associated with an increased risk of stroke (HR: 1.09; 95%CI: 0.85 to 1.40; I2=60%, p=0.04) or major bleeding (HR: 1.11; 95%CI: 0.95 to 1.28; I2=57%, p=0.03) once adjusted for underlying stroke and bleeding risks.
B.

1. RCS1: Among AF patients having a CHA2DS2-VASc ≥2, those with co-morbid SMI were less likely to be prescribed an OAC (44% vs 54%, $p < 0.001$). However, there was no evidence of a significant difference between the two groups (AF with SMI vs AF with no SMI) since 2019.

2- RCS2: Despite being at risk of stroke (CHA2DS2-VASc ≥1), 61.5% of AF patients with co-morbid SMI were not prescribed any OAC. Alcohol or substance dependency (RR: 0.87; 95%CI:0.76-0.99), and activities of daily living impairment (RR:0.90; 95%CI: 0.83-0.98) on the Health of the Nation Outcome Scale were associated with lower prescription of any OAC among people with AF and co-morbid SMI. (preliminary results).

Conclusions: Low rates of AF are reported among people with SMI suggesting under-recognition or recording gaps. AF patients with co-morbid SMI are less likely to be prescribed OAC therapy compared to non-SMI. Implementing an eCDSS for AF management in a mental healthcare setting might improve the recording of physical conditions and risks, thus might offer an opportunity for better identification, risk stratification and implementation of effective preventive measures among people with SMI.
Consent of Release of Rights I have read and agree to the above terms and conditions.

34.4 HEART FAILURE IN SEVERE MENTAL ILLNESS: CHARACTERISTICS, TEMPORAL TRENDS, AND LONG-TERM PROGNOSIS

Christoffer Polcwiartek*[1]

[1]*Aalborg University Hospital*

Background: Patients with severe mental illness (SMI) have increased cardiovascular morbidity and mortality, contributing to a reduced life expectancy of approximately 20 years compared with the general population. In this patient group, the prevalence of cardiovascular risk factors and disease is high, which may increase the risk of early heart failure (HF) development and accelerate deterioration of left ventricular structure and function in SMI. Our aim was to investigate the association between being diagnosed with SMI and long-term clinical outcomes of HF including all-cause mortality and trends in use of medical therapy, advanced implantable devices, and surgical procedures for HF.
Methods: This was a retrospective cohort study during 2002-2017. In the Duke University Health System, we included patients with incident HF who had undergone an electrocardiographic and echocardiographic evaluation. Patients were stratified by the absence/presence of SMI including schizophrenia, bipolar disorder, and severe depression. The primary outcome was all-cause mortality assessed using multivariable Cox regression. We also reported rates of implantable cardioverter-defibrillator (ICD), cardiac resynchronization therapy (CRT), left ventricular assist device (LVAD), and heart transplantation.

Using data from Danish nationwide administrative registries, we identified a similar HF cohort with/without SMI to validate findings from the Duke University Health System and to provide temporal trends in medical therapy following HF diagnosis during 1996-2019 in Denmark. Data are currently being analyzed and will be presented at the SIRS Congress 2023.

Results: In the Duke University Health System, a total of 20,906 patients with HF (SMI, n=898; non-SMI, n=20,008) were identified. Patients with SMI presented clinically 7 years earlier with HF than those without SMI. Risk of all-cause mortality was significantly different between men and women with/without SMI (Pinteraction=0.002). Excess mortality was observed among men with SMI compared with men without SMI (hazard ratio, 1.36 [95% CI, 1.17– 1.59]). No association was observed among women with/without SMI (hazard ratio, 0.97 [95% CI, 0.84–1.12]). Rates of ICD, CRT, LVAD, and heart transplantation were similar between patients with/without SMI (6.1% vs. 7.9%, P=0.095). Patients with SMI receiving these procedures for HF experienced poorer prognosis than those without SMI (hazard ratio, 2.12 [95% CI, 1.08–4.15]).

Conclusions: Our data indicate that men with SMI carry a poorer long-term prognosis of HF compared with women. Although patients with/without SMI had equal access to advanced procedures for HF, those with SMI experienced excess postprocedural mortality. These findings underscore concurrent sex- and mental health-related disparities in HF management and treatment, suggesting that patients with SMI and HF merit closer follow-up.

35. ARE PSYCHOTIC SYMPTOMS LINKED TO AN OVERWEIGHTING OF PRIOR KNOWLEDGE OR OF SENSORY INFORMATION: IS THERE A CONSENSUS?

Franziska Knolle*, Technical University of Munich*

Overall Symposia Abstract: Recent theoretical frameworks suggest that hallucinations and delusions result from errors in the way that people with psychosis combine different sources of information to inform their perceptions and beliefs. Specifically, it is thought that there is an imbalance between the reliance on prior knowledge relative to novel sensory information in psychosis. In these models, inferences are portrayed as the end product of a processing hierarchy where higher levels contain abstract information (e.g., core beliefs) while lower levels process more concrete sensations (e.g., seeing something new). Using Bayesian inference, at each level, and based on prior knowledge, the brain generates predictions about what is expected next, which is fed back to lower levels. At the lowest level, predictions are compared with perceptual inputs. Any discrepancy between predicted and perceived inputs, termed prediction error, is propagated up to higher levels to minimise future prediction errors. Whereas recent work has provided support for Bayesian models of psychosis, it is unclear whether the symptoms of psychosis are the consequences of too much reliance on prior knowledge or an overreliance on sensory information; or a combination of both. In this symposium, we will present studies providing evidence for both hypotheses, to discuss a potential consensus and necessary future studies. Marta Garrido (The University of Melbourne) investigated how the relative weighting of prior and sensory information varied with the degree of psychotic-like experiences in typical individuals. Across two large samples they found that psychotic-like experiences were associated with an overweighting of sensory information driven by greater prior imprecision, although sensory information was also less precise. Kelly Diederen (King's College London) used online adaptations of three tasks that require participants to integrate prior and novel information across different cognitive domains. Whereas hallucination-proneness was weakly associated with overreliance on prior visual information, delusional-ideation was linked to altered learning and social inference. Veith Weilnhammer (Charite Berlin) will present data investigating how internal predictions shape

the experience of partially ambiguous stimuli. In patients diagnosed with paranoid schizophrenia, the results show that hallucinations were more severe in individuals who were biased less by internal predictions. Franziska Knolle (Technical University of Munich) tested the balance between prior knowledge and sensory information in a predictive language comprehension task. Individuals with higher levels of psychotic symptoms showed a stronger weighting of prior knowledge relative to sensory information, inducing conditioned hallucination. Additionally, prior weighting was linked to increased levels of glutamate.

Taken together, the studies presented here suggest that imbalances between reliance on prior knowledge relative to sensory information depend on the processing hierarchy as well as the disease stage. For example, during higher level cognitive processing, individuals at risk for psychosis may exhibit very strong expectations which may bias processing of incoming sensations, potentially linked to increased levels of glutamate. This could provide an origin for auditory hallucinations as top-down prior knowledge may induce sensory experiences that are not real. Studies investigating lower processing levels in chronic patients, however, suggest an underweighting of prior knowledge relative to sensory information, with potential links to increased levels of dopamine and associations with hallucinations. Thus, the results: show that it is a complex interplay between overreliance on prior vs novel sensory information that gives rise to the various symptoms of psychosis. Importantly, the findings show that Bayesian approaches provide us with the tools to acknowledge the heterogeneity of psychotic symptoms and their associated computational mechanisms.

35.1 ARE PSYCHOTIC SYMPTOMS RELATED TO A GENERIC IMBALANCE IN WEIGHTING PRIOR AND NOVEL INFORMATION, OR DO THEY DEPEND ON THE AFFECTED COGNITIVE DOMAIN?

Kelly Diederen*[1], Toni Gibbs-Dean[1], Joel Vasama[1], Cheryl See[1], Carina Kuehne[1], Teresa Katthagen[2], Tom Spencer[1]

[1]*Institute of Psychiatry, Psychology and Neuroscience King's College London,* [2]*Charité-Universitätsmedizin*

Background: In recent years, it has been proposed that a generic deficit in the way that individuals integrate prior knowledge and novel information in order to shape their experiences and beliefs, gives rise to the positive symptoms of psychosis. Although recent work partially supports this hypothesis, findings are inconsistent and leave many unanswered questions. This may be in part due to the wide range of experimental tasks and symptom-scales used to investigate this hypothesis. Whereas some studies used visual and/ or auditory perceptual decision-making tasks, others have focussed on learning and on higher cognitive domains such as language and social inference. Divergence in the observed extent of aberrant weighting of prior vs novel information might depend on the cognitive domain under study, as well as on the symptom-profile of the sample under study. It is, therefore, important to investigate the integration of prior and novel information across different modalities, and samples.

Methods: We used online adaptations of three tasks that require participants to integrate prior and novel information and that have previously been demonstrated to relate to psychotic symptoms. The first task required participants to identify the location of a red dot as being on a figure or on the background of a two-tone image, before and after the two-tone image was disambiguated. In the second task, participants had to learn to identify the location where a

novel object would land, based on learning from previous trials and newly presented locations. The third task required participants to infer the intentions of an adviser who gave trial-wise information on which option to select to maximise outcomes. Auditory perception and language tasks were omitted due to difficulty to assess these modalities online. The first study (N = 503) acquired data from the general population including a DSM-V screener that incorporated psychosis, mood and anxiety disorders, and symptom measures such as hallucination-proneness, delusional ideation and subclinical paranoid delusions. In the second study (N = 151), participants were selected based on high/ low scores on psychotic-like symptoms.

Results: While there was a trend-level association between hallucination-proneness and the extent to which people relied on prior visual information in the two-tone task, this effect was only observed in the dataset where participants were selected based on their proneness towards hallucinations. Furthermore, there was no association between delusional ideation and reliance on prior perceptual information in either dataset. In contrast, delusional ideation was associated with altered reliance on novel information in the learning task, and social information in the social inference task, an effect that was most pronounced for paranoid delusions. We observed no significant relationship with hallucination-proneness in either of these tasks.

Conclusions: These findings stress the importance to investigate specific psychotic symptoms in relation to the modality (e.g., social inference) in which they occur. Furthermore, the absence of a clear relationship between the reliance on visual prior information and hallucination proneness highlights the importance to include an auditory task in future studies, as most hallucinations occur in the auditory domain. In addition, future work should further disentangle the relationship between learning and social inference on the one hand and delusional ideation and paranoid delusions on the other hand, as a more specific effect between tasks and symptoms might have been obscured. Finally, clinical studies are needed to validate the current observations.

35.2 BAYESIAN ACCOUNTS OF PERCEPTUAL DECISIONS IN THE NONCLINICAL CONTINUUM OF PSYCHOSIS: GREATER IMPRECISION IN BOTH TOP-DOWN AND BOTTOM-UP PROCESSES

Marta Garrido*[1]

[1]*The University of Melbourne*

Background: Neurocomputational accounts of psychosis propose different mechanisms for how information is evaluated and integrated into a predictive model of the world, in attempts to understand the occurrence of altered perceptual experiences. Conflicting Bayesian theories postulate aberrations in either top-down or bottom-up processing. The top-down theory predicts an over-reliance on prior beliefs/expectations resulting in aberrant perceptual experiences, whereas the bottom-up theory predicts an over-reliance on current sensory information, as aberrant salience is directed towards objectively uninformative stimuli. This study empirically adjudicates between these models by mathematically quantifying the relative reliance on both prior and sensory information.

Methods: We use a perceptual decision-making task under uncertainty in a neurotypical population with varying psychotic-like experiences. In that task, the participants were asked to make an informed guess about the position of an occluded coin that fell into a pond. Participants could see the splashes made by the coin as it fell into the pond. These splashes gave participants a clue about the coin's position and the spread of these splashes was manipulated on a trial-by-trial basis to be either small or large, corresponding to high and low precision in sensory information, respectively. The prior precision was manipulated across

blocks, by varying the true position of the coin (revealed at the end of each trial). Participants were told that the person throwing the coin aimed at the middle of the pond, hence corresponding to the prior mean. The prior precision was high when the true position of the coin was close to the middle (good thrower), and low when the coin fell further away from the middle (bad thrower). In this way, the precision (high, low) on prior and sensory information was orthogonally manipulated in a 2 by 2 design.
Results: Bayesian modelling was used to compute individuals' reliance on prior relative to sensory information across the task, revealing Bayesian-like performance, albeit non-optimal. In other words, the participants' guess about the coin's position reflected a weighted integration of prior and sensory information, with participants placing more weight on the source of information with higher precision. However, the participants' guesses differed significantly from the behaviour predicted for an optimal Bayesian observer. Across two datasets (discovery dataset n=363; independent replication in validation dataset n=782) we showed that psychotic-like experiences were associated with an overweighting of sensory information relative to prior expectations, driven by decreased precision in prior information. However, participants with greater psychotic-like experiences also encoded likelihood information with greater sensory noise.
Conclusions: Our study lends empirical support to notions of both weaker bottom-up and weaker (rather than stronger) top-down perceptual processes, as well as aberrance in belief updating that extends into the nonclinical continuum of psychosis. Our ongoing work in inpatients with psychosis will determine whether these same patterns of reliance on the relative prior vs. sensory reliability are observed in schizophrenia in a continuous or discontinuous fashion.

35.3 OVERWEIGHTING OF PRIOR KNOWLEDGE RELATIVE TO SENSORY INFORMATION IN A PREDICTIVE LANGUAGE TASK IS ASSOCIATED WITH PSYCHOTIC-LIKE SYMPTOMS

Franziska Knolle*[1], Elisabeth F. Sterner[1], Verena Demler[1], Lucy J. MacGregor[2], Christoph Mathys[3]

[1]*Technical University of Munich,* [2]*University of Cambridge,* [3]*Interacting Minds Centre, Aarhus University*

Background: The recent hierarchical Bayesian accounts of psychosis provide testable theories for the explanation of positive symptoms in psychosis. One theory suggests that an overweighing of sensory likelihood may occur at lower levels (e.g., early sensory processing areas) due to increased dopamine activity causing aberrant salience and leading to delusions, while an overweighting of prior beliefs at higher levels, potentially caused by altered glutamatergic receptor signalling, may cause hallucinations. Experimental findings report initial evidence for both, an overweighting of sensory information, as well as an overweighting of prior information, depending on disease stage and level of processing hierarchy. The interplay of prior information and sensory likelihood can be tested efficiently during language processing, due to its predictive nature. Interestingly, language processing is not only compromised in early stages of psychosis, but language processing brain regions are also activated during the occurrence of hallucinations. This study therefore investigates (1) the use of prior knowledge relative to sensory information in a predictive language task as a trait maker for early psychotic-like symptoms, (2) whether an overreliance induces conditioned hallucinations, and (3) whether the use of prior knowledge is associated with cortical and/or subcortical levels of glutamate.

Methods: In the task, two groups of healthy individuals (baseline study n=114, replication study n=53), assessed for psychotic-like symptoms, listened to sentences of varying predictability (e.g., high predictability: "Goethe was a famous German … poet"; low predictability: "Next to the window was a … hole"). The final word of each sentence (e.g., "poet" or "hole") was degraded in clarity using a noise vocoding algorithm; degradations were available in four levels from fully unintelligible to fully intelligible. After listening to the full sentence, participants were asked to report the word they perceived, assessing conditioned hallucinations. We fitted a linear Bayesian regression model to estimate the prior weight which presents the relative strength of the prior over the sensory input. The degree of psychotic-like symptoms was included as a subject-level parameter. In the replication study, we furthermore measured levels of glutamate in the anterior cingulate cortex (ACC), the bilateral putamen and the left/right dorsolateral prefrontal cortex using magnetic resonance spectroscopy (1H-MRS), and investigated associations with modelling parameters.
Results: In both studies, the modelling results showed that prior knowledge relative to sensory information was overweighed with increasing psychotic-like symptoms. Moreover, overweighting of prior knowledge with increasing psychotic-like symptoms was linked to experiencing more conditioned hallucinations. In the replication study, we found that levels of glutamate in the ACC predicted use of prior information. Furthermore, a mediation analysis revealed that this association was enhanced when glutamate levels were reduced in the bilateral putamen.
Conclusions: This study shows that experiencing conditioned hallucinations in healthy individuals with stronger psychotic-like symptoms is associated with how much they rely on prior contextual information, and, on a neurobiological level, with altered levels of cortical glutamate, specifically in the ACC. Taken together, this study provides evidence for an overweighting of prior information during higher level processing in individuals with enhanced psychotic-like symptoms, which is linked to altered levels of cortical glutamate. These findings may provide an initial mechanistic explanation of how suboptimal predictive language processing contributes to the formation of hallucinations.

35.4 USING BISTABLE PERCEPTION TO UNDERSTAND HOW ALTERATIONS IN PERCEPTUAL INFERENCE DRIVE PSYCHOTIC EXPERIENCES

Veith Weilnhammer*[1]

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Background: Adaptive perceptual inference requires an optimal integration of external sensory information with internal predictions about the sensory environment. According to predictive processing theories of psychosis, alterations in the balance between internal predictions and external sensory information may lead to psychotic symptoms such as hallucinations. However, it has remained unclear whether psychotic experiences result from over-weighting internal predictions (the strong prior account), or, alternatively, from relying too much on prediction errors that are driven by external sensory information (the weak prior account).
Methods: To measure the balance between internal predictions and external prediction errors during perceptual inference, we devised a novel experimental paradigm based on bistable perception. In bistable perception, constant and ambiguous sensory information induces dynamic changes in conscious experience. According to predictive processing views on bistable perception, these spontaneous changes in conscious experience arise from the interplay of internal prediction that determine the current interpretation of the stimulus, with prediction errors that are triggered by stimulus ambiguity.

To modulate the balance between internal predictions and externally-driven prediction errors during bistable perception, we introduced the a new experimental paradigm based on gradual ambiguity. In this paradigm, a structure-from-motion stimulus is gradually disambiguated by 3D information across multiple levels of signal-to-ambiguity. The degree of congruency between conscious experience and sensory information provides a behavioral read-out of how strongly perception is driven by external prediction errors. In parallel, the average time spent in one interpretation of the stimulus reflects the degree to which perception is biased by internal predictions.

Results: In two studies that investigated how healthy observers experience gradual ambiguity, we found ongoing fluctuations in the weight of internal predictions versus external sensory information. These fluctuations reflected two opposing modes of sensory processing: During internal mode, conscious experience was strongly driven by internal predictions, while sensory information was largely ignored. Conversely, during external mode, conscious experience closely followed external sensory information, while the impact of internal predictions was strongly reduced. Moreover, we found that ketamine, a NMDA receptor antagonist that can be used to model psychotic experiences, alters the balance between external and internal mode.
A third study investigated how patients diagnosed with paranoid schizophrenia experience gradual ambiguity. Relative to healthy controls, patients showed a stronger increase in congruent conscious experiences for increasing levels of signal-to-ambiguity. The severity of hallucinatory experiences correlated positively with the patients' sensitivity to external sensory. Moreover, the severity of hallucinatory experiences correlated negatively with the average time patients spent in one perceptual interpretation of the stimulus.

Conclusions: Our results indicate that hallucinatory experiences are associated with a shift of perceptual inference towards external sensory information and away from internal predictions. Thereby, our findings speak in favor of the weak prior account of hallucinatory experiences. However, our results cannot clearly distinguish between scenarios where the influence of internal predictions or external information on perception is selectively impaired, and scenarios where both factors are altered. Future studies could use non-invasive brain stimulation to induce virtual lesions in the respective neural correlates of internal predictions and external sensory information to causally test their relevance for psychotic experiences.

36. TARGETING IMMUNE DYSFUNCTION IN SCHIZOPHRENIA AT CELLULAR, MOLECULAR AND NEURAL SYSTEM LEVELS

Bill Deakin, *University of Manchester*

Overall Symposia Abstract: The neuroinflammatory hypothesis of schizophrenia proposes that low-level peripheral immune activation (non-pathologically raised blood cytokines and other immune mediators) found in many studies gives rise to inflammation in the brain and subsequent changes associated with psychosis. How the inflammatory theory interfaces with genetically-driven synaptic neurodevelopmental mechanisms is obscure. However, our first presentation using Mendelian Randomization shows that gene variants that predict interleukin (IL)-6 levels in the large UK Biobank cohort also predict reduced grey matter thickness in middle temporal gyrus, a brain region in which schizophrenia genes are differentially expressed compared to other brain regions. This study implies that genetically determined IL-6 levels cause neuro-developmental changes relevant to schizophrenia. Whether there is a persistent causal element will be revealed by the PIMS study, a trial of the human monoclonal IL-6 receptor antibody tocilizumab in patients selected for raised levels of IL-6. The primary outcome is reduction in anhedonia. Anhedonia has been proposed as a transdiagnostic RDoC disturbance mediated by raised inflammatory mediators since both are common to major

psychiatric diagnoses. Our second presentation introduces tumour necrosis factor as a possible target for transdiagnostic motivational deficits. In people with schizophrenia, increasing TNF levels modulated nucleus accumbens responses to reward anticipation in a functional magnetic resonance imaging paradigm and modulated effort processing responses. The results suggest that immune mediators in blood may relate to transdiagnostic aspects of schizophrenia. Our last two presentations reveal potential new markers to identify immune subtypes of psychosis, one molecular and the other cellular. Human-expressed retroviruses (HERVs) have been implicated in neurodevelopmental disorders and their expression can be increased by inflammation. Our third presentation shows that HERVs may be a target mechanism in an immune subtype of psychosis. Over-expression of HERV-W ENV in C57BL/6J mice, induced a behavioural phenotype of impaired prepulse inhibition (PPI) together with altered hippocampal gene expression. Impaired PPI also occurred in a vulnerable subset of mice exposed to maternal immune activation by poly(I:C). The vulnerable group but not the resilient showed increased expression of several ERV transcripts in hippocampus together with IL-6. Hence, maternal inflammation can induce hippocampal ERV transcription in some vulnerable subgroups, which in turn mediates a psychosis-relevant behavioural phenotypes. Our final presentation highlights the lack of attention given to immune cells to identify immune-relevant subgroups of psychosis. The study is interrogating the role of IL-6 at the cellular level in early psychosis. The presentation will show that in-vitro, exogenous IL-6 activates STAT3 in innate (monocytes), adaptive (lymphocytes type T and B, and natural killer T cells) and protective (Tregs) cell types. Pre-incubation of cells with tocilizumab prevents the abnormal intracellular activation evoked by IL-6. This probe of immune cell responsiveness to IL-6 will add a dynamic measure to standard cell counts in identifying immune-relevant subgroups of psychosis. Our discussant will stimulate a critical debate on the mechanisms and validation of immune biomarkers in schizophrenia.

36.1 INVESTIGATING THE RELEVANCE OF PERIPHERAL INFLAMMATION IN SCHIZOPHRENIA

Rachel Upthegrove*[1], Moralez-Munoz Isabel[1], John A Williams[1], Golam Khandaker[2], Stephen Burgess[3], John Suckling[3], Marwaha Stephen[1]

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Background: Immune dysfunction is implicated in the aetiology of schizophrenia with elevation of peripherally measured cytokines prior to the onset of disorder and causality suggested in genomic studies. However, the efficacy of immunomodulatory drugs is mixed, and it is not clear how we should target new and repurposed agents to better effect. There is considerable heterogeneity in the potential clinical profile of immune active psychosis; with negative, cognitive and acute symptoms variably implicated. Identifying valid, reproducible inflammation subgroups of patients with schizophrenia based on their inflammatory profile could help elucidate illness mechanisms and stratification of potential candidates of novel treatments.

Methods: This presentation will rehearse new and recently published data demonstrating the importance of affective symptoms in early stages of immune active psychosis. We assessed 3988 participants in the ALSPAC birth cohort. Group trajectories of anxiety using latent class growth analysis were conducted, with logistic regression analyses to investigate the associations of persistent anxiety with subsequent psychotic disorder, and path analyses mediating role of CRP in these associations. Further evidence of potential causality of immune

dysfunction in neurodevelopment is examined in 20688 participants from the UK Biobank database using Mendelian Randomisation.
Results: Compared to those with persistently absent anxiety, the persistently anxious group was more likely to develop psychotic disorder at age 24 (odds ration [OR]=2.70, 95%CI=1.50-4.86, p=0.001). CRP levels at 9 and 15 years exerted an overall contributing and mediating effect (bias-corrected estimate=0.000; 95%CI=0.000-0.001, p=0.041).
MR analysis in the UK BB demonstrated genetically predicted levels of IL6/IL6r and a specific association with brain structure in areas highly relevant for schizophrenia and other neurodevelopmental disorders.

Conclusions: Targeting immune modulating agents may need to be in very early stages of illness, in defined subgroups with evidence of immune activation in future trials. Transdiagnostic symptoms including affective dysfunction and anhedonia may indicate relevant clinical outcomes.
1. Moralez-Muñoz, Palmer E, Marwaha S and Upthegrove R. (2022) Persistent childhood and adolescent anxiety and risk for psychosis: a longitudinal birth cohort study Biological Psychiatry; 92:275–282

2. Williams JA, Burgess S, Suckling J,.. Upthegrove R. Inflammation and Brain Structure in Schizophrenia and Other Neuropsychiatric Disorders: A Mendelian Randomization Study (2022) JAMA Psychiatry. doi:10.1001/jamapsychiatry.2022.040

36.2 TUMOR NECROSIS FACTOR IS ASSOCIATED WITH ALTERED ACTIVATION IN VENTRAL STRIATAL AND ANTERIOR INSULA IN RESPONSE TO REWARD AND EFFORT IN PATIENTS WITH SCHIZOPHRENIA

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Background: There is limited understanding of mechanisms underlying deficits in motivated behaviors and negative symptoms in patients with schizophrenia. Inflammation has been posited to be involved in the pathophysiology of schizophrenia, and previous work has demonstrated associations between increased inflammation and negative symptoms in patients with schizophrenia. Inflammation has been shown to alter signaling in ventral striatum and anterior insula in association with motivational deficits in controls and depressed patients. We hypothesized that inflammation would be associated with motivational deficits and altered signaling in reward-relevant regions.
Methods: 37 medicated patients with schizophrenia were recruited from Grady Hospital in Atlanta, Georgia. Subjects were excluded if they had unstable medical conditions, evidence of inflammatory illness, use of anti-inflammatory medications, and/or active substance use. Negative symptoms were measured using the Brief Negative Symptom Scale (BNSS), with subscores for a motivated behavior factor as well as an expressivity factory. A subset of subjects performed a resting state connectivity scan (n=30) as well as task based fMRI (n=22) using the Monetary Incentive Delay Task (MID) and the Effort Based Decision Making Task (EBDM) in a 3T scanner. For the resting state data, imaging preprocessing was performed using standardized pipelines using the CONN software toolbox. Seed to voxel analyses were performed in second level analyses and statistics reported above were extracted from the peak of the cluster. For the task based data, A standardized preprocessing pipeline was used in SPM. For the MID, a predefined Nacc mask was used given the a priori hypothesis regarding the ventral striatum in response to reward anticipation. A whole brain analysis was used for the

EBDM task to look at the effect of increasing effort (using a parametric modulator). Linear regression models were tested to determine the relationship between inflammation and brain activation, controlling for age and sex.
Results: C-Reactive Protein (CRP), a marker of systemic inflammation, was significantly correlated with the BNSS motivation factor ($r=0.34$, $p=0.04$) but not the expressivity factor. This association was driven by the avolition subscale ($r=0.44$,$p=0.029$). These relationships remained significant after controlling for depression. Increased CRP was also associated with greater resting state connectivity between a seed in the right NAcc and activation in a cluster that included the right insula ($T=3.41$,$p<0.001$). In the task-based data, tumor necrosis factor (TNF) was significantly associated with mean bilateral activation of the NAcc (beta=-0.462,$p=0.039$) on the MID. Using a parametric modulator to investigate the effect of increasing perceived effort on the EBDM, higher TNF was associated with increased activation in the right anterior insula ($T=4.35$,$p<0.001$). Moreover, activation in the anterior insula in response to effort was correlated with NAcc activation in response to reward ($r=-0.512$,$p=0.015$).
Conclusions: These findings are consistent with studies in healthy controls and patients with depression demonstrating the impact of inflammation on the ventral striatum and anterior insula. Anterior insula may control motivational vigor and influence downstream dopaminergic signaling in the NAcc, suggesting a coordinated circuit between these regions that may be sensitive to inflammation. Future work will seek to demonstrate causal mechanisms as they relate to increased inflammation and brain regions/circuits that are associated with motivational deficits in patients with schizophrenia.

36.3 ELEVATED EXPRESSION OF ENDOGENOUS RETROVIRAL ELEMENTS AFFECTS BEHAVIORAL AND TRANSCRIPTOMIC PROFILES IN MOUSE MODELS OF PSYCHOTIC DISORDERS

Felisa Herrero[1], Joel Gruchot[2], Patrick Küry[2], Ulrike Weber-Stadlbauer[1], Urs Meyer*[1]

[1]*University of Zurich,* [2]*Heinrich-Heine-University*

Background: Endogenous retroviruses (ERVs) are remnants of germline infections that took place several million years ago and represent approximately 8% of the human genome. Accumulating evidence implicates increased expression of ERVs in the spectrum of psychotic disorders, including schizophrenia. Thus far, however, the link between increased ERV expression and psychotic disorders largely remains circumstantial. To gain more mechanistic insights into the neurobiological disease pathways affected by ERVs, we studied the role of ERVs in two complementary mouse models with relevance to psychotic disorders. The first model was based on transgenic expression of the human-specific ERV type-W envelope protein (HERV-W ENV), whereas the second model was based on maternal immune activation (MIA), a transdiagnostic environmental risk factor of psychiatric disorders.
Methods: Transgenic C57BL/6J mice with HERV-W ENV expression (HERV-W TG mice) were generated by inserting the multiple sclerosis-derived retrovirus (MSRV)-pv14env sequence under the CAG promoter into the hypoxanthine-guanine phosphoribosyltransferase (HPRT) locus and were compared to wildtype (WT) littermates. MIA was induced by maternal treatment with the viral mimetic, poly(I:C) (5 mg/kg, i.v.), given to pregnant C57BL/6N on gestation day 12. Vehicle-exposed offspring served as controls (CON). Behavioral investigations were conducted in both models and included tests assessing social approach behavior and social recognition memory, prepulse inhibition (PPI) of the acoustic startle reflex, and novel object recognition. Next-generation RNA sequencing of hippocampal tissue was used to identify genome-wide transcriptional changes in HERV-W TG mice relative to WT

controls, and subsequent immunohistochemical analyses using confocal laser scanning microscopy were conducted to estimate the density of excitatory and inhibitory synapses in hippocampal subfields. Transcripts of murine-specific ERVs and inflammatory cytokines were measured in the MIA model using quantitative real-time PCR and subjected to unsupervised cluster analysis with behavioral data.
Results: Compared to WT littermates (n = 12), adult HERV-W TG mice (n = 12) displayed a number of behavioral and cognitive abnormalities, including deficits in PPI of the acoustic startle reflex ($p < 0.01$, $F[1,22] = 8.45$), social recognition memory ($p < 0.05$, $t[22] = 2.84$), and novel object recognition ($p < 0.05$, $t[22] = 2.40$). Using a false discovery rate (FDR) threshold of 10% ($q < 0.1$), we found 68 and 131 genes to be upregulated and downregulated, respectively, in the hippocampus of HERV-W TG mice (n = 3) relative to WT controls (n = 3). Functional network prediction using Ingenuity Pathway Analysis demonstrated that the differentially expressed genes annotated with the functional nodes "neurodevelopmental disorders", "schizophrenia", "quantity of dendritic spines", "synapse formation", and "cognition". Reduced densities of excitatory (VGLUT1+/PSD-95+) and inhibitory (VGAT+/Gephyrin+) synapses were found in the hippocampal CA1 subfield of HERV-W TG mice (n = 7) relative to WT controls (n = 7; $p < 0.01$ for both analyses). In the MIA model, we found that adult offspring born to poly(I:C)-exposed dams could be stratified based on the presence (susceptible subgroup, n = 9) or absence (resilient subgroup, n = 7) of PPI and social interaction deficits. Furthermore, we revealed a concomitant increase in the expression of IL-6 ($p < 0.001$) and numerous murine-specific ERV transcripts, including ETnI ($p < 0.01$), ETnIIa ($p < 0.01$), IAP ($p < 0.001$), MusD ($p < 0.01$), SynA ($p < 0.01$) and SynB ($p < 0.05$), in the hippocampus of susceptible MIA offspring relative to resilient MIA offspring and CON offspring.
Conclusions: Our data provide converging preclinical evidence for a role of endogenous retroviral elements in disrupting brain functions relevant to psychotic disorders and beyond. Whereas the transgenic model provides insights into the causal mechanisms whereby HERV-W ENV expression changes behavioral and transcriptomic profiles, the findings obtained in the MIA model suggests that an inflammatory stimulus, even when initiated in prenatal life, has the potential of causing persistent alterations in MERV expression, particularly in those offspring that are susceptible to MIA.

36.4 CELLULAR IMMUNOPHENOTYPE OF PSYCHOSIS AND THE ROLE OF INTERLEUKIN-6; A MULTI-COLOUR FLOW CYTOMETRY APPROACH WITH FUNCTIONAL ASSAYS

Fabiana Corsi-Zuelli*[1], Zhi Li[2], Cristina Matas de las Heras[3], Elizabeth Jinks[3], Jamie Cowley[2], Ines M Morano[3], Cristina Marta Del-Ben[1], Omar Qureshi[3], Rachel Upthegrove[4], Nicholas Barnes[2]

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Background: The burden associated with schizophrenia and other psychoses is one of the largest globally, with over 21 million people affected, resulting in 15-20 years of life lost per patient. Current antipsychotic drugs are ineffective for around one-third of patients, and the same proportion display elevated blood cytokine levels. This low level of non-resolving inflammation may predict poor response to existing dopaminergic treatments. Several meta-analyses show that interleukin (IL)-6 is elevated in the blood and cerebrospinal fluid of patients, including patients in their first episode of psychosis and even before antipsychotic treatment

initiation. Large prospective studies show that increased blood IL-6 during childhood precedes the onset of psychotic symptoms and experiences during adulthood. Mendelian Randomization suggests that genetically determined elevated IL-6 is causally related to schizophrenia aetiology and brain abnormalities, irrespective of confounding by lifestyle factors or reverse causation. It is now becoming evident that not all but only a subset of patients have immune dysfunction. IL-6 induces cell activation via phosphorylation of STAT3 (pSTAT3), which can be inhibited by tocilizumab, a humanised anti-IL-6 receptor monoclonal antibody. Currently, however, there is a remarkable scarcity of investigations addressing immune mechanisms using peripheral blood mononuclear cells (PBMCs) in psychosis. We are investigating intracellular functional assessments of IL-6-related pathways (STAT3) in PBMCs to identify immune-relevant subgroups of psychosis. This study is part of the UK MRC PIMS, a multi-site experimental medicine study testing the effect of tocilizumab in psychosis pathogenesis and mechanisms.

Methods: We optimised a multi-colour flow cytometry assay that will be used to characterise the absolute number, frequency, and function of a variety of PBMC subsets isolated from the blood of patients in the early stages of psychosis and healthy controls. This deep-immunophenotyping protocol also includes an optimised phosflow assay to determine STAT3 phosphorylation in PBMCs after exogenous IL-6 exposure. Briefly, PBMCs were isolated from human leucocyte cones using SepMate density gradient centrifugation and quantified using a haemocytometer and resuspended in complete RPMI media. PBMCs (1 x 106 cells/well) were then stimulated with exogenous recombinant human IL-6 at different concentrations (0.1, 1, 10, 100 ng/mL) after incubation with tocilizumab (20 ug/mL) or vehicle. The geometric mean of fluoresce intensity (MFI) of total PBMCs was evaluated to select the optimal dose of exogenous IL-6. The proportion of pSTAT3 at different cell populations (CD14+ and/or CD16+monocytes, CD56+natural killer cells, CD3+ T cells, CD3+CD56+ natural killer T cells, CD4+ T helper, CD8+ T cytotoxic, and CD25+CD127-CD39 Tregs) was measured by multi-colour flow cytometry (CytoFLEX, Beckman Coulter) after fixation, permeabilization and staining procedures. All experiments were performed in triplicates.

Results: Exogenous IL-6 evoked increases in intracellular pSTAT3 in a dose-response fashion (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 substantially inhibited by pre-incubating cells with tocilizumab (geometric mean±SD, minimum 358.3±1.0; maximum: 611±1.12). Using IL-6 at 10 ng/mL, we observed an augmented percentage of pSTAT3 in both innate and adaptive immune cells, with a significant decrease by pre-treatment with tocilizumab. pSTAT3 inhibition among innate cells included monocytes, such as intermediate CD14+CD16+ (72.6%) and classic CD14+ CD16- (47.6%). Inhibition in adaptive immune cells included CD3+CD56+ natural killer T cells (62.2%), CD4+ T helper (54.0%), Tregs CD25+CD127-CD39- (50.8%), T cells CD3+ (45.8%), Tregs CD39+ (22.7%), and CD8+ T cytotoxic (22.3%). Less responsive cells included CD56+ NK cells (7.7%) and non-classic CD14-CD16+monocytes (8.7%).

Conclusions: Functional assessment of IL-6/STAT3 signalling in various subtypes of immune cell subsets could help in the identification of immune-dysregulated subgroups of psychosis and give better chances of effective and personalised treatments, and the development of novel targeted treatments. This optimised protocol is now being applied to patients' samples.

37. MODELS OF CANNABIS AND CHILDHOOD TRAUMA RISKS ON PSYCHOSIS: CONVERGING EVIDENCE OF RISK FROM ANIMAL MODELING TO INFLAMMATION

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Overall Symposia Abstract: Age of psychosis (PSY) onset and associated symptomatology, as well as brain morphology and function are modulated by the interaction of genetics and the environment. Data indicate that cannabis (CA) use, and childhood trauma (CHT) individually increase the risk for emerging PSY, with some evidence revealing an interactive effect of CHT and CA on risk of psychopathology in adolescence. CHT, being a risk factor for PSY and other mental illnesses, also increases the risk of substance use.
Here we present diverse perspectives on childhood trauma and cannabis in populations that span healthy controls; individuals affected by first episode psychosis; individuals affected by chronic schizophrenia; and finally, we discuss modeling trauma and cannabis in murine models.

Thus, Elisabetta del Re will be presenting data on the synergy of cannabis and trauma in a large transdiagnostic cohort of chronic psychosis subjects and the contribution of the hippocampus to risk of psychosis.

Dr. Emmet Power will present data that link inflammation and cannabis use in a large population of healthy controls.

Dr. Emily Kline will present data from a community population of first episode psychosis and the prevalence of cannabis use in this population.

Finally, Dr. Bernat Kocsis will introduce animal modeling of a two hits mechanism in inducing psychosis-like behavioral changes in mice.

The overall symposium will contribute important scientific data to inform policy and stimulate discussion; and addresses the goals defined by the United Nations for sustainable human development by the year 2030, on the ground that traumas such as 'Poverty, income inequality, interpersonal and collective violence, and forced migration are key determinants of mental disorders'.

37.1 CHARACTERIZATION OF CHILDHOOD TRAUMA, HIPPOCAMPAL MEDIATION AND CANNABIS USE IN A LARGE DATASET OF PSYCHOSIS AND NON-PSYCHOSIS INDIVIDUALS

Elisabetta C. del Re*[1], Walid Yassine[2], Victor Zeng[3], Sarah Keedy[4], Ney Alliey-Rodriguez[4], Elena Ivleva[5], Scott Hill[6], Nicole Rychagov[7], Jennifer E. McDowell[8], Jeffrey Bishop[9], Raquelle Mesholam-Gately[10], Giovanni Merola[11], Paulo Lizano[12], Elliot Gershon[4], Godfrey Pearlson[13], John Sweeney[14], Brett Clementz[15], Carol Tamminga[16], Matcheri Keshavan[17]

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Background: Cannabis use (CA) and childhood trauma (CT) independently increase the risk of earlier psychosis onset; but their interaction in relation to psychosis risk and association with endocannabinoid-receptor rich brain regions, i.e. the hippocampus (HP), remains unclear. The

objective was to determine whether lower age of psychosis onset (AgePsyOnset) is associated with CA and CT through mediation by the HP, and genetic risk, as measured by schizophrenia polygene scores (SZ-PGRS).
Methods: Cross-sectional, case-control, multicenter sample from 5 metropolitan US regions. Participants (n=1185) included 397 controls not affected by psychosis (HC); 209 participants with bipolar disorder type-1; 279 with schizoaffective disorder; and 300 with schizophrenia (DSM IV-TR). CT was assessed using the Childhood Trauma Questionnaire (CTQ); CA was assessed by self-reports and trained clinical interviewers. Assessment included neuroimaging, symptomatology, cognition and calculation of the SZ polygenic risk score (SZ-PGRS).
Results: In survival analysis, low CT and CA are associated with lower AgePsyOnset. At high CT or CA, CT or CA are individually sufficient to affect AgePsyOnset. CT relation with AgePsyOnset is mediated in part by the HP in CA users before AgePsyOnset. CA before AgePsyOnset is associated with higher SZ-PGRS and correlated with younger age at CA usage.
Conclusions: CA and CT interact to increase risk when moderate; while severe CT and/or CA abuse/dependence are each sufficient to affect AgePsyOnset, indicating a ceiling effect. Probands with/out CA before AgePsyOnset differ on biological variables, suggesting divergent pathways to psychosis.

37.2 CANNABIS USE, CHILDHOOD TRAUMA AND THEIR ASSOCIATIONS WITH INFLAMMATION AT AGE 24

Emmet Power*[1], David Mongan[2], Subash Raj Susai[1], Melanie Föcking[1], Mary Cannon[1], David Cotter[1]

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Background: Biomarkers of inflammation, cannabis exposure and childhood trauma are all associated with increased risk of mental disorders in previous research. Findings of associations between childhood trauma and inflammation have been inconsistent. There is also limited investigation of associations between cannabis use and markers of inflammation. Namely, only one previous large well-conducted study has investigated this question to our knowledge finding no association between cannabis use and a composite measure of interleukins. Widespread and increasing use of cannabis, increasing frequency of use in cannabis users, increasing Δ9-tetrahydrocannabinol content in cannabis, and rising rates of cannabis use disorder are a growing public health challenge, particularly in western countries. Danish healthcare register data indicate that cannabis use disorder is associated with 15.7 and 12.2 life years lost in males and females respectively.
In the current study, we aimed to investigate the association between frequencies of past year cannabis use and childhood trauma with classic and novel markers of inflammation.

Methods: We used a sample of 914 of healthy volunteers from the Avon Longitudinal Study of Parents and Children birth cohort study. We investigated whether interleukin 6 (IL-6), tumour necrosis factor alpha (TNFα), C-reactive protein (CRP) and soluble uroplasminogen activator receptor (suPAR) measured at age 24 were associated with cannabis use and childhood trauma subtypes in multivariate regression models adjusted for an array of confounders including sociodemographic measures, body mass index, tobacco smoking and current mental health diagnoses.
Results: We found convincing evidence of a strong association with a medium effect size between daily or near daily cannabis use and suPAR (standardized β= 0.474, P=0.001), a novel marker of chronic inflammation. We did not find any associations between cannabis use or

childhood trauma; and IL-6, TNFa or CRP. We found weak evidence for a small association between childhood emotional abuse and suPAR at age 24 (β= 0.103, P=0.034). We did not find any robust associations between other types of childhood trauma and suPAR or classic markers of inflammation.
Conclusions: In well-controlled laboratory studies Δ9-tetrahydrocannabinol decreases mitochondrial respiration, and increases cellular apoptosis, fibrosis, and oxidative stress. This is the first study to our knowledge delineating altered biomarkers of inflammation associated with daily/near daily cannabis use in a real world sample. Our findings that frequent cannabis use is strongly associated with suPAR is novel and may provide valuable insights into biological mechanisms that underpin associations between cannabis use, brain health and chronic disease morbidity. Whilst previous findings have shown that childhood trauma is predictive of low-grade inflammation in youth our results support recent methodological concerns in this area.

37.3 DUAL-HIT RODENT MODELS TO STUDY INTERACTIONS BETWEEN ADOLESCENT CANNABIS USE AND SCHIZOPHRENIA RISK FACTORS

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Background: In order to understand the potential risk of cannabis (CB) use on development of schizophrenia (SZ), it is essential to find an appropriate animal model that would allow investigating the neural mechanisms of adolescent CB exposure and its interaction SZ with risk factors carried from early life.
Methods: The introduction of "dual-hit" models were a major step in this direction. In these models, well-established animal constructs commonly used in SZ research, built on imitating genetic or early life risk factors as first hits, are combined with activation of CB1 receptors (CB1-R) as a "second hit". They provided important data on neural mechanisms involved which would be hard or impossible to obtain from human studies.
Results: Due to extremely mixed results so far, there is little consensus regarding the underlying mechanisms of how CB interacts with risk factors in early life to precipitate SZ-like abnormalities. These studies used common behavioral tasks modeling SZ-relevant cognitive deficits, such as prepulse inhibition, exploration (in maze and open field), social interaction, motivation (forced swim or sucrose preference), novel object recognition and reported both synergistic or protective relationships or no interaction between CB and risk factors disturbing embryonic (e.g. maternal immune activation, MIA) or early postnatal neurodevelopment (e.g. maternal separation, MS). Other, rather sporadic, studies used a different strategy; instead of functional tasks probing complex behaviors they used the dual-hit models with adolescent CB to examine more specific neurobiological mechanisms focusing on molecular targets. The findings were also mixed; however, CB showed both synergistic and protective effects, e.g. on 5-HT and NMDA receptor binding, or CB-induced changes in CB1-R density, in different models, including MIA and MS. Adolescent CB administration in genetic models in mice also lead to similar conclusions.
Conclusions: The validity of the "general picture" of adolescent CB effect remains not clear at this point. The uncertainty projected by these findings i.e., CB acting synergistically with or protecting from SZ risk factors, may reflect true variety in CB action in human or, alternatively, may point to limitation of rodent models requiring extension of investigations on animals to other domains. A potential candidate for such research could be targeting neural network mechanisms shown in the past decade relevant for development of cognitive deficits in human SZ and rodent models. Ample data are available for example concerning deficits of network

oscillations, in MIA, MAM, and other SZ models, and hippocampal theta and gamma rhythms are strongly reduced after acute CB1-R activation. Brain oscillations represent intermediate level of organization of neural ensembles, i.e. the "missing middle" bridging the gap between microscopic disturbances and macroscopic behavioral outcomes. Their examination, using highly translatable EEG and field potential recordings, may provide information more integrative than molecular studies on one hand and more localized to specific structures than complex behavioral paradigms on the other.

37.4 TIMING OF CANNABIS EXPOSURE RELATIVE TO PRODROME AND PSYCHOSIS ONSET IN A COMMUNITY-BASED FIRST EPISODE PSYCHOSIS SAMPLE

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Background: Cannabis use is common and consequential in the early phases of schizophrenia. A history of cannabis use among adolescents and young adults receiving treatment for a first episode of psychosis is common, both in the immediate circumstances leading to the onset of psychosis as well as more habitually throughout adolescence. Cannabis use in patients with diagnosed illness can exacerbate symptoms and serves as a very strong predictor of relapse and/or chronicity of illness. Cannabis, specifically the delta-9-tetrahydrocannabinol (THC) constituent, has also been implicated as a cause of transient psychotic symptoms and a risk factor for schizophrenia. Over the past decade, the United States has enacted policies of cannabis liberalization, with full legal access to cannabis for adult non-medical ("recreational") users in some states, and prevalence of cannabis use in adolescents and young adults has increased in the general population. There is an urgent need to better understand the prevalence, impact, and timing of cannabis use in early phase clinical psychosis samples.
Methods: The current study samples consecutive admissions (N = 246) to two United States community based first-episode psychosis services to characterize timing of cannabis use relative to psychosis and attenuated symptom onset, differences between those with and without cannabis exposure, and the association of age at first cannabis exposure with clinical and demographic variables.
Results: Both cannabis exposure (78%) and cannabis use disorders (47%) were highly prevalent at admission. In 94% of participants, cannabis use preceded the onset of both attenuated and full-threshold psychosis symptoms by several years. Earlier age at first exposure to cannabis was associated with younger age at prodrome and psychosis onset, worse premorbid functioning, and greater severity of cannabis use disorder at admission.
Conclusions: The timing of first exposure to cannabis may have individual prognostic as well as public health significance. Documenting the prevalence and impact of cannabis use in early psychosis samples, as well as the overall incidence of psychotic disorders, will be of vital public health significance as the United States and other countries enact cannabis legalization and cannabis products become more widely available.

38. TARGETING RISK: EXPLORING INTERVENTION STRATEGIES AND BIOMARKERS FOR REDUCING NEURODEVELOPMENTAL SCHIZOPHRENIA VULNERABILITY

Steven Laviolette*, University of Western Ontario*

Overall Symposia Abstract: The neurodevelopmental etiology of schizophrenia has been linked to complex intrinsic factors and exposure to extrinsic environmental insults, particularly during the pre-natal and adolescent periods of brain maturation. Emerging clinical and pre-clinical evidence is identifying a variety of neurodevelopmental risk factors for increased schizophrenia risk, including pathological disturbances in the prefrontal cortex, hippocampus, mesolimbic dopamine (DA) system and associated signaling pathways involving GABA, glutamate and the endocannabinoid systems. Identifying these biomarkers and developing effective intervention strategies to halt or reverse the pathophysiological sequence of schizophrenia etiology is of crucial importance. More importantly, can effective intervention strategies be developed to disrupt the neurodevelopmental etiology of schizophrenia? In this symposium, a variety of pre-clinical and clinical data will be presented exploring potential intervention strategies for preventing the neurodevelopmental sequelae associated with increased schizophrenia risk. Featured schizophrenia risk models will include translational neurodevelopmental animal models of pre-natal drug (cannabinoid) and toxin exposure (mitotoxin methylazoxymethanol acetate; MAM) focusing on fatty-acid signaling related pathophenotypes and GABAergic disturbances in prefrontal-cortical and hippocampal networks as well as genetic models of glutathione deficiency underlying perineuronal net and oxidative stress- induced schizophrenia-related phenotypes. In addition, clinical data will be highlighted exploring how cannabinoid exposure may alter levels of Fatty Acid Amide Hydrolase (FAAH) in neural circuits related to schizophrenia risk and associated biomarkers underlying these pathophysiological events. Topics covered in our symposium will offer the audience a diverse range of cutting-edge translational and clinical findings into exciting new discoveries with the potential for developing effective intervention strategies to reduce schizophrenia risk, particularly during vulnerable windows of brain development.

38.1 JUVENILE VS ADOLESCENT STRESS LEADS TO HIPPOCAMPAL PARVALBUMIN NEURON LOSS AND DOPAMINE SYSTEM ALTERATION, BUT IS MEDIATED VIA DIFFERENT PARVALBUMIN-REGULATED PATHWAYS IN MALE VS FEMALE RATS

Anthony Grace*[1], Felipe Gomes[2], Xiyu Zhu[1], Daniela Uliana[1]

[1]*University of Pittsburgh,* [2]*Ribeirao Preto Medical School, University of Sao Paulo*

Anthony Grace*, University of Pittsburgh*

Background: There is increasing evidence that childhood stress or trauma is a significant risk factor for the development of major psychiatric disorders in adults, including schizophrenia, depression, and anxiety. Using rodent models, we have been exploring how prepubertal or postpubertal stressors increases vulnerability to disorders in adulthood. We have found that the pathological consequences depend on the timing and intensity of the stressors, with parvalbumin (PV) neuron loss a driver of the pathology. This would result in an excitation/inhibition imbalance driving a hyperdopaminergic state observed in schizophrenia.

Methods: Male and female rats were subjected to either daily handling or daily footshock + 3 restraint sessions over 10 days from PD21-30 (prepubertal) or from PD41-50 (postpubertal) and tested as adults (>PD65). Dopamine (DA) neurons were recorded in the VTA in a cells/track protocol, and recordings were made from ventral hippocampal (vHip) and basolateral amygdala (BLA) neurons. Behavioral tests include elevated plus maze (EPM) and novel object recognition (NOR).

Results: Male rats that received combined stressors pre or peripubertally exhibited hyperdopaminergic state (increased number of DA neurons firing ($F(1,31)=9.852$, $p<0.01$) as well as anxiety (elevated plus maze $F(1,38)=6.228$, $p<0.05$) and deficits in NOR $F(1,37)=6.884$, $p<0.01$) in the adult; however female rats were resilient to the long-term effects of stressors. In contrast, exposure to stress postpubertally caused female rats to exhibit increased DA population activity ($F(1,31)=11.47$; $p<0.01$), primarily in the affect-related medial VTA; in this case the males were resilient. In both sexes, vHip activation impacted DA neuron activity (male-selective increase by PreP-S ($p<0.05$; Dunn's test) and female-selective increase by PostP-S ($p<0.01$)) and in both cases was driven by significant vHip PV neuron loss. However, in males vHip activity is correlated with loss of PV neurons in the BLA leading to BLA activation with prepubertal stress (Kruskal–Wallis test, $H=24.69$, $p<0.0001$; Dunn's test, PreP-S:Males, $p<0.0001$). In contrast, in the female preliminary results show that postpubertal stress caused elevated vHip firing rate via possible PV loss in nucleus reticularis leading to nucleus reuniens activation, presumably via the nucleus reuniens-vHip pathway.
Conclusions: These results: show that male rats are vulnerable to prepubertal stress-induced disruption of DA neuron activity and deficits in anxiety and cognition as adults due to vHip PV neuron loss, whereas females are resilient. In contrast, female rats were susceptible only to stress administered postpubertally and vHip PV loss leading to alterations only in the affect-related medial VTA, consistent with anxiety and susceptibility to depression. Furthermore, these alterations produced pathway-specific changes in males vs females. This is consistent with a resilience of females to severe schizophrenia pathology compared to males, and is driven by an excitation/inhibition imbalance throughout the circuit.

38.2 MOLECULAR TARGETS LINKING CANNABIS AND PSYCHOSIS

Romina Mizrahi*[1]

[1]*McGill University*

Background: Cannabis is the most widely used illicit drug (becoming legal in many countries), particularly by adolescents and youth, making it a growing public health concern. In the US, approximately 51.8% of young adults aged 18-24 reported life-time cannabis use, with 34.8% reporting past year cannabis use. Schizophrenia (SCZ) is a debilitating mental disorder affecting about 1% of the world population. Early cannabis use increases the risk of developing SCZ by almost twofold in vulnerable individuals making cannabis a strong risk factor for SCZ acting through an unknown molecular mechanism.
Methods: Complimentary PET studies will be presented in this panel, using validated radioligands to quantify the following molecular targets in vivo-in brain: a) Fatty Acid Amide Hydrolase (FAAH) and b) Monoamino Oxidase B (MAO-B).
Results: In this panel, using Positron Emission Tomography (PET) molecular imaging, I will present, complimentary studies showing a) significant effects of cannabis use on the brain endocannabinoid system, particularly Fatty Acid Amide Hydrolase (FAAH) which regulates anandamide levels in brain; b) published study showing a significant relationship between FAAH levels and positive psychotic sychotic symptoms; c) published work showing a significant relationship between FAAH levels and Glutamate+glutamine; and d) novel unpublished data investigating the effects of cannabis use on Monoamino Oxidase B (MAO-B), a key dopamine metabolism regulatory enzyme in psychosis patients with and without cannabis use. Preliminary data reveals a ~24.0 % reduction in MAO-B in patients with early psychosis compared to controls, with a ~19.5% lower MAO-B in those with a positive urine drug screen for cannabis, compared to those without.

Conclusions: This discovery, if confirmed in well powered studies, together with the novel FAAH data may explain the exacerbated psychotic experiences in vulnerable patients when using cannabis, perhaps earlier disease onset and higher relapse rates in patients with SCZ.

38.3 MMP9/RAGE MECHANISM AS A PROMISING TARGET FOR EARLY INTERVENTION IN EARLY PSYCHOSIS PATIENTS: A TRANSLATIONAL STUDY.

Daniella Dwir*[1], Jan-Harry Cabungcal[1], Lijing Xin[2], Basilio Giangreco[1], Enea Parietti[1], Martine Cleusix[3], Raoul Jenni[1], Paul Klauser[4], Philippe Conus[5], Michel Cuénod[1], Pascal Steullet[1], Kim Q. Do[1]

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Background: A hallmark of schizophrenia (SZ) is a dysfunction of parvalbumin-expressing fast-spiking interneurons (PVI), which are essential for neuronal synchrony during sensory/cognitive processing. Oxidative stress (OxS) and inflammation during early brain development, as observed in SZ, lead to impaired cortical circuitry, specifically the PVI and the perineuronal nets (PNN). In a translational approach both in an animal model and in early psychosis patients (EPP), we aimed (1) to identify a precise mechanism, leading to PVI/PNN impairments, and (2) to interfere with the proposed mechanism by using the antioxidant N-acetyl-cysteine (NAC) and environmental enrichment (EE) to rescue PVI maturation.
Methods: This study was conducted on a transgenic mouse model of GSH deficit (GCLM KO) with SZ related phenotype and on EPP from a well-characterized cohort. Mice were treated with a dopamine reuptake inhibitor (GBR), to mimic a social stress and induce an additional oxidative challenge, at postnatal day (P)10-20, followed by NAC/EE during juvenile/adolescent period. EPP were enrolled in a double-blind, randomized, placebo-controlled clinical trial of NAC supplementation for 6-months.
Results: We identified during peripubertal stage of GCLM KO a vicious cycle of processes involving activation of MMP9 by OxS, leading to RAGE shedding, which maintain neuroinflammation and OxS, inducing long-term impairment of PVI. These long-lasting effects were completely reversed by the NAC/EE. This recovery is mediated by NAC, via the inhibition of OxS-induced MMP9/RAGE, as it interrupts the deleterious feedforward mechanism, allowing PVI/PNN maturation. The decreased fast-rhythmic oscillations, reflecting PVI neuronal synchronization, in the GCLM KO were recovered by NAC/EE. 6-month NAC treatment decreased RAGE shedding in EPP plasma, in association with increased prefrontal GABA, improvement of cognition/clinical symptoms, suggesting similar neuroprotective mechanisms.
Conclusions: MMP9/RAGE pathway represents a key regulatory mechanism by which OxS interacts with neuroinflammation. The long-lasting effects on PVI/PNN can be reversed by a combined NAC/EE. In analogy, patients carrying genetic risks to redox dysregulation potentially vulnerable to early-life insults could benefit from a combined pharmacological and psycho-social therapy. Our findings highlight the MMP9/RAGE pathway as a promising target for novel drug development in psychiatry.

38.4 A DIETARY PERINATAL OMEGA-3 FATTY ACID INTERVENTION RESCUES SCHIZOPHRENIA-LIKE COGNITIVE AND AFFECTIVE ABNORMALITIES IN THE PREFRONTAL-CORTICAL-HIPPOCAMPAL NETWORK FOLLOWING PRENATAL CANNABIS EXPOSURE

Steven Laviolette*[1], Mohammed Sarikahya[1], Samantha Cousineau[1], Marta De Felice[1], Mina G. Nashed[1], Hanna Szkudlarek[1], Daniel B. Hardy[1], Walter Rushlow[1], Ken Yeung[1]

[1]*University of Western Ontario*

Background: Clinical and preclinical studies have demonstrated that prenatal cannabis exposure produces long-term pathological effects on fetal brain development and may increase vulnerability to certain neuropsychiatric disorders, including schizophrenia, cognitive and mood/anxiety disorders. However, the underlying mechanisms remain unknown. Research in our lab has demonstrated that fetal exposure to Δ9-tetrahydrocannabinol (THC) impairs neurodevelopment, in part, through pathological alterations in neural fatty acid signaling pathways (eNeuro. 2022 Oct 10;9(5)). Considerable evidence demonstrates that abnormal omega-3 (N3) fatty acid signaling may underlie various neuropsychiatric disorders. In addition, evidence has shown that dietary interventions with N3 fatty acids may prevent or ameliorate neuropsychiatric symptom profiles. The present study examined if perinatal supplementation with N3-fatty acids may rescue neuronal, behavioural and molecular neuropsychiatric phenotypes induced by pre-natal THC exposure.

Methods: Using a translational rodent model of maternal THC exposure in Wistar rats we compared the effects of an N3 enriched diet vs. standard control diet from gestational day 7 to postnatal day (PND) 21 of the offspring. Between PND 35-45, and PND 90-120, subsets of male/female offspring underwent behavioural tests for memory, social and novelty-induced anxiety, sensory integration, and anhedonia. We further performed in vivo electrophysiology in the Prefrontal-Cortical-Hippocampal circuit combined with molecular protein expression analyses of multiple schizophrenia-linked protein expression markers and Matrix-Assisted Laser Desorption/ionization imaging mass spectrometry (MALDI) to image and quantify levels of distinct fatty acid signaling pathways in the prefrontal-cortical-hippocampal network.

Results: We will present data showing that pre-natal THC exposure induces profound abnormalities in prefrontal-cortical-hippocampal network activity states combined with significantly decreased levels of N3 fatty acid levels within this circuitry. In addition, male and female offspring demonstrated profound cognitive and affective behavioural abnormalities into early adulthood. Remarkably, the N3 dietary intervention prevented cognitive and affective impairments in male offspring while simultaneously normalizing disturbed oscillatory and neuronal network activity patterns in later life. In contrast, N3 dietary intervention reduced anxiety-like phenotypes in females but had little effect on long-term memory impairments. In addition, N3 dietary interventions was more effective in preventing hippocampal neural activity abnormalities in males vs. females, which may account for the greater protective effects in males, specifically in terms of cognitive impacts of prenatal THC.

Conclusions: Our findings demonstrate for the first time that prenatal cannabinoid exposure leads to enduring deficits in multiple fatty acid signaling pathways directly in the prefrontal-cortical-hippocampal network that can persist into adulthood. Remarkably, we demonstrate that dietary interventions aimed at N3-fatty acid normalization may be a promising therapeutic option for cannabis-induced neurodevelopmental pathologies, with potentially broader therapeutic outcomes in male offspring.

39. THE EMERGING ROLE OF THE CEREBELLUM IN PSYCHOSIS: IMPLICATIONS IN COGNITION, PSYCHOPATHOLOGY, AND CLINICAL TRANSLATIONS

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

Overall Symposia Abstract: Although it has long been a hypothesis that the cerebellum plays a critical role in the pathogenesis of psychotic disorders, considerably less attention has been given to this structure compared to the cerebrum in psychiatric neuroscience research. However, studies of the cerebellum have clearly gained momentum in the past few years, as recent findings have started to paint a more in-depth picture of the nuanced role of the cerebellum in cognition and psychopathology. More importantly, recent studies have also provided initial evidence for the translational value of these neuroscience findings in clinical environment and started to demonstrate that the cerebellum is a promising target for the treatment of these severe mental disorders.

This symposium therefore aims to compile the most recent findings highlighting the mechanisms and clinical implications of cerebellar dysfunction contributing to psychotic disorders, and endeavors to draw the attention of the research community to the importance of this commonly overlooked "little brain" structure. We will start with a brief introduction to the history that has motivated the field, and then present four studies covering both neuroscience research and translational investigations. In the first study, Dr. Brady will present his work linking cerebellar function with cognition across the psychosis spectrum. Using a data-driven method, he will show that connectivity between the cerebellum and association cortices have the strongest brain-wide associations with processing speed and social cognition, establishing the specific cognitive domains most relevant to cerebellar dysfunction in patients. In the second study, Dr. Shinn will discuss a cerebellum-based neural mechanism that may be common to both hypoalgesia and negative symptoms. She will present data showing that patients with schizophrenia have a blunted cerebellar response to pain stimulation and that the reduction in cerebellar pain response is significantly correlated with the severity of negative symptoms. In parallel to these findings, Dr. Cao will highlight a cerebellum-based neural circuit as a promising imaging biomarker for individualized prediction of treatment response in first-episode psychosis, using two independent longitudinal datasets in which patients were clinically followed up for 12 weeks with antipsychotic monotherapies. Finally, translating these findings to clinic, Dr. Halko will present an inspiring work illustrating that functional modulation of the cerebellum with transcranial magnetic stimulation (TMS) significantly reduces negative symptoms and improves cognition in psychotic patients, pointing to the potential clinical value of the cerebellum as an interventional target.

At the end of the symposium, Dr. Ford will summarize these findings and lead the discussion on the promises and challenges of cerebellar studies in psychosis, where the panel will discuss 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.

39.1 DISTINCT PATTERNS OF CEREBELLAR-CORTICAL CIRCUIT DYSFUNCTION UNDERLIE MULTIPLE COGNTIVE DEFICITS IN PSYCHOSIS

Kathryn Lewandowski[1], Mark Halko[1], Melissa Hwang[1], Nachum Serota[2], Julie McCarthy[1], Adam Beermann[2], Jing Xie[2], Madelaine Nye[2], Dost Ongur[1], Ann Shinn[1], Fei Du[1], Mei-Hua

Hall[1], YingYing Tang[3], Larry J. Seidman[2], TianHong Zhang[3], Matcheri S. Keshavan[2], HuiJun Li[4], Robert W. McCarley[5], Margaret A. Niznikiewicz[5], Martha E. Shenton[6], JiJun Wang[3], William S. Stone[2], Susan Whitfield-Gabrieli[7], Roscoe Brady*[2]

[1]*McLean Hospital/Harvard Medical School,* [2]*Beth Israel Deaconess Med. Ctr. and Harvard Medical School,* [3]*Shanghai Mental Health Center, Shanghai Jiaotong University School of Medicine,* [4]*Florida A and M University,* [5]*Harvard Medical School, Veterans Affairs Boston Healthcare System,* [6]*Brigham and Women's Hospital, Harvard Medical School,* [7]*Northeastern University*

Background: Cognitive deficits in psychosis are among the strongest predictors of disability. These deficits are already present in the prodrome prior to conversation to psychosis and their biological basis is poorly understood. Cognitive deficits in psychosis are broad but when cognitive performance is parsed into subdomains (e.g. memory, social cognition, attention etc.), a structure emerges with two different factors: First, multiple cognitive domains in which performance is strongly correlated with impaired information processing speed. Second, independent deficits in social cognitive ability that are not correlated with processing speed. We previously reported that the strongest whole-brain fMRI correlate of social cognitive ability in psychosis was a cerebellar-parietal circuit (Brady et al. 2020). We hypothesized that deficits in other cognitive domains would be linked to distinct circuits. To test this hypothesis we examined fMRI connectivity and cognitive performance in individuals with psychosis and individuals in the prodrome.
Methods: We analyzed two datasets: Adults diagnosed with psychosis (n=103) underwent task-free ('resting state') fMRI imaging and extensive cognitive testing. We used fully data-driven multivariate pattern analysis to identify circuit correlates of information processing speed. This analysis was repeated in individuals at clinical high risk (CHR) for psychosis (n=137 including n=21 future converters).
Results: In participants with psychosis, the strongest ($r=.396$, $p< .001$) correlate of information processing speed was a cerebellar-frontal circuit. This link was stronger in antipsychotic-free individuals (n=40, $r=.52$, $p<.001$). Independent analysis in the CHR cohort replicated this result ($r=.392$, $p< .001$) and this connectivity-cognition relationship was strongest in future converters ($r=.558$ $p=.012$). Notably, the cerebellar node of this circuit is localized to the same posterior (non-motor) region of the cerebellum identified in our prior study of social cognition in psychosis. The cerebral nodes of these circuits are completely distinct.
Conclusions: Cognition in psychosis is broadly impaired but the severity of individual domains of cognitive performance suggests multiple contributing factors that are partially independent. Remarkably, data-driven approaches analyses converge on cerebellar connectivity as a common factor in multiple specific deficits. Furthermore, these brain-cognition relationships can be reliably observed even in the prodrome to psychosis. While distinct deficits have conserved cerebellar nodes, the cerebral nodes of these putative cognitive circuits are spatially distinct. Taken together, these results offer a brain-based explanation for the aggregation of diverse deficits in psychosis while also allowing heterogeneity in the severity of specific deficits. Further, the identification of a shared cerebellar substrate suggests a potential target for intervention. This will be described in the presentation by Mark Halko PhD.

39.2 DEFICIENT CEREBELLAR RESPONSE TO PAIN IN SCHIZOPHRENIA

Ann Shinn*[1], Mariesa Cay[2], Emma Golden[2], Jaymin Upadhyay[3]

[1]*McLean Hospital/Harvard Medical School,* [2]*McLean Hospital/Boston Children's Hospital,* [3]*Boston Children's Hospital/Harvard Medical School*

Background: Individuals with schizophrenia (SZ) have been reported to have hypoalgesia (reduced pain sensitivity). Hypoalgesia may impede monitoring of physical health, contribute to underreporting of potentially life-threatening yet treatable illnesses (e.g., cardiovascular disease, diabetes), and may be a contributing factor in the early mortality well-known to afflict this population. Though case reports of hypoalgesia in SZ have been described for more than a century, surprisingly little attention has been paid to understanding the neural mechanisms underlying abnormal pain perception in SZ. In the current ongoing pilot study, we used functional magnetic resonance imaging (fMRI) during noxious and non-noxious thermal stimulation to examine the neural substrates underlying dysregulated pain processing in SZ. We hypothesized that hypoalgesia in SZ is subserved by the same deficits that give rise to the characteristic blunting (e.g., of motivation/reward and expressivity) that is the hallmark of negative symptoms.

Methods: We recruited men and women, ages 18-50yo, with a SZ spectrum disorder (SZ, schizoaffective disorder, or schizophreniform disorder) as well as age- and sex-matched healthy control (HC) participants. All participants were required to be in good physical health, with no acute pain conditions or history of chronic pain syndromes, no DSM-5 substance use disorders in the previous month, and no MRI contraindications. Prior to imaging, we performed quantitative sensory testing (QST), which involved placing a thermode (Medoc, Inc.), starting at 35°C and incrementally warming at a rate of 1°C/sec, on the dorsum of the participant's right hand and measuring heat pain thresholds ('When do you first feel pain?'), heat pain tolerances ('When is the heat too painful?'), and heat pain temperatures corresponding to a 7/10 pain rating ('When is the pain a 7 on a 0-10 scale?'). Participants also underwent a comprehensive clinical evaluation including administration of the Clinical Assessment Interview for Negative Symptoms (CAINS), as well as brain MRI including two evoked fMRI scans (non-noxious, noxious), each 4 min in length. During the evoked fMRI scans, five heat stimulations were delivered to the dorsum of the right hand in a 30/15s off/on cycle. The on-condition temperature for the non-noxious scan was 40°C, while that during the noxious scan was the subject-specific temperature corresponding to a 7/10 pain rating. Using the FMRIB Software Library (FSL), we modeled the BOLD response (off-on, boxcar function) using explanatory variables convolved with a gamma function. In group-level, mixed-effects (FLAME 1) comparisons, t-test results for each voxel were thresholded at $z=3.1$, cluster size corrected at $p<0.05$. Within the SZ patient sample, we also examined the relationship between neural response to thermal pain stimuli and negative symptoms by including individual CAINS scores as covariates of interest within group-level analysis.

Results: We found that patients with SZ (n=18), compared to HC participants (n=21), showed significantly lower functional activation of the cerebellum (crus I/II, lobule VI) during the experience of 7/10 heat pain in the scanner. SZ and HC did not significantly differ in the response to non-noxious (40°C) thermal stimuli in the cerebellum or other regions in the pain circuit. In addition, we found that the blunted cerebellar response during heat pain stimulation (lobule VI) was negatively correlated with the CAINS score ($r=0.44$) such that greater severity of negative symptoms covaried with lower cerebellar activation in response to thermal pain stimuli.

Conclusions: The preliminary results from this ongoing study provide clues that link hypoalgesia and negative symptoms to a common circuit involving the cerebellum. Considering these findings in the context of 'dysmetria' (cerebellar-mediated incoordination) models of psychosis, our findings suggest that dysmetria of reward-aversion and salience processing may underlie the pathophysiology of both hypoalgesia and negative symptoms.

39.3 CEREBELLAR-CORTICAL FUNCTIONAL CONNECTIVITY AS A NEURAL SIGNATURE FOR INDIVIDUALIZED PREDICTION OF ANTIPSYCHOTIC RESPONSE IN FIRST-EPISODE PSYCHOSIS

Hengyi Cao*[1], Todd Lencz[2], Juan Gallego[2], Anita Barber[2], Michael Birnbaum[2], Delbert Robinson[2], Anil Malhotra[2]

[1]*Feinstein Institute for Medical Research and Zucker Hillside Hospital,* [2]*The Zucker Hillside Hospital*

Background: Identification of robust biomarkers that predict individualized response to antipsychotic treatment at the early stage of psychotic disorders remains a challenge in precision psychiatry. Our previous study suggested that cerebellar-cortical connectivity may be a potential predictor for long-term (2-year) treatment response. The present work aimed to further investigate if a similar circuit would predict short-term response, and if the cerebellar-cortical circuit would show the strongest signal across the whole brain connectome, using a completely data-driven method.

Methods: In a discovery sample, 49 first-episode patients with psychosis received multi-paradigm fMRI scans at baseline and were clinically followed up for 12 weeks under antipsychotic monotherapies (either risperidone or aripiprazole). Treatment response was evaluated at the individual level based on the psychosis scores of the Brief Psychiatric Rating Scale (BPRS). Cross-Paradigm Connectivity was applied to extract individualized "trait" connectomes across different fMRI paradigms. Connectome-based Predictive Modeling was subsequently employed to train a predictive model that uses baseline connectomic trait measures to predict individualized change rates of psychosis scores. The model performance was evaluated as the Pearson correlations between the predicted change rates and the observed change rates, based on cross validation. The generalizability of the prediction model was further examined in an independent validation sample of 24 first-episode patients with a similar design. Significance of prediction performance in both samples was determined by 5000 permutations.

Results: The results revealed a paradigm-independent connectomic trait that significantly predicted individualized treatment outcome in both the discovery sample (r[predicted vs observed] = 0.44, P = 0.007) and the validation sample (r[predicted vs observed] = 0.50, P = 0.005). This neural trait involved connections predominantly linking the cerebellum (especially crus 1) and multiple sensory (e.g. sensorimotor, auditory, visual) and cognitive (e.g. default-mode, frontoparietal, cingular-opercular) systems in the cerebral cortex.

Conclusions: This study discovers and validates that cerebellar-cortical functional connectivity is a promising connectomic predictor for individualized response to short-term antipsychotic treatment in first-episode psychosis. Moreover, these findings also echo our previous study showing the cerebellar-cortical circuitry in prediction of long-term response and together highlight the potential clinical value of the cerebellum in psychosis treatment and precision psychiatry.

39.4 DEVELOPMENT OF THERAPEUTIC CEREBELLAR TRANSCRANIAL MAGNETIC STIMULATION VIA TRANSLATIONAL NEUROSCIENCE

Mark Halko*[1]

[1]*Harvard Medical School/McLean Hospital*

Background: With growing evidence that cerebellar circuitry dysfunction contributes to psychotic disorders, it has become imperative to develop intervention approaches that can impact cerebellar circuitry. Network-based functional imaging has created increasingly precise cerebellar organization that can be reliably acquired within individuals. Transcranial magnetic stimulation (TMS) has a rich history of cerebellar stimulation that is consistent with cerebellar-cortical network organization.
Methods: By combining imaging with cerebellar neuromodulation we can show that effective stimulation paradigms can be developed using standard techniques. Work from our group developed the tools and techniques to reliably target individualized networks and extended these tools to cerebellar modulation. In a combined TMS-fMRI experiment, n=26 healthy participants participated in a 3 session, dose-response experiment of cerebellar iTBS. In an independent cohort, network imaging was used to identify negative symptom networks, and then in n=11 participants, cerebellar iTBS was delivered 2x daily for 5 days.
Results: These dose-response experiments validated cerebellar involvement within known networks, in nodes in frontal and parietal cortex, but also in basal ganglia and thalamic circuitry. Taken into patient populations, we show that increasing neuromodulation of negative symptom network Results: in improved negative symptoms.
Conclusions: Tools such as TMS can be applied in basic science settings to uncover cerebellar network interactions, and the same equipment can also be used in multi-day applications for therapeutic intervention. Thus, with single-session translational experiments we can predict the direction of therapeutic response in clinical populations. Taken together, these studies demonstrate the necessity of looking to basic science for the toolkits of intervention. With these toolkits, emergent imaging findings in clinical populations can be validated. This long path of development of interventions is meeting the current findings of the other symposia presenters, providing a pathway forward for clinicians and investigators to integrate these results into clinical practice using tools that are readily available today.

Plenary Session VII: Lea Davis

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

40. WHAT GENOMICS RESEARCH IN A ELECTRONIC HEALTH RECORD SETTING IS REVEALING ABOUT SCHIZOPHRENIA

Kim Do*, Lausanne University*

Overall Abstract: Dr. Davis's laboratory is at the forefront of psychiatric genomics. In this plenary session, she will discuss a novel multisite collaborative program, leveraging electronic health records to tackle the heterogeneity of psychosis in the real world. Her innovative research in EHR-based psychiatric genetics with PsycheMERGE provides a "translational sandbox" to examine how the interaction between genomic and environmental risk factors throughout development give rise to real world complexity including diagnostic delay, phenotypic heterogeneity, and multiple comorbidities. holds great promise to break new ground in our understanding of the biological processes underlying schizophrenia, paving the way towards precision psychiatry.

40.1 WHAT GENOMICS RESEARCH IN AN EHR SETTING IS REVEALING ABOUT SCHIZOPHRENIA

Lea Davis*, Vanderbilt University Medical Center*

Individual Abstract: The genetic architecture of schizophrenia is complex and includes polygenic and rare variant contributions that interact with risk-increasing environmental exposures (e.g., trauma and substance use) throughout development. Genome-wide association studies over the past decade have yielded tremendous knowledge of the variants, genes, and pathways that are involved the etiology of schizophrenia. Genomic tools, such as polygenic scores, which measure the cumulative risk for schizophrenia from common genetic variation have emerged from these decades of genetic research. While these scores are not yet ready for use in clinical practice, the EHR research setting provides a "translational sandbox" to examine how genomic and environmental risk factors together give rise to real world complexity including diagnostic delay, phenotypic heterogeneity, and multiple comorbidities. By leveraging the collaborative infrastructure of the Electronic Medical Record and Genomics (eMERGE) Network, the PsycheMERGE network aims to tackle exactly these issues. Today, with over 25 partner sites and nearly one million genotyped patients, the network is studying the utility of polygenic scores, the genetic relationship between schizophrenia and the rest of the medical phenome, and the early developmental trajectories correlated with later diagnoses of schizophrenia. During this presentation I will share findings from the network and reflections on the promise and pitfalls of EHR-based genomic research in schizophrenia.

Concurrent Symposia

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

41. DIGITAL BIOTYPING OF NEGATIVE SYMPTOMS: ADVANCES AND CHALLENGES

Jean-Pierre Lindenmayer*, New York University*

Overall Symposia Abstract: Negative symptoms are a critical symptom dimension of schizophrenia, typically associated with reduced social and instrumental functioning. Negative symptoms are present early on in the disease process, are stable during chronic phases of illness and are difficult to treat. Negative symptoms are generally assessed using clinical rating scales; however, these rating scales have several inherent limitations that impact validity and efficacy for their use in clinical trials (e.g., PANSS, SANS, BNSS, CAINS). More recently, there have been increasing attempts to digitally phenotype negative symptoms using objective biobehavioral technologies, such as computerized analysis of speech and facial behaviors. These technologies have allowed to identify precise and intricate characteristics of negative symptoms that cannot be easily identified during clinical interviews, and may yield complex features of digitally characterized negative symptoms. Additionally, digital tools may have numerous potential benefits compared to traditional assessments: they are non-invasive, ecological, do not demand extra efforts, and provide continuous access which offers timely understandings of symptom and symptom changes.

Current innovative digital approaches to assessment offer a unique opportunity to create predictive models of individual vulnerability based on the integration and interdependencies of symptoms from diverse sources of information. Therefore, this panel will present clinically relevant digital technologies assessing negative symptoms and their relationship with clinical ratings as well their potential predictive power of illness development. The panel will also address reasons for the lack of convergence between digital technologies and clinical ratings, and further demonstrate how these digital technologies may enhance measurement of negative symptoms.

41.1 LONGITUDINAL ECOLOGICAL MOMENTARY ASSESSMENTS OF THE BEHAVIORAL INDICATORS OF AVOLITION IN SCHIZOPHRENIA IDENTIFY CHANGES THAT ARE CORRELATED WITH CLINICAL RATINGS OF NEGATIVE SYMPTOMS

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Background: Negative symptoms in participants with schizophrenia (avolition) are associated with real-world social deficits. The assessment of negative symptoms is more difficult than positive symptoms because it requires self-awareness and corroborative information. Recent advances in the observational assessment of negative symptoms have employed ecological momentary assessment (EMA) which can capture momentary features of avolition, including time spent home and alone, and engagement in passive and unproductive activities. We report interim, but substantive, pilot data from the first 6 months of a 12-month longitudinal study of EMA, combined with clinical ratings of negative symptoms during an open label safety study of an antipsychotic medication in development.

Methods: Stable outpatients (PANSS ≤ 80) with schizophrenia entered an open-label treatment study of the candidate drug that included monthly clinical ratings of the PANSS and negative symptom ratings with the NSA-16. Longitudinal EMA assessments were delivered in 7-day bursts, 3 surveys per day for one week intervals monthly throughout the study. The surveys were delivered by a smartphone and queried location and social context (home vs. away; alone vs. with someone), positive and negative affect (PA, NA), hallucinations and delusions, and 1 of 3 targeted activity surveys that were customized for home alone, home with someone, and away from home. A total of 23 different activities were sampled with a sampling window of "the last hour". Participants also wore a "fit-bit" actigraph daily during EMA sampling weeks. Three NSA items were selected for analysis because they most closely defined avolition (reduced activities, reduced sense of purpose, and reduced social drive). Analyses were limited to subjects who answered at least 33% of the EMA surveys. Mixed Model Repeated-Measures Analysis of Variance (MMRM) strategies were used for EMA data analysis, including use of dynamic correlates to predict activity outcomes. Correlations (and regression analyses) with aggregated EMA variables and scores on the NSA items were also computed.

Results: A total of 7276 fully completed EMA surveys were answered to date by 169 subjects with clinical assessments during the sampling period. Scores on momentary PA as measured by EMA increased significantly ($X2=47.30$, $p<.001$). Step counts increased in concert with momentary PA ($p<.001$). The increases in PA also correlated with increases in time-synchronized at-home productive activities and decreases in passive and unproductive activities. Further, significant decreases in surveys answered at home were associated with increases in momentary PA ($p<.001$). Regression analyses indicated that answering more EMA surveys while home, alone, and engaging in unproductive activities shared 21% of the variance with NSA "reduced activity" item scores. More away from home activities, fewer EMA surveys answered home and alone, and more daily steps shared 31% of the variance with the NSA "reduced sense of purpose" item. Answering fewer EMA surveys home and alone and more surveys reporting productive activities shared 29% of the variance in the NSA item "reduced social drive". Numbers of surveys answered at home and alone, and PA all shared less than 4% variance with PANSS reduced emotional experience items.

Conclusions: These preliminary findings are the first report to document that treatment-related changes in a constellation of the behavioral indicators of avolition can be detected with EMA

surveys. The results of these surveys were substantially correlated with concurrent clinician ratings of NSA items indexing avolition (i.e., reduced emotional experience) that are the primary predictors of the social deficits associated with schizophrenia. Increases in PA after baseline were robustly detected and predicted increased engagement in positive daily activities measured on a momentary basis over a 6-month period, including more surveys answered away from home that corresponded with more productive activities and reductions in at-home unproductive activities. Increased physical activity was also longitudinally associated with increased PA. These EMA findings were validated by their convergence with clinician-rated scores on negative symptoms generated with a "gold standard" instrument (NSA-16) using a clinician-based, monthly rating strategy.

41.2 COMPUTATIONAL ANALYSIS OF FACE EXPRESSION IN SCHIZOPHRENIA

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Background: Flat facial affect is characteristic of schizophrenia(Sz), associated with functional impairment, and assessed using clinical ratings. Software-derived audio-visual biomarkers of flat affect, based on facial action coding systems, may be more informative about mechanisms, as they index specific face muscle activity.
Methods: Participants included 7 Sz patients, 10 healthy controls, and 20 individuals at clinical high risk (CHR) for psychosis, who were interviewed via HIPAA-compliant Zoom for ~30 minutes, with audiovisual recording. Time series of face expression (and gaze) features were extracted and analyzed using OpenFace software and Py-Feat. Mean amplitudes of face action units (AU) were calculated. Matrix ("distance") profiles for raw face features (in 3-4 dimensions) were used to capture self-similarity of expression (face motif repertoire) over time.
Results: Sz patients had reduced face AU amplitudes (t=-4.17,p=.0009), specifically in AU7 (t = -2.95,p =.01), which indexes the orbicularis oculi or "lid tightener," involved in "genuine" smiling and social signaling. Further, Sz patients had decreased repertoire of face expression (t=1.9,p=.09). Among CHR individuals, convergent validity with "ground truth" clinical ratings of face expression ("SIPS N3") existed for mean overall AU (r=-0.44), AU7 amplitude (r=-0.35), and repertoire metrics (r=-0.35). Clinical relevance was supported by correlations with role function ratings for AU7 amplitude (r=.30) and repertoire metrics (r=.40).
Conclusions: Automated metrics of face expression have convergent validity and clinical relevance in schizophrenia and its risk states. The specific involvement of AU7 suggests abnormal activity in dorsal midcingulate M3 and/or amygdala. Next steps include assessment of psychometrics and population variance for these promising biomarkers.

41.3 A MULTIMODAL SPEECH AND FACIAL DIGITAL ASSESSMENT TO ASSESS NEGATIVE SYMPTOMS

Jean-Pierre Lindenmayer[1], Anzalee Khan*[2], Vikram Ramanarayanan[3], David Suendermann-oeft[4], David Paulter[4], Benedicto Parker[1], Mohan Parak[1]

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Background: Negative symptoms are a transdiagnostic feature of mental illness. Current Methods: of assessing negative symptoms depend on verbal report (clinical interview) from patients and caregivers/informants. These verbal reports lack a systematic and efficient way of

incorporating behavioral and biometric observations that are strong indicators of negative symptoms and can be insensitive to change in treatment, subjective, requires extensive training and subject to cultural disparities. Speech behaviors and facial movements can inform clinicians about negative symptoms and include monotone and monosyllabic speech, few gestures, pausing, speech rates, speed of movement of certain facial areas. Facial and speech changes in negative symptom patients are difficult to track and quantify with conventional techniques. A rising number of conversational agents or chatbots are equipped with artificial intelligence (AI) architecture. Can negative symptoms in schizophrenia be meaningfully measured using AI-enabled vocal and facial analysis?
Methods: We assessed 20 inpatients at a psychiatric facility in New York, NY. At the first visit, the following instruments were administered (in the same order), including a sociodemographic and clinical questionnaire, AI vocal/speech software, PANSS, BNSS, CDSS, CGI-S, AIMS, SAS, BARS: each patient wase rated twice by the same clinician within a one week period in order to assess for test-retest reliability. The second visit included the AI vocal/speech software, PANSS, BNSS, CDSS, AIMS, SAS, BARS, CGI-S and CGI-I (severity of illness, improvement, and degree of change). For the AI software, participants were each provided a valence-neutral sentence to read; participants then be engaged in free speech where they were asked open ended probes designed to be emotionally-ambiguous in valence and content (e.g., tell me about yourself?). Concurrent, convergent, divergent and discriminative validity were assessed, along with user experience as measured by the SUTAQ (Service User Technology Assessment Questionnaire).
Results: 20 individuals (age 41.21 (SD=10.22) with schizophrenia were enrolled. Session duration for the AI software was a mean f 8:36 min (min = 5:01 min, max = 13:35 min). Significant correlations were observed between PANSS Motor Retardation and the AI software speaking rate ($r = -0.787$, $p = 0.020$) and average jaw acceleration ($r = -0.827$, $p = 0.011$), PANSS Active Social Avoidance and diadochokinetic syllable alternating motion rate (DDK-AMR) ($r = -0.850$, $p = 0.007$), PANSS Marder Negative symptom score and speaking rater ($r = -0.851$, $p = 0.007$), BNSS Avolition Internal Experience and articulation/loudness ($r = -0.818$, $p = 0.038$), BNSS Blunted Affect Vocal Expression, and Blunted Affect Expressive Gestures with the AI software speaking rate, articulation rate and DDK-AMR ($r > -0.800$, $p < 0.05$). Most participants (80%) reported satisfaction with the program.
Conclusions: Speech and facial AI technology could aid in negative symptoms assessments. Given the diverse types of data sets, feature extraction, computational methodologies, and evaluation criteria available, AI software can improve diagnostic accuracy and allow remote monitoring. Additional testing on larger sample sizes, reproducibility, and generalizability of the software is warranted.

41.4 DIGITAL BIOTYPING NEGATIVE SYMPTOMS REQUIRES A MACHINE TO THINK LIKE A HUMAN

Alex Cohen*[1]

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Background: Negative symptoms are a transdiagnostic feature of serious mental illness that reflect a public health issue. For over four decades, clinical scientists have endeavored to measure negative symptoms using “digital” technologies. If successful, these technologies could improve the reliability and validity of negative symptom measurement, expand access of quality care worldwide, decrease public burden and address structural inequalities related to negative symptom measurement and treatment. Despite dozens of studies to date employing analysis of various vocal, language, facial, geolocation, actigraphy and social media data

streams, no technology has come close to demonstrating sufficient support for clinical implementation. The use of artificial intelligence (AI) applied to large biobanks from international and multidisciplinary collaborations has not advanced clinical implementation. This talk will focus on a major omission in prior research – to systematically consider context when analyzing data from digital technologies. Context, referring to the circumstances that shape "in the moment" behavior, are indispensable for clinical evaluations of negative symptoms. In any given moment during a clinical interview, a person may appear silent, expressionless and disinterested due to a variety of contextual factors. For example, they may be: waiting patiently for their turn to talk, cognitively strained, distracted, respectfully deferring to the interviewer, concerned about power dynamics and its effects on access to care, drowsy, or bored. To effectively evaluate negative symptoms, clinicians must consider an impressively complex and dynamic set of contextual factors. The fact that high inter-rater reliability of negative symptoms can be achieved by clinicians suggests that there is a "collective wisdom" on what contextual factors underlie negative symptoms.

Methods: This talk will focus on uncovering this "collective wisdom" and applying it to AI models of negative symptoms using multimodal data from digital technologies. First, I will present several video case studies illustrating that even people with profound negative symptoms behave unremarkably most of the time. Second, I will propose two contexts, namely involving cognitive and socio-emotional factors, that are theoretically critical to the emergence of negative symptoms. Third, I will present findings analyzing speech, language and facial expression data from several large corpuses of patients with psychosis-spectrum disorders.

Results: These findings collectively highlight how negative symptoms are particularly evident during key contexts – for example, when they are under heavy cognitive or socio-emotional demands while interacting with a clinician during a clinical interview.

Conclusions: I will discuss how these contexts inform modelling, measurement and implementation of digital biotyping. Only by considering contexts that humans consider critical to negative symptoms, can machines meaningfully measure negative symptoms.

42. RUNNING IN THE FAMILY: THE INTERGENERATIONAL TRANSMISSION OF RISK FOR SEVERE MENTAL ILLNESS

Neeltje Van Haren, *Erasmus Medical Center*

Overall Symposia Abstract: Mental illness runs in the FAMILY. A family history of mental illness is the most important known risk factor for the development of mental health problems. Up to 50% of children with a mentally-ill parent will develop a mental disorder in their life course, suggesting a transfer of disease risk from affected parents to offspring. Such intergenerational transmission of risk of mental illness is rarely considered in clinical practice, and health care systems do not sufficiently embed family history of mental illness into diagnostics and care, leading to a delay in diagnosing patients and missing the time window for protective actions and resilience strengthening. Furthermore, parents with mental illness are often unaware of how their disorder may impact the well-being of their children, may be less capable of reflecting on their parenting role and style, and seldom discuss the latter with health care professionals.

Despite ample evidence that mental illness runs in families, how and when risk for mental illness is passed from parents to offspring is still poorly understood. We need to identify the underlying environmental and (epi)genetic risk factors and mediating epigenetics and neural mechanisms (i.e. what are intermediate variables on the pathway from parental to offspring mental illness), and when these factors operate, e.g. during foetal development, early

childhood, adolescence, and into adulthood. At the same time, we need to identify resilience factors that counteract an existing risk and elucidate their mechanisms of actions. Only then can we advance our understanding of the aetiology of mental illness and uncover new targets for the development of preventive strategies to break the intergenerational cycle of mental illness and to support strengths and resource building.

Obtaining reliable quantitative and qualitative metrics in parents and their offspring may be informative of the likelihood of offspring to develop mental illness. Such metrics should include clinical, behavioural, environmental, as well as biological factors. Here, we will present the work of four familial high-risk offspring cohorts, presenting on (longitudinal) clinical, behavioural, environmental, genetic and neuroimaging analyses. Also, the FAMILY consortium (funded by the European Commission) will be introduced.

Caroline Vandeleur (Lausanne, Switzerland) will present on risk of specific psychopathology in offspring that is related to disease characteristics in their parents in the Lausanne offspring cohort. Merete Nordentoft (Copenhagen, Denmark) will share important clinical and biological findings from the VIA project that have been collected over the last decade. Simon Poortman (Rotterdam, Netherlands) will present on the neurodevelopmental trajectories in the Dutch Bipolar and Schizophrenia Offspring Study (DBSOS). Finally, Alex Gonzalez (Barcelona, Spain) will share the results from analyses combining genetic, epigenetic, environmental and clinical data in The Bipolar and Schizophrenia Young Offspring Study (BASYS). Martin Maziade (Quebec, Canada) will wrap up and will introduce and lead the discussion.

In this symposium, participants represent a mix in gender (3 male, 3 female) and seniority (2 junior, 4 senior) and all come from different labs in Europe and Canada.

42.1 DETERMINANTS OF THE PARENT-CHILD TRANSMISSION OF MOOD AND PSYCHOTIC DISORDERS: FROM FAMILIAL RISK TO ADVERSE ENVIRONMENTAL FACTORS

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Background: Studies focusing on the offspring of parents affected by mood and psychotic disorders, frequently referred to as the high-risk study, provide a powerful design for the identification of risk factors and early clinical manifestations of disorders in these offspring given their elevated familial risk. This identification is of critical importance for the development of early intervention strategies that could reduce morbidity and mortality related to mood and psychotic disorder outcomes. A small body of prospective research, which is the topic of this presentation, has cast new insight into the risk factors and trajectories of early psychopathology in high-risk offspring.

Methods: One of the most robust and widely studied risk factors for the development of bipolar and psychotic disorders is a positive family history, suggesting the potential role of genetic factors. Regarding mood disorders, previous analyses of our cohort in Lausanne and Geneva have revealed a strong association between early-onset bipolar disorder (BPD) in parents, but

not the later onset subtype, and the risk of BPD in offspring. The familial aggregation of early onset major depressive disorder (MDD) was also modestly associated with the risk of MDD in offspring. Although high-risk studies have produced conflicting findings regarding antecedents of mood disorders in offspring, several studies have found the index episode of BPD to mostly be depressive. In addition, two studies have found subthreshold hypomania to be a significant predictor of subsequent BPD, and separation anxiety disorder has been found to precede the onset of MDD in offspring. Furthermore, research has shown that offspring at familial risk of psychosis have an increased risk of developing motor development and language problems, difficulties in executive cognition, or problems with social adaptation.
Results: Studies of adults have further suggested that adverse environmental factors including physical or sexual abuse and stressful life events are involved in the development of mood and psychotic disorders, although these risk factors have more seldom been studied prospectively in high-risk offspring. Regarding psychosis, already in early childhood years, children born to parents with schizophrenia have shown an increased risk of experiencing trauma. Regarding mood disorders, poor parental-rearing attitudes and early life stress have been shown to be risk factors for the development of mood episodes among the offspring of bipolar parents, but high-risk studies on the risk of MDD following early trauma are scarce. Our own high-risk data show that childhood adversity is indeed more frequent in families of patients with both BPD and MDD than those of controls. However, this adversity was not associated with the risk of BPD in the offspring of bipolar parents. Regarding MDD, we found childhood adversity to mediate the risk between parental MDD and this risk in offspring.
Conclusions: In conclusion, existing prospective research has shown that children at familial risk of mood and psychotic disorders have an increased risk of developing psychopathology already early in life. Recent research also confirms the major impact of parental BPD on the risk of BPD in offspring, with a particular emphasis on the influence of the age of onset of the parental disorder. There is also evidence of increased childhood adversity in families of parents with mood and psychotic disorders. However, our data in Lausanne show that this adversity was not associated with the risk of BPD in offspring of bipolar parents, but we did find a strong prospective association between childhood adversity and the onset of MDD in our cohort of offspring.

42.2 THE DANISH HIGH RISK AND RESILIENCE STUDY – VIA

Merete Nordentoft*[1], Mette Falkenberg Krantz[2], Maja Gregersen[3], Nicoline Hemager[4], Aja Greve[5], Birgitte K. Burton[6], Kit Melissa Larsen[7], Hartwig Roman Siebner[8], Ole Mors[9], Anne Amalie Thorup[10]

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Background: Identifying disease mechanisms and possibilities for prevention and intervention before onset of illness will be extremely valuable. As early signs of schizophrenia and bipolar disorder are rare in the general population, longitudinal studies of enriched samples such as children with familial risk of these disorders can provide unique insights into disease processes. They are at increased risk of developing the same disorders as their parents, but also for developing other severe mental disorders. Fifty percent of all people suffering from mental disorders have their first contact with mental health services before the age of 18, and the peak incidence of schizophrenia is at age 22 years. Therefore, childhood to late adolescence offers a window of opportunity for elucidating pathogenic mechanisms. A better understanding of the early phases of the development of mental disorders, associated neurodevelopmental changes and needs of these children is pivotal for initiating early intervention studies with potential for prevention or reduction of mental illness.

Methods: In 2013-2016, we established the longitudinal Danish High Risk and Resilience Study VIA 7, a large, representative cohort of 522 7-year-old children born to parents with schizophrenia (202 children), bipolar disorder (120 children) or without these disorders (controls, 200 children). The comprehensive first, second and third wave of assessment (the VIA 7 study at age 7, the VIA 11 study at age 11, and the VIA 15 study at age 15) included psychopathology, neurocognition, social cognition, motor and social functioning, home environment, socioeconomic status, genetics and epigenetics. We also measured biological processes in blood and hair samples, such as methylation risk score, immune status, sex-hormones and cortisol. Data collections in VIA 11 (2017-2020) and VIA 15 (2021-2024), featured a comprehensive brain mapping protocol, including multi-modal, structural and functional MRI of the children's brains, MEG and EEG, polysomnography (measuring sleep patterns) and accelerometric assessment of physical activity.

Our aims are with the VIA 19 study are:

1. To improve insight into early disease processes of schizophrenia and bipolar affective disorder including symptom formation and psychopathology, impairments or delays of maturation in different domains of cognitive functioning including social cognition, paralleled by changes of brain structure and of patterns of brain activation.
2. To identify the influence of genetic, epigenetic and environmental exposures.
3. To develop a prediction model and a short test battery that allow for identification of early modifiable risk factors and risk markers, such as lack of stimulation and support in the home environment, traumatic events during childhood, neurocognitive and social cognitive deficits, sleep disturbances and early signs of psychopathology

Results: Results from the VIA 7 and the VIA 11 studies revealed significant differences in almost all the above-mentioned domains, especially between children born to parents with schizophrenia and controls. Briefly, we found that compared to controls, children of parents with schizophrenia were more likely to have child psychiatric disorders, psychotic experiences, lower cognitive function, poorer understanding of language, poorer motor functioning, more traumatic life events, low level of physical activity. Moreover, they were more likely to live in inadequate home environments, and to have structural brain changes at age 11.

Comparisons between VIA 7 and VIA 11 revealed that differences between groups generally prevailed or increased. Critically, longitudinal multimodal brain imaging allowed for the first time to capture structural and functional brain changes during disease formation.

We plan to carry out the fourth wave of assessments in The Danish High Risk and Resilience Study VIA 19, when the adolescents turn 19.

Conclusions: The Danish High Risk and Resilience Study has attracted national og and international awareness of children born to parents with severe mental illness. Moreover, models for intervention have been developed and are currently being investigated in randomised clinical trials.

42.3 NEURODEVELOPMENTAL TRAJECTORIES IN ADOLESCENT OFFSPRING OF PARENTS WITH SCHIZOPHRENIA OR BIPOLAR DISORDER

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Background: Offspring of parents with severe mental illness (e.g., bipolar disorder [BD] or schizophrenia [SZ]) are at elevated risk for developing psychiatric illness, owing to both genetic predisposition and increased burden of environmental stress during childhood. Emerging evidence indicates a disruption of brain structure and neural network connectivity in young offspring of BD and SZ patients, but the neurodevelopmental trajectories in this at-risk population remain to be elucidated. Using a cross-disorder longitudinal approach we investigate brain development in child and adolescent offspring with at least one parent with schizophrenia (SZo) or bipolar disorder (BDo) and compare them to offspring of parents without mental illness (Co).

Methods: A total of 298 T1-weighted scans were obtained from 189 offspring (aged 8-18 years at baseline) of at least one parent diagnosed with BD (n=82) or SZ (n=53) and community control offspring (n=54), of which 109 underwent a follow-up scan. Follow-up duration was between 2-6 years. FreeSurfer was used to segment the brain into global and local measures of brain volume, cortical thickness, and cortical surface area. Generalized Additive Mixed Models (GAMM) was applied to allow for nonlinear fits between brain metric and age for each group, correcting for sex. Trajectories were compared between groups. A total of 286 diffusion-weighted scans were obtained from 185 offspring of at least one parent diagnosed with BD (n=79) or SZ (n=52) and community control offspring (n=54), of which 103 underwent a follow-up scan. Anatomical brain networks were reconstructed into structural connectivity matrices with the number of streamlines (threshold≥5) between each pair of brain regions taken as the weight of their connection. Graph theoretical analysis was performed to obtain the connectivity strength, global efficiency, clustering coefficient, modularity from each connectivity matrix. Linear mixed-effects models were used to examine group differences in each brain network metric, including age, age-by-group, sex and scanner site as fixed effects, and family and within-subject dependence as random effects. All analyses were corrected for multiple comparisons using false discovery rate (FDR) at alpha=0.05.

Results: Preliminary GAMM results show differential trajectories with increasing age of cortical surface area between BDo and SZo (p=0.003) and of cortical thickness between BDo and Co (p=0.006). The surface area decrease in SZo is more pronounced with increasing age

than in BDo. Cortical thickness shows a less pronounced decrease in BDo compared to Co with increasing age. Sensitivity analyses show that the pattern of findings remains largely similar after correcting for level of IQ or presence of psychopathology. The linear mixed-effects analyses of the graph theory metrics yielded no significant effects of age on any of the brain network metrics in controls nor a difference in age effects between groups after FDR correction.

Conclusions: To conclude, our preliminary analyses show suggestive evidence for subtle deviations in brain developmental trajectories in child and adolescent offspring of parents with schizophrenia and bipolar disorder. In particular, surface area change may be different between SZo and BDo, with SZo showing a decrease during adolescence while BDo show an increase.

42.4 EVALUATION OF THE GENETIC AND EPIGENETIC ARCHITECTURE OF YOUTH AT HIGH FAMILIAL RISK OF SCHIZOPHRENIA AND BIPOLAR DISORDER

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Background: Schizophrenia (SZ) and bipolar disorder (BD) are highly prevalent and impairing conditions that have differential diagnostic criteria. However, a partially shared etiology could explain their familial aggregation and overlapping clinical and genetic features. The genetic architecture of SZ and BD is highly polygenic and the overlap between these disorders is estimated to be 60-70%. Thus, the construction of polygenic risk scores (PRSs) has proven to be a useful approach in disentangling their genetic underpinnings, overcoming the limitations of candidate gene approaches.

SZ and BD are associated with a shorter lifespan, which has been linked to age-related biomarkers and physiological conditions, suggesting that patients suffer from the effects of accelerated aging. Epigenetic modifications (changes in chromatin structure, specifically methylation of CpG dinucleotides) have been closely related to gene expression, cell senescence and functionality. Methylation patterns change throughout the lifespan, following a specific timing. With the use of methylation data, epigenetic clocks can be estimated to define the biological age of an individual. Studies in SZ and BD samples show controversial and inconsistent results reporting no differences between the epigenetic and chronological age and epigenetic deaccelerations.

Methods: The offspring of patients with SZ and BD and of community controls (6-17 years) were recruited from two hospitals in Spain, and biological samples were used to construct PRSs and epigenetic clocks. Sociodemographic, clinical and cognitive and data was assessed periodically for two years. We used biological and clinical data to characterize the (epi)genetic particularities of the young individuals at high familial risk, as well as to define their role in the progression of subclinical features and their putative interplay with environmental risk factors.
Results: Our findings provide further evidence of a shared genetic vulnerability of SZ and BD, found predominantly in youth at high familial risk. Epigenetic clocks showed a biological age deacceleration in high-risk individuals compared to controls, contrary to the age acceleration hypothesis. Prospective analyses with subclinical, cognitive and functioning data led to multiple conclusions. High SZ and BD PRSs and deaccelerated epigenetic age, which were overrepresented in the high familial risk individuals, were not associated with clinical progression – measured with subclinical psychotic symptoms, cognitive and functioning scales – at two years. Nonetheless, PRS reflecting the liability for depression and cognitive performance were associated with clinical features of all individuals, regardless of their parental diagnosis. The impact of cognitive PRSs on functionality was synergically modulated by the history of obstetric complications, suggesting that gene-environment phenomena can occur from early developmental stages.
Conclusions: Our research has so far yielded intriguing results that contribute to the understanding of the determinants of subclinical features preceding severe mental disorders. Genetics and epigenetics pose as a promising source of biological data to study the mechanisms underlying psychotic and mood disorders. The characterization of the psychopathological processes and their interaction with environmental stressors at early stages can contribute to the implementation of preventive and personalized clinical interventions in individuals at high familial risk that may ultimately help improve longitudinal outcomes.

43. DOES TREATMENT AFFECT THE TRAJECTORY OF COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA? EVIDENCE FROM LOW AND MIDDLE INCOME COUNTRIES

Lawrence Yang*, New York University*

Overall Symposia Abstract: Cognitive impairments are globally recognized as a core feature of psychosis. Clinical trials of antipsychotic (AP) treatment show modest but significant improvements in cognitive functioning; however, finding are constrained by narrowly defined samples of well-educated (i.e., ≥ high-school) individuals with psychosis (IWP) with short durations of untreated psychosis (DUP; i.e., <5 years) residing in primarily high income, urban, settings. To address the paucity of evidence from diverse settings, this symposium presents findings on the effects of AP medication on cognitive functioning from primarily rural regions across three distinct low- and middle-income countries (LMIC), each with sizeable samples of IWP with longer (>5 years) DUP. Because many IWP in rural LMIC have prolonged DUP preceding first treatment contact, we have a unique opportunity to study how initiating AP treatment after prolonged DUP is associated with cognitive outcomes across varying stages of illness – including first episode psychosis (FEP) and chronic never-treated psychosis (i.e., up to 20-30 years DUP). In this symposium, we present research from the three of the most well-established community-based, first treatment contact studies of IWP in LMIC. The first presenter will present data from rural China, comparing a community-dwelling treated IWP group to chronic never-treated IWP on the extent to which they accurately understand testing instructions during a standardized cognitive assessment – a prerequisite to obtaining valid

cognition data using standardized batteries. A second presenter will present baseline (prior to AP treatment initiation) and 1-year follow-up cognition data on 120 individuals with FEP in India receiving regular AP treatment, illustrating cognitive deficits among FEP in an LMIC setting and treatment effects at 1-year follow-up. A third presenter will present baseline and 2-year follow-up data on a community-based cohort of 210 IWP in Nigeria ascertained from psychiatric treatment facilities (~50%) and traditional/faith healing services (~50%) which typically provide minimal AP treatment, enabling the comparison of cognitive functioning across different levels of AP treatment exposure at follow-up. In the final presentation, we cross-sectionally compare cognition among a community-sample of treated IWP vs. never-treated chronic IWP in rural China (aged 24-75 years), to characterize overall treatment effects on cognition and to examine whether effects differ during later age (>65 years old). We will compare findings from these three LMIC settings with first-treatment contact studies from High-Income Countries to illuminate the similarities and differences that exist in the treatment of cognitive impairments in rural LMIC where DUP may be substantially longer. Response to AP medication among IWP with prolonged DUP will further delineate how treatment may mitigate long-term functional declines in previously untreated IWP and provide crucial insights into the neurobiological course of chronic psychosis. Results will have implications for the treated course of psychosis across varying illness stages in LMIC across diverse global settings.

43.1 COMPARISON OF ABILITY TO LEARN DIFFERENT TYPES OF TEST-TAKING TASKS OF NEVER-TREATED AND CURRENTLY-TREATED INDIVIDUALS WITH CHRONIC SCHIZOPHRENIA

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Background: We conducted cognitive assessments of community-dwelling individuals with chronic never-treated schizophrenia in rural parts of China using an adapted Chinese version of the MATRICS Consensus Cognitive Battery (MCCB-CV-R). Many participants could not understand the requirements of the tests when using the original MCCB test instruction, so we developed standardized expanded instructions to ensure that respondents understood what was expected to the greatest extent possible prior to formal testing.
Methods: We enrolled 134 individuals with untreated schizophrenia (UT), 134 matched individuals currently being treated for schizophrenia (TC) and 134 matched healthy controls (HC). The mean (sd) age of the 402 respondents was 49.2 (9.2) years; 59.7% were female; 94.8% lived in rural communities; their median (IQR) years of schooling was 4 (0-7) years (27.4% had never attended school); 89.4% had never used a computer; and the mean duration of illness in patients was 20.5 (9.5) years.
Respondent's ability to learn the requirements of each test (i.e., able to independently complete the practice example or correctly state the expected requirement) was rated by the interviewer: 1=refusal to do the test; 2=unable to successfully complete the training after 6 extra instructions; 3=able to complete the training after 2 to 6 extra instructions; 4=able to complete the training after 1 extra instruction; and 5=able to complete the training after the initial instruction. This measure of training success had good interrater reliability (mean kappa=0.74, range: 0.59-0.86).

The ten tasks (nine MCCB-CV-R tests and ability to use a computer mouse) were subclassified into four types: three tasks requiring the use of paper and pencil, three tasks requiring respondents to verbally re-state test requirements, two tasks requiring manual dexterity, and two tasks involving use of a computer. Refusals were excluded from the analyses.

Results: Based on Kruskal Wallis (rank) Tests comparing mean ranks of the training success score between the 3 groups (and parallel ANOVA tests), the ability to learn all 10 tasks was best in HC, intermediate in TC, and poorest in UT. HC performed significantly better than TC except in the animal naming test, and TC performed significantly better than UT except in the 3 paper and pencil tests. The mean (sd) training scores for all 10 tasks for HC, TC and UT (4.51 [0.47], 4.13 [0.72], and 3.76 ([0.91]; $F=34.27$, $p<0.001$) were significantly different between the three groups. A similar pattern was found when comparing the means for the four types of tests. Group differences remained significant after adjustment for age. Age was a significant predictor of the mean training score for all 10 tasks (unstandardized Beta=-0.027, $t=-7.32$, $p<0.001$) and of the mean training scores of the 4 types of tests; however, the interaction term of age by group was not significant for any of these analyses.

Conclusions: This study finds that the ability to learn new tasks is significantly impaired in patients with chronic schizophrenia compared to HC. With the exception of the ability to learn task that require the use of paper and pencil, the impairment in the ability to learn tasks is significantly greater in never-treated patients than in currently-treated patients. The ability to learn new tasks decreases steadily with age in all three groups, but the rate of decline does not vary between groups. We conclude that treatment with antipsychotic medications decreases the magnitude of the impairment in the ability to learn new tasks of individuals with schizophrenia, but it does not change the downward trajectory of the ability to learn new tasks with age that equally affects persons with and without severe mental illness.

43.2 TRAJECTORY OF COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA: EVIDENCE FROM INDIA

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Background: Cognitive deficits in persons with psychosis appear to be present across the different stage of the illness. Data from India shows that 70% of the patients with schizophrenia and 40% with the first episode of psychosis have cognitive deficits (Talreja, 2013; PS Bhat,2021). This presentation is put together based on the work done at the Schizophrenia Research Foundation (SCARF) over the past 15 years. It will cover data from various studies on individuals in different stage of illness, namely first episode psychosis (FEP), early-stage schizophrenia, chronic schizophrenia and data from the INTREPID II study.

Methods: 120 individuals with FEP were recruited at two different time points to evaluate the course and outcome of their illness. Cognitive function was assessed at baseline and after one year. All individuals with FEP were on regular treatment. Around 80 individuals were able to attempt the cognitive assessments and not all of them could complete all the tasks; accordingly, the sample size varied across different tests. The mean age of the sample was 29 years, 60% of participants were female, and the mean duration of illness was around 32 weeks.

Results: Initial results include the following: full analyses will be presented at the session. Analysis of pre- post treatment data revealed that executive function (Set shifting ability, fluency, working memory) improved in persons with FEP over time. A prominent feature was that a majority of the patient's cognitive scores were not highly impaired at baseline.

Conclusions: The pattern of cognitive deficits (including contrasting results with those found in High Income Countries), role of education in evaluating cognitive deficits in persons with psychosis, and the challenges faced in assessing cognition in this sample, will be discussed.

43.3 A TWO-YEAR TRAJECTORY OF COGNITIVE IMPAIRMENTS AMONG PERSONS WITH PSYCHOSIS IN NIGERIA

Oye Gureje*[1], Olatunde Ayinde[2], Olufemi Idowu[3], Tessa Roberts[4], Georgina Miguel Esponda[5], Alex Cohen[6], Helen Weiss[7], Sujit John[8], Joni Lee Pow[9], Casswina Donald[9], Bola Olley[10], Robin Murray[11], Rangaswamy Thara[12], Gerard Hutchinson[13], Craig Morgan[14]

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Background: Cognitive impairments are commonly associated with schizophrenia, and these could cut across several domains. There is evidence that the impairments are present even among patients who are medication-naive, thus suggesting that the impairments represent core features of the disorder and may indeed have developmental origin. Even though much evidence for this association has come from studies conducted in North America, Western Europe and Australasia, there is a growing body of research from the Global South examining the same features. These studies are important in broadening our understanding of the origin, impact and course of these impairments. In particular, our understanding about the effect of treatment on the trajectory of the impairments is incomplete and in need of more explorations across diverse settings, including those with unique health system profile.
Methods: As part of the International Programme of Research on Psychotic Disorders (INTREPID) II, individuals with an untreated psychotic disorder in Nigeria were identified through a comprehensive case detection system that included professional, folk, and popular sectors. Over a two-year period, 210 such persons, resident in three defined catchment areas and aged between 18 and 64 years, were identified. Interviewed with the Schedules for Clinical Assessment in Neuropsychiatry (SCAN), they were diagnosed as having psychotic disorder based on ICD-10 criteria, with most having schizophrenia. Along with the same number of age- and sex-matched controls, these persons were assessed with the Brief Assessment of Cognition for Schizophrenia (BACS).
Results: Baseline analyses have shown that persons with psychotic disorder performed worse than controls on the BACS domains. The mean scores on the domains of BACS among cases and controls respectively were verbal memory 29.4±11.7 vs 39.1±10.8, Digit sequence 16±7.7 vs 2±1.0, Motor function 52.3±20.1 vs 73.1±20.5, verbal fluency 22.3±11.4 vs 34.9±14.4, symbol coding 18.3±17.0 vs 32.0±22.4 and Tower of London 10.1±7.5 vs 15.1±7.2. A two-year follow-up assessment has now been conducted on the 170 (82%) of the 210 cases, including a repeat of the BACS as well as symptom and functional outcomes. Because the baseline cases were recruited from biomedical service facilities (51%) and folk (traditional/faith healing) services (45%), the sample presents very important differences in their subsequent exposure to psychotropic medication over the follow-up period.
Conclusions: In this presentation, we shall be exploring how those differences affect the trajectory of their cognitive performance.

43.4 EXAMINING MEDICATION IMPACTS ON COGNITIVE FUNCTIONING AMONG PEOPLE WITH SCHIZOPHRENIA FROM YOUNG ADULTHOOD TO LATER LIFE: A CROSS-SECTIONAL COMPARISON BETWEEN TREATED AND NEVER TREATED INDIVIDUALS FROM RURAL CHINA

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Background: Clinical trials of antipsychotic (AP) treatment show modest but significant improvements in cognitive functioning - a central area of impairment among individuals with schizophrenia (IWS). For never-treated IWS advancing into later age (>65 years) who largely reside in In Low- and- Middle-Income Countries (LMIC), impairments could become even more pronounced given the combined effects of aging and illness progression. Accordingly, AP treatment may mitigate cognitive impairments that may become progressively worse as untreated IWS enter into later age. We utilize a rare opportunity in rural China (Ningxia Province) to compare cognition among a community-sample of treated IWS vs. never-treated chronic IWS to characterize overall treatment effects on cognition, and whether these may differ during later age.

Methods: The MATRICS Consensus Cognitive Battery (MCCB), adapted for use with a largely rural, under-educated Chinese sample, was administered to 134 treated IWS and 134 never-treated IWS, matched on gender, age, ethnicity, education, urban v. rural residence, and duration of illness. Respondents were: 94.8 % rural residents and 59.7 % female, with a mean age of 49.2 years, mean years of education of 4.2 (25.7% had never attended school), and mean duration of illness was 20.5 years. MCCB composite T scores were computed and adjusted for matching variables. Differences in mean predicted MCCB composite T scores were examined with independent samples t-tests. An interaction analysis subsequently tested whether AP treatment moderates cognitive impairments with increasing age.

Results: Never-treated IWS (mean= 38.8, SD = 1.2) showed significantly lower MCCB composite T scores compared to treated IWS (mean= 41.8, SD= 1.2) overall ($t[266] = 20.4$, p-value <0.001). These differences were observed both among the young- to-mid adult age group (up to 64 years old) and among those aged 65 or older. Interaction analysis results suggest that the slope of cognition decreases across age groups was approximately the same for both groups ($\beta = -0.001$, 95%CI[-0.15, 0.15], $p = 0.99$). Despite not showing differences in slopes, the treated IWS group showed higher cognition scores at young adulthood when compared with the untreated IWS group, which stayed relatively consistent through ages 65 or older (differences between treated vs. untreated IWS groups ranged from 2.4 to 3.1 from ages 24-75).

Conclusions: Findings support that treated IWS have significantly better cognitive performance compared to never-treated IWS both at the earlier and later stages of illness. AP treatment, however, does not appear to moderate cognitive impairments as age increases. Thus, while initiating treatment produces a significant boost in cognition that may persist across the stages of illness, it may not differentially impact rates of cognitive impairment as IWS age. Implications of our findings on "accelerated aging", including the untreated group showing worsened cognition earlier in life, followed by age-related decreases that can result in more severe cognitive-related impairments in older age, will be discussed.

44. DISTURBANCES OF THE SELF-OTHER BOUNDARY IN SCHIZOPHRENIA

Amy Jimenez, *VA Greater Los Angeles Healthcare System*

Overall Symposia Abstract: Characterization of disturbances of the self-other boundary in schizophrenia is well established, dating back at least to the initial identification of First Rank Symptoms (FRS) by Schneider in the last century. While not specific to schizophrenia, mounting evidence suggests these symptoms may drive other features of the illness, especially difficulties with interpersonal connections and other impairments in social functioning. Recent empirical findings from phenomenological and neuroscience research have signaled renewed interest in this topic and converging evidence suggests that self-other disruption is a fundamental aspect of the disorder. Innovative experimental designs have demonstrated alterations in several indices of self-other disturbance, including reduced white matter connectivity, an anterior to posterior shift in cortical midline neural activity during self-processing, abnormalities in perceived space between people, reduced sense of agency and body ownership, as well as fragmentation and imprecision of temporal processing at the neural level.

The four presentations in this panel will highlight recent and ongoing work in this area utilizing methodologies ranging from phenomenology to neuroscience. Dr. Holt will present findings from work examining the neural mechanisms of social distancing behavior in schizophrenia. Specifically, she will show how alterations in a parietal-frontal-subcortical network relate to variations in personal space characteristics in individuals with the disorder. Dr. Jimenez will present work showing alterations in cortical midline activity during tasks of self-related processing, including self-referential judgments. She will further show preliminary evidence that similarly altered patterns of neural activity are associated with impairments in affective and cognitive empathy. Dr. Northoff will present work on aberrant inner time consciousness, a key phenomenological feature of self-disturbance in schizophrenia. Based on results from several EEG studies, he will demonstrate abnormal random changes in phase cycle dynamics, yielding highly irregular, temporally imprecise signal in patients. Dr. Park will present findings from a series of multisensory integration experiments in virtual reality that examine self-other boundary (peripersonal space; PPS) in schizophrenia under social interactional and nonsocial (danger vs. safe) conditions to understand the function of the PPS as a protective zone between the self and the world. Finally, Dr. Nasrallah, who has been researching this topic for decades, will serve as the panel discussant. Together, these presentations will provide a well-articulated framework from which we can form a more nuanced understanding of this fundamental deficit in schizophrenia.

44.1 NEURAL MECHANISMS OF INTERPERSONAL DISTANCE IN PSYCHOTIC AND HEALTHY INDIVIDUALS: DISTINCT PATHWAYS TO A COMMON BEHAVIOR

Daphne Holt*[1], Louis Vinke[1], Mona Nasiriavanaki[1], Nicole DeTore[1], Clayton Jeffrey[1], Amritha Harikumar[1], Rachel Sussman[1]

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Background: The space immediately surrounding the body serves as an interface between the physical self and the outside world. Neurophysiological studies in humans and non-human primates have identified a frontoparietal-subcortical system that monitors the stimuli and actions that occur near the body and responds to the intrusion of others into this space. In both clinical and non-clinical populations, preferences for certain physical distances from others

("personal space") have been linked to variation in psychological traits or states, such as social anhedonia, anxiety, and paranoia. In the current study, we measured interpersonal distances and responses of the brain during personal space intrusions in order to further investigate the neural mechanisms of personal space and social functioning in individuals with and without diagnoses of psychotic disorders.

Methods: 37 individuals with non-affective or affective psychotic disorders and 60 demographically-matched control subjects (viewed 3D images of faces that appeared to approach or withdraw from them while fMRI data were collected. Resting-state functional connectivity, symptoms and personal space preferences were also measured. The fMRI data were analyzed with Freesurfer using a region-of-interest approach, focused on independently-defined sites within the superior, inferior and medial parietal cortices, dorsal and ventral premotor cortices, dorsal and ventral striatum and the amygdala.

Results: Preferred interpersonal distance was significantly correlated with a lower differential response of the inferior parietal cortex (IPS) to approaching vs. withdrawing faces in the full sample ($r = -0.26$; $p = 0.011$) and in the psychosis ($r = -0.35$; $p = 0.031$) but not the control group ($r = -0.19$; $p = 0.139$). In the psychosis group, interpersonal distances were also correlated with IPS-ventral striatal connectivity ($r = 0.35$; $p = 0.034$), whereas in the control group, interpersonal distances were correlated with IPS-amygdala connectivity ($r = 0.43$; $p < 0.001$). Lastly, in the psychosis group, IPS-ventral striatal connectivity was associated with levels of symptoms of schizophrenia (PANSS Total and General scores), social anxiety and social dysfunction (all $p < .05$).

Conclusions: These findings suggest that distinct neural pathways in psychotic and non-psychotic individuals, involving the ventral striatum and amygdala, respectively, influence a common neural-behavioral phenotype: the regulation of personal space by the inferior parietal cortex. Understanding the role of this model system in social behavior may generate new insights about the neurobiological mechanisms of social dysfunction in psychotic illness.

44.2 NEUROIMAGING OF IMPAIRED EMPATHY IN SCHIZOPHRENIA IMPLICATES CORE DISTURBANCE AT THE SELF-OTHER BOUNDARY: PRELIMINARY ANALYSES

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Background: Self disturbance is a fundamental characteristic of schizophrenia, with important clinical and functional implications. Reduced sense of self has downstream effects on cognitive abilities such as empathy, the ability to understand and share the mental states of others. Empathy is an emergent phenomenon that integrates both low and high level social processes, including perspective taking. Empathy requires one to draw upon their own experiences and self-knowledge to understand the experience of others. At the same time, empathy requires the ability to control and inhibit self-focus and reorient to focus on others. Thus, optimal empathic response requires adequate self-other distinction. In healthy controls, empathy is associated with activation in several midline cortical regions also implicated in self-processing, including medial prefrontal cortex (mPFC) and posterior cingulate (PC), as well as ventrolateral prefrontal cortex (vlPFC). Several aspects of empathy are consistently impaired at both the behavioral and neural level in schizophrenia; however, whether this impairment extends to perspective taking has not been fully explored.

Methods: A preliminary sample of 22 individuals with schizophrenia and 13 healthy controls completed a visual perspective-taking task during fMRI in which a "director" asks them to move an object on a shelf. To respond accurately, participants must take the perspective of the director, which is either the same or different from their own. The primary behavioral outcomes were accuracy and response time. The primary imaging outcome was the contrast between different versus same perspective during experimental trials. Mean beta values were extracted from the three key regions of interest (ROIs) associated with empathy described above. Repeated measures ANOVA was used to examine within- and between-group effects.
Results: Data collection is currently ongoing; results from the current preliminary sample are provided here. In terms of behavioral data there was a significant main effect of group ($F(1,33) = 20.53$, $p < .001$) and a group by condition interaction ($F(1,33) = 6.63$, $p < .05$) for accuracy. Specifically, individuals with schizophrenia were less accurate than controls overall. In addition, whereas accuracy did not vary by condition for controls, patients performed worse when required to take a different perspective from their own. For the imaging data, all ROIs showed a significant main effect of condition, indicating greater activation when taking a different perspective compared to one's own. For mPFC there was a main effect of group ($F(1,33) = 9.27$, $p < .01$), indicating reduced activation across conditions in patients compared to controls. For vlPFC there was a group by condition interaction ($F(1,33) = 5.91$, $p < .05$) indicating that activation varied by condition for controls (i.e., greater activation for different compared to same perspective) but not for patients.
Conclusions: The current study extends previous findings of impairment in some aspects of empathy in schizophrenia (i.e., reduced ability to make complex inference about another's beliefs, feelings, and intentions) to show that simple visual perspective taking to infer which objects someone else sees is also reduced. This deficit was reflected in blunted mPFC activation, a region consistently implicated in both empathy and self-processing, as well as reduced responsivity to task demands in vlPFC, a region critical for inhibition and reflexive reorienting. Although preliminary, the current findings add to a growing body of literature implicating a core disturbance of self as a potential basis for impaired empathy in schizophrenia.

44.3 SCHIZOPHRENIA AND THE SELF - TEMPORAL FRAGMENTATION AND IMPRECISION

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Background: Schizophrenia is characterized by a basic self-disturbance the neural correlates of which remain unclear yet. One key phenomenological feature of the basic self-disturbance is abnormal inner time consciousness which is often experienced fragmented. What are the neural corelates of such temporal fragmentation of self? This is the goal of our study.
Methods: Method: We investigate 20 schizophrenic patients and 20 healthy controls; both groups underwent EEG during resting state and a self-other enfacement task which requires temporal integration on the psychological level. Temporal integration on the neuronal level was measured by the autocorrelation window (ACW) that reflects the brain's intrinsic neural timescales (INT). Moreover, we obtained phenomenological markers using the EASE for the basic self-disturbance. Finally, we support the assumption of temporal disturbances on the phenomenological level by presenting data from our newly developed scale for time-space experience in psychosis (STEP).
Results: We show significant changes in temporal integration on the psychological level as by altered self-other distinction with prolonged self in the enfacement task in schizophrenia. This

is accompanied by prolonged ACW during task and decreased ACW rest-task difference indexing abnormal temporal integration on the neuronal level. Finally, we present phenomenological data on the STEP showing the diagnostic specificity of temporal fragmentation experience for schizophrenia.
Conclusions: Conclusion: Our data demonstrate temporal irregularity and imprecision with temporal fragmentation and abnormal temporal integration on neural, psychological, and phenomenological levels. This is supported by present data as well as other which will be indicated in my talk. Together, the basic self-disturbance may be traced to temporal abnormalities, e.g., irregularity and imprecision on neural, psychological and phenomenological levels of activity in schizophrenia. In short, schizophrenia may essentially be a temporal disorder on the millisecond range.

44.4 SELF-OTHER BOUNDARY UNDER PHYSICAL AND SOCIAL THREAT IN SCHIZOPHRENIA

Sohee Park*[1], Hyeon-seung Lee[1], Tatiana Baxter[1], Michael Sangimino[1], Lauren Buck[2], Robert Bodenheimer[1]

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Background: An implicit awareness of clearly defined self-boundary is a prerequisite for adaptive interactions with the external world. In individuals with schizophrenia (SCZ), however, disrupted self-other boundary complicates the process of distinguishing one's own behavior from those of others, thereby undermining adaptive social interaction, which further erodes interpersonal relationships and exacerbates self-disturbances. Despite the chronicity and prevalence of self-other processing and social impairments in SCZ, mechanisms underlying disrupted self-other distinction have not been extensively investigated due to scarcity of tools to quantify the subjective phenomenology of self-disturbances. To address this gap, two studies were conducted. First, we examined phenomenology of self-disturbances in relation to psychosis-risk. Second, we investigated implicit multisensory action space around the self that determines one's self-other boundary (peripersonal space; PPS) in SCZ.
Methods: Study 1: An online anonymous survey of psychosis-risk and anomalous self-other boundary was distributed. Psychosis-risk was assessed with the Prodromal Questionnaire (PQ-16; Ising et al., 2012). A picture-based inventory of bodily-self aberrations (B-BODI; Benson et al., 2019) was used to document two key aspects of self-boundary disturbance: breach or loss of self-boundary and intrusion into self-space. Study 2: A multisensory integration task in virtual reality (VR) (Lee et al., 2021) was used to estimate the size and the gradient (shape) of the PPS in SC and matched control group (CO) for physical interactions with a safe or a dangerous object. Study 3: A similar multisensory task was used to estimate PPS in SC and CO for social interactions with an avatar that could be either threatening or neutral. Symptoms, paranoia, anxiety and loneliness were assessed in SC and CO.
Results: In Study 1, 58% reported experiencing intrusion into self-space, 41% reported loss of self-boundary and 29% reported both. Participants at-risk for psychosis reported significantly greater B-BODI scores for both loss of self-boundary and intrusion into self-space than the low-risk group. In Study 2, (perceived) physical danger sharpened the self-other boundary and reduced false-alarm errors of SC. These findings suggest that physical danger might diminish the group difference between SC and CO. In Study 3, social threat did not change the sizes of PPS overall but the changing pattern of slopes were significantly different across conditions. PPS gradient changed depending on the perceived danger of the social encounter for both groups but in the opposite direction. Self-other boundary became more diffuse and uncertain under social threat in SC. In contrast, self-other boundary was sharpened under social threat in

CO. Across both groups, paranoia was associated with sharper self-other boundary under social threat. Lastly, SC were more likely to report experiencing intrusion into their PPS.
Conclusions: Systematic examination of the self-other boundary may be a first step towards identifying the role of self-disturbances in components of disrupted social behavior. In Study 1, we found that whilst subjective experience of disrupted self-boundary is relatively common in the general population, those at risk for schizophrenia reported much greater rates of intrusion into self-space and loss of self-boundary than low-risk individuals. The two multisensory experiments allowed us to estimate PPS size and shape in response to perceived physical and social threat. Weakened self-other boundary under social threat in SC suggests a maladaptive response to impending danger. Lastly, paranoia may serve a protective function since it appears to sharpen self-other boundary in both groups. Elucidating how maladaptive social interactions may arise from basic problems of multisensory integration (i.e. disrupted self-other boundary) could lead to a more precise treatment targets, and therefore, contribute towards reducing social disability of individuals with conditions that disrupt self-other processing such as schizophrenia.

45. NEUROBIOLOGICAL HETEROGENEITY OF BRAIN STRUCTURE AND FUNCTION IN SCHIZOPHRENIA SPECTRUM DISORDERS: TURNING A CHALLENGE INTO AN OPPORTUNITY FOR BIOMARKER DISCOVERY AND TREATMENT INNOVATION.

Colin Hawco*, Centre for Addiction and Mental Health, University of Toronto*

Overall Symposia Abstract: Behavioural and neurobiological heterogeneity in people with a Schizophrenia Spectrum Disorder (SSD) has, thus far, been a major obstacle to the identification of consistent biomarkers. The cross-sectional, case-control approach has not adequately accounted for heterogeneity; traditional case-control comparisons assume DSM-based diagnostic categories are relatively homogeneous within a diagnosis and with limited between-diagnoses overlap, which does not appear to be the case. Both non-psychiatric controls and people with psychiatric illnesses have significant variability in brain structure and function. For example, group-level differences in SSD network connectivity may be partially explained by spatial shifts in cortical network organization/topology as opposed to reduced connectivity. Yet group-level differences remain a primary focus of the majority of research, despite recent data from large-scale consortia studies showing small effect sizes and lack of diagnostic separation at the individual level. Research may be reaching a point of diminishing returns on cross-sectional studies with case-control comparisons, with recent work published in Nature suggesting thousands of participants may be required for replicable group-level brain-behavior associations. Therefore, a shift is needed to advance clinical and neurobiological research using MRI in psychiatric illnesses. We propose an examination of individual variability and neurobiological heterogeneity not as an obstacle for biomarker discovery, but an opportunity to consider differences at the individual level. Heterogeneity will be examined through multiple perspectives. First, Dr. Phil Homan will examine functional frontostriatal dysconnectivity during model-based learning as a phenotype explaining heterogeneity in psychotic symptoms in early psychosis. Dr. Ángeles Tepper will examine functional connectomes' inter and intra-individual heterogeneity using several metrics with a test-retest approach in first episode psychosis relative to controls, related to symptom characteristics and medication. Ms. Julia Gallucci will examine a metric of individual variability and idiosyncrasy during a cognitive task in both SSD and bipolar disorder, as well as relationships with cognitive function and progressive illness effects in SSD. Lastly, Drs. Christos Davatzikos and Mathilde Antoniades will examine machine learning approaches to uncovering novel subgroups of SSD based on brain structure, through a lens considering

deviation from a control group. Together, this symposium will demonstrate that effects observed at the group level are not present in many individuals with SSD, that variability and individual deviation from the norm can represent a powerful measure of brain structure and function with potential implications for treatment outcomes, and that by leveraging the heterogeneity observed across individuals with SSD we can gain novel insights into the neurobiology and diversity observed in these individuals.

45.1 NEUROCOMPUTATIONAL PHENOTYPING OF EARLY-PHASE PSYCHOSIS

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Background: Neurocomputational phenotypes of early psychosis might capture variability in treatment response to antipsychotics. Here, we assumed that one such phenotype, clinically showing persistent delusions of persecution, can be formally characterized by impaired updating of internal models of a threatening world – a phenomenon known as uncorrectability. We used reinforcement learning and computational modeling in an aversive context to quantify this impairment of model-updating. By using functional magnetic resonance imaging (fMRI) we probed how model-based learning is related to connectivity between prefrontal and subcortical areas in a transdiagnostic cohort of early psychosis patients. We hypothesized that functional connectivity between the triad of ventrolateral prefrontal cortex (VLPFC), dorsal anterior cingulate cortex (ACC) and ventral striatum is associated with impaired model-based learning in an aversive context.
Methods: We recruited a cohort of transdiagnostic patients with early psychosis (defined as a cumulative exposure to antipsychotics of less than two years) and healthy controls. On a single day, both groups had a comprehensive clinical assessment including a cognitive battery before a scan of resting state functional connectivity followed by a two-stage reinforcement learning task during functional magnetic resonance imaging (fMRI) in an aversive context. The reinforcement learning task allowed us to contrast model-free habitual learning versus the more cognitively demanding model-based goal directed learning, and to compare computational models of various complexity to find an optimal fit to these data.
Results: Preliminary results in early psychosis patients (N=31) and healthy controls (N=12) showed that a model with distinct learning rates for model-free and model-based learning best explained the data in both groups. More impaired model-based learning was associated with lower ventrolateral prefrontal cortex connectivity to the putamen but with higher ventrolateral prefrontal cortex connectivity to the anterior cingulate cortex. We also found that the impairment in model-based learning increased with psychotic symptoms.
Conclusions: These results suggest that a neurocomputational phenotype of impaired model updating is associated with frontostriatal dysconnectivity and with the variability in psychotic symptoms.

45.2 INTRA AND INTER-INDIVIDUAL VARIABILITY IN FUNCTIONAL CONNECTOMES OF PATIENTS WITH FIRST EPISODE OF PSYCHOSIS

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Background: Schizophrenia is a heterogenous mental disorder with high variability in clinical profiles displayed by patients. Not only two people diagnosed with this disorder may show different clinical presentations (inter-individual variability), but also a single patient may show different symptomatic patterns along their medical history (intra-individual variability). In fMRI studies, functional connectomes have been shown to carry individual-level information, which can be associated with cognitive and behavioral variables. Moreover, functional connectomes have been used to identify subjects within a group, as if they were fingerprints. For the particular case of patients with Schizophrenia, previous cross-sectional studies have shown that there is reduced connectome stability as well as higher inter-individual variability.
Methods: We studied connectomes' inter and intra-individual heterogeneity with a test-retest approach of two resting-state fMRI scanning sessions (17.51 ± 6.31 weeks between sessions), and related them to clinical variables measured at these two times (PANSS total score and antipsychotic's dose, (AP dose)). Our sample consisted of 30 patients with First Episode of Psychosis and 32 Healthy Controls and we computed three measures: Deviation from Mean Healthy Connectome (correlational distance to the mean connectome of the healthy controls' group); Iself (correlation between the two sessions of the same subject); and intra-group Iothers (mean of all pairwise correlations between subjects in the same group).
Results: In our patients' group, and correcting all of our analyses for age, sex and framewise displacement, we found increased deviation from mean healthy connectome ($p = 0.040$) and increased intra-group inter-subject variability (reduced Iothers, $p = 0.002$). This last measure was associated with symptoms' levels ($p = 0.021$) and antipsychotic's dose ($p = 0.043$), indicating that patients with higher PANSS scores and higher AP doses are less similar to other patients. Regarding intra-subject variability, we were unable to replicate previous findings of reduced connectome stability ($p = 0.151$, Iself between groups comparisons), presumably due to lack of statistical power for this analysis in which we cannot profit from repeated measures (by definition, we get only one Iself measure per subject).
Conclusions: Our findings of higher inter-subject variability in Schizophrenia are consistent with the clinical heterogeneity of the disorder. Such high variability can be a crucial factor for group-means comparisons, where brain regions with low inter-subject variability are more likely to reach statistical significance than regions with higher inter-subject variability. Our results then, highlight the relevance of variability characterization in Schizophrenia as a necessity for developing accurate diagnostic tools as well as precision clinical treatments.

45.3 LONGER ILLNESS DURATION IS ASSOCIATED WITH GREATER INDIVIDUAL VARIABILITY IN FUNCTIONAL BRAIN ACTIVITY IN SCHIZOPHRENIA, BUT NOT BIPOLAR DISORDER

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Background: Individuals with schizophrenia exhibit greater inter-patient variability in functional brain activity during neurocognitive task performance. Some studies have shown associations of age and illness duration with brain function; however, the association of these variables with variability in brain function is not known. In order to better understand the progressive effects of age and illness duration across disorders, we examined their relationship with individual variability in brain activity. We hypothesized that a longer illness duration would be associated with greater variability uniquely in the schizophrenia group. Further, we anticipated the effects of aging on variability may be more pronounced in the schizophrenia group compared to the bipolar disorder and control groups.
Methods: Neuroimaging and behavioural data were extracted from harmonized datasets collectively including 212 control participants, 107 individuals with bipolar disorder, and 232 individuals with schizophrenia (total n=551). Functional activity in response to an N-back working memory task (2-back vs 1-back) was examined. Individual variability was quantified via the correlational distance of fMRI activity between participants; mean correlational distance of one participant in relation to all others was defined as a 'variability score'. A hierarchical regression was performed to evaluate the nonlinear effects (quadratic and cubic) of age and illness duration on mean correlational distance.
Results: Greater individual variability was found in the schizophrenia group compared to the bipolar disorder and control groups (p=1.52e-09). Individual variability was significantly associated with aging (p=0.027), however, this relationship was not different across diagnostic groups. In contrast, in the schizophrenia sample only, a longer illness duration was associated with increased variability (p=0.027).
Conclusions: A recently completed follow-up study examining changes following brain stimulation indicate that variability can be reduced by transcranial magnetic stimulation, demonstrating clinical relevance for the observed variability and possible utility as a treatment target. Considered in its entirety, our results shed light on several present topics within the field of schizophrenia research. For instance, the heightened amount of variability found endorses the biological findings in psychiatry that have revealed the expression of schizophrenia is not an all-or-none phenomenon and there is immense heterogeneity among patients. As current literature stresses the necessity of a more in-depth analysis at the subject level, our findings support the use of individual metrics that can better characterize variability as well as improve our understanding of schizophrenia for more accurate diagnosis and treatment. Further, the increase in variability observed in the schizophrenia group was related to illness duration, beyond the effects of normal aging, implying illness-related deterioration of cognitive networks. This has clinical implications for considering long-term trajectories in schizophrenia and progressive neural and cognitive decline which may be amiable to novel interventions.

45.4 DEEP LEARNING METHODS REVEAL DISTINCT NEUROANATOMICAL PATTERNS OF SCHIZOPHRENIA

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Background: Patients diagnosed with schizophrenia display substantial heterogeneity in terms of their clinical characteristics and symptoms, treatment response, and long term prognosis.

This heterogeneity stems at least partially from distinct subtypes of patients with differentially affected neurobiology and neuroanatomy.
Methods: We investigated neuroanatomical heterogeneity in a multi-site, multi-ethnic cohort using a semi-supervised machine learning method called HYDRA. HYDRA seeks to cluster illness effects by modelling differences from healthy controls rather than clustering patients directly. HYDRA was applied to 145 harmonized regional gray matter volumes from 364 healthy controls and 307 patients with schizophrenia from 3 sites in the PHENOM consortium (Chand et al., 2020).
We then extended this research to a larger sample within the PHENOM consortium and re-applied HYDRA as well as a novel semi-supervised clustering method called SmileGAN to regional gray matter volumes from 1068 healthy controls and 1178 patients with schizophrenia spectrum or psychotic disorders from 12 sites. Combining generative adversarial learning with a clustering algorithm, SmileGAN learns one-to-many mappings to generate fake patient data that is equivalent to real patient data and identifies subtypes that are independent from one another.

Results: The initial HYDRA analysis on the smaller dataset revealed two distinct neuroanatomical patterns (Chand et al., 2020). Pattern 1 showed widespread lower gray matter volumes, most prominent in the thalamus, nucleus accumbens, medial temporal, medial prefrontal/frontal and insular cortices. Pattern 2 showed increased volume in the basal ganglia and internal capsule, and otherwise normal brain volumes. There were no differences in age, sex, illness duration, antipsychotic dose, age of onset or PANSS score between the neuroanatomical subgroups. Pattern 1 had a positive correlation between illness duration and gray matter volume and a lower educational attainment than Pattern 2.
When the same HYDRA method was applied to the larger sample, we also found an optimal solution of k=2 with neuroanatomical patterns characterized by widespread increases and decreases, respectively.

However, preliminary results from the SmileGAN analysis suggest a more fine-grained parsing of heterogeneity with a 4-pattern solution. Here, Pattern 1 had increased volume in the basal ganglia, ventricles and internal capsule and reduced volume in hippocampal and fronto-temporal regions. Pattern 2 had increased basal ganglia and thalamic volumes and widespread increases in cortical regions but reduced ventricle volume. Pattern 3 was characterized by increased volume in the pallidum and ventricles and decreased hippocampal, thalamic, nucleus accumbens and cortical regions. Lastly, Pattern 4 had widespread cortical reductions in volume, except for increased volume in the ventricles.

Conclusions: Our results define novel neuroanatomical patterns of schizophrenia and suggest that previous case-control reports of widespread subtle volumetric deficits and subcortical enlargement are unlikely to be present in all patients. These neuroanatomical subgroups could contribute to precision clinical care that accounts for biological heterogeneity in diagnosis, prognosis, and treatment.

46. ADVANCES IN DIGITAL HEALTH INTERVENTIONS FOR EARLY PSYCHOSIS CARE

Wanda Tempelaar*, Erasmus University Rotterdam, the Netherlands*

Overall Symposia Abstract: The importance of early detection and treatment of psychosis is recognized globally. However, young adults with early psychosis symptoms face significant barriers to accessing care in a timely manner and staying engaged with Early Psychosis Intervention (EPI) Services. Previous results show young adults with early psychosis are

interested to use digital support, such as web-based resources, texts or smartphone apps, to enhance care. These digital tools have the potential to support engagement in EPI, yet studies of integration of digital interventions within EPI services are lacking. This symposium will explore novel, digital interventions for EPI services, and will consider challenges and opportunities to enhance EPI services.

First, N. Kozloff (University of Toronto, Canada) will present results from a pragmatic mixed-methods evaluation of virtual delivery of Early Psychosis Intervention (EPI) services during the COVID-19 pandemic. Interviews and validated measures were used to assess patient, family member and clinician experience and program fidelity. Service engagement (N=155) was examined in electronical medical records. The results show evidence of program fidelity, effectiveness and satisfaction of an adapted virtual model of EPI services compared to in-person care. Early use of supported employment and education and not being engaged in education, employment or training were significantly associated with risk of disengagement. Key themes from the qualitative analysis will be discussed.

Second, S. Lal (University of Montreal, Canada) will describe different phases of adaptation, implementation and evaluation of an innovative, online psychological and social therapy intervention called Horyzons-Canada for young adults with early psychosis. HoryzonsCanada is adapted from the successful Australian Horyzon program and consists of web-based resources and interventions to build strengths and resilience, social connectedness, and provides access to support from peers and clinicians. Qualitative and quantitative data from the different phases including outcomes from focus groups, pilot assessments, and implementation and evaluation data show promising results including increased engagement.

Third, B. Buck (University of Washington, US) will showcase the development of a mobile health tool that has been tailored to support help-seeking in young adults with early psychosis. Findings from interviews (N=21) revealed several barriers to treatment but also showed that young adults are interested in a mobile health tool. Patient's preferences were assessed and essential components were incorporated into the development of a novel mobile support tool. Results from subsequent usability testing showed high acceptability.

Then, G. Foussias (University of Toronto, Canada) will focus on the potential of a text messaging intervention to improve engagement in EPI services. Interestingly, data from this mixed-methods evaluation of feasibility and acceptability of a text messaging intervention (N=61) show the intervention was well received by young adults with psychosis but did not lead to improved engagement. Some improvement in medication acceptance was observed.

The findings and their implications will be synthesized by our discussant, S. Bucci (University of Manchester). She will lead a discussion how integration of digital tools can advance early psychosis care and highlight future directions.

46.1 VIRTUAL DELIVERY OF EARLY PSYCHOSIS INTERVENTION SERVICES: A MIXED-METHODS: EVALUATION

Nicole Kozloff*[1], Wanda M. Tempelaar[2], Melanie Barwick[3], Allison Crawford[1], Donald Addington[4], Jean Addington[4], Tallan Alexander[1], Crystal Baluyut[1], Sarah Bromley[1], Janet Durbin[1], George Foussias[1], Lauren de Freitas[1], Anne Kirvan[1], Paul Kurdyak[1], Andrea Morizio[1], Alexia Polillo[1], Rachel Roby[1], Eva Serhal[1], Sanjeev Sockalingam[1], Alexandra Sosnowski[5], Vicky Stergiopoulos[1], Victoria Villanueva[1], Wei Wang[1], Aristotle Voineskos[1]

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Background: Early psychosis intervention (EPI) programs rapidly transitioned to delivering services virtually during the COVID-19 pandemic with little evidence from prior research at the time. We used mixed qualitative and quantitative methods to evaluate virtual delivery of EPI services, including patient and provider experience, impact on fidelity, and service engagement.

Methods: We conducted a pragmatic mixed-methods evaluation of virtual delivery of EPI services at the Centre for Addiction and Mental Health (CAMH), Canada's largest EPI program, between April 2020-March 2022. We reviewed data from the CAMH-wide Virtual Client Experience Survey and Virtual Provider Experience Survey, validated measures that inquire about format of delivery, ease of use, beliefs about the effectiveness of virtual care, and satisfaction with care. We assessed fidelity to the EPI model using the First Episode Psychosis Services Fidelity Scale (FEPS-FS) before and after the transition to virtual delivery. We examined electronic medical record data, extracting demographic and clinical data and information on service disengagement. We modelled time to disengagement using Kaplan-Meier curves, and Cox regression using backwards selection to examine the association of demographic and clinical factors with disengagement. We conducted qualitative interviews with EPI service users and family members and a focus group with clinicians, covering a range of topics related to experiences of virtual care, and coded transcripts using thematic content analysis.

Results: Most patients, family members and providers surveyed indicated that they thought virtual care was just as effective as in-person care. Fidelity to the EPI model increased in some areas and decreased in others. Among 155 patients enrolled in EPI services over the first 8 months of virtual delivery, 15.5% (n=24) disengaged from services, 12.3% (n=19) during the first 9 months of EPI treatment. Early use of supported employment and education was significantly associated with decreased risk of disengagement, whereas not being engaged in education, employment or training were significantly associated with increased risk of disengagement. A key theme from the qualitative analysis was the convenience of receiving care virtually and the ability to integrate virtual EPI services with other priorities, including education/employment, facilitating ongoing service engagement. However, there were concerns that an element of the therapeutic relationship was missing, and that virtual services were less appropriate during crises or symptom exacerbations. Service providers raised concerns about access to equipment and digital literacy as potential barriers to service engagement.

Conclusions: Virtual delivery of EPI services appears to be viable, with patients, family members and providers indicating positive experiences, no significant net worsening in model fidelity, and low rates of service disengagement. Some individuals may experience difficulty accessing or navigating virtual services, however, suggesting that digital health equity must be prioritized if EPI services are going to continue to be delivered virtually. Furthermore, additional strategies including augmentation with in-person care may be required in specific situations.

46.2 ADAPTING, IMPLEMENTING, AND EVALUATING A DIGITAL HEALTH INNOVATION TO SUPPORT RECOVERY IN ADULTS RECEIVING TREATMENT FOR PSYCHOSIS: THE HORYZONS-CANADA RESEARCH PROGRAM

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[1]*University of Montreal,* [2]*Australian Catholic University,* [3]*The University of Melbourne,*
[4]*McGill University,* [5]*Orygen, The University of Melbourne*

Background: Young people receiving treatment for a first-episode psychosis (FEP) face many barriers to accessing a comprehensive range of psychological, social, and vocational interventions throughout their process of recovery. For example, barriers include limited availability of trained professionals, models restricted to 1:1 format and delivered in person, scheduling conflicts, and engagement challenges. Technology can play a role in helping to reduce these barriers, especially given that research has shown that individuals experiencing a FEP are receptive to using technology for mental health care. Yet, the integration of technology-enabled services and interventions within early psychosis care remains limited.
Methods: In this presentation, we will describe 3 phases of a research program to adapt, implement and evaluate an innovative, online psychological and social therapy intervention (originally developed in Australia) called Horyzons-Canada (HoryzonsCa) for individuals that have experienced a FEP. HoryzonsCa consists of web-based resources and interventions to build strengths and resilience, social connectedness, and provides access to peer support and mental health professionals. Phase 1 consisted of a mixed-methods adaptation study (focus groups and consultations) with 11 patients diagnosed with psychosis and 15 clinicians in Quebec and Ontario. Phase 2 consisted of piloting a live version of the adapted intervention with 20 patients (8-week follow-up) recruited from an early psychosis intervention program. Phase 3 (currently underway) is implementing and evaluating HoryzonsCa with 100 English and French-speaking adults receiving outpatient mental health services for psychotic disorders (12-week follow-up).
Results: Our Phase 1 adaptation study showed that patients and clinicians appreciated the strengths-based approach and social media features of HoryzonsCa, however clinicians had concerns about their capacity to deliver HoryzonsCa as part of their daily responsibilities. Several adaptations to Horyzons were made to optimize its transferability to the Canadian context and prepare it for a live pilot study. Our Phase 2 pilot study showed that the majority of participants had a positive experience with Horyzons (85%). There were no adverse incidents, and 90% perceived the platform to be safe and confidential. There were concerns and recommendations expressed regarding limited social engagement on the platform and limited critical mass of participants on the website at any given time. During our Phase 3 study, we have placed more emphasis on moderator training, support, participant onboarding, and engagement strategies, which are showing promising results with some participants continuing to engage with the intervention well-beyond the 3 months follow up time-frame (e.g., > 1 year).
Conclusions: Overall, results: from our three phases of research, thus far, support the acceptability of using an adapted version of Horyzons for the Canadian context to increase access to psychological, social, and vocational support to individuals experiencing a FEP. Ongoing efforts will need to be considered in relation to moderator training and support, as well as participant engagement strategies.

46.3 DEVELOPMENT OF NORTH: USER-CENTERED DESIGN OF AN MHEALTH INTERVENTION TO SUPPORT HELP-SEEKING AMONG YOUNG ADULTS WITH EARLY PSYCHOSIS

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Background: A long duration of untreated psychosis is linked with a more chronic course of illness as well as reduced effectiveness of early intervention programs. Young adults with early

psychosis face significant barriers to accessing care in a timely manner, including a lack of information about programs or stigmatizing beliefs about help-seeking. Many young adults with early psychosis seek information online, but a small proportion of these individuals report imminent plans to seek care at brick-and-mortar services. There is a need for digital tools that provide informational resources, support for seeking care and self-guided tools to improve symptom self-management in the interim. Mobile health (mHealth) provides a widely accessible, engaging, and low-cost way to support help-seeking among young adults at risk of psychosis.

Methods: Our team conducted a user-centered needs assessment, prototyping, and iterative development process to build NORTH, an mHealth tool optimized to support help-seeking in young adults at risk for psychosis. We remotely recruited young adults at risk for psychosis in multiple iterative steps, including (1) a qualitative needs assessment (N = 20) and (2) usability testing of an initial prototype (N = 15). These study activities build on our team's preliminary survey work identifying features of interest to prospective NORTH users. We purposively sampled individuals who were engaged and not engaged in services to better understand the potential role for technology in supporting pathways to care. Results were synthesized into design requirements for the initial version of NORTH.

Results: Needs assessment interviews revealed several barriers to treatment that aligned with existing literature on pathways to care, including limited treatment options (e.g. scheduling concerns, waitlists), cost, and negative attitudes toward treatment for (e.g. stigma or a preference for secrecy or self-sufficiency). Participants also identified key themes in an ideal mobile support tool, including on-demand coping skills reminders, symptom tracking, and a guide providing actionable steps to help-seeking. In the second phase, a study prototype was developed based on these design objectives and presented to participants, who reported overall high acceptability of the proposed intervention (overall score = 8.63 [SD = 1.44] on a 10-point Likert scale of usability). Participants' preferences for updates included maintaining detailed information while reducing unnecessary text, adding visual appeal, and increasing content delivered through multimedia (i.e. audio and video). In a second iterative sprint incorporating these suggested design changes, a beta version of NORTH has been developed in preparation for final usability testing and a randomized controlled trial in 2023.

Conclusions: Young adults with early psychosis are interested in mHealth tailored to the experience of help-seeking and identify key features to optimize such an mHealth intervention. NORTH, now a fully functional app, has the potential to provide immediate support to young adults experiencing symptoms of psychosis and considering whether to seek formal care. Given its grounding in user-centered design, NORTH may be well-suited to engage young adults at risk for early psychosis. This tool has the potential to provide self-guided symptom self-management tools, challenge stigmatizing beliefs about psychosis and treatment, and provide actionable information to support help-seeking.

46.4 A PILOT SMS TEXT MESSAGING INTERVENTION TO ENHANCE ENGAGEMENT IN EARLY PSYCHOSIS SERVICES – PRELIMINARY EFFICACY AND FEASIBILITY FINDINGS

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Background: Among youth experiencing early psychosis approximately one third prematurely discontinue treatment. While short message service (SMS) text messaging has shown promise

in enhancing treatment engagement for individuals with psychotic disorders, data from early psychosis populations is lacking. To address this, the current pilot trial investigated the preliminary efficacy and feasibility of a weekly SMS text messaging intervention to improve engagement in youth receiving early psychosis care. We hypothesized that SMS text messaging would result in improved clinic attendance rates and engagement, along with secondary benefits in therapeutic rapport, attitude towards medications, clinical symptoms, and functioning. Structured and qualitative feedback was also collected to evaluate participants' experience of the intervention and areas for future development.

Methods: Youth between the ages of 16 and 29 presenting for early psychosis treatment were recruited and randomized to either an active or sham SMS text messaging intervention, delivered as brief weekly check-ins over nine months in addition to usual care. Participants were evaluated using measures of clinical engagement and therapeutic rapport, attitudes towards medication, psychopathology, functioning, and quality of life over the course of nine months. Clinic appointment data was collected from participants' electronic medical records. Open-ended and quantitative feedback was collected throughout the study. Primary and secondary outcomes were evaluated with linear mixed models, descriptive analyses were used to examine quantitative feedback, and thematic analysis for qualitative intervention feedback.

Results: Sixty-one participants were enrolled to either the active (n=32) or sham (n=29) SMS text messaging intervention, with 44 participants (22 per group) completing the trial. Primary analyses revealed an unexpected decrease in attendance rate over time in the active SMS group compared to the sham group (beta= -0.207, SE=0.08, CI 95%= -0.22 - -0.08, p= .007), and no difference in clinician-rated engagement between groups. Secondary analyses revealed a significant improvement in attitude towards medications in the active compared to sham SMS group. There also emerged a significant difference in the rate of change in social functioning between groups, with functioning remaining stable in the active SMS group but improving in the sham group. Participant feedback revealed high usability and functionality ratings for the SMS text messaging intervention, and moderate to high satisfaction ratings. Themes emerging from qualitative feedback revealed a satisfaction theme, including positive experiences with messaging parameters and diary function of the SMS conversations, and an improvement theme, including a desire for increased diversity of questions and personalized messages, as well as appointment and medication reminders.

Conclusions: This study sought to evaluate the preliminary efficacy and feasibility of a weekly SMS text messaging intervention to improve treatment engagement for youth receiving early psychosis care. Contrary to our hypotheses, the intervention did not lead to improved attendance or clinical engagement, albeit with some improvement in attitude towards medication. Intervention feedback revealed that such an intervention was well received by youth experiencing early psychosis, and a desire for more functionality to enhance to utility of the intervention beyond a simple SMS text messaging check-in. The findings of this pilot study provide important insights on potential avenues for further development of digital interventions to augment care for early psychosis.

Oral Sessions: Cognitive Mechanisms and Clinical Research in Psychosis

1. THE ASSOCIATION BETWEEN PTSD, COMPLEX PTSD AND PSYCHOTIC SYMPTOMS IN ADULT SURVIVORS OF DEVELOPMENTAL PSYCHOLOGICAL TRAUMA: MIXED METHOD FINDINGS FROM THE MULTICENTRE IMPACT STUDY

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Background: Childhood maltreatment, a form of developmental psychological trauma, is a risk factor for post-traumatic stress disorders and psychosis. However, little research has measured the effect of both ICD-11 PTSD and complex PTSD (CPTSD) on positive and negative psychotic symptoms. We sought to investigate this relationship within a multi-site international study using quantitative and qualitative measures from online questionnaires and clinical interviews.

Methods: We recruited 1273 individuals from the UK and Republic of Korea who had experienced developmental trauma as described by the childhood trauma questionnaire (CTQ). Conducted online, we measured PTSD symptoms using the International Trauma Questionnaire (ITQ) and psychotic symptoms using the Community Assessment of Psychic Experiences (CAPE). We used linear regressions to examine whether meeting diagnostic threshold for PTSD and CPTSD predicted positive and negative psychotic symptoms. A subsample of individuals from the UK with subclinical psychotic symptoms also underwent a trauma-intrusion interview and Comprehensive Assessment of At-Risk Mental States (CAARMS) to provide quantitative data from subjective measures (0 to 100) and qualitative data. Thematic analysis, correlations and t tests were conducted to examine the relationship between trauma intrusions and psychotic symptoms.

Results: Overall, 41.5% of participants met caseness for CPTSD compared to 5% for PTSD. Meeting CPTSD caseness predicted overall psychotic symptom severity (B= 27.32, SE=1.56, p<.01), affecting the severity of both positive (B=14.53, SE= 0.94, p<.01) and negative (B= 12.80, SE= 0.88, p<.01) symptoms independently. Meeting PTSD caseness did not predict overall psychotic symptom severity (B=-10.63, SE= 3.82, p=0.01). Within the UK subsample of individuals interviewed (n=24), some participants experienced psychotic symptoms with direct content related to their trauma intrusions. Preliminary themes raised included threat, shame, distress, intrusiveness, distrust of others, and dissociation. The subjective scales found significant associations between experiencing intrusions in the here and now, with the severity of perceptual abnormalities (n=22, r=0.66, p=0.005), unusual thought content (n=22, r=0.414, p=0.049), and voice hearing (n=23, t=6.81, p=0.00). There were also associations between experiencing intrusions with physical sensations like the event, with the severity of perceptual abnormalities (n=23, r=0.53, p=0.007), unusual thought content (n=23, r=0.55, p=0.005) and voice hearing (n=23, t=9.54, p=0.00). Hearing voices was also associated with increased emotional intensity (n=19, t=19.11, p=0.00) and vividness (n=24, t=23.79, p=0.00) of trauma intrusions.

Discussion: This is the first multicentre study to find specific effects of CPTSD on psychotic symptoms in adults who have experienced developmental trauma. Considering that little research has examined the relationship between CPTSD and psychosis, our results suggest the need to further explore this association. The mixed methods findings suggest that multiple

characteristics of trauma intrusions are related to voice-hearing, with experiencing intrusions in the here and now and with physical sensations similar to the event also being associated with the severity of perceptual abnormalities and delusions. These findings suggest the need to further investigate the trauma-psychosis relationship, firstly through screening survivors of developmental trauma for PTSD and CPTSD.

2. THREAT-BASED BIOLOGICAL AND COGNITIVE MEDIATORS OF THE DEVELOPMENTAL TRAUMA-PSYCHOSIS ASSOCIATION: A POPULATION-BASED COHORT AND INTERNATIONAL BEHAVIOURAL STUDY

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Background: There is growing evidence that developmental trauma (DT) - psychologically traumatic events during childhood and/or adolescence – is causally associated with an increased risk of psychotic experiences (PE) in adulthood (Morgan et al., 2016). However, an understanding of the precise mechanisms underlying this is lacking. Consistent with biopsychosocial and computational theories of psychosis (Freeman et al., 2005, McCrory and Viding 2015, Linson et al., 2020), multiple lines of evidence converge on the role of aberrant threat processing in the mechanistic pathway linking DT and psychosis (Bloomfield et al., 2021). In a population-based birth cohort (Study I), we examined the effect of DT on volumes of brain structures involved in threat processing, and in a large international behavioural study (Study II), we examined the effects of DT on dissociable components of threat processing. We then examined whether alterations in threat processing played a mediating role in the association between DT and PE.

Methods: In Study I, we used data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a large population-based cohort in the United Kingdom (n=418). Data on DT, representing exposure to trauma between ages 0 and 17 years, and PE, assessed using the psychosis-like symptoms semi structured interview at 18 years, were derived from assessments completed by the parents or self-reported by participants. Magnetic resonance imaging (MRI) was used to measure volumes of whole brain and structures involved in threat processing (ROIs) including the amygdala, vmPFC, and the striatum in adulthood. In Study II, we recruited (n=1488) participants from the United Kingdom and Republic of Korea, and assessed exposure to DT (Childhood Trauma Questionnaire) and PE (Community Assessment of Psychic Experiences). Participants completed separate tasks to assess 1) threat recognition, using an emotional recognition task that measures discriminability, i.e. the ability to identify the emotion in facial stimuli morphed from neutral to 100% intensity for six basic emotions, 2) threat response, using a facial affect ratings task that measures subjective valence and arousal ratings for neutral, happy and angry faces, and 3) threat attention, using an emotional dot probe task that measures attentional bias for happy and angry faces. We used logistic regression, hierarchical linear regression and mediation analyses, controlling for confounding variables, to examine the associations between DT, ROIs, threat processing and PE.

Results: In Study I, we found that the severity of developmental trauma was associated with reduced left amygdalar volumes in adulthood ($B=-.01$, $p<.01$), with evidence supporting a dose-response association, whereby exposure to three or more types of trauma ($B=-.004$, $p<.05$), and exposure to trauma during both childhood and adolescence ($B=-.003$, $p<.05$), had

a greater effect compared with exposure during childhood or adolescence only. Developmental trauma was not associated with alterations in vmPFC and striatal volumes. Reduced left amygdalar volumes were in turn associated with increased severity of psychotic experiences (B=-3.25, p<.01). Mediation analyses revealed that reduced left amygdalar volumes played a mediating role in association between developmental trauma and psychotic experiences (mediation effect: B=0.04, p=.015, direct effect: B=.24, p=.02).
In Study II, the severity of developmental trauma was associated with (1) poorer recognition of angry faces (B=-.004, p<.001) and (2) more negative valence responses (B=-.001, p<.001) and increased arousal responses to neutral faces (B=.004, p=.01). Developmental trauma was not associated with alterations in threat attention. These alterations in threat processing were in turn associated with increased severity of psychotic experiences in adulthood, when controlling for the severity of developmental trauma (recognition: B=-3.28, p<.001; valence: B=-10.95, p=.001; arousal: B=1.34, p<.001). Mediation analyses revealed that these alterations in threat processing played a mediating role in the association between developmental trauma and psychotic experiences (threat recognition mediating effect, B=.008, p=.016, direct effect, B=.470, p<.001; valence responses mediating effect, B=.012, p<.001, direct effect, B=.470, p<.001, arousal responses mediating effect, B=.006, p=.036, direct effect, B=.470, p<.001).

Discussion: We found evidence that DT was associated with (1) reduced left amygdalar volumes in adulthood and (2) impaired emotional recognition of threatening emotional stimuli and more negative valence responses to neutral emotional stimuli. Importantly, these biological and cognitive alterations in threat processing played a mediating role in the association between DT and PE. These findings provide evidence in support of the hypothesis arising from biopsychosocial and computational accounts of a causal association between DT and altered threat processing that underlies vulnerability to PE. Importantly, our identification of threat-based biological and cognitive mediators of the trauma-psychotic experience relationship informs strategies for secondary and tertiary prevention of psychosis associated with DT.

3. SELF-DETERMINATION THEORY IN TREATMENT STUDIES OF SCHIZOPHRENIA: A SCOPING REVIEW

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Background: Schizophrenia is the most disabling of all psychiatric disorders, imposing impairments in both social and occupational functioning. Research suggests that motivation is an important determinant of treatment engagement, adherence to a treatment regimen, and treatment efficacy, all of which are associated with functional improvements in schizophrenia. Although negative symptoms, including amotivation, have been widely studied in schizophrenia, fewer studies have investigated patient motivation and the factors that drive and maintain it in the treatment context. Self-Determination Theory (SDT) is a well-established theory of human motivation (ranging from amotivation to extrinsic to intrinsic) and emphasizes the satisfaction of three basic psychological needs (autonomy, competence and relatedness) as core factors in maintaining motivation. This theory has been applied in other psychiatric disorders to understand treatment engagement but has been studied in schizophrenia-spectrum disorders only in the last 20 years. To better understand how patient motivation, as formulated by SDT, impacts treatment engagement and outcomes in schizophrenia-spectrum disorders, we conducted a scoping review.
Methods: This scoping review was developed in reference to the Preferred Reporting Items for Systematic Review Protocols (PRISMA-P) Statement and the PRISMA Extension for

Scoping Reviews (PRISMA-ScR). The research question was "To what extent has the literature examined core concepts of SDT in the context of treatment engagement and outcomes in schizophrenia-spectrum disorders?" Relevant studies were identified using search strategies adjusted for PsycINFO 1803-Ovid, MEDLINE 1946-Ovid, and Web of Science Core Collection. Inclusion criteria included a publication date before 2023, publication in a peer-reviewed journal, written in English, and empirically evaluating patient motivation in the context of treatment in an adult schizophrenia-spectrum population. After deduplication, a two-phase selection process was completed by two researchers using Cadima systematic review software. In Phase 1, articles were screened for inclusion based on titles and abstracts, and in Phase 2, articles included from phase one were screened for inclusion based on the full text. General study characteristics (e.g., type, design, measures), demographics, and participant clinical presentations were extracted and charted in tabular form. Study findings were synthesized using a narrative approach to summarize what has been previously published, and to identify general themes and gaps in knowledge.

Results: An interim analysis of papers published by June 2022 yielded 52 (n = 6947 participants) that met the inclusion criteria. The following general themes were found: 1) autonomous and intrinsic motivations are associated with better treatment engagement and outcomes; 2) patient motivation for treatment is a dynamic construct that can evolve during treatment; and 3) patient motivation can be enhanced through modifications of intervention designs. Most studies assessing patient motivation on the SDT continuum, ranging from amotivation to extrinsic to intrinsic, were conducted in the context of interventions targeting neurocognition, although a significant subset evaluated the effects of motivation on social and vocational functioning, psychiatric symptoms, and treatment engagement. There is a lack of studies investigating how the basic psychological needs that drive and maintain motivation (i.e., sense of autonomy, competence, and relatedness) influence treatment engagement and outcomes. The full dataset of papers published by the end of 2022 will be included in the analyses presented at the meeting.

Discussion: This scoping review highlighted that patient motivation, as conceptualized by SDT, is an important factor in predicting treatment engagement and outcomes. General themes lend further credence to using SDT as a guiding framework to help inform treatment development, increase patient engagement, and maximize treatment outcomes. Individuals who are motivated based on values and goals (autonomous) or inherent interest and enjoyment (intrinsic) have better treatment engagement, which in turn produces better outcomes. Importantly, as patient motivation is malleable, treatment designs can enhance motivation for change by incorporating elements, such as motivational interviewing. Implications and directions for future research and practice will be provided.

4. COMPARING A COMPUTERIZED DIGIT SYMBOL TEST TO A PEN-AND-PAPER CLASSIC

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Background: People with psychosis have consistent impairments in processing speed with digit symbol tasks repeatedly being shown to have the largest effect size among cognitive tasks in individuals with chronic schizophrenia (Dickinson et al., 2007; Schaefer et al., 2013). A deficit has also begun to be established in individuals at clinical high risk (CHR) for psychosis (Hauser et al., 2017; Catalan et al., 2021; Cannon et al., 2016), with digit symbol tasks even discriminating between people who convert to psychosis and those who do not (Hedges et al., 2022; Millman et al., 2022). Given the environment of increased remote assessments, it is important to understand how computerized versions of this task compare to the traditional pen-and-paper assessment. In this study we aim to 1) assess the correlation of the paper and computerized digit symbol versions, 2) compare the effect sizes of these two tests compared to controls, and 3) explore the causes of any observed differences in performance on these tasks, such as motor deficits.
Methods: 48 healthy controls and 91 CHR individuals completed at least one of these digit symbol measures. The BACS Symbol Coding was used for the paper test and the novel Test My Brain Digit-Symbol Matching Test was the computerized version. First, a correlation of each test's raw scores was completed. Then Hedge's G effect sizes were calculated for the CHR scores compared to controls. Finally, linear models and mediation analyses were used to assess whether finger tapping speed and self-reported motor deficits explained any differences in how well the tests discriminated CHR individuals from controls.
Results: The computerized and paper digit symbol tests' raw scores were positively correlated ($r = 0.466$, $p = 3.35e\text{-}8$). The BACS test had a significantly larger effect size ($g = -0.232$) compared to the computerized assessment ($g = 0.053$). However, neither finger tapping nor self-reported motor functioning predicted the paper or computerized version of digit symbol tasks. Finger tapping and motor functioning also did not mediate the relationship between group membership and digit symbol performance on either task.
Discussion: While the computerized test does relate to the traditional version, the pen-and-paper digit symbol task reigns superior compared to the computerized version for discriminating individuals at CHR for psychosis from healthy individuals. As of now, it is not clear why the paper test has more ability to parse the deficits in this population. It may be that deficits are more subtle in the high-risk population and that the pen-and-paper task has a greater degree of difficulty, but future work is necessary to test this possibility. In the future, evaluating computerized versions of digit symbol tasks should be done carefully, which is critical given recent shifts in the field to this medium.

5. DIFFERENCES AND SIMILARITIES IN TEMPORAL ORDER JUDGMENTS IN SCHIZOPHRENIA AND BIPOLAR DISORDERS

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Background: Ordering events in time is inherent to conscious mental activities. It is part of how conscious thoughts are organized in time, and it is no surprise that order and asynchrony perception difficulties in individuals with schizophrenia have been found to relate to clinical disorganization. Ordering events in time is also involved in the understanding of causal relationships between successive events. Faulty causal interpretations can lead to false beliefs, which might eventually result in an altered perception of reality. These symptoms belong to the psychosis spectrum that is shared by schizophrenia (SZ) spectrum and bipolar (BP) disorder. These pathologies further share neurobiological and genetic risk factors. Phenomenology suggests differences in time experience in individuals with SZ and BP, though.

Time would be fragmented or "disappearing" for individuals with SZ, while time would be limited to a permanent present in individuals with BP.
Previous studies showed an altered perception of temporal order in individuals with SZ. To the best of our knowledge, there is no data on the processing of the temporal structure in individuals with chronic BP. We compared the processing of temporal order between individuals with SZ and BP.

Methods: Twenty-four individuals with SZ, 20 individuals with BP and 31 neurotypical individuals were recruited for this study. We investigated explicit and implicit measures of order discrimination using the temporal order judgment task (TOJ). Two squares appeared on the screen with a short delay and participants had to judge which stimulus appeared first. We used stimulus onset asynchronies (SOAs) of 100 ms (suprathreshold), 17 ms (subthreshold), or 0 ms (synchronous, control condition). Explicit measures relate to the correct response rate on the TOJ task (i.e., "right" response for "right then left" order, and vice versa). Implicit measures relate to the influence of a previous trial on the response given on a current trial. Here, we focused on how large asynchronies (previous trial: SOA = 100 ms) facilitated temporal order judgment for small asynchronies (current trial: SOA = 17 ms).
Results: Explicit temporal order effects replicated previous findings showing that for long SOAs (100 ms) individuals with SZ performed worse as compared to neurotypical individuals. Further, individuals with BP revealed no differences in explicit measures compared to neurotypical participants or to individuals with SZ. Implicit order effects replicated improved performance in case of identical as compared to different relative order between two successive trials. Importantly, there were no differences between the groups regarding implicit order effects.
Discussion: This study brings further evidence for a difficulty in temporal order processing in individuals with SZ. This difficulty may originate from an impairment in consciously ordering events in time, as suggested by the impairments in the explicit measure for suprathreshold asynchronies. In contrast, we find a relative preservation of trial-to-trial effects shown in the implicit measure. Further, we show that individuals with BP do not reveal such an explicit order impairment. The results are consistent with the phenomenological descriptions that suggest a difference in time experience in individuals with SZ and BP.

6. SEVERE SYMPTOMS AND SUICIDAL IDEATION IN PEOPLE WITHOUT A PSYCHIATRIC DIAGNOSIS: FINDINGS FROM AN ONLINE COHORT STUDY

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Background: Many people experiencing mental illness are unable to access treatment due to stigma, lack of insurance coverage, and other structural and psychosocial factors. In this investigation, we examined clinical and demographic differences between participants diagnosed with a psychiatric disorder and non-diagnosed participants in a cohort of online study participants.
Methods: Data was derived from an online data collection protocol between 2017-2020. Participants were recruited from online and community advertising initiatives and were compensated for their time. Participants were asked to provide basic demographic information, psychiatric diagnosis, and symptom self-assessments. Psychiatric symptomatology was captured through the Quick Inventory of Depressive Symptomatology (QIDS-SR), the Community Assessment of Psychic Experiences (CAPE-15), and the Perceived Deficits

Questionnaire 5-item (PDQ-5). Participants could provide weekly follow-up responses up to 15 times, although we only analyzed baseline data for this analysis. Per literature standards, we defined major depressive severity as a score ≥ 9 on the QIDS, minor depressive severity as ≥ 7 on the QIDS, and psychosis as a response of ≥ 1.3 on the CAPE-15. Demographic and clinical data were compared by diagnosis status and symptom severity status. We defined Suicidal Ideation (SI) as a score > 1 on QIDS item 12, "Thoughts of my own death or suicide". We used the chi-square test for comparison of categorical variables and the Wilcoxon rank-sum test to compare continuous variables. We constructed a multivariable log-binomial model to test the relationship between reported symptom outcomes and SI. An alpha of 0.05 was used for all significance testing.

Results: A total of 4,134 participants enrolled in the protocol, over one-third of whom did not report a psychiatric diagnosis (1,546/4,134, 37.4%). Non-diagnosed participants were more often female ($p < 0.001$), Caucasian ($p < 0.001$), and non-Hispanic ($p < 0.001$). They also had lower median baseline ratings on the QIDS ($\mu = 9$, IQR = 6-12 vs. $\mu = 14$, IQR = 11-15; $p < 0.001$), CAPE-15 ($\mu = 0.8$, IQR = 0.4-1.1 vs. $\mu = 1.5$, IQR = 0.7-1.9; $p < 0.001$), and PDQ-5 ($\mu = 6$, IQR = 4-9 vs. $\mu = 10$, IQR = 8-11; $p < 0.001$) compared to those listing they had a psychiatric diagnosis. Notwithstanding, almost sixty percent (911/1,533, 59.4%) of non-diagnosed participants reported symptoms that met severity criteria for major depression or psychosis, and almost half reported any SI at baseline (724/1532, 47.3%). Non-diagnosed participants who met severity criteria for either major depression or psychosis were more commonly male (458/911, 50.3% vs. 252/622, 40.5%; $p = 0.002$) and Black/African American (280/911, 30.7% vs. 120/622, 19.3%; $p < 0.001$) in relation to those who did not meet severity criteria. In a log-binomial model controlling for age, sex, and race, both major depression (prevalence ratio [PR] = 1.60, 95% confidence interval [CI], 1.47-1.75), and psychosis (PR = 1.23; 95% CI, 1.15-1.31) were positive predictors of SI in non-diagnosed participants,

Discussion: A significant portion of non-diagnosed participants endorsed severe symptoms, pointing to a potential deficit in the surveillance and treatment of mental illness. Furthermore, non-diagnosed black and male participants more commonly reported severe symptoms. Together with our finding that symptom severity is associated with higher prevalence of SI, and recent literature pointing to an increase in suicides among Black US residents before and during COVID-19 lockdowns, our results accentuate the need for expanded mental health treatment accessibility for key underrepresented groups.

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7. MODIFIABLE CORRELATES OF IMPULSIVE AGGRESSION IN PEOPLE WITH SCHIZOPHRENIA

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Background: Impulsive aggression is an extreme form of social dysfunction that can result in serious consequences for people with schizophrenia. Several factors including demographic, historical, and clinical status (e.g., positive symptoms) may increase the risk of violence. Illuminating modifiable factors that may be associated with aggression may guide efforts to pre-empt violent acts or develop therapeutic approaches decrease future aggression. Deficient

cognitive control and social-emotional abnormalities have been linked to impulsive aggression in schizophrenia. The current study therefore examined their behavioral sequalae--cognitive and social cognitive deficits, impulsivity, negative affect, emotion regulation capacity, and alexithymia— and psychotic symptoms as potential correlates of aggression in schizophrenia.
Methods: The study sample comprised 130 individuals with schizophrenia or schizoaffective disorder receiving services at two inpatient intermediate care psychiatric facilities-New York Presbyterian Westchester Behavioral Health Center (WBHC) and Manhattan Psychiatric Center (MPC). Participants ranged from age 18 to 60 and had to have at least one confirmed incident of assault within the past year or a score of at least 5 on the first five items of the Life History of Aggression (LHA). Participants completed the MATRICS Consensus Cognitive Battery (MCCB) as a measure of cognition. Two measures of social cognition--the Reading the Mind in the Eyes Task (Eyes Task), and the Emotion Recognition-40 (ER-40) served to assess mentalizing capacity and facial affect recognition respectively. The assessment battery included two measures of impulse control—the go/no go task and the emotional stop task. Participants were also administered the Positive and Negative Affect Scale (PANAS), a measure of trait positive and negative emotionality (using the past 7 days reporting time frame) and the Toronto Alexithymia Scale (TAS) to assess deficits in the recognition and communication of affective states. A subset of participants (N=37) completed an emotion regulation task during which they viewed pictures selected from the International Affective Picture System (IAPS) while participants' heart rate variability (HRV), respiration, and skin conductance where recorded. Symptom severity was assessed with the Positive and Negative Syndrome Scale (PANSS). All participants completed behavioral tasks of reactive aggression--the Taylor Aggression Paradigm (TAP) and the Point Subtraction Aggression Paradigm (PSAP). Participants' incidences of inpatient aggression were recorded and quantified using the Overt Aggression Scale Modified (OAS-M). We used exploratory factor analysis with Promax rotation to examine the patterns of associations among measures of past and current aggression, cognitive and social cognition measures, symptoms, affect, impulse control, and alexithymia. We used comparative fit index (CFI), Root Mean Square Error of Approximation (RMSEA), and Standardized Root Mean Square Residual (SRMR) to evaluate the goodness-of-fit of the selected factor solution.
Results: The EFA identified four interpretable factors with indicator variables that produced factor loadings greater than 0.40. The first factor was interpreted as Correlates of Past Aggression. Variables loading on this factor included the LHA score, MCCB global score, Eyes Task, ER-40, and accuracy on the Go/No go task. The second factor was interpreted as Correlates of Current Aggression. Variables loading on this factor included assault against others, property destruction, verbal assaults, overt irritability, and alexithymia subscale scores. The third factor labeled Correlates of Autoaggression included assault against self, suicidal tendencies, Positive Symptoms, Emotional Distress, and the Excitement/Agitation subscales of the PANSS. The fourth factor was interpreted as Correlates of Lab-based Aggression and these included performance on the TAP, PSAP, heart rate variability and respiration rate during the emotion regulation task, and PANAS hostility and irritability scores. The accepted factor solution showed acceptable goodness-of-fit to the research data (CFI = 0.92, RMSEA = 0.092, SRMR = 0.06).
Discussion: These results indicate that potential contributors to aggression show differential patterns of association with aggression measures. For example, whereas cognition and social cognition measures were more related to a life history of aggression or violence, trait hostility and irritability, and lab-based indices of emotion regulation were more related to lab-based measures of aggression. Alexithymia was remarkably linked to current aggressive behavior whereas PANSS subscales better self-aggression. The association of cognitive and social

cognitive deficits, alexithymia, emotion regulation abnormalities, and impulsivity with aggression suggests areas for future therapeutic development.

8. EFFECTS OF KETAMINE ON METACOGNITION: COMPARISON WITH SCHIZOPHRENIA AND SCHIZOTYPY

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Background: Metacognition is defined as the ability to reflect upon one's own thoughts and knowledge and to monitor the quality of ongoing cognitive or perceptual processes. Impairments in metacognition have been observed in schizophrenia and are targeted by tailored psychotherapeutic approaches. However, the neurotransmitter systems underlying metacognition and their alterations in schizophrenia remain elusive. In this talk, I will present evidence of the effects of the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine on metacognition, and I will compare the findings from this pharmacological model of psychosis to data from schizophrenia spectrum populations including individuals with high levels of schizotypy.

Methods: In a first double-blind, placebo-controlled study with between-subjects design, N=53 healthy participants completed an episodic memory task with trial-by-trial confidence ratings in functional magnetic resonance imaging (fMRI). A second double-blind, placebo-controlled fMRI study of N=45 healthy individuals investigated ketamine effects on brain function during a perceptual discrimination task. In both studies, ketamine was applied intravenously with a target plasma concentration of 100ng/ml. To more directly relate these pharmacological challenge studies to schizophrenia spectrum data, the episodic memory paradigm was investigated in a large sample (N=330) for correlations with multiple dimensions of schizotypy, and the study was complemented by a preregistered, systematic literature review of previous research on the role of metacognition in schizotypy.

Results: Regarding episodic memory, acute ketamine administration during retrieval impaired metacognitive sensitivity (meta-d') and enhanced metacognitive bias, with retrieval performance and metacognitive efficiency (meta-d'/d') being unaffected. At the level of BOLD, ketamine elicited higher activation of posterior cortical areas, including superior and inferior parietal lobe and occipital cortex. Regarding perceptual metacognition, ketamine impaired metacognitive performance, whilst perceptual performance and metacognitive bias remained unaffected. Psychophysiological interaction (PPI) analysis of BOLD data revealed altered functional connectivity during metacognitive confidence ratings under ketamine. Schizotypy was associated with diminished introspective insight and an overly self-referential and maladaptive metacognitive style, in keeping with the systematic literature review. Interestingly, low task-based metacognitive efficiency was associated with high levels of cognitive disorganization, whereas overconfidence (i.e., increased metacognitive bias) was related to positive schizotypy.

Discussion: Together, these findings confirm the existence of altered metacognitive patterns in the schizophrenia spectrum and provide evidence of a glutamatergic contribution. Ketamine, a widely used and convincing model of psychosis, induces impairments in mnestic and perceptual metacognitive performance, without affecting cognitive or perceptual performance. Findings on metacognitive bias i.e. the tendency towards overconfidence, however, are less consistent. Findings from schizotypy point to a differential pattern of associations, with the cognitive disorganised dimension being associated with metacognitive efficiency whereas higher levels of positive schizotypy are characterised by a tendency towards overconfidence.

Oral Sessions: Molecular Mechanisms and Symptom Formation

9. NEURAL VARIABILITY IN THREE MAJOR PSYCHIATRIC DISORDERS

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Background: Across the major psychiatric disorders (MPDs), shared disruptions in brain physiology are suspected. Here we investigate disruption of neural variability at rest, one well-established behavior-relevant marker of brain function, and establish its basis in gene expression and neurotransmitter receptor profiles across the MPDs.

Methods: We recruited 279 healthy controls and 219 patients with schizophrenia, major depressive disorder, or bipolar disorders (manic or depressive state). The standard deviation of blood oxygenation level-dependent signal (SDBOLD) obtained from resting-state fMRI was used to characterize neural variability. Transdiagnostic disrupted SDBOLD patterns and their relationships with clinical symptoms and cognitive functions were tested by partial least-squares correlation. Spatial correlation tests were used to examine correlations between disrupted patterns of SDBOLD and postmortem gene expressions, Neurosynth meta-analytic cognitive functions, and neurotransmitter receptor profiles.

Results: Two transdiagnostic patterns of disrupted SDBOLD were found. Pattern 1 is exhibited in all diagnostic groups and most prominent in schizophrenia, characterized by higher SDBOLD in the language/auditory networks but lower SDBOLD in the default mode/sensorimotor networks. In comparison, pattern 2 is only exhibited in unipolar and bipolar depression, characterized by higher SDBOLD in the default mode/salience networks but lower SDBOLD in the sensorimotor network. The severity of pattern 1 is positively related to clinical symptoms and cognition deficit across MPDs. Two disrupted patterns spatially correlated with expressions of different genes (e.g., neuronal projections / cellular processes), distinct meta-analytic cognitive functions (e.g., language/memory), and profiles of different neurotransmitter receptors (e.g., D2/opioid receptors). In conclusion, neural variability is a potential transdiagnostic biomarker of MPDs with a substantial amount of its spatial distribution explained by gene expressions and neurotransmitter receptor profiles.

Discussion: The pathophysiology of several MPDs can be traced through the measures of neural variability at rest, with varying clinical-cognitive profiles arising from differential spatial patterns of aberrant variability.

10. FRONTOSTRIATAL RESTING-STATE FUNCTIONAL CONNECTIVITY ABNORMALITIES CORRELATE WITH MOTIVATION AND PLEASURE DEFICITS IN SCHIZOPHRENIA

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Background: Negative symptoms, comprising two distinct dimensions of motivation and pleasure (MAP) and expressivity (EXP) deficits, are one of the core symptoms of schizophrenia (SCZ). Abnormalities in frontostriatal connectivity have been implicated to the development of negative symptoms. However, previous studies investigating the relationship between negative symptoms and the resting-state frontostriatal connectivity mainly adopted traditional negative symptoms ratings without evaluation of the MAP and EXP dimensions. It remains unclear whether these two dimensions of negative symptoms associate distinctively with the altered frontostriatal connectivity. This study aimed to examine the relationships between the MAP and EXP deficits and the corresponding altered frontostriatal connectivity in patients with SCZ based on a second-generation assessment of negative symptoms.
Methods: Seventy-three SCZ patients and 28 healthy controls (HC) were recruited from the Beijing Chaoyang Hospital. We administered the Clinical Assessment Interview for Negative Symptoms (CAINS) and the Positive and Negative Syndrome Scale (PANSS) to assess the severity of psychopathological symptoms of SCZ patients. All participants underwent the resting-state functional MRI (rs-fMRI) scans. The rs-fMRI data were processed using the standard preprocessing pipeline in the CONN toolbox. To obtain the frontostriatal connectivity, a seed-based analysis was performed using 6 subdivisions of the striatum in each hemisphere as seeds. Mean time-series BOLD signals were calculated for each seed region and the voxel-wise resting state functional connectivity (rsFC) analyses between the striatum seed regions and the frontal lobe were performed. Group differences in rsFC were then conducted controlling for age and head motion. Statistical significance was based on a cluster-level FWE-corrected height threshold of $p < 0.05$. We extracted the rsFC values that showed significant difference between groups. Partial correlation analysis was conducted to investigate the relationships between these rsFC values and the CAINS total score, and the scores on CAINS two factors (the MAP and EXP factors) in SCZ patients.
Results: Compared with HC, SCZ patients showed significant hyper-connectivity between the right dorsal striatum and the left anterior cingulate gyrus (ACC), between the right ventral striatum and the left inferior frontal gyrus, between the right ventral striatum and the right orbitofrontal cortex. SCZ patients also exhibited hypo-connectivity between the left dorsal striatum and the left superior frontal gyurs, between the left dorsal striatum and the right middle frontal gyrus, between the right ventral striatum and the right superior frontal gyrus. The altered rsFC between the right dorsal striatum and the left ACC was associated with the CAINS total score ($r = 0.264$, $p = 0.042$), the CAINS MAP factor ($r = 0.281$, $p = 0.030$), but not the EXP factor ($r = 0.104$, $p = 0.428$) after controlling for age, illness duration, antipsychotic medication and other psychopathological symptoms.
Discussion: The present findings suggested that SCZ patients exhibited altered frontostriatal connectivity. In particular, the hyper-connectivity of right dorsal striatum and left ACC was associated with the MAP deficits in SCZ patients. These findings highlight that the altered frontostriatal connectivity may play a crucial role in understanding MAP deficits in SCZ patients. However, future study recruiting larger first-onset SCZ is required to verify the present findings.

11. PERSONAL SPACE REGULATION IN SCHIZOPHRENIA PREDICTS FUNCTIONAL OUTCOME AND SYMPTOM SEVERITY AFTER 6 MONTHS

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Background: Schizophrenia spectrum disorders are typically characterized by poor social and functional outcome. Among other factors, the course of the disorder, and symptom severity contribute to the poor outcome. Here, we assessed the prognostic value of Personal Space Regulation as a biomarker in early identification of patients that are likely to improve in outcome. In particular, we examined whether impaired interpersonal space at baseline could predict functional outcome and symptom severity at 6-month follow up in patients with schizophrenia.
Methods: We employed a modified version of the stop-distance paradigm to assess changes in interpersonal distance at baseline and at 6-month follow-up in 137 patients with schizophrenia. Patients indicated their preferred interpersonal distance between them and a confederate in four different conditions: (1) in the Active-Approach condition patients walked towards the confederate and stopped when they felt uncomfortable, whereas (2) in the Passive-Approach condition, the confederate walked towards the patients and they had to say stop when the confederate reached at an uncomfortable distance. The two conditions were carried out with (3) eye-contact and (4) no eye-contact. Preferred IPS was measured with a laser distance sensor after each trial. In addition, symptom severity and outcome measures were assessed at baseline and after 6-months. Outcome was assessed with the Social and Occupational Functioning (SOFAS) and the Global Assessment of Functioning (GAF). No intervention other than medication was applied during the 6-month interval.
Results: Patients were divided into groups of normal and high distances according to the cut-off value of 1.58 meters. Baseline measures showed that patients with increased distance had significantly poorer functional and general outcome than those with normal distance. Moreover, both groups of patients with increased and normal distances improved in outcome and symptom severity after 6 months. This improvement in function was significantly associated with a decrease in patients' interpersonal distance. Importantly, IPS at baseline predicted functional outcome and symptom severity at 6-month follow-up. Patients with normal distance at baseline improved more, in that they showed better functioning and less symptom severity at 6month follow up, compared to those with increased distance.
Discussion: Overall, findings showed that interpersonal space at baseline is associated with the outcome and symptoms after 6 months. Schizophrenia patients, and especially those with normal space regulation improved significantly in outcome and symptom severity within the course of 6 months, compared to those with impaired space regulation. As such, Personal Space Regulation assessed with a simple task like the stop-distance paradigm, might serve as a biomarker in early identification of schizophrenia patients that are likely to improve or decline in outcome.

12. THE EFFECT OF STOPPING CANNABIS USE ON THE RISK FOR DEVELOPING PSYCHOTIC DISORDERS: A CASE-CONTROL ANALYSIS FROM THE EU-GEI STUDY

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Background: Cannabis is the most widely used recreational drug globally, after alcohol and tobacco. As more countries legalise or decriminalise use there is a growing need to understand possible risks associated with cannabis use, particularly with high potency or very frequent use. Cannabis use is associated with increased risk of psychosis. There is evidence that cannabis

users who stop using cannabis after developing a psychotic disorder have better clinical and functional outcomes than those who continue using it. With this in mind, we used data from the EU-GEI study to investigate the relationship between time since stopping cannabis and risk of psychotic disorder.

Methods: We used data from work package 2 of the EU-GEI study, a multi-centre case-control study with 901 first-episode psychosis patients (FEP) and 1,235 controls. All included subjects completed a modified version of the Cannabis Experiences Questionnaire (CEQ-EUGEI). In this paper. Included measures of cannabis use patterns are: lifetime cannabis use (0=never used, 1=used at least once throughout your lifetime), current cannabis use (former users=0, currently using=1), frequency of use (0= never and rare use, 1=more than once a week, 2=daily use), potency of cannabis used (1=low potency (THC<10%), 2=high potency (THC≥10%). In addition, we created a combined frequency/potency variable (0=never use, 1=rare use low potency, 2=rare use high potency, 3=weekly use low potency, 4=weekly use high potency, 5=daily use low potency, 6=daily use high potency the time in weeks since having stopped cannabis. Time since stopping cannabis was recorded in weeks.

Results: In keeping with previous literature, more FEP reported using cannabis ever and being current cannabis users compared to controls. In addition, more FEP reported using high potency cannabis compared to controls.

We find that lifetime cannabis use increased risk for psychotic disorder (OR= 1.7; 95% CI 1.39-2.13; p<0.001). Current daily users were at the highest odds of developing a psychotic disorder compared to never users (OR 2.8; 95% CI 1.78-4.39; p<0.001), exhibiting nearly a three-fold increase in their risk. Those who stopped using cannabis <50 weeks before the time of assessment had a comparable risk for psychotic disorder (OR 1.6; 95% CI 1.21-2.25; p<0.001). However, ex-users who stopped cannabis use between 50-250 weeks before assessment had significantly decreased odds of psychotic disorder compared to those who stopped more recently (OR 0.6; 95% CI 0.40-0.79; p<0.001). Ex-users who had stopped at least 250 weeks before the time of assessment were no different in their odds for developing psychotic disorders compared to never users (OR 0.9; 95% CI 0.47-1.85; p=0.867).

Using the frequency-potency composite variable, we demonstrate that previous daily users of high potency cannabis had the highest baseline probability of developing psychosis (OR 5.49; 95% CI 3.65-8.42; p<0.001). The pattern of differences in probabilities for psychotic disorders remains unchanged up to 500 weeks since stopping cannabis. Those cannabis users who had stopped using cannabis for 500 weeks or longer reduce their probability of psychotic disorder independently of their frequency and type of the cannabis previously used.

Discussion: This is the first study to show that cannabis use cessation is associated with a reversibility of acquired risk for psychotic disorder. These findings confirm the previous evidence of the adverse effects of cannabis use on mental health, especially daily cannabis use and high potency types. Importantly, this is the first study that observes the changes in risk profile for developing psychosis as a measure of time since quitting cannabis. Thus, our findings suggest that quitting cannabis is a clinically significant challenge that requires sustained public health efforts and greater attention in treatment and research.

13. MOLECULAR SIGNATURES OF RELAPSE IN EARLY-STAGE PSYCHOSIS USING BIOPSIED NEURONAL CELLS

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Background: The trajectory of psychotic disorders after onset is heterogeneous, and many cases show deteriorating courses. One of the major determinants of poorer prognosis is the occurrence of symptom exacerbation, often referred to as “relapse”. One-third to half of the patients experience relapse in early-stage psychosis. Studying the molecular signature of relapse could help us understand the cause and consequences of relapse, which are important for developing therapeutic strategies to revert the disease course at an early stage.
One bottleneck in studying the molecular mechanisms underlying the progression of psychiatric disorders is the difficulty in obtaining appropriate biospecimens from living subjects. Recent studies showed that olfactory neuronal cells (ONCs) are useful surrogate cell modes for studying neuronal molecular signatures in humans. ONCs can be obtained repeatedly through nasal biopsies from living patients and healthy controls, thus especially suitable for studying disease progression, such as relapse. Their neuronal identity (similar to excitatory neurons in the anterior cingulate cortex and dorsolateral prefrontal cortex) and homogeneity have been well characterized. Due to their homogeneity, ONCs are also very useful for bulk-level next-generation sequencing studies, which have higher accuracy and coverage at the whole-genome level with cheaper costs, compared with single-cell sequencing.

Methods: We obtained bulk RNA-Seq data from ONCs of 64 healthy controls (HC) and 62 patients with early-stage psychotic disorders (onset within 24 months). Among 62 patients, 30 of them experienced relapse (hospitalization due to psychotic symptom exacerbation) after the onset (referred to as the R group), while the other 32 patients didn’t experience any relapse between the onset and nasal biopsy (referred to as the NR group). Differential expression analysis was conducted to identify significant alterations in the R group, compared with the NR group and HC. Gene co-expression network analysis was further performed to assist in the interpretation of the biological changes associated with relapse. Confounding effects of age, sex, race, smoking status, medication, and duration of illness were evaluated and adjusted in the analyses as appropriate.
Results: The R group had a larger deviation from HC than the NR group. The 25 genes were differently expressed in the R group compared to healthy controls, while 14 genes were differently expressed in the NR group compared to HC. Notably, only 8 genes were differently expressed when total patient sample was compared with HC, suggesting heterogeneity within the patient cohort. The gene co-expression network analysis revealed that the calcium signaling pathway was a central hub of alterations observed in the R group compared with HC. Interestingly, the member of synaptotagmin gene family, which mediates calcium-dependent regulation of membrane trafficking in synaptic transmission, was the top gene with the most significant change between the R and NR groups.
Discussion: GWAS studies identified the calcium signaling pathway as one of the most important pathways for schizophrenia and bipolar disorder. However, its biological significance in specific clinical contexts of these diseases remains to be elucidated. Our study provides a novel insight that this pathway may be involved in the process and outcome of relapse.

14. SYNAPTIC DYSFUNCTION IN SCHIZOPHRENIA: COMPLEMENTARY TESTS IN VIVO USING [11C]UCB-J POSITRON EMISSION TOMOGRAPHY

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Background: The synaptic dysfunction hypothesis of schizophrenia is highly influential. However, it has been unclear whether synaptic alterations are present in vivo, when they emerge in the course of illness, or whether they are linked to glutamatergic function in vivo in schizophrenia. We addressed these questions in complementary clinical studies. First, we used [11C]UCB-J positron emission tomography (PET) to investigate whether levels of synaptic vesicle glycoprotein 2A (SV2A), a marker of synaptic terminal density, are altered in patients with chronic schizophrenia (SCZ), or antipsychotic naïve/free patients recruited from first-episode services (FE-SCZ) compared to healthy volunteers (HV). Second, we explored whether SV2A levels are related to markers of glutamatergic function in patients and healthy volunteers.

Methods: Sixty-one volunteers (SCZ n=18, FE-SCZ n=21, HV n=22) underwent [11C]UCB-J PET, estimating grey matter [11C]UCB-J volumes of distribution (VT) and distribution volume ratio (DVR), and proton magnetic resonance spectroscopy, estimating creatine-scaled glutamate (Glu/Cr) and glutamate+glutamine (Glx/Cr) in the anterior cingulate cortex (ACC) and hippocampus. We collected clinical data including PANSS score, chlorpromazine-equivalent antipsychotic dose (CPZ) and duration of illness (DOI).

Results: Comparing SCZ and HV groups, 2-way ANOVA revealed significant group-by-region interaction ($F_{2, 68}=7.472$, $p=0.001$), group ($F_{1, 34}=6.170$, $p=0.02$) and ROI ($F_{2, 68}=426.0$, $p<0.0001$) effects on VT, with significantly lower VT in the SCZ group by large effect sizes in the frontal cortex (FC, SCZ=16.93 [0.80]; HV=19.50 [0.64]; $t=2.51$, $df=34.0$, $p=0.03$, Cohen's $d=0.8$) and ACC (SCZ=19.55 [0.75]; HV=22.49 [0.72]; $t=2.83$, $df=34.0$, $p=0.02$, $d=0.9$), but not in the hippocampus (SCZ=14.09 [0.59]; HV=15.44 [0.50]; $t=1.75$, $df=34.0$, $p=0.09$, $d=0.6$). Furthermore, we found significant group-by-region interaction ($F_{2, 68}=7.97$, $p=0.0008$), group ($F_{1, 34}=8.1$, $p=0.007$) and ROI ($F_{2, 68}=510.9$, $p<0.0001$) effects on DVR, with significantly lower DVR in the SCZ group in the FC (SCZ=2.93 [0.17]; HV=3.48 [0.09]; $t=2.89$, $df=34.0$, $p=0.01$, $d=1.0$), ACC (SCZ=3.39 [0.17]; HV=3.99 [0.09]; $t=3.05$, $df=34.0$, $p=0.01$, $d=1.0$) and, additionally, hippocampus (SCZ=2.40 [0.12]; HV=2.74 [0.07]; $t=2.32$, $df=34.0$, $p=0.03$, $d=0.8$). There were no significant relationships ($p>0.05$) between VT and GMV, PANSS score, DOI and CPZ. Comparing FE-SCZ and HV groups, we found no significant effects of group on [11C]UCB-J VT or DVR in any region of interest ($d=0.0$-0.7, $p>0.05$). PANSS total score was negatively associated with [11C]UCB-J VT in the hippocampus in the FE-SCZ group ($r=-0.48$, $p=0.03$). There were no significant differences between groups in Glu/Cr or Glx/Cr in the ACC or hippocampus ($p>0.05$). Analyses with Pearson's product moment correlation coefficient revealed that [11C]UCB-J DVR was significantly positively associated with Glu/Cr (ACC: $r=0.53$, $p=0.01$; hippocampus: $r=0.68$, $p=0.0005$) and Glx/Cr (ACC: $r=0.72$, $p=0.0002$; hippocampus: $r=0.48$, $p=0.03$) in the HV group but not the SCZ group ($p>0.05$).

Discussion: These findings provide evidence that synaptic terminal density levels are lower, and that the normal relationship between glutamate and synaptic terminal density is lost in vivo in schizophrenia in patients with chronic illness. They show for the first time that large differences in synaptic terminal density are not present early in schizophrenia. Thus, taken together, these findings may indicate that synaptic density changes during the course of schizophrenia, potentially leading to lower levels of glutamatergic terminals and/or a lower glutamatergic-to-GABAergic terminal ratio.

15. PREDICTING REMISSION, RECOVERY AND RELAPSE IN SCHIZOPHRENIA USING BLOOD-BASED BIOMARKERS - A MACHINE LEARNING ANALYSIS OF NEUROFILAMENT LIGHT-CHAIN AND ASSOCIATED FACTORS

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Background: Disruptions of neuronal macro- and microcircuits in schizophrenia (SCZ) have been attributed to pathologies of neuronal connectivity. We hypothesized that during acute psychosis structural damage to axons and synapses occurs in a subset of patients, rendering them more susceptible to poor short- and long-term treatment outcomes.

Methods: Neurofilament light-chain protein (NfL), a marker of axonal and synaptic damage, was quantified in sera of acutely ill unmedicated schizophrenia patients (SCZ, n=98) at hospital admission (T0) and after 6 weeks of inpatient treatment (T6), compared to healthy controls (HC, n=132). Additionally, we analyzed blood cell counts, the levels of 171 serum biomarkers, clinical symptomatology and functioning at T0 and at T6. Furthermore, long-term treatment outcome (remission, recovery, relapse) was assessed during a 5-year follow-up phase. Univariate analysis and support vector machine learning was employed to identify SCZ with increased NfL, interrogate the relationship between biological factors and NfL and examine whether NfL and associated biological factors can predict response to pharmacological treatment as well as long-term recovery and relapse. The models were all tested for generalizability using an external validation cohort (n=50).

Results: NfL was increased in SCZ versus HC ($p=0.014$), correlated positively with positive and negative syndrome scale-positive scores (Rho=0.265, P=0.019) and inversely with global assessment of functioning-scores (Rho=-0.365, P<0.001) at T0. Decreased NfL at T6 (P<0.001) did not correlate with administered cumulative antipsychotic dosage. NfL levels were predicted with a balanced accuracy (BAC) of 73.43 % (sensitivity 60.71%, specificity 86.14%, P<0.0001) using a serum biomarker set, in which higher levels of insulin-like growth factor binding protein 2 (IGFBP-2), alpha-1-antitrypsin (AAT), segmented neutrophils count, total granulocyte count and Interleukin-1 receptor antagonist (IL-1RA) predicted elevated NfL (NfL+), whereas transferrin and resistin predicted normal NfL levels (NfL-). Taken together with psychopharmacological information, these factors predicted response to (measured by PANSS reduction) and recovery after (measured by GAF reduction) 6 weeks of psychopharmacological treatment with a BAC of 64.57% (sensitivity 86.27%, specificity 42.86%, P=0.017) and 64.91% (sensitivity 59.09%, specificity 70.73%, P=0.013), respectively. NfL and these associated factors also predicted psychotic relapse during 5-year follow-up with a balanced accuracy of 68.38% (sensitivity 80.00%, specificity 56.76%, P=0.0382). These findings were fully replicated in the external validation cohort.

Discussion: NfL anchors a set of blood-based biomarkers related to synaptic plasticity, inflammation response, glucose and cholesterol metabolism as well as haemodynamics. In this biomarker set, elevated NfL levels and associated proteins suggest neurodestructive processes in acute psychosis. Furthermore, this set can be used to robustly predict short- and long-term

treatment outcome in schizophrenia thus pointing towards innate immunity--based acutely destabilized neuronal circuits as an endophenotype for future therapy and disease monitoring in schizophrenia.

16. LEVELS OF MATRIX METALLOPROTEINASE 9 (MMP-9) ARE ELEVATED IN SCHIZOPHRENIA AND BIPOLAR DISORDER: THE ROLE OF MODIFIABLE FACTORS

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Background: Individuals with schizophrenia and bipolar disorder have a 10-15 year shortened life span largely related to increased rates of cardiac and pulmonary diseases. Cigarette smoking and obesity have been identified as risk factors for these conditions. However, the pathways associated with these conditions have not been fully identified. Matrix metalloproteinases (MMPs) are a diverse set of enzymes associated with inflammation and tissue destruction. MMP-9 has been associated with increased levels of mortality relating to cardiopulmonary diseases in non-psychiatric populations. Furthermore, MMP-9 levels have also been associated with health factors such as tobacco smoking and obesity.
Methods: Sensitive enzyme immunoassays were employed to measure the levels of MMP-9 in blood samples obtained from 1121 individuals: 440 with schizophrenia, 399 with bipolar disorder, and 282 without a psychiatric disorder. We estimated the odds of clinical diagnosis associated with MMP-9 demographic variables, tobacco smoking, and obesity, and also the partial explained variance using logistic and linear regression methods. We also determined the association between psychiatric medications and MMP-9 levels in the individuals with psychiatric disorders.
Results: Individuals with elevated MMP-9 levels had higher odds of a diagnosis of schizophrenia (OR 8.2, SE 2.72, $p<.001$) compared with the non-psychiatric group adjusted for age, sex, and race Partial correlation analyses indicated that smoking, obesity and their interaction explained 59.6% of the elevated odds. Smaller but significant associations were found for bipolar disorder. We also found that the levels of MMP-9 were substantially lower in individuals who were receiving valproate, particularly in those receiving relatively high doses. Ongoing studies also suggest that increased levels of MMP-9 are associated with premature mortality in this population.
Discussion: Individuals with higher levels of MMP-9 have significantly higher odds of a diagnosis of schizophrenia or bipolar disorder. Individuals receiving valproate had substantially lower levels of MMP-9, possibly related to its ability to inhibit histone deacetylation. Some but not all of the variance in clinical disorders associated with MMP-9 can be attributed to tobacco smoking or obesity as well as psychiatric medications. Interventions directed at decreasing the rate of smoking and obesity might reduce the morbidity and mortality associated with elevated levels of MMP-9 and improve the health outcomes of individuals with these disorders.

Oral Sessions: Interventions, Side Effects, and Outcomes

17. CLINICAL RECOVERY AND LONG-TERM EFFECTS OF SPECIALIZED EARLY INTERVENTION SERVICES VS TREATMENT AS USUAL: A 20-YEAR

FOLLOW-UP OF THE OPUS TRIAL FOR PATIENTS WITH A FIRST EPISODE OF SCHIZOPHRENIA

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Background: To date, the OPUS trial is the largest randomized controlled trial (RCT) testing two years of early intervention services with 20 years of follow-up among patients with a first episode of schizophrenia. Short-term effects of early intervention services have been confirmed. Still, knowledge is sparse on the very long-term effects of early intervention services.

Methods: A total of 547 individuals were included into the RCT (OPUS I trial) between January 1998 - December 2000 and allocated to either two years of early intervention services or treatment as usual. Participants aged 18-45 years with a diagnosis of first episode schizophrenia were included into the study. Individuals were excluded if treated with antipsychotics (>12 weeks of treatment prior to randomization), substance induced psychosis, mental disability (IQ lower than 70) or organic mental disorders. Clinical and trained staff, blinded to the original treatment allocation, have assessed the five, ten and 20-year follow-up. The early intervention service consisted of two years of assertive community treatment including social skill training, psychoeducation and family groups for two years delivered by a multi-disciplinary team (caseload 1:10). The standard treatment was based on the available community mental health treatment (1:20 –1:30).): In accordance with the prespecified protocol the primary outcomes were psychopathological and functional outcomes, mortality, days of psychiatric hospitalizations, number of psychiatric outpatient contacts, use of supported housing/homeless shelters, symptom remission and clinical recovery.

Results: A total of 164 participants (30%) of 547 were interviewed at the 20-year follow-up, (mean [SD] age, 45.9 [5.6] years, 51.8% female sex). No significant differences were found between the early intervention group (OPUS-group) compared to the TAU-group on global functional levels (estimated mean difference -3.72 [95% CI, -7.67 - 0.22], P=.06), psychotic (estimated mean difference, 0.14 [95% CI, -0.25 - 0.52], P=.48) and negative symptom dimensions (estimated mean difference, 0.13 [95% CI, -0.18 - 0.44] P=.41). The mortality rate was 13.1% (OPUS-group) and 15.1% (TAU group), P=.47. Likewise, no differences were found ten to 20-years after randomization between the OPUS-group and TAU-group on days of psychiatric hospitalizations (Incidence Rate Ratio (IRR), 1.20, 95% CI 0.73 - 1.20, P=0.46), or number of outpatient contacts (IRR: 1.20, 95% CI 0.89 - 1.61, P=0.24). Of the entire sample, 40% were in symptom remission and 18% were in clinical recovery.

Discussion: In this 20-year follow-up study among individuals with a first episode of schizophrenia we found no evidence that two years of early interventions services could alter long-term illness course compared to treatment as usual. The main strength of this study is the 20-year clinical and longitudinal data assessed among a large sample of individuals diagnosed with a first episode of schizophrenia spectrum disorders. Furthermore, we are the first RCT testing early intervention services to report on long-term outcomes among individuals with schizophrenia. The all-cause mortality rate was markedly high in this relatively young cohort, which calls for actions in order to improve suicide prevention and long-term physical health among individuals with schizophrenia. Even though we did not find any long-term differences between the groups after 20 years of follow-up, a 40% symptom remission and an 18% clinical recovery rate was found among observed cases at 20 years of follow-up, contributing to

optimism and hope among individuals diagnosed with schizophrenia and ultimately reducing stigma.

18. EAS-SZ: A METHOD FOR QUANTIFYING EARLY CHILDHOOD ADVERSITY AS A RISK FOR SCHIZOPHRENIA

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Background: Understanding the relative environmental and genetic contributions to risk of schizophrenia is critical. This is difficult, in part, due to the confounding situation that children of parents with schizophrenia are exposed to adverse environments more commonly than children of healthy parents. Additionally, a wide range of adversities has been implicated as risks for schizophrenia. We propose a method for ranking adverse environments, to derive a risk prediction measure which can be used to help untangle environmental and genetic risks.
Methods: We used prospectively collected data for 430,000 children born 1980–2001 in Western Australia, and for their parents. Follow up continued until 2015 using linked State registers, identifying 1,620 children with schizophrenia. A 40% random sub-sample was used to develop our scale, through Cox modeling. Numerous constructs of adversity exposure up to age 10 were grouped into broad domains and screened for independent association ($p<0.2$) with adult schizophrenia diagnosis. Augmented backwards elimination identified, for each domain, an optimal combination of constructs to predict schizophrenia; the corresponding sum of the log hazard ratios provided a summary measure of the domain. A final multivariable Cox model combined the domain summaries and the resultant sum of the log hazard ratios produced our risk prediction measure, EAS-Sz. The remaining 60% of our cohort, not used in developing the scale, was randomly divided into two testing subsets. Discrimination was assessed with Harrell's Concordance and graphical tools were used to assess calibration.
Results: Application of the scale to test data showed dose response. Harrell's Concordance values were 0.66 and 0.62. Predicted time to diagnosis curves were mostly contained within observed 95% Kaplan Meier bounds.
Discussion: Our method objectively combines many constructs of early childhood exposures to adversity into a single risk prediction measure for adult schizophrenia which displays dose response and predicts association considerably above chance.

19. PSYMATIK: A DIGITAL TOOL TO FACILITATE PERSONALISED AND EVIDENCE-BASED ANTIPSYCHOTIC PRESCRIBING

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Background: Side-effects of antipsychotics impair quality of life, contribute to mortality/morbidity rates, increase stigma, and lead to poor treatment concordance and thus psychotic relapse. Risk of side-effects is a key factor that people wish to discuss as part of antipsychotic prescribing decisions, and this approach is recommended by regulatory bodies. However, considering all side-effects of all available antipsychotics is a complex multidimensional process, complicated further by the need to tailor discussions to the individual. As such, there is a pressing need for a digital tool that facilitates comprehensive,

evidence-based, and personalised antipsychotic prescribing decisions based on drug side-effects.

Methods: First, we created a database of antipsychotic side-effects. We performed an umbrella review, searching Pubmed from inception to August week 4 2022 for meta-analyses that rank antipsychotics based on side-effects. Effect size magnitude data were extracted from the largest meta-analyses. Where there were insufficient data, ordinal ranking data were extracted from national/international guidelines. Second, we constructed an interface that allows the user to select multiple side-effects and assign each a degree of relative concern. This user input data is then integrated with the database of side-effect magnitudes, ultimately providing the user with a personalised ranking of treatments from best to worst in terms of overall side effect severity.

Results: Of 2060 citations, 9 meta-analyses met inclusion criteria. After removing overlapping/small studies, we extracted data from 2 network meta-analyses, supplemented by ordinal data from 6 guidelines. Data were extracted for 32 antipsychotics and 13 side-effects. This database was incorporated into the Psymatik digital tool, which is accessed at https://psymatik.com. Within Psymatik, the user selects which antipsychotic side-effects they wish to avoid and the degree of concern for each side-effect. User weighting and effect size data are synthesised using the TOPSIS multi-criteria decision-making method, which ranks antipsychotics from best to worst. The output is a heatmap, where the first column represents the TOPSIS ranking; the remaining columns correspond to unweighted effect size magnitudes for those side effects selected by the user.

Discussion: We have developed a digital application that supports patients and prescribers to make evidence-based, personalised, and comprehensive antipsychotic prescribing decisions based on drug side-effect profiles. The tool facilitates gold-standard care, and as such we expect it to form a key part of future psychiatric practice.

20. TREATMENT-RESISTANT SCHIZOPHRENIA AND GUT MICROBIOME ASSOCIATIONS

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Background: One third of people with schizophrenia don't respond to first-line treatment with atypical antipsychotics. Half of these treatment-resistant patients also have an inadequate response to clozapine, the medication reserved for treatment-resistant schizophrenia due to its high effectiveness in reducing psychotic symptoms. The gut microbiome has recently been implicated in mental illness and schizophrenia specifically. We investigated whether the gut microbiome was associated with schizophrenia diagnosis, treatment-resistance and response to clozapine.

Methods: We collected stool from 97 participants (25 non-psychiatric controls, 24 people with schizophrenia taking first-line atypical antipsychotics, 26 people with treatment resistant schizophrenia responding to clozapine, 22 people with treatment resistant schizophrenia not responding to clozapine) which was sequenced through shotgun metagenomics with a depth of 3Gbp per sample. Multivariate analysis was used to investigate the association of common and rare bacterial species with schizophrenia diagnosis, treatment resistance and response to clozapine. Bacterial richness, alpha diversity, and beta diversity measures were compared

between groups. Differences between groups in bacterial abundance was assessed through Analysis of Composition of Microbiomes (ANCOM).
Results: After adjusting for age, sex, BMI, stool type, diet and physical activity, multivariate analysis found large and significant associations between common and rare bacterial species and schizophrenia diagnosis (30% variance, SE=13%, p=7.88E-05 and 82% variance, SE=15%, p=1.6E-08, respectively), and common and rare species and treatment-resistance (27% variance, SE=0.18, p=8.71E-03 and 68% variance, SE=0.25, p=3.15E-04, respectively). However, there was no evidence for association of microbiome composition with response to clozapine. People with schizophrenia had decreased microbial richness and significantly different beta diversity compared to non-psychiatric controls. People with treatment resistant schizophrenia therefore taking clozapine had significantly higher beta diversity than people with schizophrenia not taking clozapine. Clozapine responders had decreased richness compared to clozapine non-responders, but no other differences. There were 4 bacterial species which were significantly differentially abundant in people with treatment-resistant schizophrenia when compared to people with schizophrenia taking first-line atypical antipsychotics.
Discussion: Consistent with previous research, we found differences between the gut microbiome composition of people with schizophrenia and non-psychiatric controls. In addition, amongst people with schizophrenia, those with treatment resistant schizophrenia have a different microbiome composition compared to those not taking clozapine. Therefore, our findings strongly suggest that clozapine use may influence the presence of rare microbial species. Longitudinal studies in patients prior to and post clozapine treatment are needed to disentangle whether those gut microbiome differences pre-exist in treatment resistant individuals or are in fact due to clozapine exposure.

21. CHECK THE EFFECTS - SYSTEMATIC ASSESSMENT OF ANTIPSYCHOTIC SIDE-EFFECTS

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Background: Antipsychotic medicines are the mainstay of treatment for those with a diagnosis of schizophrenia. However, these medicines are associated with a varying range of side-effects which can influence attitudes and subjective well-being negatively. This can result in poor adherence to treatment which occurs in up to 80% of those with schizophrenia resulting in relapse and rehospitalisation. Individuals may underreport antipsychotic side-effects as a result of embarrassment, misattribution of symptoms or forgetfulness. Thus, routine monitoring using systematic enquiry with a validated rating scale is recommended. While regular and systematic assessment of antipsychotic side-effects is part of good clinical care, it is uncommon in practice. In an effort to bring the evidence to the individual, we aimed to assess systematically for antipsychotic side-effects and their associated distress in an inpatient cohort.
Methods: Eligible individuals prescribed an antipsychotic for at least two weeks were invited to
have their side-effects assessed systematically using the Glasgow Antipsychotic Side-effects Scale (GASS) or the GASS for clozapine.

Results: 208 individuals were assessed systematically for antipsychotic side-effects. 71.5% (n = 138) had not reported side-effects to their clinician prior to the assessment. Daytime drowsiness (75%), dry
mouth (58.2%), weight gain (50.0%) and polyuria/polydypsia (48.1%) were the most commonly reported side-effects, while erectile dysfunction (35.0%), sexual dysfunction (26.3%), amenorrhoea (26.3%), galactorrhoea (25.0%) and sedation (21.5%) were reported to be the most distressing side-effects. There was no evidence of an association between side-effect severity, number of side-effects reported or distress caused by those taking high dose/combination antipsychotic therapy compared with standard dose monotherapy.

Discussion: In order to establish the true experience of an individual taking antipsychotic medicine, side-effects must be regularly and systematically assessed using a validated rating scale. Additionally, as it is the distress caused by a side-effect that is directly linked with poor adherence, associated distress must also be established. Based on the lack of correlation between high dose/combination antipsychotics and side-effects, treatment should be tailored to the individual based on response/tolerance and dose reduction or avoidance of polypharmacy should not be recommended to minimise side-effects.

22. CYTOKINE AND CHEMOKINE DIFFERENCES AND CHANGES DURING CLOZAPINE TREATMENT IN BLACK PATIENTS BY ACKR1 GENOTYPE

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Background: Polymorphisms on the Atypical Chemokine Receptor 1 (ACKR1) gene lead to differences in absolute neutrophil counts (ANC) but not in neutrophil function. Clozapine has a low but serious risk of severe neutropenia, and our group has been studying the safety of clozapine in those with the ACKR1 genetic variant, rs2814778 (C-C, Duffy Null), the group known to have a low ANC. However, ACKR1 binds to many chemokines, exclusively expressed in cerebellar neurons, venular endothelial cells and erythrocytes. Neutrophils play a pivotal role in inflammatory response and also contribute to the activation of inflammatory cytokines. Given the roles of inflammation in the pathophysiology of schizophrenia and clozapine's role in inflammation, it is important to understand more about the impact of ACKR1 genotype and clozapine on inflammation.

Methods: This is secondary data analysis of a 6-month, open-label clinical trial of clozapine use in African-descent adult patients with schizophrenia spectrum disorders with or without

the Duffy-Null genotype, conducted at three sites (2 US and one Nigeria). We examined differences in cytokine and chemokines by genotype at baseline and during treatment with 24 weeks of clozapine treatment for the US participants. Single-Nucleotide Polymorphism (SNP) genotyping was performed on gDNA isolated from blood using TaqMan polymerase chain reaction (PCR) technology. Chemokines and cytokines identified as being associated with neutrophil function or clozapine treatment were analyzed using Millipore Sigma multiplex (Luminex technology) and log transformed due to abnormal distribution. These included chemokines (EGF, FGF_2, TGF-a, G-CSF, Flt-3L, GM-CSF, fractalkine, IFN-a2, IFN-g GRO, MCP-3, MCP-1, MIP-1a, MIP-1b, RANTES, TNF-a, TNF-b, VEGF, MDC, PDGF-AA, PDGF-AB-BB, sCD40L), and cytokines (IL-17A, IL-1RA, IL-1a, IL-9, IL-1b, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12p40, IL-13, IL-15). IL-8 was the primary cytokine in the grant application as it was known to be related to neutrophil function and effected by clozapine.
Results: We enrolled 274 participants, of which 61 (22.2%) US clozapine participants had inflammatory marker data (N=42, 69% CC Duffy-Null, N=19 CT/TT genotype). At baseline the Duffy-Null (CC) group had significantly higher GRO and RANTES and significantly lower eotaxin and MCP-1 ($p<0.05$). A significant genotype by time interaction showed that IL-8 decreased only in the Duffy Null group ($F=4.68$, $df=1,58$, $p=0.035$). Other genotype by time interactions showed that the TC/TT allele group had a significant increase in eotaxin and IL-1RA and decreases in FGF2, IL-12p40, IL5 and IFN-a2 not seen in the Duffy-Null group. Irrespective of genotype clozapine treatment was associated with a 143% increase in mean sCD40L 74% increase in EGF and a 36% increase in IL-6.
Discussion: There are differences in inflammatory marker presentation by genotype particularly in GRO, RANTES, eotaxin and MCP-1. We also find IL-8 increases during treatment only in the Duffy-Null (CC) group. Previously clozapine was found to selectively inhibit IL-8 mediated polymorphonuclear chemotaxis, likely by interfering with elements of the signaling cascade. Additionally, the Duffy-Null genotype has less overall chemokine and cytokine change during 24 weeks of clozapine treatment than the CT/TT group, albeit clozapine has some effect on increasing sCD40L, IL-6 and EGF independent of genotype. These findings may help elucidate genetic differences in inflammatory risk with clozapine and provide another clue that IL-8 may play in the lower neutrophil count seen in the Duffy-Null group.
Funding Source: This study was funded by NIMH R01MH102215 (Kelly PI), R01 MH102215-02S2 (Kelly PI). Leponex (clozapine) was provided by Novartis in Nigeria at a reduced cost to the investigators. Clozapine was purchased for the US sites.

23. CLOZAPINE IN BLACK PATIENTS WITH TARDIVE DYSKINESIA: RESULTS OF A 24 WEEK OPEN LABEL CLINICAL TRIAL

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Background: Tardive dyskinesia (TD) is characterized by involuntary athetoid or choreiform movements that is associated with neuroleptic medications and is potentially irreversible. Treatment options are limited but may include dose reductions of the current psychotropic, which may increase risk of relapse of schizophrenia symptoms, or switching to a different agent, such as clozapine. Considered the 'gold standard' for treatment-resistant schizophrenia, clozapine has also been shown to reduce severity and seldom exacerbate TD. Current literature is limited in determining risk factors associated with TD and predictors of response using clozapine, especially in Black patients. To our knowledge, our data is the largest Black population with schizophrenia treated with clozapine to date. We sought to determine risk factors associated with tardive dyskinesia in Black patients and examine the rate of clinical response to clozapine for tardive dyskinesia in Black patients when switching from antipsychotics to clozapine.

Methods: This is a secondary analysis of a three-center prospective open-label study that enrolled 274 patients treated with clozapine for six months. The occurrence of tardive dyskinesia at baseline was defined by the Glazer-Morgenstern (GM) criteria as a score of 3 or greater on the Abnormal Involuntary Movement Scale (AIMS). We examined clinical variables associated with TD including medication use, demographic information (gender, age, race, education level, BMI), diagnosis, smoking status, substance use history, ACKR1 genotype, extrapyramidal symptoms (Simpson Angus Scale) and psychiatric symptoms using the Brief Psychiatric Rating scale (BPRS). We also examined the efficacy of clozapine in reducing TD and distress from TD. TD response was defined as a 50% reduction in total AIMS scores.

Results: Of the 274 enrolled participants (150 US, 124 Lagos, Nigeria), 271 had baseline AIMS scores for the analysis. Twenty-two of 271 (8%) met criteria for TD using GM criteria. Those with TD had an older age ($t=12.0$, $p=0.00054$) and higher SAS scores ($t=7.1$, $p=0.00760$). Fewer in the TD group were treated with first-generation antipsychotics ($x2=5.7176$, $p=0.0168$) and antihistamines ($x2=t=4.6110$, $p=0.0318$) and more in the TD group were taking vitamins ($x2=5.6143$, $p=0.0178$). During the 24-week study, 20/22 (91%) had a ≥50% reduction in TD scores. Mean scores in the TD group decreased by over 70% from 11.1 ± 7.6 at baseline to 3.1 ± 5.4 at endpoint ($F=19.01$, $p<0.0001$).

Discussion: We see a low rate of TD in this chronic patient group (8%) suggesting that rates of TD in chronic patients ready for clozapine may be lower than reported elsewhere, due to differences in rater training or differences in criteria used in reports. Participants meeting criteria for TD were more likely to be older and having extrapyramidal side effects prior to clozapine treatment. Having TD was associated with lower use of first-generation antipsychotics, less anticholinergic use, and higher vitamin usage. We see a robust response to clozapine as over 90% at baseline with TD had a ≥ 50% reduction and an average of 70% reduction in total scores from baseline. Clozapine is a highly effective treatment for chronic patients with TD, particularly as seen in this Black population.

This study was funded by NIMH R01MH102215 (Kelly PI), R01 MH102215-02S2 (Kelly PI) and 5R21MH093300-02 (Wonodi PI). Leponex (clozapine) was provided by Novartis in Nigeria at a reduced cost to the investigators.

24. NON-PRESCRIPTION OF CLOZAPINE FOR OUTPATIENTS: THE CLINICIANS' PERSPECTIVE

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Background: Clozapine remains the gold standard for treating treatment-resistant schizophrenia (TRS); however, it is continuously underused in most parts of the world. Previous research have found that some of the most frequently mentioned barriers to clozapine utilization are the patients' refusal of treatment due to blood sampling or side effects.
Studies on patients' perspectives, on the other hand, have found that patients in clozapine therapy are satisfied with their treatment and do not consider blood sampling an issue.

It is suggested that there is a discrepancy between the prescribers' expectations regarding patients' attitudes – and the patients' actual attitudes towards clozapine treatment and that these presumptions constitutes the most significant barriers for clozapine-prescribing.

However, current evidence primarily consists of surveys of clinicians' general perceptions of barriers for clozapine treatment, which may not reflect the impact of individual barriers in real-world settings. The objective of this study is to address these gaps in current evidence.

Methods: (Ongoing study) Medical records of 128 outpatients with schizophrenia and a prescription of non-clozapine antipsychotic polytherapy were screened. Forty-three eligible clozapine-naïve patients were identified. Clinicians (psychiatrists and primary care providers) completed questionnaires on symptom severity (CGI), functioning (GAF) and their perceptions of current treatment, reasons for non-clozapine treatment and initiatives that might facilitate clozapine treatment. Based on questionnaire responses, focused explanatory interviews will be conducted in order to further explore clinicians' responses. Qualitative data from interviews will be analyzed using content analysis.
Results: (Preliminary) In total, 66 questionnaires concerning 37 patients were returned. The respondents were 13 psychiatrists and 19 care providers. The median CGI rating of patients was 5.5 (IQR 5.0-6.5) and their median GAF was 31 (IQR 21-38.5). The most cited reason for non-prescribing of clozapine was the expected non-compliance with blood-monitoring requirements; however, the reason most frequently chosen as the most important one was the perceived sufficiency of current treatment (12/58 responses). Expected refusal due to blood-monitoring or side-effects was the chosen main reason in six responses only. When the clinicians were asked to choose between proposed clozapine facilitating interventions, the most frequent answer (25/58) was that no interventions were relevant. This statement was often explained with a perceived sufficiency of current treatment. When divided into psychiatrist/non-psychiatrist responses, the choice of both most important reason and relevant intervention differed between groups with non-psychiatrists emphasizing blood-monitoring barriers and facilitators in contrast to psychiatrists who maintained their weight on current treatment status. Further analysis on the qualitative components of this study is ongoing and results will be presented at the conference.
Discussion: The preliminary results of the study confirms the hypothesis that expected patient refusal is not the main barrier to clozapine treatment, however, the low utility rating of purposed facilitators were unexpected. This study is expected to provide new insights into real-world reasons for non-prescribing of clozapine making it an important contribution to clinical research.

Oral Sessions: Focus on Early Psychosis

25. MEASURES OF SOCIAL AND OCCUPATIONAL FUNCTION IN EARLY PSYCHOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Deficits in social and occupational function are widely reported in psychosis, yet no one measure of social and occupational function is currently agreed upon as a gold standard in psychosis research. The aim of this study was to carry out a systematic review and meta-analysis to determine which measures of social and occupational function were associated with largest effect sizes when measuring differences between groups, changes over time, or response to treatment.
Methods: Literature searches were conducted based on PsycINFO, PubMed and the reference lists of relevant articles to identify studies for inclusion. Cross-sectional and longitudinal observational studies and intervention studies of early psychosis (defined as ≤ 5 years since diagnosis) that included social and occupational functioning as an outcome measure (either primary or secondary) were considered. A series of meta-analyses were conducted to establish differences in effect sizes across measures for changes in function over time and in response to intervention. Subgroup analyses and meta-regression were carried out to account for variability in study and participant characteristics.
Results: Of 240 studies reviewed, 116 studies met inclusion criteria, of which 46 studies provided data (N=18,647) relevant to our meta-analysis. Of the global measures most frequently used, smallest effect sizes for changes in function over time and in response to treatment were observed for the GAF, while more specific measures of social function showed the largest effect sizes. Notably, among the brief measures considered, NEET status (not in employment, education or training) showed larger effect sizes than longer, more global measures of social and occupational functioning. Differences in effect sizes between functioning measures remained significant after variability in study and participant characteristics were accounted for.
Discussion: These findings highlight some the difficulties in measuring social and occupation function in psychosis. They suggest that more detailed and specific measures of social function (as opposed to impressionistic global measures) are better able to detect changes in function over time and in response to treatment in early psychosis.

26. EXPLORING PARENTHOOD IN FIRST EPISODE OF PSYCHOSIS PATIENTS: THE POTENTIAL ROLE OF THE OFFSPRING IN THE OUTCOME OF WOMEN.

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Background: It is well known that patients with schizophrenia spectrum disorders, particularly men, have significantly fewer offspring than the general population. Estimates of parenthood in individuals with psychosis range from 27 to 63% while in general population ranges from 64 to 79%. Some previous studies have focused on how to address successfully parenthood in cases of severe mental illness. However, there is a lack of research on what represent having children in the outcome of first episode of psychosis (FEP) patients.

Methods: The aim of this study was to explore the role of parenthood in FEP patients at illness onset and at 3-year follow-up. For this purpose, the parenthood circumstances of 665 FEP patients that between 2001 and 2018 enrolled PAFIP (Program for the Attention of Early Phases of Psychosis) were explored. The groups of FEP men and women, with and without children, were compared on premorbid, sociodemographic, clinical and neurocognitive characteristics at baseline and 3 years later. Attending the interest of a previous research in our group, comparisons between women under and over 40-year-old were conducted as secondary analyses.
Results: A total of 123 (18.49%) of FEP patients were parents at the time of admission, being 107 out of 294 women (36.39%) mothers, while only 16 out of 351 men (4.55%) were fathers. When comparing FEP women with and without children at baseline, the former were significantly older (40-year-old vs 30-year-old), presented less severe negative symptoms and percentage of cannabis consumption was lower (12.3% vs 25.7%). FEP women with children, despite presenting lower levels of education than those without children (elementary education in 51.4% vs 32.4% respectively) they have significantly better global function at 3-year follow-up.
Discussion: FEP women were more likely than FEP men to be parents. The reason behind this result could be the differences in age at illness onset between men and women. In addition, FEP women with children presented a less severe debut of the illness and a more favorable outcome. Our findings contrast with earlier studies in reflecting that children involvement in the recovery of their parents after a FEP could be highly recommended and underscore the need for family intervention programs. Finally, our results: make FEP men situation more visible and sensible to be considered in the treatment process attending that parenthood could be central to personal and social identity.

27. SUICIDALITY IN FIRST EPISODE PSYCHOSIS OVER TEN YEARS: TRAJECTORY AND REGISTRY LINKED APPROACH

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Background: Prediction of suicidality in patients with severe mental illness represents a crucial and challenging public health issue. Few studies investigated the development of the complex phenomenon of suicidality over time in first episode psychosis (FEP). Using a trajectory based approach we aimed to study the patterns of changeability and variability across the whole spectrum of suicidality from ideation to death by suicide in this important clinical group at high risk of suicidal behavior.

Methods: We used longitudinal data from the TIPS (Early Treatment and Intervention in Psychosis) ten years prospective follow-up study linked to death registries of two countries, Norway and Denmark. Participants with FEP (N=301) were recruited consecutively at baseline from 1997 to 2001 and followed up at one, two, five and ten years. We used SCID for diagnosis, PANSS for symptom assessment, the premorbid adjustment scale (PAS) for premorbid functioning and Global Assessment of Functioning Scale (GAF) split version for current symptom levels and functioning. We assessed suicidality in the clinical interview at baseline and every follow up by asking the participants if they currently or in the previous four weeks experienced suicidal ideations, plans, or attempts. Finally, we linked our data to the central registries of cause of death to include data on completed suicide over ten years (N=17) in our sample. All participants had provided written informed consent. The regional committees of medical research ethics approved the study. In order to identify trajectories of suicidality in the first 2 years of illness, we conducted growth mixture modeling (GMM) analysis. Multinomial logistic regression was applied to examine baseline predictors of the potential trajectories. In turn, trajectories' associations with suicidality and death at ten years were estimated.
Results: We identified four trajectories of suicidality in the first two years of illness: The stable non-suicidal trajectory represents most of the study sample (N=217, 72.09%), followed by stable suicidal ideation (N=45, 14.95%), then improving suicidal behavior (N=21, 6.98%), and finally worsening suicidal behavior (N=18, 5.98%). Compared to the stable non-suicidal trajectory, the stable suicidal ideation trajectory group was associated with a longer duration of untreated psychosis (DUP) (OR=1.24, p=0.033), poorer premorbid childhood social adjustment (OR=1.33, p=0.039), depression (OR=1.10, p=0.016), and substance use (OR=2.33, p=0.011). The improving suicidal behavior trajectory was associated with more severe depression (OR=1.12, p=0.040), lower GAF symptoms (OR=0.93, p=0.035) and function (OR=0.93, p=0.009). On the other hand, no baseline characteristics differentiated the worsening suicidal behavior trajectory group from the stable non-suicidal group. At the ten-year follow-up, the trajectory of stable suicidal ideation was associated with persistent suicidal behavior 3 times higher than the stable non-suicidal group (OR=3.12, p=0.008). The worsening trajectory was associated with increased risk of death by suicide 7 times higher than the stable non-suicidal group (OR=7.58, p=0.013).
Discussion: The trajectory approach in assessing suicidality in FEP revealed that the pattern of suicidality, notably over the first two years of illness, appears to be an important clinical predictor for the risk of future suicidal outcomes. Routine identification of persistent and worsening patterns of suicidality could help key health professionals in providing early and appropriate interventions for at-risk individuals.

28. OFFER AND UPTAKE OF PSYCHOLOGICAL THERAPIES FOR FIRST-EPISODE PSYCHOSIS IN DIFFERENT ETHNIC GROUPS: A REPORT FROM THE CRIS-FEP STUDY

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Background: Higher rates of psychotic disorders and poor clinical outcomes are well documented in minority ethnic group patients. Psychological therapies (PT) are recommended as the first line of treatment for first-episode psychosis (FEP). However, there are inequalities in access to PT. In this study, we investigated whether ethnicity, sociodemographic and clinical characteristics influenced the offer and uptake of psychological therapies (PT) in a FEP sample.
Methods: We used data from the Clinical Record Interactive Search-First Episode Psychosis (CRIS-FEP) study. The study was conducted at the South London and Maudsley NHS Trust

between 2010 and 2014. Descriptive statistical tests were used to determine associations between sociodemographic, clinical and PT offer/uptake. In addition, we performed multivariable logistic regression to estimate the odds of being offered a PT by ethnicity, adjusting for confounders.
Results: We identified 558 FEP patients. Of these, 193 (34.59%) patients were offered a PT, and 182 accepted the offer. Patients were more likely to be offered cognitive behavioural therapy (84.10%) than group therapy (13.33%). Patients who accessed mental health services via early intervention services (EIS) were more likely to be offered a PT compared to those in non-EIS ($X2 = 16.06$, $df=1$, $p < .001$). Among the patients that received an EIS, there was substantial evidence that black African (adj. OR=0.08; 95% CI=0.01 -0.79) and black Caribbean (adj. OR= 0.08; 95% CI=0.01 -0.87) patients were less likely to be offered CBT compared with their white British counterparts.
Discussion: Accessing EI services increased the likelihood of being offered a PT. However, treatment inequalities remain by ethnicity. Our findings are relevant to policymakers, clinicians, patients and carers.

29. DEEP-BRAIN SHAPE MORPHOLOGY UNIQUELY RELATES TO MOTOR DYSFUNCTION IN EARLY PSYCHOSIS

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Background: Motor dysfunction is a well-documented presentation in early-psychosis and tied to basal ganglia circuits. Understanding how the morphology of these critical deep-brain structures mediates motor performance is relevant to characterization of motor control and are relatively understudied. This project aimed to examine the relationship between bilateral motor performance and surface shape features of the basal ganglia and thalamus in a sample of patients with early psychosis. It was hypothesized that individuals with early psychosis would demonstrate patterns of abnormal basal ganglia and thalamic shape that would correspond with motor performance and is distinct from healthy individuals.
Methods: Participants included 97 patients with early psychosis (EP) and 45 healthy control (CON) individuals from the Human Connectome Project for Early Psychosis who underwent T1-weighted magnetic resonance imaging and neuropsychological testing; only right-handed participants were included. Motor function was assessed using the NIH Toolbox Motor Domain dominant and non-dominant age-corrected standard scores. Surface shape of the caudate, putamen, globus pallidus and thalamus was characterized using Large Deformation Diffeomorphic Metric Mapping. ANOVA models tested group differences on motor function, vertex-wise statistical surface t-maps evaluated group differences in subcortical shape deformation, and statistical surface Pearson correlation maps evaluated the relationship between vertex-wise shape deformation and motor performance in each structure for each group; all maps were corrected using an integrated random-field theory approach.
Results: Groups significantly differed in motor performance for both the dominant ($F=7.53$, $p=0.007$) and non-dominant ($F=10.53$, $p<0.001$) scores. Subcortical comparisons between SCZ and CON revealed significant inward deformation in medial right putamen, lateral right thalamus and posterior left thalamus. Results from correlation surface maps for both dominant and non-dominant scores in CON were similar and revealed negative correlations in tail of left caudate, bilateral ventral/posterior globus pallidus, and right LGN of thalamus. Positive correlations were seen bilaterally in head and body, and tail of left caudate, left anterior globus

pallidus, bilateral anterior and posterior putamen, right anterior thalamus, and bilateral posterior thalamus. Results from correlation surface maps for both dominant and non-dominant scores in SCZ were also similar and revealed negative correlations in bilateral anterior tail of caudate and left posterior putamen. Positive correlations were observed in bilateral head and tail of caudate, anterior right globus pallidus, posterior left globus pallidus, bilateral anterior and posterior putamen, and bilateral anterior and posterior thalamus.
Discussion: Results indicate motor performance is strongly related to the morphology of the basal ganglia circuit in early psychosis and suggests a potential substrate for the behavioral abnormalities in the disorder. Pattern differences revealed disruption to the typical brain-motor relationship of motor control, with more extensive basal ganglia circuit involvement in EP, which may indicate broader recruitment of circuit resources for task engagement. Further characterization of these abnormalities has potential to guide future clinical applications for early identification and management of motor dysfunction in the early course of psychosis.

30. THE CALIFORNIA COLLABORATIVE NETWORK TO PROMOTE DATA DRIVEN CARE AND IMPROVE OUTCOMES IN EARLY PSYCHOSIS (EPI-CAL): FEASIBILITY AND PRELIMINARY FINDINGS

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Background: Team-based "coordinated specialty care" (CSC) for early psychosis (EP) is highly effective in promoting clinical and functional recovery. NIH's EPINET project (https://nationalepinet.org/) seeks to join EP programs across the US to facilitate large-scale data collection and analysis to promote rapid dissemination of best practices. As an EPINET hub, California's EPI-CAL project (https://epical.ucdavis.edu) joined 5 university- and 13 county-based EP programs to create a sustainable learning health care network and contribute de-identified data to the NIMH EPINET database. Interim goals of EPI-CAL to assess feasibility focused on: 1) implement Beehive in EP programs to enroll 70% of eligible EP clients, which includes clients opting into data sharing 2) collect outcomes data from a core battery of evidence-based measures, and 3) report on outcomes prioritized by community-partners, including symptoms, functioning, and quality of life.
Methods: After an initial training series, Beehive was implemented in 18 EP programs to begin outcomes data collection from staff, clients, and families. Fifteen programs serve both FEP and CHR clients, two programs serve only FEP clients, and one program serves only CHR clients. Participants who use Beehive within their clinic can opt-in to data sharing for research purposes. Descriptive analyses summarize the demographic and outcomes data collected to

date, with a particular focus on symptoms (Modified Colorado Symptom Index (MCSI); functioning, and quality of life (Personal Wellbeing Index; PWI). Symptoms and quality of life were client self-report surveys, while the functioning measures were rated by clinicians [Global Functioning Social and Role scales (GF:S; GF:R) or the MIRECC-GAF social functioning and occupational functioning scale] per clinic preference.

Results: To date, 18 EPI-CAL clinics have registered 575 clients in Beehive. Of those 575 clients who have been registered, 61% (n = 348) have completed their Beehive end user license agreement (EULA) and are considered enrolled in Beehive. Of those who have completed their EULA, 85% (n = 295) have agreed to share their de-identified data with NIH, 89% percent (n = 309) have agreed to share their limited data with UCD, and 88% (n = 306) have completed at least one survey. We only report data for those who agreed to share their data with UCD for research purposes. At baseline, 86 clients completed the MCSI (M = 24.77, SD = 15.02). A total of 187 MCSI surveys were completed across all time points by 155 unique individuals, with 24 clients reporting data at more than one time point. At baseline, 110 clients completed the PWI (M = 5.02, SD = 2.37). There were 250 completed life outlook surveys from 206 unique individuals (34 clients completed the survey at more than one time point), which included single-item quality of life index from the PWI. There were 112 clinic-completed functioning measures (96 GF:S/GF:R and 16 MIRECC GAF) completed on 97 unique individuals (15 clients with more than one timepoint rated). Forty-two GFS (M = 5.67, SD = 2.08) and GFR (M = 5.24, SD = 2.41) scales were rated for clients at baseline. Five MIRECC GAF social (M = 51.00, SD = 8.92) and occupational (M = 54.20, SD = 12.09) scales were rated for clients at baseline.

Discussion: Data collection via a co-designed application for research and clinical care is feasible across community and university-based EP programs. Furthermore, a large majority of clients are willing to share their data for research purposes even when required to opt-in to this type of data sharing. Future analyses will include longitudinal examination of key outcomes as data collection continues across EPI-CAL sites and results from an increased sample will be reported. Differences between FEP and CHR clients will also be examined.

31. IMPORTANCE OF LIVED AND LIVING EXPERIENCE INTEGRATION IN EARLY PSYCHOSIS COORDINATED SPECIALTY CARE: FOSTERING A CLIMATE OF RECOVERY

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Background: Fidelity to coordinated specialty care (CSC) has been an important development in the field in order to best identify what components of CSC are most supportive to clients' recovery. A significant barrier for many programs is lack of funding or insurance coverage for particular roles, such as peer support specialists (PSS). Peers with lived experience with psychosis/other lived experience and family partners or advocates, who have a loved one with mental illness, share some similar roles on CSC teams, however, each have quite unique areas of expertise they bring to support clients and their families. The role of the PSS, family partner, along with supported employment and education specialists (SEES), family involvement, and conducting comprehensive needs assessment, may foster a climate of support and recovery for individuals with early psychosis (EP).

Methods: As part of the Early Psychosis Intervention Network of California (EPI-CAL), a hub of EPINET with 19 EP clinics, we examined 126 multidisciplinary EP staff and providers' beliefs about psychosis, help-seeking, and recovery – completing our "Clinician Attitudes of

Recovery and Stigma" (CARS) measure. Each program also participated in a First Episode Psychosis Services (FEPS-FS-1.1) and/or Clinical High Risk for Psychosis Services (CHRPS-FS-1.1) Fidelity Scale assessment. Individual scores for select fidelity items were analyzed dichotomously and continuously.

Results: On average, staff and providers had low-levels of stigma towards individuals across the psychosis-continuum, positive attitudes about seeking treatment, and attitudes supporting recovery-oriented care. However, these varied by staff and clinic characteristics, including race, bilingual ability, clinic role, level of education, and clinic setting (University or Community). Ten clinics reported peers and/or family advocates were part of their team at baseline assessment, and according to fidelity standards for peers on CSC teams, only four teams had a peer hired on their team. Preliminary data of CARS scores by team composition suggest there were significant differences on the CARS Discrimination and Devaluation Scales depending on the presence of a peer or family advocate/partner on the team. Other results related to FEPS-FS and CHRPS-FS items of interest, including family involvement, role of SEES, and whether a comprehensive needs assessment was completed, will be reported in association with CARS ratings. Possible moderators will also be discussed.

Discussion: Clinic staff stigma towards psychosis and beliefs about recovery could be a barrier to clients seeking care, affect treatment provision, and could impact clients' continued engagement. Results support the possible benefits of persons with lived or living experience on CSC teams that could reduce stigma and bias and increase a clinic's climate of being more recovery oriented. Other components of EP CSC care, such as support from SEES, may also play a role. These findings may support recommendations for insurance providers and funders to support CSC models that fund these vital roles. Limitations will also be discussed.

32. IMPROVED IN COGNITION AND SOCIAL COGNITION FOLLOWING TARGETED COGNITIVE TRAINING IN INDIVIDUALS AT RISK FOR PSYCHOSIS

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Background: Individuals at clinical high risk (CHR) for psychosis have neurocognitive deficits which impact broad domains of cognition and social cognition and are associated with functional disability and poorer overall outcome. Research has shown that targeted cognitive training (TCT) is effective at improving cognition and social cognition in individuals with schizophrenia and therefore may also be an effective therapeutic intervention to improve cognition in CHR individuals and better support social and role functioning. This study investigated whether cognitive and social cognitive TCT in CHR participants would improve their overall cognition, social cognition and functioning.

Methods: 102 CHR individuals were randomly assigned to targeted cognitive and social-cognitive training (TCT) or an equivalent amount of a computer game control condition (CG). N=98 participants were randomized and N=65 completed the assigned intervention which consisted of 40 hour-long sessions over approximately 8-10 weeks of either an online cognitive and social cognitive TCT or the control computer games. Participants completed a battery of social and cognitive tests at four timepoints (baseline, mid-training, post-training and 9 months post-training) and N=29 healthy controls (HC) also completed the baseline assessment. The primary outcome measures were the MATRICS Consensus Cognitive Battery (MCCB), as well

as the MSCEIT specifically to assess social cognition measure, and the Global Functioning Scales.
Results: CHR participants at baseline demonstrated significantly lower overall MCCB cognitive composite scores than HC ($t=-3.67$, $p<.001$) as well as lower MSCEIT scores ($t=-2.54$, $p=.02$). There was a significant group by time relationship on the overall MCCB cognitive composite score such that individuals who received TCT improved over the course of the training compared to those who received CG ($F(1,116)=4.07$, $p=.04$). Furthermore, these gains were maintained at the 9-month followup ($F(1,156)=3.98$, $p=.04$). The MSCEIT also showed a significant group by time interaction with improved performance in the TCT group compared to the CG group over the course of training and followup ($F(1,116)=9.45$, $p=.002$). However, there were no significant group by time interactions on the Global Functioning Scale: Role or Global Functioning Scale: Social.
Discussion: These results suggest that the TCT exercises were associated with improvements in overall cognition as well as social cognition and that these improvements continued following the cessation of the training program. This study supports the use of behavioral treatment like TCT to address potential cognitive and social cognitive impairments in CHR individuals. Further research is necessary to determine how best to translate these gains in cognition to improvements in overall functioning.

Oral Sessions: Genetics and Models of Schizophrenia

33. ALTERED PERSONAL SPACE IN SCHIZOPHRENIA: A SCOPING REVIEW OF PERIPERSONAL SPACE AND INTERPERSONAL DISTANCE

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Background: To protect the body and to adaptively engage with the environment, it is vital to accurately estimate the extent of our personal space. Aberrant appraisal of self-space could impair one's ability to distinguish self-generated actions and intentions from those of others, resulting in bodily self-disturbances. In turn, anomalous self-other distinction impacts social interactions. The space around the self (personal space) is represented by the peripersonal space (PPS), which refers to the multisensory interface within the reaching distance from the body, and we regulate the space between self and others (i.e., interpersonal distance; IPD) flexibly to optimize social interactions. Growing evidence indicates aberrant PPS and IPD in individuals with schizophrenia (SZ) and these altered personal distances are associated with clinical symptoms. Although self-disturbances and social impairments are core features of SZ, personal space dysregulation has not been extensively examined in this population due to the diversity of conceptualizations and methodologies that have resulted in a wide range of results and interpretations. This study aimed to review empirical studies of personal space in SZ to expand our understanding of self-other boundaries.
Methods: Based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher et al., 2015), literature search through database such as Pubmed, Web of Science, PsycInfo and Google Scholar was conducted. Keywords include "personal space", "interpersonal distance", "peripersonal space", "schizophrenia", "schizotypy" and "psychosis". Titles and abstracts of search-returned articles were reviewed using Rayyan software. Published works or accepted preprints in peer reviewed journals from 1950 to January 2022, written in English were included. The included research empirically measured

the personal space as a dependent variable in schizophrenia spectrum disorders or assessed schizotypy level of the general populations. A total of 21 articles met inclusion criteria.
Results: Eleven studies reported abnormally extended IPD of SZ regardless of the affective features of the environment; SZ prefer a longer distance between themselves and others, and 5 studies found the size of personal space for SZ and matched controls (CO) to be similar. In contrast, the PPS estimated from multisensory integration tasks appears to be contracted in in SZ (n=2) and those with high schizotypy (n=2). Importantly, the extended gradient of the PPS of SZ suggests that the border between the self and other is ill-defined or blurred. Indices of personal space, such as the size, gradient and variability of space representation, were closely associated with schizophrenia symptoms.
Discussion: Multisensory PPS is associated with goal-directed perceptual-motor behavior toward the environment. Smaller size of the PPS and blurred self-other boundary may have socially relevant consequences. Reduced clarity of the self-other boundary, precipitated by disrupted multisensory processing, may lead SZ to prefer enlarged IPD to keep others at bay and protect the self. In other words, weakened self-other distinction, indicated by shallow gradient of PPS, could result in a preference for larger IPD. Aberrant spatial self-processing, therefore, may derail social self-consciousness. Clinically, weakened self-other boundary may lead to a misattribution of self-generated actions as other-generated and thereby contributing towards social hallucinations and delusions.

34. ABERRANT SALIENCE IN AUDITORY PROCESSING IN SCHIZOPHRENIA: EVIDENCE FOR ABNORMALITIES IN BOTH SENSORY PROCESSING AND EMOTIONAL REACTIVITY

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Background: Misophonia is an unclassified disorder characterized by heightened sensitivity to repetitive, mostly human-produced sounds (throat-clearing, pen-tapping, etc.) that results in an emotional response and avoidance behaviors. Behavioral, electrophysiological, and fMRI measures implicate abnormalities in salience processing in the heightened emotional responses characteristic of misophonia. Like misophonia, psychosis is associated with the abnormal attribution of salience to stimuli. Researchers have proposed that delusions are a mechanism by which people with psychosis make sense of odd experiences of salience. There is also evidence that the auditory hallucinations in schizophrenia stem from an overinterpretation of background noise or as manifestations of increased salience attribution to mundane stimuli. Based on evidence that elevated salience signaling is characteristic of both psychosis and misophonia, investigating relations among misophonia measures, self-reports of domain-general salient experiences, and other clinical and behavioral variables is of interest in patients with psychosis.
Methods: Participants included 30 patients with schizophrenia or schizoaffective disorder (SZ) and 28 healthy controls (HC) between the ages of 18-64. Misophonia symptoms and emotional reactivity were measured using the Misophonia Questionnaire (MQ). The Sensory Processing Scale (SPS) was used to assess sensory over-responsivity/under-responsivity. We assessed psychopathology, the experience of odd perceptions and cognitions, and the frequency and severity of adverse childhood experiences using the Brief Psychiatric Rating Scale, the Aberrant Salience Inventory, and the Childhood Trauma Questionnaire, respectively.

Results: Misophonia symptoms did not significantly differ between SZ (M = 0.975, SD = 0.829) and HCs (M = 0.857, SD = 0.782; t = 0.554, p = 0.582); however, SZ patients (M = 0.996, SD = 0.617) exhibited greater misophonia emotional behavior than HC (M = 0.343, SD = 0.271; t = 4.889, p < 0.001). SZ participants also reported greater sound sensitivity on the MQ (M = 4.741, SD = 3.717), when compared with HC (M = 2.478, SD = 2.213; t = 2.658, p = 0.011) and scored higher (M = 0.251, SD = 0.169) than HCs (M = 0.101, SD = 0.106) on both sensory over-responsivity (t = 4.082, p < 0.001) and sensory under-responsivity (M = 0.250, SD = 0.185 for SZs; M = 0.136, SD = 0.106 for controls; t = 2.912, p = 0.005) on the SPS. Additionally, misophonia symptoms from the MQ correlated with BPRS unusual thought content (r = 0.373, p < 0.05). Misophonia emotional behavior from the MQ correlated with heightened emotion from the ASI (r = 0.429, p < 0.05) and with hallucination severity ratings from the BPRS (r = 0.415, p < 0.05). Finally, self-reported sound sensitivity from the MQ correlated with physical neglect scores from the CTQ (ρ = 0.426, p < 0.05).
Discussion: Although SZ patients reported similar misophonia symptom ratings compared to HC, they reported significantly higher misophonia emotional behavior. The presence of greater misophonia emotional behavior in SZ patients might point to a higher prevalence of misophonia than in the general population. Alternatively, it may suggest that the heightened emotional reactivity to sounds does not reflect "true" misophonia. Future studies, using neuroimaging techniques, could help elucidate similarities and differences among mechanisms of aberrant salience in misophonia and psychosis. In any case, these results: recapitulate the centrality of emotional reactivity to schizophrenia psychopathology – modulated by factors such as the experience of childhood trauma – and highlight the importance of emotional reactivity to symptoms as a treatment target.
Funding Source: This study was partially funded MPower funds from the University of Maryland.

35. DECONSTRUCTING THE EXPECTED VALUE OF CONTROL IN SCHIZOPHRENIA: A NOVEL MECHANISTIC MODEL OF NEGATIVE SYMPTOMS

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Background: Although negative symptoms are a central contributor to functional impairments in schizophrenia (SZ), extant treatments largely do not lead to sustained and clinically meaningful improvements in these symptoms. This has resulted in an intense search for novel mechanisms underlying negative symptoms in SZ. A growing body of work has identified that impairments in reward-processing may be critical mechanisms underlying negative symptoms and goal-directed behavior. Research has shown that people with SZ have difficulty engaging in decision-making processes needed to effectively identify when it is most advantageous to exert effort for rewards and that these deficits are associated with greater negative symptoms severity. However, little is known about the processes underlying these effort allocation impairments in SZ and consequently, the most critical elements to target in novel interventions. The current study leverages the novel Expected a Value of Control model to investigate the mechanisms behind effort allocation impairments in SZ. Based on this computational model, people allocate effortful cognitive control depending on 1) how much reward they expect for doing so 2) and whether their performance matters for obtaining rewards (efficacy).

Methods: We evaluated the independent and joint impact of reward and efficacy expectations on performance (reaction time, accuracy) in a novel experimental paradigm that dissociates expectations of reward and efficacy associated with a cognitive control task (i.e., the Stroop task) in SZ (n = 43) and healthy controls (CN; n = 44). Specifically, at the beginning of each trial, the monetary reward (high, $1.00 vs. low, $.10) and the efficacy level (high, reward is contingent on performance vs. low, reward is random) associated with the trial's Stroop task is presented. We also tested how efficacy and reward expectations interacted with negative symptoms and neurocognition to predict task performance.
Results: In SZ but not in CN, we observed a significant interaction between efficacy and reward. When expected rewards were high, SZ were faster to respond when rewards were contingent on performance (high efficacy) than when they were random (low efficacy). However, this patten was reversed when rewards were low. The interaction between efficacy and reward was further modulated by motivation and pleasure negative symptoms and global neurocognition (ps < .03). Specifically, in SZ with higher motivation and pleasure negative symptoms or poorer neurocognition, when rewards were random (low efficacy), task accuracy was lower when rewards were high than when rewards were low.
Discussion: These findings suggest that while SZ are sensitive to both reward and efficacy cues, they may have trouble integrating both cues to determine when it is most beneficial to allocate effortful cognitive control. Further, when rewards are high but efficacy (i.e., probability of success determined by performance) is low, SZ with high motivation and pleasure negative symptoms or poor cognition may fail to allocate sufficient effort despite the high potential payoff. For these individuals, effort may be too costly when efficacy is low and stakes (e.g., rewards) are high, leading them to reduce their control allocation. Together, these findings suggest that difficulty integrating efficacy and reward cues may account for diminished effort allocation in SZ with a certain clinical profile (i.e., high motivation and pleasure negative symptoms or poor cognition).

36. USING ELECTRONIC HEALTH RECORDS TO CHARACTERIZE THE INTERACTION BETWEEN SEXUAL ASSAULT AND GENETIC RISK IN SCHIZOPHRENIA

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Background: Epidemiological studies have established sexual assault as an important non-genetic risk factor for schizophrenia. Schizophrenia is highly heritable with a significant polygenic contribution; however, few studies have examined the joint impact of sexual assault and genetic predisposition on schizophrenia risk.
Methods: This study included 77,566 genotyped patients with linked electronic health records from the Vanderbilt University Medical Center biobank (BioVU). Sexual assault exposure was determined using a validated keyword-based phenotyping algorithm applied to de-identified clinical notes. Sexual assault was studied as an environmental exposure interacting with schizophrenia polygenic score in logistic regression models of schizophrenia clinical diagnosis. Analyses were conducted separately in individuals with European (N=65,261) and African (N=12,305) ancestry.
Results: European-ancestry analysis demonstrated a significant gene-environment interaction effect on schizophrenia diagnosis ($p<0.05$) with a greater association between schizophrenia polygenic score and diagnosis in individuals without disclosures of sexual assault (OR=1.93, 95% CI=1.65, 2.26) compared with survivors of sexual assault (OR=1.21, 95% CI=0.87,1.69). Sexual assault was associated with increased odds of schizophrenia in the African-ancestry

cohort (OR=49.9, 95% CI=35.5-70.1), but no significant interaction effect was observed in this group.
Discussion: This work suggests that schizophrenia polygenic score may be a greater risk factor in the absence of additional risk factors including traumatic environmental exposures such as sexual assault. Further work is needed to elucidate the joint contributions of polygenic risk and sexual assault across additional ascertainment settings and ancestral groups.

37. GENETICS, INFLAMMATION AND CHILDHOOD TRAUMA: EFFECTS ON COGNITION IN PATIENTS WITH SCHIZOPHRENIA AND HEALTHY PARTICIPANTS

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Background: Recent studies have reported a negative association between exposure to childhood physical neglect (PN) and cognitive functioning in patients with schizophrenia (SCZ). Change in immune response is hypothesised as one potential mechanism by which PN may negatively impact both disease risk and cognitive function. Proinflammatory markers, including interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF-α) and C-reactive protein (CRP) have been found to be particularly elevated in SCZ patients who have experienced PN. In recent studies, elevated levels of IL-6 has been shown to mediate the association between PN and cognition. However, it is not yet known whether this mediating effect is specific to IL-6 or extends more broadly to other inflammatory markers such as CRP and TNF-α. Further, interactions between genetic risk for SCZ and PN on the association between inflammation and cognition have yet to be investigated. The purpose of the present study was therefore to better model the association between PN and cognition in terms of the mediating effects of inflammatory response and the moderating effects of genetic risk for SCZ.
Methods: A total of 278 Irish participants (102 patients with SCZ and 177 healthy controls) were included in this study. Structural equation modelling (SEM) was used to examine whether the mediating effects of inflammation on the association between PN and cognition was better captured by IL-6 alone, or by a combined inflammatory latent variable. This latent variable of inflammation was derived from basal plasma levels of IL-6, TNF-α and CRP. PN was measured using the Childhood Trauma Questionnaire and cognition was assessed across three domains including full-scale IQ, logical memory and the emotion recognition task (ERT). Following this, we tested whether any associations described above were moderated by an individual's genetic susceptibility to SCZ, which was grouped according to high vs low SZ-polygenic score (SZ-PGS) carrier status. SEM analyses were performed in R (version 4.1.2) using the Lavaan package.
Results: Significant indirect effects of the latent variable of inflammation were found across all SEM models, such that the inflammatory marker fully mediated the associations between physical neglect and ERT, and partly mediated the association between physical neglect and both FSIQ and logical memory. When the latent variable was replaced with IL-6, the mediation model for physical neglect and FSIQ was no longer significant (Indirect effect= -0.027, p= 0.056). In contrast, the mediation model for logical memory and ERT remained significant but explained considerably less variation in cognition compared to the latent proinflammation variable (4.1% vs 2.1% for logical memory and 4.6% vs 2.2% for ERT). When genetic risk for SCZ (SCZ-PGS) was included as a moderator in the model, this was observed to significantly

moderate the relationship between physical neglect and logical memory (Indirect effect= -0.212, p= 0.002), such that individuals carrying a higher SZ risk burden and greater exposure to physical neglect demonstrated poorer performance on the logical memory test.
Discussion: This study provides evidence that the role of inflammatory response in mediating the relationship PN and cognitive performance extends beyond that of IL-6 alone. This study also provides novel evidence that the relationship between physical neglect and memory performance is moderated by genetic risk for SCZ. To conclude, increased inflammation and higher genetic risk for SCZ represent an important mechanism linking adverse early experiences to later cognitive deficits in patients with SCZ and controls.

38. RCT OF VIRTUAL REALITY JOB INTERVIEW TRAINING IN IPS SUPPORTED EMPLOYMENT FOR INDIVIDUALS WITH SCHIZOPHRENIA AND OTHER DISORDERS

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Background: Approximately 10-15% of the 9 million adults with schizophrenia and other mental illnesses (SMI) are employed. This employment rate increases to 50% in adults with schizophrenia and other SMIs enrolled in the Individual Placement and Support (IPS) model of supported employment. A notable gateway to employment for individuals in IPS and other forms of supported employment is the job interview. However, individuals with schizophrenia and other SMIs have notable impairments in their social skills that make it difficult to navigate the job interview. A recent employment framework shows that active job-seeking behavior (e.g., completing job interviews) is an essential treatment target for employment services. Moreover, adults with schizophrenia have poor interviewing skills and want training to alleviate their fears related to interviewing. Currently, IPS provides few resources to train their "Employment Specialist" counselors to deliver the most common form of job interview preparation which is role-playing job interviews. Moreover, only about 47% of employment specialists provide role-play training as this training is time and resource intensive and is not included within the fidelity framework of IPS. To address this issue, we developed Virtual Reality Job Interview Training (VR-JIT, a commercially available tool) which is a computerized job interview simulator (that facilitates 4 levels of automated feedback). Subsequently, VR-JIT has established efficacy (via 5 RCTs) at enhancing job interview skills and competitive employment outcomes among individuals with schizophrenia and other serious mental illnesses. The presentation will report on the outcomes from an intent-to-treat randomized controlled trial that assessed the real-world effectiveness of VR-JIT when delivered within IPS for individuals with schizophrenia and other SMIs.
Methods: This NIMH-funded randomized controlled trial (R01 MH110524) included 90 participants with schizophrenia and other SMIs. Participants were randomly assigned to IPS+VR-JIT (N=54) or IPS as usual (N=36), completed pretest and posttest assessments, and an employment evaluation at 9-months post-randomization. Intent-to-treat chi-square analysis, multivariable logistic regression, Cox proportional hazards models, and mixed-effects linear regressions were conducted. Fifty-one percent of participants were categorized as IPS nonresponders (i.e., they did not obtain employment within their first 90 days of IPS) and 49%

were recent IPS enrollees (i.e., fewer than 90 days in IPS). Primary outcomes were competitive employment and time-to-employment by nine-month follow-up. Secondary outcomes were job interview skills, job interview anxiety, and job interview self-confidence. Notably, the enrollment for this study ended prematurely due to the covid-19 pandemic.
Results: IPS+VR-JIT participants did not have significantly higher employment rates, compared with IPS-as-usual participants (41% vs. 28%, p=.07). Subgroup analyses revealed that IPS nonresponders (N=46) in the IPS+VR-JIT group had greater odds of obtaining employment (odds ratio [OR]=5.82, p=0.014) and shorter time to employment (hazard ratio=2.70, p=0.044), compared with IPS nonresponders in the IPS-as-usual group. Meanwhile, recent IPS enrollees in the IPS+VR-JIT group did differ from recent IPS enrollees in the IPS-as-usual group with respect to their employment outcomes. Regarding secondary outcomes in the full sample, mixed-effects linear analyses indicated that IPS+VR-JIT, compared with IPS-as-usual, significantly improved job interview skills (p=0.006), job interview anxiety (p=0.019), and job interview confidence (p=0.013).
Discussion: Vocational rehabilitation services within community mental health agencies could potentially benefit from an evidence-based practice targeting job interview skills for individuals with schizophrenia and other SMIs. Based on the results of this RCT, VR-JIT appears to be an option to fill this service gap for individuals who may linger in employment programming without obtaining employment (which is at least 50% of clients receiving those services). In addition, VR-JIT trainees more broadly had significantly improved interview skills, interview confidence, and interview anxiety, which speaks to the effectiveness of VR-JIT for these outcomes above and beyond the services provided within IPS. Notably, more research is needed to understand why VR-JIT is effective and to identify optimal implementation strategies when delivering it within employment services. To this end, although the scale of IPS is still expanding domestically and internationally, most employment services lack the fidelity and supports of IPS. Thus, evidence-informed methods such as VR-JIT could be used to help elevate such services.

39. ASSOCIATION OF TREATMENT-RESISTANCE WITH SCHIZOPHRENIA POLYGENIC RISK SCORES

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Background: Many schizophrenia patients continue to exhibit psychotic symptoms even after taking at least two antipsychotic medications. They are regarded as treatment-resistant, and clozapine is often prescribed. Therefore, clozapine therapy can be utilised to identify individuals who are resistant to pharmacological treatment.A number of genetic studies have attempted to examine the genetic factors underlying treatment resistance, with most previous candidate gene studies focusing on neurotransmitter system genes. Three recent studies reported association between treatment resistance and polygenic risk score (SCZ-PRS) for schizophrenia based on summary statistics from the Psychiatric Genomics Consortium Phase 2 genome-wide association study (GWAS), while one did not report this association.
Methods: We performed polygenic risk score analysis of treatment resistance using the latest (Phase 3) schizophrenia GWAS summary statistics in our sample of 195 patients of European ancestry with diagnosis of schizophrenia or schizoaffective disorder according to DSM-IV. We calculated standardized SCZ-PRS based on summary statistics from the latest schizophrenia GWAS (leave-one-out; Trubetskoy et al, 2022) using the PRS-CS method. We ran logistic regression, with treatment resistance (based on clozapine use status) as the dependent variable,

SCZ-PRS as the independent variable, and sex and first two principal components as covariates.
Results: Polygenic risk scores for schizophrenia are significantly associated with treatment resistance status (beta=0.57, SE=0.21, p=0.007). Patients scoring in the top 10th percentile in SCZ-PRS are 4.76 times as likely to be treatment resistant as patients in the other 90 percentiles (p=0.005), taking into consideration sex and population structure.
Discussion: Our findings provide further support for the potential use of the genetic risk scores for schizophrenia in the prediction of treatment outcomes.

40. RARE DAMAGING VARIANTS AND PHENOTYPIC VARIABILITY IN SCHIZOPHRENIA

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Background: One of the greatest barriers to clarifying the core biological processes that underlie schizophrenia (SCZ) and improving patient outcomes is the clinical and genetic heterogeneity of the disorder. For example, while psychosis onset is most common in early adulthood, some patients experience psychotic symptoms as early as childhood. Similarly, while cognitive functioning is impaired on average among SCZ patients compared to controls, there is considerable variability between patients. Determining whether differences in clinical features between patients can be explained by distinct genetic profiles, such as differential burden of damaging variants in disease-associated genes or in genes involved in different aspects of brain development, is a key question with implications for personalized medicine approaches to intervention.
Methods: We used whole exome sequencing to identify rare, protein-truncating variants (PTV) in 402 patients with SCZ spectrum disorders. Linear or logistic regression tested associations between cognitive function, age of psychosis onset, and burden of PTV in genes associated with autism spectrum disorder (ASD), broader neurodevelopmental disorders, or SCZ, or in genes involved in distinct neurodevelopmental processes. Neurodevelopmental process gene-sets were defined previously via weighted gene co-expression network analysis of transcriptomic data from 1,061 brain samples from the developing human brain (Forsyth et al., 2020).
Results: Total burden of PTV in genes previously associated with ASD and SCZ were associated with lower cognitive functioning among SCZ spectrum patients. Burden of PTV in genes involved in establishing neuronal excitability during perinatal development additionally predicted borderline intellectual functioning. Burden of PTV in ASD-associated genes was nominally associated with earlier psychosis onset.
Discussion: Results suggest that poor cognitive functioning among SCZ patients is associated with greater burden of rare, damaging variants in genes that have been previously associated with ASD and SCZ, as well as in genes involved in establishing neuronal excitability. Efforts to confirm these findings in a larger sample are underway.

Oral Sessions: Somatic and Environmental Factors

41. HEARING LOSS IN SCHIZOPHRENIA: THE ROLE OF MEDICAL AND PSYCHIATRIC FACTORS

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Background: Recent findings of increased rates of hearing loss (HL) in community-dwelling adults with schizophrenia have identified an unrecognized and unmet service need. Unaddressed, hearing impairment can have significant psychosocial, mental and cognitive health impact. Several barriers may impact assessment, prevention and treatment of HL in people with schizophrenia. One concern is the validity of audiology assessment when psychotic symptoms such as hallucinations are also present. Another concern is the role of medical comorbidities in the HL found in people with schizophrenia, given that non-psychiatric cohorts with HL have higher rates of certain medical conditions. This study sought to understand the role of psychiatric and medical factors in the hearing of people with schizophrenia, with the goal of informing assessment and risk mitigation.

Methods: This study used the Shoebox portable audiometry system to evaluate the hearing of 40 older adults ages 50-70 years with a schizophrenia-spectrum diagnosis. Hearing threshold (dB) was characterized as a continuous variable by the better ear pure tone average measured across 500 to 8000 Hz. Severity of hearing loss was classified categorically using standard cut points. The Tinnitus Handicap Inventory (THI) assessed a second aspect of audiologic functioning. The presence of medical comorbidities that might impact hearing ability was obtained via records review and frequency counts of medical conditions were examined with respect to HL severity category. The Positive and Negative Syndrome Scale (PANSS) was used to examine the cross-sectional relationship between psychiatric symptom severity and audiologic performance. A subset of participants retested on audiometry to obtain a reliability estimate were asked directly about symptom interference during testing using item P3 (Hallucinatory behavior) from the PANSS.

Results: The mean (SD) age of the sample was 59.79 (5.66) years, 62.5% (n=25) were male, and most self-identified as non-white (77.5%, n=31) and non-Hispanic/Latinx (80%, n=32). Mean (SD) hearing threshold (HT) was 24.48 dB (12.66); 30% (n=12) of the sample evidenced no HL, 35% (n=14) evidenced subthreshold HL (15< HT ≥25), and 35% (n=14) evidenced HL in the mild to severe range (HT>25 dB). Severity of impairment on the THI was significantly correlated with HT (r=0.48, p=0.002) though only 12.5% reported more than slight impairment due to tinnitus. Medical comorbidities included diabetes/prediabetes (50%), cardiovascular disease (7.5%), and hypertension (52.5%). Presence of HL varied at a trend level of significance with presence of medical comorbidities (Fisher's Exact Test = 4.76, p=0.084). Neither PANSS positive (r=0.07) nor negative (r=0.14) symptom totals were correlated with HT. While 36% of participants retested on audiometry reported auditory hallucinations (AH) during testing, presence of AH did not significantly change the classification of HL severity from test to re-test.

Discussion: Compared to similar aged non-psychiatric cohorts, adults with schizophrenia ages 20-70 years have higher rates of HL and elevated hearing threshold. Results suggest that the presence of HL is not simply an artifact of psychiatric symptoms and HL demonstrated on audiologic testing is independent of auditory hallucinations during testing. Health comorbidities such as diabetes, cardiovascular disease and hypertension that are known risk factors for age-related HL in non-psychiatric cohorts were present in this sample and associated with their HL. These findings have relevance for addressing assessment and prevention of HL in schizophrenia.

42. COMPUTATIONAL SEMANTIC AND SYNTACTIC ANALYSIS IN SCHIZOPHRENIA: A CLUSTER ANALYSIS SEEKING LINGUISTIC SUBGROUPS

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Background: Oddities in speech are common in schizophrenia, but not all patients exhibit them. This makes the analysis of speech patterns an important means to investigate heterogeneity in this illness. Previous work has suggested that computerized analysis of speech can detect several disturbances within this population. In particular, semantic content density, pronoun use, as well as morphology/syntax appears to be affected in the early phases of the illness. We utilize these features to parse the heterogeneity of first episode psychosis and identify subgroups of individuals with distinct linguistic profiles.

Methods: 147 subjects (39 healthy controls (HC), 72 with first episode psychosis (FEP), 18 with chronic schizophrenia for >3 years (SCZ), and 18 clinical high risk (CHR)) from an ongoing study (TOPSY) were included in this study. Picture description task from the Thought and Language Index (TLI), was used to elicit 1-minute of speech. Speech data was then transcribed to text and analyzed for semantic and syntactic variables of speech which were then transformed into quantitative scores for various speech variables. We chose 7 variables to be included in final analysis that capture syntactic complexity, semantic content, and pronoun use. These variables included mean length of sentence (MLS), mean length of T-unit (MLT), mean length of clause (MLC), clauses per sentence (CS), number of subjects per clause (nsubj/cl), number of ideas, and pronoun density. A hierarchical cluster analysis was conducted in R. Analysis included all 147 subjects and their 7 speech variables. Nbclust was used to determine the optimal number of clusters from the dataset. Once the optimal number of clusters was determined, subjects were then divided into their subgroups and the variables were compared between groups to determine any notable features.

Results: Nbclust suggested three clusters as optimal from the sample. Group 1 consisted of 51 subjects (9 CHR, 18 FEP, 17 HC, 7 SCZ; 35.29% FEP), group 2 consisted of 66 subjects (8 CHR, 32 FEP 19 HC, 7 SCZ; 48.48% FEP), and group 3 consisted of 30 subjects (1 CHR, 22 FEP, 3 HC, 4 SCZ; 73.33% FEP). The clusters did not differ significantly in terms of age or PANSS score (total, positive, and negative scales). Notably, group 3 consisted of a disproportionate number of FEP subjects (73.33% compared to 48.98% in overall sample) and FEP of this subgroup displayed higher scores on MLS, MLT, CS, and number of ideas ($p < 0.001$).

Discussion: The findings from this hierarchical cluster analysis expand on previous work analyzing speech data in schizophrenia. Most notably, we identified a subgroup of individuals with a distinctive linguistic profile: they have higher complexity of syntax and density of ideas and are mostly represented by patients with FEP. This cluster was not associated with higher symptoms, pointing to the existence of specific language profiles, distinct from clinical profiles. These findings support the presence of stage-specific language disturbances in schizophrenia, with a subgroup of acute psychosis exhibiting a linguistic profile that is distinct from both prodromal and chronic schizophrenia. This raises the question of whether certain fundamental changes in syntax and semantics result in acute psychotic symptoms.

43. RISK OF ADVERSE OBSTETRIC AND NEONATAL OUTCOMES IN PREGNANT WOMEN WITH SCHIZOPHRENIA-SPECTRUM DISORDER: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Schizophrenia-spectrum disorder (SSD) is a severe mental illness that profoundly jeopardizes the reproductive health of women in young adulthood. Accumulating evidence revealed higher risk of obstetric and neonatal complications in women with SSD, compared to those without SSD. This study aimed to conduct an updated comprehensive meta-analysis to quantitatively synthesize estimates of increased risk of adverse obstetric and neonatal outcomes among women with SSD relative to the general population.

Methods: We performed a comprehensive search of EMBASE, MEDLINE, Cochrane and WOS databases for relevant English full-text articles from inception up to September 24, 2021. Two reviewers evaluated evidence that compare risk of obstetric and neonatal complications in women with and without SSD and performed formal assessment of the methodological quality of the studies using the Newcastle-Ottawa Scale. Adjusted relative risk (RR) was pooled across studies using the random-effect models. Heterogeneity was assessed by the chi-square Cochran's Q-test and I2 statistic. Publication bias was examined using the funnel plot and Egger's regression asymmetry tests.

Results: Sixteen studies were included in the review, comprising 35,913,532 pregnant women (including 39,246 women with SSD). Women with SSD had increased risk of placental complications (RR=1.40 [95% CI: 1.12–1.75]), induction of labor (1.30 [1.10–1.52]), caesarean delivery (1.21 [1.11–1.32]), fetal distress (1.09 [1.03–1.14]) and stillbirth (1.39 [1.16–1.67]) than controls. Infants born to mothers with SSD displayed elevated risks of preterm birth (1.38 [1.24–1.54]), small for gestational age (1.26 [1.13–1.40]), low birth weight (1.40 [1.21–1.62]), low Apgar scores at 1 minute (1.41 [1.22–1.63]) and at 5 minutes (1.67 [1.27–2.20]), neonatal death (1.77 [1.33–2.35]) and post-neonatal death (2.38 [1.52–3.73]) relative to those born to mothers without SSD. Significant heterogeneity was observed across studies in most outcomes. No publication bias was noted.

Discussion: Our findings confirmed the increased risk of some important adverse obstetric and neonatal outcomes in women with SSD and thus underscore the importance of coordinated antepartum care that manages the health and wellbeing of women with SSD during pregnancy. Future studies should also assess moderators and mediators for the excess pregnancy complications in SSD women and hence more information can be gathered to guide healthcare resources allocation to optimize obstetric and neonatal outcomes in this vulnerable group of patients.

44. THE ROLE OF SOCIAL DETERMINANTS OF HEALTH IN ASSOCIATIONS BETWEEN MARGINALIZED RACIAL IDENTITIES AND PSYCHOTIC-LIKE EXPERIENCES IN THE ABCD STUDY

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Background: Previous work has linked marginalized racial and ethnic groups to an increased endorsement of psychotic-like experiences. According to social determinants frameworks, marginalized racial and ethnic groups are at increased risk for exposure to socio-environmental risk factors, including structural factors (such as poverty and poor housing conditions), as well as social stressors (such as discrimination). We have begun to examine the extent to which socio-environmental risk factors partially account for associations between racial/ethnic groups with psychotic-like experiences.

Methods: Analyses included a total of 10,257 individuals from the Adolescent Brain Cognitive Development study. Analyses examined individual socio-environmental risk factors and stressors, as well as the first component derived from principle component analyses for socio-environmental risk factors and cumulative stressors. These analyses included mediation models examining whether cumulative stress assessed at 1-year follow-up indirectly links baseline socio-environmental exposures to distressing PLEs assessed at 2-year follow-up, as well as serial mediation models examining whether these socio-environmental exposures and cumulative stress indirectly link racial/ethnic groups to distressing PLEs.
Results: Analyses revealed evidence that cumulative stress indirectly linked socio-environment exposures, including poverty and exposure to crime, to distressing psychotic-like experiences. There was also evidence that for Black and Hispanic groups, greater socio-environmental risk factors were associated with greater cumulative stress, and these factors indirectly linked being Black or Hispanic with distressing psychotic-like experiences.
Discussion: The analyses provide evidence that the relationship between marginalized racial and ethnic identities with the endorsement of PLEs partially reflects the sequelae of structural racism. Findings further our understanding of contributors to early psychosis spectrum symptoms, underscoring the importance for both clinicians and researchers to incorporate structural factors and social stressors in conceptualizations of PLEs in individuals from marginalized groups.

45. LIFE COURSE TRAJECTORIES OF NEIGHBOURHOOD SOCIAL DEPRIVATION AND POPULATION DENSITY BEFORE AND AFTER FIRST DIAGNOSIS OF PSYCHOTIC DISORDERS: A NESTED CASE-CONTROL STUDY IN SWEDEN

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Background: People with psychosis are more likely to be born and live in densely populated and socially deprived environments, but it is unclear whether this association is a cause or consequence of disorder. Consequently, we sought to define trajectories of exposure to neighbourhood-level population density and deprivation before and after first diagnosis of severe mental illness [SMI], and to investigate whether these were associated with psychotic disorder or non-psychotic bipolar disorder.
Methods: We conducted a nested case-control study of all individuals born in Sweden between January 1, 1982, and December 31, 2001, with no SMI diagnosis before their 15th birthday. Cases included all cohort members who received a first diagnosis of International Classification of Diseases, Tenth Revision [ICD-10] psychotic disorder (F20-29, F30/1.2, F32/3.3) or non-psychotic bipolar disorder (F30/3.x) between their 15th birthday and cohort exit, up to December 31, 2016. We randomly selected one birth-year-sex matched control per case. Exposure variables were quintiles of neighbourhood social deprivation and population density at the Small Area Marketing Statistics (SAMS) area-level. Group-based trajectory modelling was used to derive trajectories of each exposure from: birth until age 13 years old, and from age at diagnosis until cohort exit. Logistic regression was used to examine associations with outcomes, adjusting for the following confounders: birth year; sex; biological parental history of SMI; parental migrant status; and number of residential moves.
Results: We included 26,729 cases and 26,729 controls. From birth to early adolescence, we observed independent dose-response relationships between membership of a greater deprivation or population density trajectory and psychotic disorder, with those in the most versus least deprived (adjusted odds ratio [aOR]: 1.21; 95%CI: 1.11-1.31) and densely

populated (aOR: 1.49; 95%CI: 1.34-1.66) trajectories at greatest risk, after multivariable adjustment. Compared with those in the most deprived trajectory, experiencing moderate (aOR: 0.92; 95%CI: 0.84-1.02) or strong upward (aOR: 0.84; 95%CI: 0.75-0.93) mobility corresponded with lower risk. Following diagnosis, only 2.3% of participants experienced active downward social drift to more deprived environments. Compared with controls, people with psychotic disorder were more likely to belong to this trajectory (aOR: 1.38; 95%CI: 1.16-1.65) or remain living in the most deprived trajectory (aOR: 1.37; 95%CI: 1.25-1.50). Less consistent patterns were evident for non-psychotic bipolar disorder.
Discussion: Greater deprivation and population density during upbringing increase risk of psychotic disorder, but this may be modifiable via upward social mobility during early life. The preponderance of people with psychotic disorders in deprived areas can largely be explained by social causation and passive drift processes, with active social drift following diagnosis not playing a strong role. For effective allocation of healthcare resources, prevention and treatment efforts should be preferentially located in these deprived areas.

46. PHYSICAL HEALTH IN CLINICAL HIGH RISK FOR PSYCHOSIS INDIVIDUALS: A CROSS-SECTIONAL STUDY

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Background: The CHR-P (Clinical High Risk for Psychosis) phase represents an opportunity for prevention and early intervention in young adults, which might also be focused on important physical health trajectories. There are different reasons to promote good physical health and lifestyle in CHR-P individuals, including recent evidence that low levels of physical activity during childhood and adolescence could be considered as an independent predictor of psychosis, or comorbid psychiatric disorders (e.g. affective and substance use disorders) which are also linked to significant physical health conditions.
Methods: We conducted a clinical register-based cohort study, according to the Reporting of studies Conducted using Observational Routinely collected health Data (RECORD) Statement. The primary outcome was the physical health in CHR-P individuals recruited from January 2013 until October 2020, at the South London and Maudsley (SLaM) National Health Service Foundation Trust, UK.
Smoking status, alcohol use, diet, and physical activity were investigated with Fagerström Test for Nicotine Dependence (FTND), AUDIT (Alcohol Use Disorder Identification Test), DINE (Dietary Instrument for Nutritional Education), IPAQ (International Physical Health Questionnaire).

Results: The final database included 194 CHR-P subjects, 90 (46%) females and 104 (54%) males. The mean age was 23.70±5.12 years. The percentage of tobacco smokers was 41% (significantly higher than the value of 24% found in the general population, in the same age group). 49% of the subjects who consumed alcohol had an AUDIT-C score above 5 (hazardous drinking), with an average score of 4.94 (significatively higher than the value of 2.75 in the general population). Investigation of diet revealed low fiber intake in the majority of the sample

and high saturated fat intake in 10% of the individuals. 47% of CHR-P subjects met the recommended physical activity guidelines in the UK (significantly lower than the value of 66% found in the general population). Average physical parameters were 71.53±16.04 kg for weight, 1.72±0.10 m for height, 24.45±4.50 for BMI, 82.29±13.04 cm for waist circumference, 69.42±11.57 bpm beats for heart rate, 17.93±5.32 apm for respiratory rate, 115.81±12.00 mmHg for systolic pressure and 72.24±9.32 mmHg for diastolic pressure. Physical parameters were not significantly different from the general population.
Discussion: Our study showed that the percentage of smokers in CHR-P subjects was twice as high as the general population and those who consume alcohol have drinking behaviors that might be more dangerous and possibly lead to abuse and addiction. Also, CHR-P subjects had an unbalanced diet, with high proportions of low fiber intake and high saturated fat intake, while subjects meeting the recommended physical activity guidelines were a low proportion (47% vs 66% of young adults of the same age in the UK). This evidence corroborates the need for monitoring physical health parameters and lifestyle in CHR-P subjects, to implement tailored interventions which target daily habits.

47. A SPECIALIZED PRIMARY CARE MEDICAL HOME IMPROVES THE HEALTH CARE AND PHYSICAL HEALTH OF PATIENTS WITH SERIOUS MENTAL ILLNESS

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Background: People with serious mental illness (SMI) have rates of premature mortality three times higher than the general population, mostly due to cardiovascular disease and cancer. This population is often not well engaged in primary care and do not receive high-value medical services, but are high utilizers of hospital and emergency services. While services to address this problem have been implemented by numerous healthcare organizations, most have not been studied using experimental designs, and few have been effective. This project studied the implementation and effectiveness of a novel primary care medical home designed for patients with SMI and physical health risk.
Methods: A hybrid implementation-effectiveness study, this is a cluster controlled trial of a medical home, the SMI Patient-Aligned Care Team (SMI PACT), to improve healthcare of patients with SMI. The SMI PACT included systematic patient enrollment, proactive nurse panel management, a collaborative care psychiatrist, and a primary care physician providing care that included psychiatric treatment. Within one geographic region of the Department of Veterans Affairs, one medical center was assigned to SMI PACT and two to usual care. Patients were recruited based on having elevated medical risk; a diagnosis of schizophrenia, bipolar disorder, major depression with psychosis, or persistent severe post-traumatic stress disorder requiring antipsychotic medication; and stable psychiatric disorder. Medical risk was calculated using the CAN score, which measures risk for hospitalization or death within 6 months. Stability of psychiatric disorder was measured using the Milestones of Recovery Scale (MORS). Linear mixed effects repeated measures models compared the intervention over time to control on access and treatment appropriateness, perceived chronic illness care and care experience, psychiatric symptoms, and health-related quality of life. Formative evaluation studied patients, providers, organizational context and treatments.

Results: Thirty-nine clinicians and managers enrolled. 331 patients with SMI enrolled for a median of 401 days. 28% had schizophrenia, with others divided between major depressive disorder with psychosis (4%), bipolar disorder (36%), and disabling PTSD requiring antipsychotic medication (32%). Participants had a mean CAN risk percentile of 85. Sixty-five intervention patients (40%) moved all psychiatric care to the PACT. No adverse events were attributable to the intervention. Compared with control, intervention patients had greater improvement over time in appropriate screening for body mass index, lipids, and glucose ($\chi 2$ = 6.9, 14.3, and 3.9; P's < .05); greater improvement in all domains of chronic illness care (activation, decision support, goal-setting, counseling, coordination) and care experience (doctor-patient interaction, shared decision-making, care coordination, access; F for each 10–24, P's < .05); and greater improvement in mental health-related quality of life (F = 3.9, P = .05) and psychotic symptoms (F = 3.9, P = .05).
Discussion: A specialized medical home for patients with SMI can be feasible, safe and effective. This SMI medical home was well received by patients and clinicians. Processes and tools were developed to support dissemination. This care model addresses healthcare challenges faced by this high cost, high need population.

48. WHY AND HOW TREATMENT WORKS? EXPLORATION OF SUBJECTIVE EXPERIENCES AND PERSPECTIVES OF 'MENTAL HEALTH SERVICE' USERS WITH PSYCHOSIS AND PROVIDERS IN ETHIOPIA

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Background: Traditional health services remain the preferred choice for the treatment of mental illnesses in Africa. In Ethiopia, 85% of patients access traditional health services for mental illness. This is in contrast to only 10% of patients with mental illness accessing 'modern' mental health services. This has called for the need to increase collaboration between traditional and modern mental health services in search for a viable hybrid model. The proposed modalities of collaboration range from a 'task-shifting' model where some functions of treatment, like prescribing medications, is done by traditional practitioners to a fully integrated model where both services are provided at one visit. This study explored the question: what subjective experiences and perspectives of users and providers determine why and how treatment works? Our hypothesis was, by exploring the subjective experiences, explanatory models and perspectives of patients, family members, and providers of existing mental health provision models, it is possible to capture a knowledge base that could be used to further develop a hybrid model of mental health care that incorporate the best of traditional and modern models for care of persons with schizophrenia spectrum disorders.
Methods: The study was conducted at two sites in Ethiopia where the Department of Psychiatry at Addis Ababa University provides service. Entoto St. Mary's church holy water treatment site is where the department has a collaboration where patients attending holy water treatment are offered the option of a psychiatric evaluation and treatment at a nearby clinic. The outpatient psychiatry clinic at the Tikur Anbessa Hospital is the nation's referral hospital. We employed qualitative methodology with an interpretive paradigm using in-depth 45-60 minute interviews of patients, family members and providers who attended the two clinics, and purposive sampling to identify participants. Consent and ethics approval was acquired. The 25 interviews conducted to reach saturation included 5 spiritual practitioners, 5 family members, 5 patients who were only on holy water treatment, 5 patients who were on both holy water treatment and medications, and 5 holy water attendants who support the clergy. All interviews

were conducted in Amharic, tape recorded, transcribed and translated to English and coded for thematic analysis.
Results: Collaborative approach, embracing explanation, community centredness, spirituality, and diagnostic paradigm, were the themes that emerged from our thematic analysis. A collaborative approach and attitude to care was found to be the norm at the holy water treatment site. Patients, family members, and providers expressed a culture of practice where all are involved in ensuring that the needs of the patient are met. An all-embracing perspective about treatment effectiveness through the attribution of cure as an endowment from the almighty was given as a reason why participants have a positive attitude towards all forms of treatment including modern psychiatric care. The experience of patients at the holy water site was described as being situated in the community values of sharing and supporting one another which was described in direct contrast with care provided at a psychiatric hospital where patients are isolated from a social milieu. The trust family members have for the social system is also described as one reason why the treatment sites were preferred. Spirituality served as the overarching, binding factor.
Discussion: Collaboration between traditional and modern mental health services is an area of global mental health that is that is not given enough emphasis. The lack of viable model for the type of collaboration is a contested subject. The question of effectiveness of traditional Methods: is also debatable. Despite the controversies and the lesser attention given to its exploration, traditional medicine remains not only the commonest but also the preferred choice of treatment for patients and families in Ethiopia, even for severe mental illness including schizophrenia. This calls for a deeper exploration of experiences and perspectives of the various actors regarding why and how it remains their preferred choice. Our exploration sheds light on some of these and identified areas for further empirical explorations.

Oral Sessions: Cognition and Intermediate Phenotypes

49. PROGESTERONE MODERATES THE RELATIONSHIP BETWEEN SCHIZOTYPAL TRAITS AND NEGATIVE AFFECT IN YOUNG WOMEN

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Background: Individuals with or at-risk for psychosis demonstrate a tendency towards negative affective states. Increased stress sensitivity and greater negative affect are observed in individuals diagnosed with schizophrenia and are associated with poorer functioning. Similarly, individuals high in schizotypal personality traits, which may reflect latent illness vulnerability experience greater stress reactivity and higher negative affect. Evidence from both human and animal work indicates that ovarian hormones play a role in affect regulation, and data from patient and clinical high-risk samples also point to a protective effect of estrogen (and possibly progesterone) in women with psychosis. Ovarian hormones thus stand to moderate the relationship between negative affect and psychosis risk. However, results from patient samples are complicated by antipsychotic use, which impact ovarian hormone levels. Furthermore, existing studies investigating psychosis risk, affect, and ovarian hormone associations are cross-sectional, making it impossible to disentangle within-person from

between-person processes. In the current study we aim to triangulate relationships between negative affect, ovarian hormone levels, and schizotypal traits using a 45-day daily diary study of young women from a general population sample. Specifically, we examined the possible risk-buffering effects of ovarian hormones on the association between schizotypy and negative affect.

Methods: 563 regularly menstruating young women (ages 15-24) who were not using hormonal contraceptives or other medications that could influence ovarian hormones were included in these analyses. Over a 45-day period, women provided daily saliva samples for ovarian hormone measurements as well as daily ratings of positive and negative affect using the Positive and Negative Affect Schedule. Additionally, women completed the Multidimensional Personality Questionnaire (MPQ); the Absorption subscale provided an index of schizotypal personality traits. Correlational analyses were used to relate average positive and negative affect ratings with MPQ Absorption scores. Multilevel modeling was used to explore same-day within-person effects of ovarian hormone levels (estrogen and progesterone) on negative affect and to test whether the effect of trait schizotypy on daily negative affect was moderated by ovarian hormone levels.

Results: As predicted, MPQ Absorption scores were significantly and positively associated with higher average negative affect ($r=0.21$, $p<0.001$). In our multilevel models, we found an interaction effect between progesterone and MPQ Absorption ($t=2.29$, $p=0.02$) on daily negative affect. Within individuals, the effect of schizotypal traits on negative affect was weaker during periods of higher progesterone levels. There were no interactions between estrogen and schizotypal traits on negative affect, or interactive effects between progesterone and estrogen on negative affect. Progesterone effects remained significant when estrogen was included in the models.

Discussion: These data provide novel evidence for the importance of progesterone levels in moderating schizotypy-negative affect relationships and suggest that within-person progesterone levels may operate as a protective factor in the context of psychosis risk. They furthermore highlight the importance of disentagling within-person from between-person processes in exploring the link between hormones, affect, and psychosis risk. Combined, these results have important implications for understanding mechanisms of psychopathology in women.

50. LONGITUDINAL PROGRESSION OF AUDITORY DYNAMIC RANGE DEFICITS AND ASSOCIATED DISEASE MORBIDITY IN EARLY PSYCHOSIS

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Background: Despite accounting for significant disease morbidity in schizophrenia, the neuropathological basis of negative symptoms remains poorly understood and options for treatment limited. Accurate perception of the auditory soundscape is critical for real-world functioning as the sensorium is the interface between the physical world and the internally constructed representation of the environment, and its importance compounded by the highly verbal nature of human interactions. The current investigation examined auditory cortex (AC) dynamic range, the scaling of cortical activity to stimulus intensity, and its relationship to

clinical outcomes among individuals with a schizophrenia spectrum disorder (FESz) during the first 6 months of illness.
Methods: Twenty-six FESz and 38 healthy controls (HC) were tested at baseline and at a 6-month follow-up. Magnetoencephalography was recorded during binaural presentation of tones at 3 intensities (75dB, 80dB, 85dB). MRIs were obtained to enhance cortical localization of MEG sensor-level activity. Clinical assessments included MATRICS cognitive battery (MCCB) and Global Functioning: Role and Social (GFR/GFS) scales for all participants and the Positive and Negative Syndrome Scale for patients.
Results: FESz exhibited a blunted response to increasing tone intensity relative to HC ($F2,122=5.27$, $p=.006$). While this deficit did not change over time, recovery of right-hemisphere AC dynamic range (85dB – 75dB AC response) was associated with reduced negative symptoms ($\rho=-.54$, $p=.005$). Diminished dynamic range was also associated with impaired GFS ($\rho=.65$, $p<.001$), GFR ($\rho=.51$, $p=.007$), and MCCB ($\rho=.49$, $p=.012$) at baseline and increased negative symptoms at baseline ($\rho=-.53$, $p=.006$) and follow-up ($\rho=-.51$, $p=.008$).
Discussion: Despite persistent dynamic range deficits in FESz over the early course of their disease, recovery of this AC response property was associated with significant reduction in negative symptoms. Given the laterality of this deficit and its robust relationship to impairments in socialization, the blunted sensitivity of AC to sound intensity likely reflects prosodic language deficits. Identification of a functional neural deficit that tracts progression of negative symptoms during a critical period for disease intervention and modification is critical to successful treatment endeavors. Auditory remediation paradigms designed to target dynamic range deficits merit further investigation.

51. CHOICES OF REFERENCE MARKERS IN THE VERBAL PRODUCTIONS OF PEOPLE WITH SCHIZOPHRENIA SPECTRUM DISORDERS

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Background: People with schizophrenia present with language disfunctions, yet we know little about their use of reference markers (indefinite, definite, pronouns or names), an important aspect of language production.
Methods: Twenty-five (25) participants with schizophrenia and 25 healthy controls completed two distinct referential communication tasks during which they had to verbally present some series of images to an interaction partner. The tasks involved presenting a series of movie characters (character identification task) or movie scenes (narration task), respectively, and a manipulation was introduced such that half of the movies could be considered as Likely-Known by the interaction partner, whereas the other half was Likely-Unknown. The reference markers that the participants used to refer to the movie characters where coded as either an indefinite marker (e.g. “a warrior”), a definite marker (“the hero”), a pronoun (e.g. “he”) or the character’s name (e.g. “Leonidas”).
Results: No significant effect of group or group by condition interaction emerged for the first task (character identification task). For the second task (narration of movie scenes), people with schizophrenia used fewer names ($F(1, 55)=6.05$, $p = .017$) and more definite references ($F(1, 108)=4.42$, $p = .038$) when they introduce the characters as part of their narration. Moreover, they did not adjust their use of these definite reference to the same extent as the healthy controls depending on the likely knowledge of the interaction partner, as shown by a significant group by condition interaction ($F(1, 125)=7.36$, $p = .008$). No significant effect of group or group by condition interaction emerged for the other stages of narration, i.e. when the participants

subsequently maintained the characters in focus or when they reintroduced the characters at a later point in the narration.
Discussion: These results suggest that the choices of reference markers are affected in very specific conditions in people with schizophrenia, namely when introducing a character as part of a narration.

52. INSULAR AND STRIATAL CORRELATES OF UNCERTAIN RISKY REWARD PURSUIT IN SCHIZOPHRENIA

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Background: Risk-taking in specific contexts can be beneficial, leading to rewarding outcomes. Schizophrenia is associated with disadvantageous decision-making, as subjects pursue uncertain risky rewards
less than controls. However, it is unclear whether this behavior is associated with more risk sensitivity or less reward incentivization. Matching on demographics and IQ, we determined whether risk-taking was more associated with brain activation in regions affiliated with risk evaluation or reward processing.
Methods: Subjects (30 schizophrenia/schizoaffective disorder, 30 controls) completed a modified, fMRI Balloon Analogue Risk Task. Brain activation was modeled during decisions to pursue risky
rewards and parametrically modeled according to risk level.
Results: The schizophrenia group exhibited less risky-reward pursuit despite previous adverse outcomes (Average Explosions; $F(1,59)=4.06,p=.048$) but a comparable point at which risk-taking was
volitionally discontinued (Adjusted Pumps; $F(1,59)=2.65,p=.11$). Less activation was found in
schizophrenia via whole brain and region of interest (ROI) analyses in right ($F(1,59)=14.91,p<0.001$) and left ($F(1,59)=16.34,p<0.001$) nucleus accumbens (NAcc) during
decisions to pursue rewards relative to riskiness. Risk-taking correlated with IQ in schizophrenia,
but not controls. Path analyses of average ROI activation revealed less statistically-determined
influence of anterior insula upon dorsal anterior cingulate bilaterally (left: $\chi2=12.73,p<.001$; right: $\chi2=9.54,p=.002$) during risky reward pursuit in schizophrenia.
Discussion: NAcc activation in schizophrenia varied less according to the relative riskiness of uncertain rewards compared to controls, suggesting aberrations in reward processing. Lack of activation
differences in other regions suggest similar risk evaluation. Less insular influence on anterior cingulate may relate to attenuated salience attribution or inability for risk-related brain region collaboration to sufficiently perceive situational risk.

53. FACE PROCESSING DEFICITS AS A DETERMINANT OF SOCIAL DISCONNECTION: AN ERP STUDY OF PEOPLE WITH SCHIZOPHRENIA AND SOCIALLY DISCONNECTED MEMBERS OF THE COMMUNITY

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Background: A large component of the overall disability in schizophrenia (SCZ) involves social disconnection (SD), defined as the objective, longstanding lack of social and familial relationships. Social disconnection is also a major public health concern among those in the general community due to its association with serious mental and physical health consequences. Substantial gaps exist in our understanding of the mechanisms that uniquely contribute to social disconnection in these two groups. The current study examined face processing, indexed by the N170 event related potential (ERP) component, as a determinant of social disconnection across a spectrum of severity, including people with SCZ and people from the community who self-identified as being socially disconnected. We predicted that SCZ participants would have reduced N170 amplitudes in response to faces compared with community participants, but similar N170 amplitudes to buildings. As an exploratory aim, we examined group differences in N170 amplitudes to happy, angry, and neutral facial expressions.

Methods: Electroencephalography from 64 clinically-stable outpatients with SCZ and 126 individuals from the community was recorded. A SD composite score was calculated for each participant from clinician-rated interviews and self-report scales. Using this composite score, the community sample was divided into two groups: participants with longstanding disconnection (SD-High) (n = 63) and participants who were socially connected (SD-Low) (n = 63). The N170 paradigm was modified from our prior studies. Participants performed three different classification tasks while viewing color images of faces or buildings. In separate blocks, participants identified the emotion of a face (angry, happy, neutral), the gender of a face (male, female), or whether a building was one or two stories. N170 waveforms were created by averaging all accepted trials separately for face images (from the gender and emotion task) and building images, and for each facial expression (from the emotion task). The N170 was calculated as mean amplitude from 130 to 200 ms following the images from a cluster of six bilateral parieto-occipital electrodes.

Results: Our main analyses were conducted in two steps. First, we compared the groups on their level of social disconnection. The SCZ group was more disconnected than the SD-Low group, $t(125) = 6.13$, $p < .001$, but less disconnected than the SD-High group, $t(125) = -6.49$, $p < .001$. Second, we conducted a 3 (Group) x 2 (Condition: face, building) rm-ANOVA for N170 mean amplitude. There was a main effect of Condition [$F1,187 = 626.55$, $p < .001$, $\eta p2 = .77$], which was qualified by a significant Group x Condition interaction effect [$F2,187 = 5.71$, $p < .01$, $\eta p2 = .06$]. The Group x Condition interaction effect was because the SCZ group had significantly smaller N170 amplitudes than both community groups for faces [SD-Low: $t(125) = 2.42$, $p = .02$, Cohen's $d = .43$; SD-High: $t(125) = 2.03$, $p = .04$, Cohen's $d = .36$] but not buildings [SD-Low: $t(125) = 0.33$, $p = .75$, Cohen's $d = .06$; SD-High: $t(125) = 0.36$, $p = .72$, Cohen's $d = .06$). For the exploratory aim, we conducted a 3 (Group) x 3 (Condition: angry, happy, neutral) rm-ANOVA for N170 mean amplitude. The Group x Condition interaction was not significant.

Discussion: This study evaluated face processing, indexed by the N170 ERP component, as a determinant of SD across a spectrum of severity, including people with SCZ and those from the general community. Our data showed that people with SCZ fell in the middle of the SD

spectrum. However, as expected, the SCZ group had reduced N170 amplitudes to faces (but not buildings) compared with the community groups. These results suggest that facial processing abilities may be a rate-limiting factor for establishing and maintaining social relationships, but only among those with prominent social cognitive impairment. These results can guide treatment development in SCZ by targeting reduced face processing ability is a key independent determinant of SD.

54. DAMPENED SOCIAL MOTIVATION IN THE INDIVIDUALS WITH NEGATIVE SCHIZOTYPY AND SCHIZOPHRENIA

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Background: Schizophrenia (SCZ) is characterized by motivational impairments, which lead to social dysfunctions. Previous studies have suggested that SCZ patients consistently exhibited impaired effort-based decision making, but it remains largely unclear whether this motivational dysfunction can be extended to the social context, which is more closely related to psychosocial outcomes. Additionally, to improve the understanding of psychopathology, it is important to adopt dimensional conceptualizations from the Research Domain Criteria (RDoC) framework to understand social motivational dysfunction in the schizophrenia spectrum, which represents the positive valence domain of the RDoC framework. In the present study, we aimed to examine the social effort-based decision making and its relation to anhedonia in negative schizotypy (NS) and SCZ patients.

Methods: We recruited 25 individuals with NS (Score of Chapman Social Anhedonia Scale ≥ 20), 45 patients with a diagnosis of DSM-5 SCZ and 68 healthy controls (HC). The Mock Job Interview Task was administrated to all the participants to examine participants' willingness to expend effort (i.e., in a highly intense and challenging interview context) to obtain rewards (i.e., job offer). The proportion of high-effort choice and a range of subjective ratings across three levels of bonus points (low: 5/medium: 15/high: 25) were obtained to determine potential group differences. Subjective ratings were recorded to assess the participants' effort expenditure and the level of perceived stress during the interview as well as their valence and arousal experience while receiving the feedbacks. Chapman Social Anhedonia Scale was used to assess social hedonic capacity.

Results: There was a significant Group x Bonus points interaction ($F(4, 270) = 5.428$, $p < .001$, partial eta2 = 0.074). Compared with HC, both individuals with NS and SCZ patients were less willing to expend high-effort in pursuit of the job opportunity in the medium bonus points condition (ps < .001), whereas only patients with SCZ were less willing to choose the hard-effort option when a high bonus was provided (ps < .001). The proportion of high-effort choice in the medium condition was negatively correlated with social anhedonia level in SCZ patients ($r = -0.298$, $p = 0.047$). In addition, Lower arousal experience was observed in the individuals with NS than in SCZ patients regardless of interview outcomes (ps < .093), but there was no group difference in arousal experience between HC and SCZ patients. No significant Group differences were observed for valence rating, perceived stress level and self-evaluation of effort expenditure (ps > .286).

Discussion: In line with most previous studies indicating impaired effort-based decision making in SCZ, similar motivational dysfunction is also present in the non-clinical individuals

with NS. This suggests that aberrant social effort-based decision making might be a potential mechanism for amotivation in the schizophrenia spectrum, which might in turn assist in more accurate identification of schizophrenia.

55. TRAJECTORIES OF SOCIAL COGNITION DURING A RANDOMIZED CONTROLLED TRIAL OF SOCIAL COGNITIVE TRAINING IN PEOPLE WITH SCHIZOPHRENIA

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Background: Social cognition training (SCT) is one of the few evidenced-based interventions for remediating deficits in social cognition in schizophrenia. However, heterogenous responses to SCT have been observed, and little is known about individual patient characteristics that predict response to inform a personalized medicine approach. We therefore examined trajectories of response to SCT and predictors of social cognitive gains using a data-driven modeling approach.

Methods: Seventy-six clinically stable adults with schizophrenia underwent computerized SCT (SocialVille) as part of the randomized Treatment of Social Cognition in Schizophrenia Trial (TRuSST). The intervention consisted of 40 training sessions over 12 weeks targeting affect perception, social cue perception, theory of mind, self-referential style, and empathy. Assessments occurred at baseline, mid-training, and post-training. Social cognition was measured with a social cognition composite score from six social cognition tests, collectively assessing facial emotion recognition (The Penn Emotional Recognition Test), prosody identification (The Prosody Identification Test), immediate and delayed memory for faces (the Penn Faces Memory Test), the Mayer-Salovey-Caruso Emotional Intelligence Test managing emotions subscale and the Empathic Accuracy Task. Additional assessments included demographics, symptoms, functioning, motivation, and additional measures of social cognition. Latent class growth analyses were used to identify trajectories of social cognition in response to SCT. A random forest machine learning model was trained with a nested 10-fold cross-validation procedure and the Generalized Threshold Shifting (GHOST) protocol, which addresses class imbalance, to predict membership. The most important baseline characteristics predicting response to SCT were identified using the Boruta feature selection algorithm and Shapley values.

Results: A latent class trajectory growth model with five groups was the best fit to the data. Group 1 (29% of participants) began with slightly above average social cognition, and this ability significantly improved with SCT. Group 2 (9% of participants) was approximately one standard deviation above the sample mean social cognitive ability at baseline but did not improve with training. Groups 3 and 4 (18% and 36% of participants, respectively) began with average to slightly below-average social cognition and showed non-significant trends toward improving with training. Finally, Group 5 (8% of participants) had a baseline social cognitive ability approximately one standard deviation below the sample mean and experienced statistically-significant deterioration in this ability, despite SCT. The random forest model predicted Group 1 membership (i.e., robust response to SCT) versus membership in all other groups with an area of the curve (AUC) of 0.73 (SD=0.24; 95% CI [0.51-0.87]). The most

important baseline variables for predicting Group 1 membership were abilities in social cognitive domains of inferring beliefs and intentions of others, managing emotions, emotion recognition, and prosody detection, as well as better functional capacity.
Discussion: These findings – while preliminary due to the small sample size - suggest that there are distinct patterns of response to SCT in schizophrenia and indicate that those with slightly above average social cognitive abilities at baseline may be most likely to experience cognitive gains. Further research on how to best promote robust treatment response in individuals with lower baseline social cognition is warranted.

56. A DETAILED EXAMINATION OF PITCH DISCRIMINATION DEFICITS ASSOCIATED WITH AUDITORY VERBAL HALLUCINATIONS IN SCHIZOPHRENIA

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Background: Individuals with schizophrenia spectrum disorders (SSD) and a history of experiencing auditory verbal hallucinations (AVH) reportedly exhibit poor pitch discrimination relative to those with an SSD but no AVH history. It has been theorised that these exacerbated pitch discrimination deficits may contribute to the manifestation of, as well as the prosodic processing and source monitoring deficits associated with, AVH. The present study extended this research, asking if a lifetime history, and the current status, of AVH exacerbated the pitch discrimination challenges that are seen in SSD.
Methods: Participants completed a pitch discrimination task, where the tones presented differed in pitch by either 2%, 5%, 10%, 25% or 50%. Pitch discrimination accuracy, perceptual sensitivity, reaction time (RT) and intra-individual RT variability (IIV) were examined in individuals with SSD and AVHs (AVH+; n=46), or without AVHs (AVH-; n=31), and healthy controls (HC; n=131). Secondary analyses split the AVH+ group into state (i.e., actively experiencing AVH; n=32) and trait hallucinators (i.e., a history of, but not actively experiencing, AVH; n=16). To address the ceiling effects commonly seen in pitch discrimination tasks, hierarchical linear modelling was used to analyse data.
Results: Relative to HC, significantly poorer accuracy and sensitivity was detected in individuals with SSD at 2% and 5% pitch deviants (all $p > 0.54$, all $d > 0.40$), and in hallucinators at 10% (all $p < 0.05$, all $d = 0.47$). However, no significant differences in accuracy, sensitivity, RT nor IIV were found between AVH+ and AVH- groups (all $p > 0.54$, all $d < 0.14$). No differences between state and trait hallucinators were observed (all $p > 0.25$, all $d < 0.32$).
Discussion: A general SSD deficit drove the current findings. This may represent a deficit in early auditory perception in all individuals with SSD, which ultimately leads to the aberrant processing of higher-level linguistic information. The outcomes of the present study provide some directions for future research into auditory processing, prosodic and source monitoring deficits in AVH+ individuals.

Oral Sessions: Biomarkers and Clinical Outcomes

57. CLINICAL RECOVERY AMONG INDIVIDUALS WITH A FIRST EPISODE SCHIZOPHRENIA AN UPDATED SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Through decades the clinical recovery outcomes among individuals diagnosed with schizophrenia have been highly inconsistent ranging from 13.5%-57%. The primary objective of this updated examination was to report the pooled estimate and explore various moderators in order to improve the understanding of the course of schizophrenia.

Methods: A systematic literature search was setup on PubMed, PsycInfo and EMBASE until January 13th, 2022. Both observational and interventional studies among cohorts of individuals with a first episode of schizophrenia (less than 5 years of illness) reporting on clinical recovery was included. The PRISMA 2020 statement was used and data was extracted for a random-effects meta-analysis, meta-regression and sensitivity analyses. Risk of bias was assessed using The Newcastle-Ottawa Scale.

Clinical recovery was defined as measures for both a clinical dimension (e.g. symptom rating scales, absence of psychotic symptoms, no relapses or use of psychiatric hospitalization etc.) and a social/functional dimension (e.g. social/functional rating scales, social, occupational or educational domains) with a duration of at least 12 months on either clinical or social/functional dimensions. In studies that did not specifically state the word recovery we extracted data from study texts and tables in order to satisfy our recovery criteria.

Results: A 20.8% (95% CI=17.3%-24.8%) recovery rate was found among 26 unique study samples (mean trial duration, 9.5 years) including 3877 individuals (mean age, 26.4 years). In meta-regression none of the following study characteristics could uncover the diverse reported recovery rates; age at inclusion (P = .84), year of inclusion (P = .93), follow-up time (P = .99), drop-out rate (P = .07) or strictness of the recovery criteria (P = .35). Furthermore, no differences in recovery were found between early intervention services (19.5%; 95% CI=15.0%-24.8%) compared to other interventions (21%; 95% CI=16.9%-25.8%), P=.65.

Discussion: In this up-dated review and meta-analysis we found a 20.8% recovery rate among individuals with a first episode of psychosis within the schizophrenia spectrum.

The analysis was done in accordance with a pre-published protocol with rigid description of definitions and analysis plan adhering to the PRISMA guidelines. To enhance clinical importance, we had strict definitions of inclusion criteria and definitions of outcomes, excluding affective psychosis, and assuring that the definition of recovery included a functional component and a criteria of duration.

Today most clinicians no longer perceive schizophrenia as a progressive deteriorating illness. Still, we found no improvements in recovery rates in accordance to year of inclusion or follow-up time. Furthermore, when comparing studies with early intervention services to other interventions no difference was detected implying that modern era treatment facilities have not enhanced outcomes. After comparing recovery rates between studies mixing individuals with first and multiple episodes of psychosis and studies only including first episode psychosis, we

found no significant differences. Therefore, urgent new initiatives for individuals in all illness stages are needed in order to improve the rate of recovery.

As implication for future research, we suggest that alternative moderators and mediators are searched for, in order to understand the recovery process and develop more effective interventions. Some proposed factors could be substance abuse, level of psychotic and negative symptoms, duration of untreated psychosis and adherence to treatment, all factors we were unable to explore due to lack of information. Exploring these in future systematic reviews including individual-level data, may improve the knowledge gap.

58. WOMEN WITH SCHIZOPHRENIA-SPECTRUM DISORDERS AFTER MENOPAUSE: A VULNERABLE GROUP FOR RELAPSE

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Background: Throughout the life stages of women with schizophrenia-spectrum disorders (SSD), lower estrogen levels are associated with more severe disease course. At perimenopause in the mid-forties, estrogen levels decline to remain persistently low after menopause. This period is hypothesized to increase relapse risk and reduce antipsychotic effectiveness in preventing relapse.
Methods: The cohort of persons with schizophrenia/schizoaffective disorder was identified from Finnish nationwide registers (N = 61 889) and stratified by sex and age <45 vs. ≥45 years. Hospitalizations for psychosis were defined per 5-year age group during the follow-up 1996–2017. Risk of psychosis hospitalization (Adjusted Hazard Ratio, aHR) was assessed using within-individual design, by comparing antipsychotic monotherapy use to nonuse periods in the same individuals for seven dose categories in defined daily doses (DDDs/day).
Results: Starting at age 45–50, women were consistently more often hospitalized for psychosis than their male peers. Women ≥45 had significantly higher aHRs than women <45 at antipsychotic monotherapy >0.6 DDDs/day, and than men at >1.1 DDDs/day. This female-specific age-dependent decrease in effectiveness was present for clozapine doses >0.6 DDDs/day, olanzapine doses >1.4 DDDs/day, and for specific doses of quetiapine (0.9–1.1 DDDs/day) and risperidone (0.6–0.9 DDDs/day).
Discussion: While younger women have a lower risk of relapse and generally need a lower antipsychotic dose to prevent rehospitalization than men, antipsychotic effectiveness declines in women after the age of 45. Starting in mid-forties, older women with SSD should be regarded as a vulnerable group that deserve special attention.

59. TIME-TO-EVENT ANALYSIS OF TOTAL ANTIOXIDANT CAPACITY AND VITAMIN D IN SCHIZOPHRENIA BASED ON ONSET AGE AND ILLNESS DURATION

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Background: Schizophrenia is one of the severe mental illnesses with high morbidity and mortality. However, the underlying pathophysiology of schizophrenia is still poorly

understood. In recent decades, it was hypothesised that the imbalance between oxidative and antioxidative systems may be involved in clinical course of schizophrenia. In addition, vitamin D deficiency was also postulated in increasing the risk of schizophrenia as it is vital in brain function, antioxidative and anti-inflammatory systems. Vitamin D receptor gene (VDR) single nucleotide polymorphisms (SNPs) may cause the impairment of VDR leading to abnormal activities of vitamin D. Age at onset and illness duration may give impact on certain outcomes of schizophrenia. Hence, the present study aimed to investigate the interactive effects between total antioxidant capacity (TAC), vitamin D level and VDR SNPs, and age at onset and illness duration, respectively.

Methods: A total of 106 patients with schizophrenia were enrolled and blood samples were collected. Serum was separated and used to analyse TAC using assay kit and vitamin D level using enzyme-linked immunosorbent assay. DNA was extracted from whole blood and used to analyse VDR SNPs using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Kaplan-Meier method with log-rank test was conducted to assess the effects between TAC, vitamin D level and four VDR SNPs (rs7975232, rs1544410, rs731236 and rs2228570), where age at onset and illness duration were served as time-to-event variables. In the analysis of TAC, patients with schizophrenia were categorised into two groups based on median TAC level (<1.078, ≥1.078mM UAE/L) whereas in analysis of vitamin D level, patients with schizophrenia were categorised into two groups based on median vitamin D level (<31.42, ≥31.42ng/ml). Meanwhile, patients with schizophrenia were categorised into three groups according to the genotypes in analysis of each VDR SNP.

Results: From overall findings, in the analysis with age at onset as time-to-event variable, no significant difference was observed between groups of TAC (p=0.786), vitamin D level (p=0.404) and VDR SNPs [rs7975232 (p=0.618), rs1544410 (p=0.363), rs731236 (p=0.060) and rs2228570 (p=0.722)], respectively. On the other hand, duration of illness was not significantly different between groups of vitamin D level (p=0.108) and VDR SNPs [rs7975232 (p=0.992), rs1544410 (p=0.566), rs731236 (p=0.968) and rs2228570 (p=0.643)], respectively. Duration of illness led to the only significant difference between two groups of TAC (p=0.02), in which TAC <1.078mM UAE/L was observed in the group with longer illness duration [18.70 years (95% CI: 13.50-23.90) vs 12.20 years (95% CI: 6.90-17.50)].

Discussion: This finding was in line with previous review demonstrating longer duration of illness was associated with higher levels of inflammation and oxidative stress in schizophrenia. Our previous meta-analysis in schizophrenia also showed that longer illness duration was associated with elevated oxidative damage. It was assumed that patients with longer duration of illness may take more antipsychotics in which certain antipsychotics may contribute the effects on oxidative stress. The significant interaction between low TAC level and longer illness duration suggested the role of oxidative stress in clinical course of schizophrenia. More longitudinal studies may be conducted in future to identify the source (endogenous or exogenous) and mechanism of oxidative stress in pathophysiology of schizophrenia.

60. AGENCY IS IN THE EYE OF THE BEHOLDER: MISMATCHES IN PERCEIVED EFFICACY BETWEEN INDIVIDUALS WITH FIRST EPISODE PSYCHOSIS AND THEIR CAREGIVERS

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Background: Personal agency is a key element of recovery from psychotic disorders. Similarly, caregiver perceptions of affected relatives' agency are an important factor in interpersonal systems that support or inhibit recovery. Agency in this context can be

operationalized as efficacy to manage symptoms and social behaviors. Previous research has indicated that caregivers provide less effective social support when they perceive their affected relatives to have low efficacy to manage symptoms. However, no studies have yet examined perceptions of efficacy within families, to determine whether caregiver perceptions of efficacy match (or even relate to) individual perceptions of efficacy. The present study therefore examined perceived efficacy within families to determine whether individuals with FEP and their caregivers agree or disagree in their perceptions of efficacy, and on what information individuals and caregivers base their perceptions of efficacy (i.e., which related variables are associated with individual and caregiver efficacy ratings).
Methods: Individuals with first episode psychosis (FEP, n=46, mean age=22.6, median DUP=11.6 months) completed the Self-Efficacy Scale for Schizophrenia (SESS) and measures of symptom severity, social functioning, social quality of life, stigma, and discrimination. Caregivers (n=42) completed a caregiver version of the SESS assessing perceptions of their affected relative's self-efficacy. Analyses examined individual-caregiver agreement in terms of mean comparisons and correlations between individual and caregiver efficacy ratings. To test which sources of information were most relevant to individual and caregiver perceptions of efficacy, analyses tested simple relationships and incremental effects of variables linked to efficacy in previous research (positive symptoms, negative symptoms, depression, social functioning, social quality of life, stigmatization, and discrimination).
Results: Individuals with FEP perceived themselves to have more efficacy across all domains (positive symptoms, negative symptoms, and social behavior) than did their caregivers (d=0.53 to 0.92). Individuals' and caregivers' efficacy ratings were correlated in the social behavior domain, but not in the positive or negative symptom domains. Efficacy ratings were most associated with depression and stigmatization when rated by individuals with FEP, but with social functioning when rated by caregivers.
Discussion: Perceptions of efficacy to manage symptoms and social behavior were mismatched in individuals with FEP and caregivers, both in terms of mean differences and correlations. Notably, the pattern of relationships with covariates suggests that individuals and caregivers may base perceptions of efficacy on different sources of information. These findings highlight specific targets for psychoeducation, social skills training, and assertiveness training to enhance supportive family systems.

61. PERSISTENT CHILDHOOD INFLAMMATION AND RISK OF DEVELOPING PSYCHOSIS AND OTHER MENTAL AND PHYSICAL HEALTH PROBLEMS IN ADULTHOOD: A LONGITUDINAL BIRTH COHORT STUDY

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Background: There is a growing body of evidence showing that inflammation or changes in the immune system play a key role in certain mental health disorders. The evidence is particularly strong for psychosis and depression. However, a potential causal link between inflammation and psychosis is yet to be proven, and less is known about the trajectories, nature and degree of inflammation that might have an impact on mental health. The aim of this study was to characterize the inflammatory trajectories within a large general population across childhood and adolescence, and how these trajectories would associate with a range of mental and physical health conditions in young adulthood. This would help identify which mental

health disorders and other physical health outcomes in young adulthood are linked with early life inflammation. We hypothesized that there would be sub-group of young people who have different and raised levels of inflammation, and that this group would be at highest risk of developing certain mental health conditions, namely psychosis and depression, as well as related cardio-metabolic psychical health conditions such as diabetes and associated insulin resistance.

Methods: We used data from the Avon Longitudinal Study of Parents and Children (ALSPAC) study, which has data from over 14,000 individuals at birth. Groups of inflammatory trajectories across childhood and adolescence were identified using latent class growth analysis (LCGA). Inflammation was assessed via blood samples of CRP measures at ages 9, 15 and 17. Scores above 10 were excluded to rule out the impact of acute infection, with all CRP-measures z-transformed and LCGA carried out on the z scores to provide classes of different inflammatory trajectories across childhood and adolescence.

We also investigated the prospective associations between inflammatory trajectories identified by LCGA, and different mental health (including psychosis, various severities of depression, hypomania, generalised anxiety disorder, social phobia, panic disorder, mild depression, alcohol abuse or cannabis misuse) and physical health (including diabetes, asthma, arthritis, stroke, kidney disease, or "any health problem") outcomes at age 24. As well as predefined outcomes, we also calculated the Homeostatic Model Assessment for Insulin Resistance (HOMA score) at age 24 from recorded insulin and glucose measures. We used regression analyses across binary (e.g. diagnosis) and continuous (e.g. HOMA scores) outcome measures. Further, we controlled for gender, preterm, family diversity index score, ethnicity, child health age 8 and 13, and hospitalization at age 8. To deal with missingness, we applied inverse probability weighting.

Results: We identified 3 trajectories of inflammation across childhood and adolescence. Class 1 had persistently low levels of CRP (Low Group - 93% of cohort), which was used as the comparison group in the subsequent logistic regression analyses. Further, there were two divergent groups, both with persistently raised levels of CRP. Class 2 had a persistently raised level of CRP with a peak earlier at age 9 (Early Peak - 5% of cohort) and Class 3 had persistently raised CRP levels and a peak later at age 17 (Late Peak - 4% of cohort).Logistic regressions were used to compare odds ratio (OR) of outcomes between the Early Peak and Late Peak groups and the comparison group (Low Group). The Early Peak was 4 times more likely to develop psychosis at age 24 (4.13, CL 95% 1.66-10.46, p=0.003), nearly 4 times more likely to develop severe depression (OR 3.69, CL 95% 1.39-10.84, p=0.009) and more than twice as likely to develop moderate depression (OR 2.15, CL 95% 1.97-3.87, p=0.01) than the Low Group. The Early Peak group showed no significant results for hypomania, generalised anxiety disorder, social phobia, panic disorder, mild depression, alcohol abuse or cannabis misuse. No significant results were found for the Late Peak group for any outcomes, compared with the Low Group.

Overall, there were no significant results for increased risk for diabetes, asthma, arthritis, stroke, kidney disease, or "any health problem" in either group. Finally, and using linear regressions, we found a significant association between the Early Peak group and higher levels of HOMA scores at age 24.

Discussion: Our findings from a large population cohort show that specific trajectories of low grade systemic inflammation across childhood and adolescence are related to later onset of mental health disorders, particularly psychosis and depression, with early rather than later inflammation potentially holding importance. Our results also show specificity in the

development of psychosis and depression, and not all or other mental health disorders. Finally, our results show that the early peak group is also at higher risk of developing certain cardio-metabolic disorders such as insulin resistance. This study adds new information about the chronicity and timing of inflammation predating illness, and provides insight into the co-occurrence of related cardio-metabolic disorder that may be useful in developing targeted preventive interventions.

62. SPEECH ILLUSIONS IN PEOPLE AT CLINICAL HIGH RISK FOR PSYCHOSIS LINKED TO CLINICAL OUTCOME

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Background: We assessed the incidence of hearing speech in noise in people at clinical high-risk of psychosis (CHR) and examined whether this was associated with adverse clinical outcomes.
Methods: At baseline, 344 CHR participants and 67 healthy controls (HC) were presented with computerised white noise (with or without speech) and asked whether they heard speech, and whether speech was neutral, affective or whether they were uncertain about its valence. Two years later we assessed whether participants transitioned to psychosis, or remitted from the CHR state, and their level of functioning. We assessed associations between performance on the white noise task and outcome.
Results: CHR participants had a lower sensitivity than HC on the task. Logistic regression revealed that in CHR participants, a bias towards hearing speech was associated with remission (OR=.21, p=.042). Hearing speech illusions with uncertain valence was associated with reduced likelihood of remission (OR=7.72. p=.007). When we assessed only participants who did not take antipsychotic medication at baseline, the association between hearing speech illusions with uncertain valence at baseline and remission remained (OR=7.61, p=.043) and this variable was additionally associated with a greater likelihood of transition to psychosis (OR=5.34, p=.029).
Discussion: In CHR participants, hearing speech in white noise, and uncertainty about the affective valence of this speech, is associated with adverse outcomes. This task could be used in a low-burden battery of cognitive markers to stratify CHR participants according to their future outcomes.

63. CONCORDANT STRUCTURAL BRAIN SIGNATURES OF IMMUNE-RELATED BLOOD BIOMARKERS AND SUBCLINICAL PSYCHIATRIC SYMPTOMS IN YOUTH

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Background: Youth seeking treatment for mental health concerns are at increased risk of developing severe mental illness later in life. In search of early risk biomarkers, tests of peripheral blood offer a cheap and minimally-invasive option. Studies in individuals with schizophrenia and bipolar disorder have found differences in stress- and immune-related peripheral proteins, though it is not known if or how these differences relate to early risk. Here we integrate peripheral blood measures, MRI, and behavioral assessments from two youth cohorts - one treatment-seeking for psychiatric concerns, and the other a non-clinical population sample - to test if patterns of brain structure associated with levels of peripheral biomarkers mirror those found in younger children with emergent mental health symptoms.

Methods: We first analyzed 73 participants from the Toronto Adolescent and Youth Cohort Study (TAY), an ongoing longitudinal clinical cohort study of psychiatric treatment-seeking youth aged 11-24. Participants had 26 proteins quantified in peripheral plasma and underwent MRI at baseline. Linear models tested for cross-sectional associations between each protein with cortical thickness (CT) across 68 regions, covarying for age, sex, ethnicity, and intracranial volume. We also tested associations of proteins with psychosis spectrum symptoms (PSS). Independently, we analyzed data for 11,235 youth aged 9-10 from the Adolescent Brain and Cognitive Development (ABCD) general population-based study who had baseline MRI and Child Behavior Checklist (CBCL) data. We modeled associations between 11 CBCL syndrome scales and CT across the same regions tested in TAY, including the same covariates. Association t-statistics for biomarker effects on CT (TAY) and CBCL effects on CT (ABCD) were then correlated, considering brain regions as observations, for each pair of biomarkers and CBCL scales. P-values were corrected for false discovery rate (pFDR).

Results: In TAY, blood-to-brain associations were strongest between peripheral Resistin, growth differentiation factor 15, interleukin-6 (IL-6) and CT of inferior frontal, inferior temporal, and superior frontal regions, respectively. Increased IL-6 was also nominally associated with greater probability of PSS (uncorrected p=0.02). In ABCD, several CBCL scales were associated with CT; e.g. attention problems with left parahippocampal gyrus (pFDR=4.9x10-5). Correlating effects of biomarkers (TAY) and CBCL scales (ABCD) between datasets revealed significant concordance between neural signatures of peripheral brain-derived neurotrophic factor (BDNF) and IL-6 and both attention and thought domains of the CBCL. The strongest concordance was observed for thought problems (BDNF correlation r=0.55, pFDR=3.8x10-4; IL-6 r=0.44, pFDR=0.041). Selecting one region as an illustrative example; higher BDNF was associated with thinner left parahippocampal cortex in TAY, which in turn was significantly associated with thought problems in ABCD.

Discussion: We found associations between several peripheral stress- and immune-related markers and both brain structure and PSS in treatment-seeking youth. Importantly, we also show that the neural signatures of these markers are highly concordant with those associated with subclinical mental health symptoms in younger children in the general population. These findings 1) demonstrate potential for monitoring risk of psychopathology in youth via peripheral markers, 2) propose a map for evaluating the neurostructural basis of this risk, and 3) identify brain regions co-varying with peripheral markers that may be useful for optimizing non-invasive interventions. Validation with repeated measures in a larger clinical sample is needed.

64. HETEROGENEITY IN THE LONG-TERM COURSE OF PSYCHOSIS: EXPLORING THE ROLE OF SUBSTANCE USE

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Background: There is substantial heterogeneity in the course of psychotic disorders and in the long-term development of psychotic symptoms.
Systematic data-driven classification of long-term symptom trajectories and identification of trajectory-associated risk factors could assist treatment planning and improve long-term outcomes. Knowledge about mechanisms underlying individual differences in trajectories is still limited. Medication adherence and abuse of cannabis and stimulants are among the most replicated risk factors for psychotic relapse but have not been adequately investigated in this context.

Methods: A sample of 192 individuals with first-episode psychosis from the Norwegian Thematically Organized Psychosis (TOP) study was followed-up after ten years. Psychotic symptom trajectories were estimated based on the time spent in psychosis during each of the ten follow-up years using growth mixture modeling. Associations between the resulting trajectory-based groups, putative risk factors assessed at baseline, and substance use during the first and the second half of the follow-up period were investigated.
Results: Four distinct trajectories were identified: (1) Stable remission (54.2%), (2) Delayed remission (15.6%), (3) Relapse (7.8%), (4) Persistent psychosis (22.4%).
At baseline, all unfavorable symptom trajectories (2, 3, 4) were characterized by higher rates of schizophrenia diagnosis and higher symptom load compared to the Stable remission group (1). The Persistent and Delayed remission trajectory groups were further linked to daily nicotine intake and recent use of cannabis and stimulants. Additionally, impaired clinical insight distinguished both the Persistent and the Relapse trajectory groups from Stable remission. No differences were found in medication adherence at baseline.

Analyses of substance use during the two parts of the follow-up period indicated that the Persistent trajectory was associated with frequent cannabis intake during the first half (OR: 5.04, p = .007) but not with cannabis intake during follow-up per se.

The Delayed remission and the Relapse trajectory groups had several similarities, including higher rates of stimulant use during the entire follow-up period and higher rates of cannabis use during the first half. The Delayed remission trajectory was, however, specifically related to frequent use of cannabis (OR 7.00, p = .004) and stimulants (OR 7.42, p = .035) during the first half of the follow-up period only, and the Relapse trajectory to the occasional use of stimulants during the entire follow-up period (first half: OR 7.06, p =. 004; second half: OR 5.81, p = .027).

Discussion: These findings expand existing evidence on the heterogeneity in the long-term course of psychosis and demonstrate that distinct trajectory subtypes can capture this heterogeneity. In preliminary analyses, the subtypes differed in terms of substance use, indicating that at least some of the observed inter-individual differences in psychotic symptom trajectories are shaped by patterns of substance use. Substance use seemed to play a more prominent role for the Relapse and the Delayed remission trajectory than the Persistent

trajectory. This suggests that a persistent course of psychosis may primarily be linked to factors other than substance use.

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65. BENCHMARKING OBSERVATIONAL ANALYSES AGAINST RANDOMIZED TRIAL RESULTS: AN APPLICATION TO FIRST EPISODE PSYCHOSIS

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Background: Conducting randomized trials in first episode psychosis (FEP) is challenging. Thus, clinical decision making often relies on analyses of observational data. To increase confidence in observational analyses, one could first benchmark the observational analyses against existing trial results and then, more confidently, extend the results to answer clinical questions not originally considered in that trial.
Methods: The FEP-CAUSAL Collaboration is an international consortium of observational cohorts of individuals with FEP. We analyzed data from four FEP-CAUSAL cohorts in North America (current N=1,081) to emulate a target trial similar to the EUFEST randomized trial. EUFEST found a higher average 1-year hazard ratio (HR) of treatment discontinuation in haloperidol compared with olanzapine and quetiapine, but similar 1-year probabilities of hospitalization and mean Clinical Global Impressions-Severity (CGI-S) scores. We replicated the results from EUFEST and then extended the emulation to include aripiprazole and risperidone.
Results: After applying EUFEST eligibility criteria to our data, we included 623 initiators of an antipsychotic included in this study. Compared with haloperidol, the HR (95% confidence interval) of treatment discontinuation was 0.38 (0.24-0.59) for olanzapine and 0.24 (0.13-0.44) for quetiapine. The 1-year mean of CGI-S for haloperidol, olanzapine, and quetiapine were 3.5, 3.4 and 4.2, respectively, and the 1-year risks of hospitalization were 24.2 (16.2-35.0), 25.4 (18.8-34.0), and 28.2 (21.6-34.2), respectively. Compared with haloperidol, the HR of treatment discontinuation was 0.18 (0.12-0.26) and 0.21 (0.13-0.34) for risperidone and aripiprazole. The 1-year hospitalization risk for aripiprazole was 33.0% (24.7-43.6) and for risperidone, 29.3% (22.0 - 37.6).
Discussion: Our observational estimates were similar to those from the EUFEST randomized trial, and so the benchmarking was considered successful. After benchmarking known effect estimates, we estimated a greater 1-year hospitalization risk for aripiprazole compared with all other drugs, something not originally studied in the randomized trial. Our findings suggest that this observational dataset may be used to estimate treatment effects in FEP research.

66. NEUROCHEMICAL SIGNATURES OF REGIONAL CEREBRAL BLOOD FLOW ALTERATIONS IN SCHIZOPHRENIA AND THE CLINICAL HIGH-RISK STATE FOR PSYCHOSIS

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Background: Functional magnetic resonance imaging (fMRI) studies have shown regional alterations in resting regional cerebral blood flow (rCBF), a proxy for baseline neuronal activity, in patients with schizophrenia (SCZ) and individuals at clinical high-risk for psychosis (CHR). Understanding how these differences in rCBF are related to dysfunction at the molecular level has potential to inform the discovery of new therapeutic strategies. Recently, positron emission tomography (PET)-derived neuroreceptor binding atlases are becoming more freely available. The combination of such PET-derived neuroreceptor maps with other neuroimaging modalities, including fMRI, has been used to validate pharmacologically induced changes in rCBF in healthy volunteers. However, this approach has not yet been applied to examine the underlying molecular mechanisms of rCBF alterations in psychosis. The goal of this study was to identify the spatial profiles of neuroreceptor densities that track rCBF CHR and SCZ-related rCBF differences.

Methods: We used a novel neuroreceptor mapping approach to identify the molecular signatures of regional rCBF maps of 129 CHR individuals compared to 58 matched healthy controls (HC), and of 122 patients with SCZ compared to 117 HC. rCBF data was obtained with arterial spin labelling (ASL) and pre-processed with the CBFBIRN pipeline (SZvsHC) (Shin et al. 2011, IRSMRM) and the ASL Toolbox (Abad et al., 2016, Magn Reson Imaging). Case-control statistical test maps of CHR vs HC and SCZ vs HC were derived using SPM12. Next, these maps were tested for spatial associations with neuroreceptor binding distribution of 40 freely available PET atlases for several neurotransmitter systems: 13 serotonergic, 2 cannabinoid, 8 dopaminergic, 3 GABAergic, 4 glutamatergic, one histaminergic, and 8 cholinergic receptors. We segmented each rCBF case-control difference map (CHR vs HC, SCZ vs HC) and receptor atlas into 82 regions of the Desikan-Killiany atlas. Pearson's correlations determined associations between the mean receptor binding values in each region and the parcellated blood flow difference maps.

Results: The spatial distribution of CHR>HC case-control differences in rCBF were significantly associated with the distribution of dopamine, acetylcholine, NMDA, and a subset of serotonin receptors (all pFDR<0.05). The spatial distribution of SCZ>HC case-control differences was associated with a similar receptor distribution pattern to those found between CHR and controls, and additionally included a wider range of serotonin receptors as well as GABAa5 receptors (pFDR<0.05), while no relationship was found with NMDA receptors.

Discussion: This study is first to use a receptor-informed fMRI approach in CHR and SZ patients. We identified that case-control rCBF differences are spatially related to the distribution of unique and overlapping neurotransmitter systems in CHR and SCZ. All dopaminergic tracers spatially correlated with CHR and SCZ rCBF differences, while receptor densities involved in excitation-inhibition balance were distinct between patient groups (i.e., NMDA receptors involved in CHR>HC rCBF maps, GABAa5 involved in SCZ>HC rCBF maps). These results provide evidence that bridges knowledge across modalities and scales to inform the underlying neurochemical pathways involved in key neuroimaging markers of schizophrenia and the CHR state, and which may be used in the future to non-invasively stratify mechanisms of risk, and which may be amenable to pharmacological intervention.

67. GENETIC FACTORS UNDERLYING INTELLIGENCE QUOTIENT IN PATIENTS WITH FIRST EPISODE PSYCHOSIS AND THEIR FIRST-DEGREE RELATIVES

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Background: In previous research with first episode of psychosis (FEP) patients and their first-degree relatives, we found that intelligence quotient (IQ) had a 25% of familial aggregation. That is, the IQ of the participants could be explained to a low-moderate degree by shared familial factors. However, it remains unclear what degree of such resemblance is due to genetics or environment. In this work, we calculated polygenic risk scores for schizophrenia (PRS-SCZ) and polygenic scores for educational attainment (PS-EA) in FEP patients, their first-degree relatives, and a group of controls. We aimed to explore whether genetic loading for these traits explained the participants' IQ and in what proportion.

Methods: The sample from PAFIP-FAMILIAS (Santander, Spain) consisted of 122 FEP patients, 131 parents, 94 siblings, and 176 controls. All provided a DNA sample, sociodemographic information and completed a neuropsychological battery. Quality control and imputation prior to PRS calculation were carried out according to standard procedures. PRS-SCZ and PS-EA were calculated by the method of PRS continuous shrinkage using the latest respective genome-wide association study as discovery sample. A linear mix model (LMM) was estimated with IQ as the dependent variable, family code as random effect, PRS-SCZ and PS-EA as fixed effects, and age, years of education, and sex as covariates.

Results: FEP patients had a significantly higher PRS-SCZ than all other participants ($p<0.001$), while their siblings and parents showed higher PRS-SCZ than controls ($p<0.001$). PS-EA did not differ between groups but correlated with years of education ($r= 0.290$, $p<0.001$). The LMM was significant ($p<0.001$) and replicated previously reported effects of family membership on IQ, as the random effect was statistically significant ($p<0.001$). PS-EA (coef. =22.52, $p<0.001$) but not PRS-SCZ was a significant predictor of IQ, along with age (coef. =0.25, $p<0.001$), and years of education (coef. =1.2, $p<0.001$). For controlling the possible effect of antipsychotics, we estimated a simple linear regression model in the subset of FEP patients. PS-EA, age, years of education and chlorpromazine equivalent dose at baseline were introduced as predictors of IQ. Only PS-EA and years of education were significant, explaining 18.6% of the IQ variance (R-squared= 0.186, $p<0.001$).

Discussion: Schizophrenia polygenic risk was differentially distributed according to disease status in our sample but was not related to IQ. Thus, the disorder may affect neurocognition via complex pathological processes rather than a direct genetic result. For example, a neurodevelopmental disruption might better explain a low IQ. PS-EA indicated that the FEP patients had a genetic potential for educational attainment like their relatives. Nonetheless, their academic and cognitive outcomes are worse. Therefore, failing to reach cognitive family potential might be strongly related to psychosis. The results from family studies provide valuable insights into treatment and prevention strategies in FEP.

68. ASSESSMENT OF LINGUISTIC FACTORS DURING ANTIPSYCHOTIC NAïVE FIRST-EPISODE PSYCHOSIS WITH LATER VOCATIONAL AND SOCIAL OUTCOMES IN THE FIRST YEAR OF TREATMENT

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Background: Several disturbances in speech are present in psychosis; however, the relationship between these disturbances during the first episode of psychosis (FEP) and later vocational functioning is unclear. Demonstrating this relationship is critical if we expect speech and communication deficits to emerge as targets for early intervention.
Methods: We analyzed three one-minute speech samples using automated speech analysis and Bayes networks in an antipsychotic-naive sample of 39 FEP patients and followed them longitudinally to determine their vocational status (engaged or not engaged in employment education or training - EET vs. NEET) after 6-12 months of treatment.
Results: Five linguistic variables with prior evidence of clinical relevance (total and acausal connectives use, pronoun use, analytic thinking, and total words uttered in a limited time frame) were included in a Bayes network along with longitudinal NEET status and and Social and Occupational Functioning Assessment Scale (SOFAS) scores to determine dependencies among our variables. We also included clinical (Positive and Negative Syndrome Scale 8-item version (PANSS-8)), social (parental socioeconomic status,) and cognitive features (processing speed) at the time of presentation as covariates. The Bayes network revealed that only total words spoken were directly associated with NEET and had an indirect association with SOFAS, with a second set of dependencies emerging among the remaining linguistic variables. The primary (speech-only) model outperformed models including parental socioeconomic status, processing speed or both as latent variables.
Discussion: In conclusion, impoverished speech, even at subclinical levels, may hold prognostic value and warrant clinical consideration when treating first-episode psychosis.

69. EVOLUTION OF THE CLINICAL HIGH RISK FOR PSYCHOSIS SERVICES FIDELITY SCALE

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Background: After three decades of research into the identification, treatment and outcome of patients at clinical high risk for psychosis, we have an extensive evidence base on specific treatments summarized in systematic reviews. Treatments are most often delivered by early psychosis intervention teams although there are no randomized controlled trials of team-based treatment. There are no published fidelity scales that specifically assess the adherence of programs to evidence-based treatment for those at clinical high risk. The First Episode Psychosis Services Fidelity Scale is a widely used measure, but it focuses on those with a psychosis rather than those at clinical high risk for psychosis. The aim of this study was to develop a fidelity scale suitable for evaluating team-based care for patients at clinical high risk of psychosis.
Methods: Literature review, a type of review which uses published materials that provide examination of current literature. We identified systematic reviews and clinical practice guidelines to identify evidence-based treatments for those at clinical high risk of psychosis. Results were compared with the treatment components used in the First Episode Psychosis Services Fidelity Scale. First Episode Psychosis Services Fidelity treatment components were

either deleted, modified, or new components added. A separate evidence base was reviewed to identify anchor points for each component using a 1-5 Likert scale.
Results: The Clinical High Risk for Psychosis fidelity scale comprises 32 components 21 of which overlap with the components of the First Episode Psychosis Services Fidelity Scale. Components describing team function were unchanged. The scale emphasizes key differences in treatment approaches including different assessments, the identification of multiple treatment targets and a stepped care approach beginning with psychosocial treatments.
Discussion: The evidence base for specific treatments is sufficient to identify evidence-based treatment components for treatment seeking individuals at clinical high risk for psychosis. This first version of the scale is suitable for validation and refinement using a Delphi consensus process and piloting in early psychosis programs that deliver care for those at clinical high risk for psychosis. It can be used in combination with the First Episode Psychosis Services Fidelity Scale to evaluate components of care in programs that deliver care for patients with a first episode psychosis and those at clinical high risk. The scale can be used to evaluate components of care in randomized controlled studies and prospective studies, with the results used to modify the scale and support changes in practice.

70. EXPLORING LONGITUDINAL SYMPTOM TRAJECTORIES IN FIRST EPISODE PSYCHOSIS: A NETWORK ANALYSIS APPROACH

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Background: Clinical outcomes in first episode psychosis (FEP) are known to be greatly improved via early intervention paradigms. However, selecting targets for intervention remains a challenge. The recent adoption of network approaches in psychopathology provides a novel approach for understanding symptom interactions in early psychosis, which can help guide therapeutic interventions by highlighting key symptoms to target. In the network analysis framework, symptoms are not viewed as indicative of a common latent variable, but rather as complex systems of dynamic, causal interactions among the symptoms themselves. In other words, psychiatric disorders are the result of the active interplay between psychiatric symptoms in a network. The network analysis approach is especially relevant in the context of therapeutic interventions, as it can be used to parse out the most central symptoms in the network as viable targets for treatment. To explore symptom networks in FEP, we examined the relationships between delusions and other psychotic symptoms at baseline and longitudinally.
Methods: Our study used network analysis to investigate symptom interactions in 678 individuals with a FEP. Specifically, we (1) estimated regularized partial correlation networks of FEP symptoms at baseline and month 12 using the 'EBICglasso' algorithm, (2) identified the most central symptoms in each network, and (3) compared baseline and month 12 symptom networks to examine changes in structure and connectivity. Additionally, we explored the role of delusional content in early psychosis symptomatology by investigating the centrality of delusional themes in the networks.
Results: At baseline, the most central symptoms were depression, affective flattening, and anxiety. At month 12, the most central symptoms were persecutory delusions, hallucinations, and delusions of thought insertion. Additionally, while network structures did not differ significantly between timepoints ($M = 0.174$, $p = 0.08$), we observed that the month 12 network was more highly connected compared to baseline ($S = 1.496$, $p < 0.01$). Only two edges were significantly different between baseline and month 12 ($p < 0.01$). Specifically, the edge

“Persecutory delusions—Somatic delusions” was not present at baseline but was present with a strength of 0.15 at month 12; conversely, the edge “Delusions of reference—Anxiety” was present at baseline with a strength of 0.15 but was not present at month 12. Analysis of specific delusional themes revealed that, at baseline, delusions of influence (i.e., delusions of being controlled, thought withdrawal, thought broadcasting, thought insertion, and mindreading) were among the top six delusional themes with the highest strength centrality.
Discussion: These results capture shifts in illness trajectory over time, wherein transdiagnostic symptomatology at baseline becomes more consolidated around psychotic symptoms in those with persistent syndromes. Consistent with previous principal component analyses of early psychosis symptomatology, baseline delusions of influence were more strongly correlated with other psychotic symptoms compared to the remaining delusional themes. For clinicians, attention to affective and anxiety symptoms may be appropriate when intervening at the earliest stages of illness, while targeting symptoms more specific to psychosis, such as delusions and hallucinations, may be necessary in those with persistent symptom burden.

71. MOZART: A CLINICAL RISK PREDICTION MODEL FOR TREATMENT RESISTANT SCHIZOPHRENIA FROM ROUTINELY COLLECTED, OBJECTIVE BIOMEDICAL PREDICTORS AT FEP ONSET

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Background: Around a quarter of people who experience a first episode of psychosis (FEP) will develop treatment-resistant schizophrenia (TRS). TRS is associated with reduced quality of life, substantial societal burden, and up to tenfold higher healthcare costs. It is not currently possible to predict accurately whether someone with FEP will develop TRS. This is important because there is evidence that clozapine, the only treatment licensed for TRS, is more effective the sooner it is prescribed. Yet, in clinical practice there are often long delays before clozapine is considered. This highlights the need to identify treatment resistance as soon as possible.
We aimed to explore the predictive potential for TRS of routinely collected, objective biomedical predictors at FEP onset, and to externally validate the model in a separate clinical sample of people with FEP.

Methods: We developed and externally validated a forced-entry logistic regression risk prediction Model fOr cloZApine tReaTment, or MOZART, to predict up to 8-year risk of TRS from FEP using routinely recorded information including age, sex, ethnicity, triglycerides, alkaline phosphatase levels, and lymphocyte counts.
TRS was assessed using clozapine use as a proxy.

The model was developed using pooled longitudinal data from patients enrolled in the Cambridgeshire and Peterborough Assessing, Managing and Enhancing Outcomes (CAMEO) psychosis EIS or the Birmingham EIS. Model validation was performed using data from the Clinical Records Interactive Search (CRIS) resource to capture anonymised data from South London and Maudsley NHS Foundation Trust (SLaM) EIS. Predictors were assessed within 100 days of patient EIS enrolment.

Model performance was assessed primarily with measures of discrimination (the ability of the model to distinguish participants with the outcome from those without), such as the C statistic, and calibration (the extent to which the outcome probabilities predicted by the model in

specified risk-defined subgroups are similar to those observed in the validation dataset), assessed by inspection of calibration plots (presented as figures).

Additionally, where performance at external validation differed from internal validation performance, we considered logistic recalibration plus revising a single predictor in the model.

MOZART was developed in 785 patients, and validated externally in 1,110 patients.

Results: MOZART predicted TRS well at internal validation (C statistic: 0.70; 95%CI 0.63,0.76). At external validation, discrimination performance reduced (C: 0.63; 0.58,0.69) but recovered after re-estimation of the lymphocyte predictor (C: 0.67; 0.62,0.73). Calibration plots showed good agreement between observed and predicted risk in the forced-entry model. We also present a decision-curve analysis and an online data visualisation tool for both the original and recalibrated models, which allows to interactively explore the effect of each predictor and their combinations on the risk of clozapine use based on the predictors included in this study. See https://eosimo.shinyapps.io/trs_app/

Discussion: Decision curve analysis showed that the forced-entry model shows clinical net benefit at lower propensity to intervene thresholds, such as between 10-20%. This model cannot yet be recommended for clinical use and requires prospective validation, health technology assessment, and regulatory approval. However, subject to these steps, in future our model could allow to implement low-risk strategies, e.g., stratifying patients at higher-than-average risk of developing antipsychotic resistance for closer psychiatric monitoring for the presence of TRS. These strategies have very low, if any, risk of causing harm, and might show potential at earlier recognition and treatment of TRS. However, given the higher risk and licensing conditions of clozapine, and the lower sensitivity of the model at higher risk thresholds, this model alone will not be useful for initiating higher-risk interventions, such as starting clozapine.

Further, we conclude that the use of routinely collected clinical information including blood-based biomarkers taken at FEP onset can help to predict the individual risk of clozapine use, and should be considered equally alongside other potentially useful information such as symptom scores in large-scale efforts to predict psychiatric outcomes.

72. PATHWAYS TO EARLY INTERVENTION SERVICES AND SUBSEQUENT URGENT HEALTH SERVICE USE: A 2-YEAR COHORT STUDY

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Background: The implementation of early intervention services (EIS) for young adults with psychosis has represented a significant innovation in psychiatric care internationally. With a focus on providing comprehensive care around illness onset, EIS are associated with improved clinical and functional outcomes when compared to standard care models. While EIS aspirationally, prioritize earlier detection of psychosis and timely provision of treatment, many patients experience significant treatment delay prior to referral to EIS. Delays in treatment are associated with increased use of urgent/acute health services, negative treatment outcomes, and increased burden and cost for health systems.

Young adults experiencing psychosis often navigate confusing healthcare services that can be ineffective at detecting illness before urgent care is needed. Prior research has suggested that accessing EIS via urgent/acute health services increases one's risk of having negative or traumatic healthcare experiences, and concern has been raised that these experiences could further contribute to negative treatment outcomes. Despite this, limited research empirically

assessed the relationship between patients' referral sources and clinical outcomes has been conducted.

The current study sought to address these gaps by examining the relationship between patients' referral source to EIS and their subsequent urgent healthcare use following referral to EIS while controlling for clinical characteristics and biological sex.

Methods: This study used a retrospective cohort design to assess the relationship between EIS patients' referral source and the rate of emergency department visits and inpatient hospitalizations for two years following their referral to the Nova Scotia Early Psychosis Program in Canada. Participants (n = 500) included all past and present patients who consented to having their data used for research purposes (approximately 75% of the total patient population).

The study follow-up period was determined to be two years to coincide with the minimum duration of EIS in Canada. Emergency room visits and hospitalizations were chosen as the outcome of interest as they have a low risk of measurement error and are indicative of acute illness. Patients' referral sources were categorized as either self-referrals, primary care referrals, outpatient mental health referrals, referrals from the child EIS, and urgent care referrals (referred via emergency or inpatient). Referral sources were categorized in this way as they represent different levels of healthcare.

Negative Binomial models were used to fit the relationship between referral source and urgent health service use over the follow-up period. In an effort to control for illness severity at referral, participants' symptom severity (measured by PANSS Marder et al., dimension scores), and general functioning (measured by SOFAS) were included in analyses. Additionally, biological sex was included as a predictor in analyses.

Results: Our sample (n = 500) was comprised of 129 (26%) Females and 371 Males (74%). 58 (12%) of participants were referred by primary care physicians, 26 (5%) were self-referred, 48 (9%) were referred from the child EIS, 88 (18%) were referred from outpatient mental health services, and 280 (56%) were referred from urgent care services. The mean number of hospitalizations for the sample over the two-year follow-up period was 1.24 (SD = 2.30). Participants referred via child EIS services had significantly higher mean symptom severity scores (PANSS) compared to other referral source groups. No other differences between referral source groups, or male and female participants were detected.

Bayesian model averaging was used for model selection and the BIC criterion was used to assess model fit. The most parsimonious model included measures of functioning (SOFAS) and severity of disorganized thoughts (Marder et al., PANSS dimensions, $p < 0.05$). Functioning (RR = 0.98 per unit increase, $p < 0.05$), and severity of disorganized thoughts (RR = 1.02 per unit increase) significantly predicted the outcome. Referral source to EIS, also significantly predicted the outcome. Compared to the reference group, those referred via urgent services had a significantly greater rate of hospitalizations per person-year (RR = 3.08, $p < 0.001$). No other referral source categories significantly predicted the outcome.

Discussion: A strong association between urgent care referral and subsequent urgent healthcare use was found over the study period while controlling for illness severity. Nonetheless, this study had limitations: Data on additional potential confounders (e.g., SES, race, and social support) were not available. Furthermore, the degree to which factors upstream from patients' referral source may be responsible for this effect is unclear. Assuming a patient's

referral source increases their risk for future urgent health care use, specific interventions to modify this reality may be difficult to develop. In addition to developing further understanding of the relationship between patients' referral source and outcomes, future research should focus on identifying whether additional support is appropriate for those with specific referral experiences.

Oral Sessions: From Brains to Societies

73. RACIAL DISPARITIES WITH PRN MEDICATION USAGE IN INPATIENT PSYCHIATRIC TREATMENT

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Background: Racial disparities in psychiatric diagnoses and treatment have significant public health implications, contributing to inequalities in healthcare outcomes. The intended use as-needed (PRN) medications on inpatient psychiatry units are to modify behaviors and calm or sedate individuals who are disruptive and/or violent towards others. It has not yet been explored whether there are racial discrepancies in the use of PRN medications. The authors looked at 14,616 inpatient encounters across two years within a United States community hospital inpatient psychiatric setting aiming to assess racial disparities regarding the use of PRN medications.

Methods: All inpatient encounters from 2019-2020 were pulled and analyzed by race, further narrowing data analysis for Black and White patients due to small sample size of other races. All PRN medication administrations were also pulled and analyzed by race and medication category. Primary outcomes included likelihood of receiving a PRN during an inpatient admission, and comparisons across PRN medication class including all antipsychotics vs non-antipsychotics, all antipsychotics vs hydroxyzine, and all antipsychotics vs. lorazepam.

Results: Of admissions with a PRN, 77.8% were White patients and 22.2% Black patients compared to 80.4% and 19.6% respectively for admissions without PRN exposure ($p<0.001$). Of 6,631 antipsychotic PRNs administrations, 62.5% for White patients and 37.5% Black patients compared to non-antipsychotic PRNs (N=58,241) 80.1% for White patients and 19.9% for Black patients ($p<0.001$). Black patients were 65% more often given antipsychotic PRNs over non-antipsychotic PRNs (OR
1.65, $p<0.001$), and 37% more often given antipsychotics over lorazepam (OR 1.37, $p<0.001$) when controlled for sex, age, and diagnosis.

Discussion: These findings provide novel data regarding racial disparities with PRN medication usage. There were statistically significant differences in PRN exposure comparing admission data, and increased probability of antipsychotics over other PRN medications for Black patients, which persisted even when controlling for sex, age, and diagnosis. This information provides a basis for further investigation and uncovering disparities in patient centered data arising from implicit bias.

74. CONTROLLABILITY OF FUNCTIONAL BRAIN NETWORKS AND ITS CLINICAL SIGNIFICANCE IN FIRST-EPISODE SCHIZOPHRENIA

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Background: Disrupted control of brain state transitions may contribute to the diverse dysfunctions of cognition, emotion, and behavior that are fundamental to schizophrenia. Classical control theory provides the rationale and mathematical procedures for evaluating both brain connectivity and its dynamic change over time. Its model and methods are rooted in the idea that energetic input modulates transitions from a current state of activity to another desired state to improve system function relevant to current demands. Human brain regions and the networks they comprise can alter functional states and drive transitions to different states, which corresponds to state transformations in the engineering control process framework. Considering control processes from a bioengineering framework may provide a useful biological framework for understanding the causes of widely observed cognitive control deficits in schizophrenia.

Methods: Controllability measurements of functional brain networks included average controllability which represents the inverse of the average impulse response energy (control input) that supports the transition of brain states; And modal controllability which evaluates the ability of nodes to drive shifts into difficult-to-reach brain states. Both measurements were calculated and compared between 125 first-episode never-treated patients with schizophrenia and 133 healthy controls (HCs). Associations between controllability metrics and clinical symptoms were evaluated using sparse canonical correlation analysis.

Results: Compared to HCs, patients showed significantly increased average controllability and decreased modal controllability in dorsal anterior cingulate cortex (dACC). General psychopathology symptoms and positive symptoms were positively correlated with average controllability in regions of default mode network (DMN) (medial prefrontal cortex, orbitofrontal cortex, posterior cingulate cortex, and parahippocampal gyrus) and negatively associated with average controllability in regions of sensorimotor (SMN) (postcentral gyrus), dorsal attention (DAN) (intraparietal sulcus and precuneus), and fronto-parietal networks (FPN) (dlPFC and supramarginal gyrus).

Discussion: dACC is a crucial region for cognitive control, cognitive flexibility, and error detection, and has been related to disturbances of cognitive control in many schizophrenia studies. The dysfunction of dACC observed in the present study in managing state transitions is consistent with the notion that dACC alterations may represent a causal factor in the disruption of optimal large-scale network function and cognition in schizophrenia. Our multivariate correlation analysis revealed that positive and general psychopathology symptoms in patients were related to network controllability in SMN, DAN, FPN, and DMN. These associations were present with average but not modal controllability. This pattern of findings suggests that distractibility and exaggerated behavioral flexibility seen in acute psychosis may be more state related than due to the regulation of higher cognitive function in schizophrenia. In conclusion, our study documented that altered controllability in the dACC represents a significant alteration of the functional brain connectome in schizophrenia, and that altered average controllability in SMN, DAN, FPN, and DMN is associated with symptoms of psychosis. Dysfunction in the ability to switch network states for optimal brain function may be an important mechanistic feature underlying the prominent neurocognitive and neurobehavioral alterations in schizophrenia.

75. QUANTIFYING 18F-DOPA PET SIGNAL IN THE MOUSE MIDBRAIN, AND APPLICATION TO A MODEL OF SCHIZOPHRENIA-RELEVANT HYPERDOPAMINERGIA

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Background: There is robust evidence that people with schizophrenia show elevated dopamine (DA) synthesis capacity in the striatum. This finding comes from positron emission tomography (PET) studies using radiolabelled l-3,4-dihydroxyphenylalanine (18F-DOPA). One study has found that DA synthesis capacity was also elevated in the midbrain of people with schizophrenia compared to healthy controls (Howes et al., 2013). A recent meta-analysis also found that neuromelanin - an accumulated product of cytosolic DOPA and DA - was elevated in the midbrain of people with schizophrenia, compared to healthy controls (Ueno et al., 2022). These studies suggest that striatal hyperdopaminergia may originate in the midbrain. To determine the contribution of midbrain dopaminergic dysfunction to schizophrenia-relevant neurobiology and phenotypes, it is necessary to utilise animal models of schizophrenia. While 18F-DOPA uptake is routinely quantified in the striata from preclinical PET scans, there is currently no reliable method for such quantification in the midbrain. Therefore, the first aim of this work is to define the parameters for quantifying 18F-DOPA uptake in the midbrain from mouse PET scans. The second aim of this work is to apply this novel method to a mouse model of striatal hyperdopaminergia. The sub-chronic ketamine model results in elevated 18F-DOPA uptake in the striatum (Kokkinou et al., 2020). If this model also reveals elevated DA synthesis capacity in the midbrain, it could be used to assess whether normalizing dopaminergic dysfunction in the midbrain can rescue dopaminergic abnormalities in the striatum and ameliorate schizophrenia-relevant phenotypes.

Methods: Adult male C57Bl6 mice were treated daily with either ketamine (30mg/kg, i.p.) or vehicle (saline) for 5 days. On day 7, animals were scanned in an Inveon PET/CT scanner. Briefly, animals underwent a 10-minute CT scan, followed by PET imaging with the 18F-DOPA radioligand (delivered i.p.) over 140 minutes. Following reconstruction, data were analysed using Inveon Research Workplace. The saline-treated group were used to define the midbrain parameters which resulted in the greatest consistency between animals, based on the lowest coefficient of variation (CV%) and standard deviation (SD). The two parameters which can be altered are the size of the midbrain ROI, and the time window used for the extended Patlak modelling to calculate KiMod. Three different bilateral midbrain ROI sizes – 1.1mm3, 2.1mm3, and 3.2mm3 - were compared. The cerebellum (the reference region) was 1.1mm3, as established previously. A range of start (T*) and end (Tend) times were compared using the Patlak algorithm, with the CV% providing an indication of how well the model fitted the data points. Based on these findings, the optimised parameters from the saline-treated animals were then applied to the scans taken in ketamine-treated animals.

Results: Comparison of different parameters revealed the 3.2mm3 ROI resulted in the lowest CV% and SD in the saline-treated group. A range of T*-Tend windows – 10-140, 15-140, 20-140 and 25-140 minutes - for calculating KiMod produced similar CV% and SD values. We therefore utilised the 20-140 minute window which has been previously established as the optimal T*-Tend window for the striatum. Using these parameters, CV% and SD values for KiMod were not significantly different between the striatum and the midbrain, indicating that it is feasible to reliably quantify 18F-DOPA uptake in the mouse midbrain. When applying these parameters, we found that KiMod was elevated in the midbrain of ketamine-treated animals in comparison to saline-treated animals ($t(22)=2.4$, $p=0.02$). For the saline-treated

group, there was also a positive correlation between DA synthesis capacity in the striatum and in the midbrain (r2=0.83, p<0.0001). However, this correlation was absent in ketamine-treated animals (r2=0.02, p=0.62), suggesting that the normal relationship between dopaminergic compartments is disrupted in this model.
Discussion: This work is the first to establish a method for reliable quantification of 18F-DOPA uptake in the mouse midbrain, and therefore provides a foundation for assessing this region in other preclinical models of schizophrenia. As a proof-of-principle, we applied this method to the sub-chronic ketamine model. We found that elevated striatal DA synthesis capacity in this model extends to the midbrain. Interestingly, the disconnect between the midbrain and striatal DA synthesis capacity seen in this model is also evident in the clinical population; where healthy controls show a positive correlation between these two regions, this is absent in people with schizophrenia. This finding makes this model extremely valuable for understanding the nature of the midbrain dysfunction, and its downstream effects. This model may therefore also be ideal for assessing the effects of novel compounds which are designed to modulate pre-synaptic DA synthesis capacity, such as Trace Amine-Associated Receptor 1 (TAAR1) agonists. This could reveal a new direction for the treatments of schizophrenia, with enormous implications for the treatment of this disorder.

76. THE IMPACT OF CUMULATIVE PRENATAL COMPLICATIONS AND CHILDHOOD TRAUMA ON BRAIN VOLUME IN YOUNG PEOPLE WITH PSYCHOTIC EXPERIENCES

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Background: Psychotic experiences (PEs) occur in 5-10% of the general population and are associated with exposure to childhood trauma and pre/perinatal obstetric complications. However, it is not known whether these environmental risk factors lead to psychosis via effects on brain structure.
Methods: Using the Avon Longitudinal Study of Parents and Children (ALSPAC), we examined healthy controls (HC n=275) and those with PEs (n=49 suspected, n=53 definite, n=36 psychotic disorder). Voxel-based morphometry assessed whether MRI measures of grey matter volume at age 20 were associated with i) PEs, ii) cumulative childhood trauma, iii) cumulative pre/peri-natal risk factors for psychosis, iv) interaction between PEs and cumulative trauma or pre/peri-natal risk.
Results: PEs were associated with smaller left posterior cingulate (pFWE<0.001; Z=4.19) and thalamus volumes (pFWE=.006; Z=3.91). Cumulative pre/perinatal risk was associated with smaller left subgenual cingulate volume (pFWE=.031, Z=4.13). A significant interaction between PEs and cumulative pre/perinatal risk found smaller right insula/operculum volumes in PE groups in a dose-dependent manner, whereas HC showed larger volumes as pre/perinatal risk increased (pFWE=<0.001; Z=4.79). Cumulative childhood trauma associated with larger left dorsal striatum (pFWE<.001; Z=4.02), right prefrontal cortex (pFWE<.001; Z=4.90) and bilateral medial frontal gyrus volumes in all participants, and no interaction with PE group.

Discussion: Pre/perinatal complications appear to lead to reduced insula/operculum volume but only in those with PEs. Such volume reductions may be a neurodevelopmental biomarker of poor mental health outcomes. Conversely, cumulative childhood trauma is associated with larger frontal and dorsal striatum volumes in all participants regardless of PE status, which may reflect adaptive changes.

77. MITOCHONDRIAL COMPLEX I LEVELS IN SCHIZOPHRENIA RELATIVE TO CONTROLS AND THE RELATIONSHIP TO SYMPTOMS: A POSITRON EMISSION TOMOGRAPHY STUDY USING 18F-BCCP-EF

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Background: Schizophrenia is associated with widespread impairment in cortical metabolism, and there is genetic and post-mortem evidence that this may be related to lower mitochondrial protein levels. However, this has not yet been directly tested in vivo. This study aimed to test the hypothesis that the volume of distribution of 18F-BCPP-EF, a novel PET tracer that binds specifically to mitochondrial complex one (MC1), is lower in schizophrenia compared to controls.

Methods: We used 18F-BCPP-EF positron emission tomography and T1-weighted magnetic resonance imaging to investigate levels of MC1 in the anterior cingulate cortex, frontal cortex and hippocampus in 66 subject. 25 were controls and 41 people were diagnosed with schizophrenia, 21 of whom were untreated at the time of the scans. Clinical data included the Positive and Negative Symptom Scale (PANSS), duration of illness, chlorpromazine equivalent antipsychotic dose, and time since last antipsychotic treatment for those who were not taking medication. We analysed PET images using MIAKAT software version 4.3.7 (http://www.miakat.org/MIAKAT2/index.html), which uses functions from MATLAB (Mathworks Inc., Natick, MA, USA), FSL (version 5.0.10; FMRIB, Oxford, UK) and Statistical and Parametric Mapping 12 (SPM12, Welcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm). We calculated 18F-BCPP-EF Volume of Distribution (VT) for each region of interest using multilinear analysis 1 (MA1) modelling, which required the creation of time activity curves and arterial input function derived from metabolite analysis of continuously sampled arterial blood. To test our main hypothesis that 18F-BCPP-EF VT is reduced in patients relative to controls, we conducted a mixed-model ANOVA, with patient group as the between-subjects factor, and ROI as a within-subjects factor, with 18F-BCPP-EF VT results for the hippocampus, frontal cortex and anterior cingulate cortex making up the three levels. Post-hoc t-tests to determine the ROIs where there was a significant difference between patients and controls. All analyses were conducted using SPSS Version 26.0 (Armonk, NY, 2019 [42]).

Results: We found significant a significant main effect of group on 18F-BCPP-EF volume of distribution [F1, 61=12.52, p<.001], with significantly lower levels in patients relative to controls in the frontal cortex [mean (SD) ml/cm3: patients=21.70 (3.9); controls=24.45 (3.62); t62 = -2.97, p=.007, Cohen's d=-.72], anterior cingulate cortex [patients=21.50 (3.4); controls 24.88.08 (4.1); t61 = -3.55, p<.001, d=-.922] and hippocampus [patients=18.00 (2.59); controls 20.40 (3.04); t62 = -3.34, p=0.001, d=-.87]. Unmedicated patients had significantly lower 18F-

BCPP-EF distribution volume compared to controls in the anterior cingulate cortex [unmedicated patients 22.31 (3.13); controls 24.87 (4.05); t42 = -2.32, p=.026, d= -.70] and hippocampus [unmedicated patients 18.55 (2.16); controls 20.40 (3.04); t42 = -2.27, p=.029, d= -.67]. In unmedicated patients, we found inverse correlations between negative symptoms and 18F-BCPP-EF distribution volume in the frontal cortex [r= -.574, p = .007] and hippocampus [r = -.520, p= .019]. Duration of illness, chlorpromazine equivalent dose, or time since last antipsychotic did not significantly correlate with 18F-BCPP-EF volume of distribution in any region of interest.

Discussion: This is the first in vivo evidence consistent with lower MC1 levels in schizophrenia patients in comparison with controls, and that lower levels are related to higher negative symptom severity in unmedicated patients. Strengths of this study included the large size of the schizophrenia group compared to other PET imaging studies in the disorder, and the inclusion of a sub-group of unmedicated patients. The inverse correlation between MC1 levels and negative symptoms was only seen in the unmedicated sub-group and not in the schizophrenia group overall, and so we call for replication of this finding in new unmedicated samples. Overall, this study extends prior evidence indicating reduced metabolic activity in many brain regions in schizophrenia to show that such findings may be related to lower MC1 in schizophrenia. Thus, MC1 may be a promising therapeutic target in schizophrenia.

78. LOST IN TRANSLATION? DECIPHERING THE ROLE OF LANGUAGE DIFFERENCES IN THE EXCESS RISK OF PSYCHOSIS AMONG MIGRANT GROUPS

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Background: Migration is a well-established risk factor for psychotic disorders, and migrant language has recently been proposed as a novel factor that may improve our understanding of this relationship. Our objective was to examine the association between multiple indicators of linguistic distance and the risk of psychotic disorders among first-generation migrant groups.

Methods: Using health administrative data, we constructed a retrospective cohort of first-generation migrants to Ontario over a 20-year period. Linguistic distance of the first language was categorized using several approaches, including language trees, estimated language acquisition time, syntactic distance scores, and lexical distance scores. First onset non-affective psychotic disorders were identified using a validated algorithm, with a 5- to 25-year follow-up period. We used Poisson regression models to compute incidence rate ratios (IRR) for each language variable, after adjusting for English fluency at arrival and other factors associated with the risk of psychotic disorders.

Results: Our cohort included 1,863,803 first-generation migrants, and nearly 700 languages were represented in the dataset. Our findings suggest that migrants whose first language is in a different language family than English had higher rates of psychotic disorders (IRR=1.08, 95%CI=1.01,1.16), as did those who had a higher estimated language acquisition time (IRR=1.19, 95%CI=1.11,1.28), relative to those whose first language was English. Similarly, migrants in the highest quintile of linguistic distance based on lexical distance scores had an elevated risk of psychotic disorder (IRR=1.15, 95%CI=1.06,1.24), but we did not find evidence of an effect for syntactic distance scores. We did not find evidence of effect modification by

age at migration, but there was some evidence of stronger effects for family reunification migrants.
Discussion: We found some evidence to suggest that language may play a role in the risk of psychosis among migrant groups, however the effects are small an unlikely to fully explain the excess risk. Elevated rates of psychosis among migrant groups have persisted for nearly a century with little progress toward prevention. These findings help identify modifiable markers of risk for psychotic disorder to inform public mental health strategies.

79. COLLABORATIVE SHARED CARE FOR PSYCHOSIS DELIVERED BY TRADITIONAL/FAITH HEALERS AND BIOMEDICAL PRACTITIONERS IN NIGERIA: STAKEHOLDERS' PERSPECTIVES ON BENEFITS, FACILITATORS, BARRIERS AND SUSTAINABILITY.

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Background: Psychotic disorders contribute a significant proportion to the global burden of mental disorders and are a cause of considerable personal suffering and economic loss. In many low- and middle-income countries, traditional and faith healers are the main source of care for affected persons. A collaborative shared care (CSC) for these conditions delivered by primary health care providers (PHCP) and traditional/faith healers (TFH) was found to improve clinical outcomes and to be cost-effective. Here, we report the findings of the process evaluation in which the perspectives of the TFH, PHCP, service users and their families were sought about this model of care.
Methods: Key informant interviews were conducted with 15 PHCP, 11 TFH, 21 service users and 19 caregivers. Participants had all been involved in providing or receiving the CSC which was implemented in 11 local government areas in Ibadan, Nigeria. CSC was a manualized model of intervention in which PHCP worked with TFH to improve the quality and safety of care provided to persons with psychosis who were receiving in-patient treatment at TFH facilities. The interviews elicited information about perceived benefits of CSC, barriers to its implementation, factors that facilitated its delivery and those that could help or hinder its sustainable adoption. Data was analysed using Framework Analysis approach along pre-determined themes.
Results: The mean ages of the service users and caregivers were 33.7 years and 52.0 years, respectively. Mean numbers of years of experience of the PHCP and TFH were 20.2 and 17.6, respectively. Among the reported benefits of CSC was that it was holistic, affordable and accessible, and generally met the needs and expectations of both patients and caregivers. Other benefits include reduction in harmful treatment practices by TFH; improvement in patient' hygiene, safety and nutritional status and reduction on level of experienced stigma. Healers reported improved understanding of mental illness; boost in their patronage and income, as well as enhancement in their status in the community. PHCP reported improved relevance of their service to society. Identified facilitators of the CSC model include absence of threat to TFH' means of livelihood; initial training of the collaborating partners; mutual respect between healers; clear delineation of roles and boundaries; willingness of partners to cooperate; provision of coordination, support and oversight to the partners; clear communication; support from peers of the PHCP and facility managers as well as financial incentives to the PHCP. Stakeholders identified a number of potential barriers to the sustainable implementation of the

CSC model: mistrust; scarcity of trained and dedicated PHCP; logistic challenges; unfavourable work environment; differences in the explanatory models of psychosis between healers and biomedical practitioners; negative stereotypes; medication stock out and poor incentives. Proffered solutions to the barriers include a reform of the health system governance and improved health workforce and health financing.
Discussion: The study demonstrates that a model of collaborative shared care which had earlier been shown to be effective and cost-effective was generally found to be satisfactory to persons with psychosis and their caregivers and to be acceptable fit-for-purpose by collaborating TFH and PHCP. Its sustainability will depend on reform to the mental health system that takes account of governance, workforce and financing.

80. MACRO-LEVEL EXPOSURES AND PSYCHOSIS RISK AMONG MIGRANTS AND ETHNIC MINORITY GROUPS ACROSS FIVE EUROPEAN COUNTRIES (AN EU-GEI STUDY): DO MIGRANT INTEGRATION POLICIES AND AREA-LEVEL SOCIOECONOMIC CONDITIONS PLAY A ROLE?

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Background: An increased risk for psychosis among ethnic minority populations has long been reported in the literature. Previous evidence suggests that these findings should be interpreted in light of a socio-developmental psychosis pathway, considering the ways how social factors intersect for specific populations. Known social determinants of psychosis such as family breakdown, social and economic disadvantage, discrimination and social exclusion have been reported to partially explain the higher psychosis risk among these populations. However, previous studies reported a great variation in risk depending on the population group and host country, suggesting that environmental contexts (conceptualized under a multilevel eco-epidemiological paradigm) may play a very important role. For instance, country-level policies implemented to facilitate or regulate the integration of migrants are likely to have a profound impact on the day-to-day realities of individuals belonging to minoritized communities and have been reported to influence the public opinion about immigrants and immigrant's integration in their host country, their well-being and self-reported health. Despite their relevance, macro-level exposures have received considerably less attention in previous studies exploring psychosis risk among minoritized populations, compared to individual-level risk and protective factors. We aimed to investigate whether migrant integration policy scores (as measured by the Migrant Integration Policies Index [MIPEX]), as well as other area-level aspects pertaining to populations' socioeconomic conditions were associated with psychosis risk and whether taking these aspects into account would explain a previously reported excess of psychosis risk among minoritized communities.
Methods: This study analysed incidence data (n = 2159) from the European Network of National Schizophrenia Networks Studying Gene-Environment Interactions study (EU-GEI), a multisite study implemented between 2010 and 2015. Case status was determined by the presence of a non-organic psychotic disorder diagnosis as per ICD-10 (International Classification of Diseases) criteria. Population at risk was estimated based on local demographic data. Exposures of interest included ethnic minority status, MIPEX score (0-100, higher scores indicating stronger integration policies), and area-level proxies of socioeconomic status including unemployment and low education (broken down by ethnic migrant status and sex), and owner-occupied housing. Sex and age were considered as a priori confounders. Poisson mixed-effects regression models were fitted to calculate the association between the individual and area-level exposures with psychosis incidence.

Results: In multinomial models controlling for age and sex, higher MIPEX scores (IRR: 0.90; 95 % CI 0.89 – 0.93) and a higher percentage of owner-occupied houses (IRR: 0.98; 95 % CI 0.96 – 0.99) were associated with lower psychosis rates, whereas a higher area-level percentage of unemployment (IRR: 1.04; 95 % CI 1.03 – 1.05) and of low education levels (IRR: 1.01; 95 % CI 1.01 – 1.02) were associated with higher psychosis incidence rates. Ethnic minority status was associated with higher psychosis risk in models adjusting for age and sex (IRR: 1.41; 95 % CI 1.27–1.56), but this effect was no longer significant when area-level exposures were added to the model (IRR: 1.01; 95 % CI 0.92 – 1.19).
Discussion: This study highlights the relevance of considering macro-level environmental factors, including previously unexamined ones like country-level integration policies, in understanding psychosis risk. Our study highlights that social determinants like unemployment may also act at an area-level, particularly when considering their differential rates for minority versus non-minority populations.

Oral Sessions: Neurobiology of Psychosis

81. DATA DRIVEN TAXONOMY FOR ANTIPSYCHOTIC MEDICATION: A NEW CLASSIFICATION SYSTEM

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Background: There are over 25 licensed antipsychotic medications, and all primarily exert their effects on psychotic symptoms via dopamine D2 receptor blockade. Nevertheless, they have diverse pharmacological and clinical profiles. Antipsychotics are commonly described as either ‘typical’ or ‘atypical’, but this classification is primarily based on the date of compound discovery and does not accurately reflect pharmacological profiles. There is thus a need for an antipsychotic classification scheme suitable for clinicians and researchers which maps onto both pharmacological and clinical effects. Although a ‘Neuroscience Based Nomenclature’ was developed to address this issue, its categorisation relies to a significant extent upon expert opinion. The aim of the present study was to develop a classification system that is data-driven and based systematically upon compound pharmacology.
Methods: We analysed the affinities of a total of 27 antipsychotics for a total of 42 receptors from 3,325 receptor binding studies. We used a clustering algorithm to group antipsychotics based on their pattern of receptor affinity. Principal components analyses were performed to identify the receptor affinity and side effect profiles of these clusters. Using partial least squares regression, we examined the ability of the clustering to predict 13 common antipsychotic-induced side effects.
Results: 4 clusters were defined, with the following properties:

Group 1 - Muscarinic (M3-M5) receptor antagonism; Cholinergic and metabolic side effects.

Group 2 - Dopamine (D2) partial agonism and adrenergic antagonism; Globally low side effect burden.

Group 3 - Serotonergic and dopaminergic antagonism; Globally moderate side effect burden.

Group 4 - Dopaminergic antagonism; Extrapyramidal and motor side effects.

Groups 1 and 4 were more efficacious than clusters 2 and 3. Using partial least squares regression, this novel classification was superior to existing classification schemes (neuroscience based nomenclature, and typical/atypical grouping) in predicting side effects.

Discussion: A data-driven classification approach has the potential to benefit both patients and researchers by guiding treatment and informing drug development.

82. BRAIN STRUCTURAL NETWORK CONNECTIVITY OF FORMAL THOUGHT DISORDER DIMENSIONS IN AFFECTIVE AND PSYCHOTIC DISORDERS

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Background: The psychopathological syndrome of formal thought disorder (FTD) is present in schizophrenia (SZ) but is also highly prevalent in major depression (MDD) and bipolar disorder (BD). It remains unknown how alterations in the structural white matter connectome of the brain correlate with psychopathological FTD dimensions across affective and psychotic disorders.

Methods: Using FTD items of the SAPS and SANS, we performed exploratory and confirmatory factor analyses in N=864 patients with MDD, BD or SZ to identify psychopathological FTD dimensions. We used T1 and diffusion-weighted magnetic resonance imaging to reconstruct the structural connectome of the brain. To investigate the association of FTD sub-dimensions and global structural connectome measures we employed linear regression models. We used network-based statistic (NBS) to identify subnetworks of white matter fiber tracts associated with FTD symptomatology.

Results: Three psychopathological FTD dimensions were delineated, i.e. disorganization, emptiness, and incoherence. “Disorganization” and “incoherence” were associated with global dysconnectivity. NBS identified subnetworks associated with FTD dimensions “disorganization” and “emptiness” but not with “incoherence”. Post-hoc analyses on subnetworks did not reveal diagnosis x FTD dimension interaction effects (also using Bayes statistics). Results remained stable after correcting for medication and disease severity. Confirmatory analyses showed a substantial overlap of nodes from both subnetworks with cortical brain regions previously associated with FTD in SZ.

Discussion: We demonstrated diagnoses-shared FTD symptomatology to be correlated with impaired communication between a set of bilateral nodes and edges in both temporal and frontal regions. This maps on the old disconnectivity hypothesis of SZ patients in general and their speech impairments in particular. Results open an avenue for transdiagnostic, psychopathology informed, dimensional studies in pathogenetic research.

83. THE IMPACT OF PSYCHOTIC EXPERIENCES AND AUTISTIC TRAITS ON BRAIN STRUCTURE

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Background: Increased prevalence rates of psychotic experiences (PEs) have been observed in individuals who present with autistic traits (Jones et al., 2012). Despite their shared clinical and genetic features, few neuroimaging studies have directly compared structural brain alterations in subjects with comorbid symptomology. This study examines subthreshold autistic traits in a birth cohort study to determine if brain alterations overlap with those identified in psychosis, and whether comorbidity uniquely alters brain structure.

Methods: Participants were sampled from the UK Avon Longitudinal Study of Parents and Children (N = 237, age range at scan 19-24 years). Autistic traits were assessed using the Social Responsiveness Scale (SRS, short version), PEs were assessed using the Psychosis-Like Symptom Interview. Using voxel-based morphometry in SPM 12, we explored grey matter differences in subjects with high scores on the SRS (i.e., top 10%, n = 26), PEs (n = 48) and healthy controls (n = 163). Within the autistic traits sample, we conducted additional analyses co-varying for the presence of PEs (n = 12 / 26). A significance threshold of $p < 0.001$ was selected at the voxel-level, while family-wise error $pFWE < 0.05$ was selected for the correction of multiple comparisons at the cluster level. Age, gender and total intracranial volume were included as covariates.

Results: A chi-square test of independence confirmed a significant association between autistic traits and PE samples ($X2$ (1, N = 237) = 6.71, $p = 0.01$). High scores on the SRS were associated with increased grey matter volume relative to healthy controls in the left middle cingulate ($pFWE = 0.002$; -17, -38, 39; 525 voxels; $Z = 4.12$) and right middle frontal gyrus ($pFWE = 0.044$; 24, 44, 21; 284 voxels; $Z = 3.84$). When covarying for PEs, only the latter result remained significant but at a less stringent FDR threshold ($qFDR = 0.041$; 23, 44, 20; 161 voxels; $Z = 3.66$), along with grey matter increases in the left occipital lobe ($qFDR = 0.041$; -14, -87, 14; voxels = 189; $Z = 4.58$), right temporal lobe (qFDR = 54, 9, -18; 158 voxels; $Z = 4.03$), and left cerebellum ($qFDR = 0.041$; -33, -75, -44; 169 voxels; 3.52). In contrast, PEs were associated with reduced volume in the right cerebellum only ($pFWE < 0.000$; 14, -65, -59; 1102 voxels; $Z = 4.18$).

Discussion: Autistic traits were associated with regional increases in grey matter, whereas PEs were associated with regional reductions. Typically, psychotic symptoms are associated with general grey matter reductions, however we observed an increase in the left middle cingulate when subjects were comorbid for PEs and autistic traits. Difficulties in social information processing are common to both autism and psychotic disorders, and the middle cingulate may be responsible for some of these deficits e.g., atypical social valuation and monitoring the decision-making of others. While findings on the anterior cingulate cortex have predominated research in autism and psychosis, the middle cingulate cortex may be a unique region associated with dual PEs and autistic traits, offering a potential target biomarker for comorbid research.

84. ASSOCIATION BETWEEN BRAIN NETWORK STRATIFICATION AND COGNITION IN SCHIZOPHRENIA SPECTRUM DISORDERS (SSD)

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Background: Schizophrenia Spectrum Disorders (SSD) have been associated with dysconnectivity in "lower-order" (e.g., visual, auditory) and "higher-order" (e.g., default-mode and frontoparietal) cortical networks (Dong et al., 2018; Oliver et al, 2021). Previous studies used diffusion map embedding (Margulies et al., 2016) to characterize different levels of cortical and subcortical hierarchy by gradient principal components in SSD (Dong et al., 2020; Wang et al., 2020). These studies found SSD showed less dissociation between the lower- and the higher-order networks which was captured by compression of the first gradient. This gradient was correlated with the severity of clinical symptoms (Dong et al., 2020; Wang et al., 2020) and processing speed (Wang et al., 2020). However, as psychiatric disorders are strongly related to both neurocognitive (i.e., non-social) and social cognitive deficits, little is known about how such cortical and subcortical hierarchy is related to cognition more broadly.

Methods: We analyzed behavioural measures (non-social and social cognitive scores) and resting-state functional magnetic resonance imaging (fMRI) data from the 'Social Processes Initiative in Neurobiology of the Schizophrenia(s) (SPINS)' study (248 stable participants with SSD and 172 healthy controls, ages 18-55). Three gradient components are extracted from parcellated connectomes (Ji et al., 2019; Margulies et al., 2016) and are then correlated with 6 non-social and 8 social cognitive measures. Next, by using partial least square correlation (PLSC; Krishnan et al., 2011), we decomposed this correlation pattern into uncorrelated dimensions that best capture their associations. In PLSC, each dimension is composed of 1) two sets of latent variables, which represent the participants on this dimension, with respect to the two sets of variables (i.e., behavioural and gradients), and 2) two sets of variable loadings, which describe how they contribute to this dimension. To examine how a dimension is related to clinical measures, including functioning, quality of life, and symptoms, in SSD, we performed Pearson's correlation tests (with false discovery rate correction) between these measures and the two sets of latent variables.

Results: PLSC analysis identified one significant dimension (explaining 67.4% of the variance) as determined by the permutation test ($p < .001$). This dimension differentiated the healthy controls from the participants with SSD and is characterized by a positive correlation between network differentiation and general cognitive performance (i.e., both social and neuropsychological). Specifically, the cognitive deficits in SSD are related to decreased differentiation between lower- and higher-order networks (Gradient 1), between different lower-order networks (i.e., auditory and sensorimotor vs. secondary visual) (Gradient 2), and between the lower-order networks and striatum (Gradient 3). Furthermore, this dimension was positively correlated with frequencies of negative symptoms in SSD.

Discussion: In this study, we used PLSC to identify cognition-related differences in the network hierarchy. These results suggest a potential role of decreased differentiation of brain networks in functional impairment in SSD; more specifically, the decreased differentiations between the lower- and higher-order networks and between different lower-order networks are associated with both social and non-social cognitive impairments in SSD.

85. INVESTIGATING THE EFFECTS OF MINOCYCLINE AND APOCYNIN ON CENTRAL AND PERIPHERAL MARKERS RELEVANT TO COGNITIVE IMPAIRMENTS IN THE SUBCHRONIC PHENCYCLIDINE MODEL

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Background: Due to the heterogeneous nature of schizophrenia, finding relevant animal models challenges all stages of drug development. These challenges in translation may contribute to the high failure rate of treatments that showed promise in pre-clinical testing. To counteract these outcomes, researchers and clinicians have suggested stratifying patients based on peripheral markers. Therefore, there may be a need to characterise central and peripheral markers in models relevant to cognitive impairment associated with schizophrenia (CIAS). The subchronic phencyclidine (scPCP) model induces sustained cognitive and pathological deficits. Previous studies of NMDA receptor antagonist models have identified increased inflammation and oxidative stress, which may contribute to the observed synaptic and GABAergic pathologies in the models linked to CIAS. Here we aimed to characterise the effect of scPCP-dosing on synaptic and GABAergic markers and levels of central and peripheral inflammation and oxidative stress. We also assessed the impact of minocycline and apocynin, an antibiotic/anti-inflammatory and an antioxidant, on behaviour and pathology.

Methods: 60 female Lister Hooded rats were dosed bi-daily for 7 days with PCP (2 mg/Kg, i.p.; n=50) or saline (n=10). After a washout week, 40 scPCP-treated animals were dosed for 7 days with apocynin (10 mg/Kg, i.p., n=20), or minocycline (40 mg/Kg, p.o., n=20). The remaining scPCP-treated (PV) and the scVehicle (VV) groups were dosed with vehicle (i.p.; n=10 each). One day after treatment cessation, the novel object recognition (NOR) task was used to assess cognition. The VV, PV, and half of the scPCP/minocycline (PM7) and scPCP/apocynin (PA7) (n=10 per group) were culled immediately after NOR testing. The remaining animals underwent a further washout week, tested with NOR and culled (scPCP/minocycline and apocynin with 1 week washout = PM14 and PA14, respectively). The discrimination index (DI) was calculated from exploration times in the NOR test to provide a ratio of time spent at the novel compared to the familiar object. Markers relevant to synaptic (SNAP-25 and PSD-95) and GABAergic (parvalbumin and GAD67) function were measured using simple western analysis (WES) in the prefrontal cortex (PFC) and dorsal hippocampus (DH). Levels of lipid peroxidation (MDA assay) were measured in the DH, whereas superoxide dismutase (SOD) activity and interleukin-6 (IL-6) were measured in the DH and plasma to assess levels of oxidative stress and inflammation. Normally distributed data were assessed with one-way ANOVA with Tukey or Dunnett post hoc tests. Non-parametric data was assessed with a Kruskal Wallis test followed by pairwise comparisons. For correlations, Spearman's bivariate coefficient was used.

Results: scPCP dosing causes a cognitive deficit in the NOR test compared to VV animals ($p=0.034$). 7 days of apocynin or minocycline reversed the cognitive deficit (PA7: $p=0.002$, PM7: $p=0.007$, pc). However, after a 1-week washout, PA14 had a significantly reduced DI compared to PA7 ($p=0.003$) and PM14 trended towards a decrease compared to PM7 ($p=0.058$). In both the PFC and the DH, scPCP treatment reduced SNAP-25 levels compared to VV ($p<0.05$). PV, PA7 and PA14 decreased PSD-95 levels in the PFC relative to VV ($p=0.010$, $p=0.005$, $p=0.003$, respectively). The PFC parvalbumin levels reflected behavioural observations; PV reduced parvalbumin compared to VV ($p=0.002$). Interestingly, the parvalbumin increased in the PM7 group from PV levels ($p=0.045$) and remained increased, though not significantly in PM14 ($p=0.100$). In apocynin-treated groups, there was an initial increase in PA7 compared to PV ($p=0.006$); however, the PA14 groups did not sustain this increase. scPCP reduced PFC and DH GAD67 ($p<0.05$), although, in the PFC, there were insignificant trend towards a recovery in PA7 and PM7. There was no treatment effect on MDA concentration; however, there was a negative correlation between DI and MDA concentration in the PV only, indicating lipid peroxidation is a predictor NOR performance. SOD activity and IL6 assays for brain and plasma are ongoing.

Discussion: This study indicates that cognitive deficits in the scPCP model can be alleviated by 7-day treatment with minocycline and apocynin. This may be mediated by changes to predominately PFC markers for GABAergic function. However, this improvement is not sustained after a washout period. Further studies are required to understand the mechanisms for the sustained pathology of the scPCP model and the necessary intervention to reverse deficits substantially.

86. EFFECT OF A REMOTE ADAPTED PHYSICAL ACTIVITY PROGRAM (E-APA) ON HIPPOCAMPI IN PATIENTS WITH SCHIZOPHRENIA

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Background: Physical activity (PA) in patients with schizophrenia (SZPs) has emerged as an interesting adjuvant non-pharmacological intervention in schizophrenia. At the same time, PA could reverse the reduction of hippocampus (HCP) volume reported in patients with schizophrenia. However, most PA programs do not consider patients' physiological capacities and their achievements are difficult due to the low level of patients' motivation. Thus, we propose on one hand to investigate a new kind of PA adapted to the cardiorespiratory capacities and delivered by a videoconference coach (e-APA) and on the other hand to test its impact on hippocamus volumes in SZPs after a 16-week program.
Methods: Thirty-five SZPs (DSM-5) were randomized either in the e-APA group or in a control group (following health education training- (e-HE)) and received both programs in the same condition with two 60-minute sessions per week during 16-week with a total of 32 sessions. High-resolution T1-weighted brain volume in the sagittal plane and two high-resolution oblique coronal T2w brain volumes aligned orthogonally to the main axis of the left HCP were proceeded in pre- and post-intervention (MRI 3-T, Philips). The final population per protocol for imaging analyses was 15 SZPs-APA vs. 14 SZPs-HE. Cardiorespiratory capacity measured by VO2max was evaluated in pre- and post-intervention, as well as the total HCP volumes (left and right) and their subfields with Automatic Segmentation of Hippocampus Subfields software (ASHS). Analyses of covariance were performed to determine intervention and/or diagnostic effects on relative variation (RV) of aerobic fitness and HCP volumes.
Results: The retention rate was 89.6%. SZPs of e-APA group presented a greater RV of VO2max compared to SPZs-HE ($p < 0.05$). The most relevant result revealed a positive and greater RV of the left subiculum volume of +3.4% in SZPs-APA in comparison with SZPs-HE (-2.5%) ($p = 0.0005$).
Discussion: This study is the first one demonstrating the feasibility and acceptability of a remote APA program and its impact on the volume of the left subiculum in SZPs. This result suggests that this non-pharmacological approach could increase the brain plasticity and support its benefits as an add treatment in schizophrenia. Further studies are necessary to better understand the cerebral mechanisms underlying the APA effects.

87. RESTING-STATE FUNCTIONAL HYPOCONNECTIVITY OF POSTERIOR-LATERAL SUBDIVISIONS OF THE BASAL FOREBRAIN CHOLINERGIC NUCLEI IN PATIENTS WITH SCHIZOPHRENIA

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Background: The cholinergic system has recently drawn increasing attention as a potential treatment target for schizophrenia. Consistent evidence, ranging from molecular imaging to pharmacological interventions, indicates that the cholinergic system is altered in patients with schizophrenia. Furthermore, in vivo structural neuroimaging studies have shown that the basal forebrain cholinergic nuclei (BFCN), the main source of cholinergic innervation to the cortex, are also altered in schizophrenia. Specifically, lower BFCN volumes have been observed in patients compared to healthy controls, and patients' lower volumes mediated attentional deficits. Beyond structural alterations, it remains to be determined whether the BFCN also show functional alterations in patients with schizophrenia. Potential alterations can be examined with functional connectivity (FC) derived from resting-state functional magnetic resonance imaging (rs-fMRI) data. Notably, FC findings in healthy participants indicate that the BFCN are functionally organized into distinct anterior-medial (aBFCN) and posterior-lateral (pBFCN) subdivisions. The aBFCN were characterized by connectivity with the hippocampus, ventromedial prefrontal cortex and posterior cingulate cortex, whereas the pBFCN showed more pronounced connectivity with the insula, dorsal anterior cingulate cortex, and thalamus—in line with the expected functional topography. In this study, we aimed to investigate the FC of the BFCN in patients with schizophrenia and evaluate possible alterations in the functional topography of these regions compared to healthy controls.

Methods: We examined differences in the FC profiles of the aBFCN and pBFCN with the whole brain between healthy controls (N=73; M(age)=38.6; female=27.4%) and schizophrenia patients (N=51; M(age)=35.2; female=15.7%) using seed-based functional connectivity analysis. Data were derived from the COBRE open-source database. Using second-level one-sample t-tests in SPM12, we calculated initial cluster-to-voxel FC maps for each group and seed separately. We quantified group differences with two-sample t-tests. For both analyses, age and gender were included as covariates of no interest. To control for potential influences of smoking, anticholinergic burden scores (ACB) and chlorpromazine equivalent doses of antipsychotic medication (CPZ), we performed several control analyses.

Results: Cluster-to-voxel FC profiles of healthy controls matched previously characterized FC maps of the aBFCN and pBFCN in healthy subjects. Differences in cluster-to-voxel FC between healthy controls and schizophrenia patients emerged only for the pBFCN seed (p(FWE)=0.011, kE=38), with patients showing decreased FC with regions covering the right insula and dorsolateral prefrontal cortex. This effect was independent of sex and age. Control analyses revealed no significant correlations between altered pBFCN FC profiles, smoking, ACB scores, and CPZ doses.

Discussion: To the best of our knowledge this is the first study that investigated the FC of the BFCN in patients with schizophrenia. We demonstrate that 1) FC can be used to study BFCN function, as we replicated previously reported FC profiles of the aBFCN and pBFCN in healthy subjects, and 2) alterations in FC of the pBFCN exist in schizophrenia patients. Intriguingly, we found reduced FC between the nucleus basalis Meynert and a cluster covering the insula, which are in line with the functional topography of these regions. This data adds a functional level to previous structural findings of a dysregulated cholinergic system in patients with

schizophrenia. Complementary to lower BFCN volumes, the FC of the BFCN is also altered in patients with schizophrenia, which enhances its potential as a treatment target.

Oral Sessions: Treatment Directions in Schizophrenia

88. REAL-WORLD OUTCOMES AND PRACTICE PATTERNS FOR LONG-ACTING INJECTABLE VS. ORAL ANTIPSYCHOTIC AGENTS AMONG HOSPITALIZED PATIENTS WITH SCHIZOPHRENIA IN THE UNITED STATES

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Background: Treatment options for schizophrenia include oral antipsychotic agents (OAs) and long-acting injectable antipsychotic agents (LAIs). Previous studies have reported that patients taking LAIs have a lower probability of relapse and re-hospitalization; however, a greater proportion of patients are prescribed OAs than LAIs. LAI use early in the treatment journey, when the course of disease is more easily modified, could potentially lead to better outcomes. Here, we explore the overall re-hospitalization rates between patients discharged from a schizophrenia-related hospitalization taking LAIs vs OAs.

Methods: The study included adults in the Premier Hospital Database (a US hospital-based, service-level, all-payer database containing records collected for billing purposes at the hospital level) with a schizophrenia-related hospitalization between December 2019 and June 2021 who were prescribed LAIs or OAs at discharge. The date of the first schizophrenia-related hospitalization during the study period is defined as the index date. Prescribing patterns and re-hospitalization risk were analyzed during the ≥3-month pre- and post-index periods.

Results: Of the 27,629 patients analyzed, 23,336 (84%) were prescribed OAs at discharge vs 4293 (16%) prescribed LAIs. Of the patients prescribed LAIs at discharge, 1,303 (30%) were prescribed atypical LAIs vs 2,990 (70%) prescribed typical LAIs. The most common OA prescribed at discharge was risperidone (26%), and the most common LAI prescribed at discharge was haloperidol (haloperidol LAI + haloperidol OA, 37%; haloperidol LAI only, 7%). Patients prescribed OAs at discharge had an average length of hospital stay of 11 days vs 18 days for those prescribed LAIs. There was a significantly greater proportion of patients with re-hospitalizations within 30, 60, and 90 days when prescribed OAs at discharge (11%, 15%, and 18%, respectively) vs LAIs (8%, P<.0001; 12%, P<.0001; 15%, P<.0001), and when prescribed typical LAIs at discharge (9%, 13%, and 16%, respectively) vs atypical LAIs (7%, P=.012; 10%, P=.004; 13%, P=.004). Compared with patients prescribed OAs at discharge, patients prescribed LAIs had 18%, 14%, and 10% reduced risk of re-hospitalization within 30, 60, and 90 days, respectively; patients prescribed atypical LAIs at discharge had 35%, 32%, and 26% reduced risk of re-hospitalization within 30, 60, and 90 days.

Discussion: Most patients with schizophrenia-related hospitalizations were prescribed OAs at discharge. However, patients prescribed OAs at discharge had significantly more re-hospitalizations than those prescribed LAIs. Of those prescribed an LAI at discharge, most were prescribed a typical LAI. Patients prescribed an atypical LAI had the lowest risk of re-hospitalization. These results suggest that prescribing an atypical LAI at discharge may result

in lower relapse/re-hospitalization rates for patients with schizophrenia; however, OAs and typical LAIs were prescribed more often than atypical LAIs.

89. LONG-TERM EFFICACY AND SAFETY OF PALIPERIDONE 6-MONTH FORMULATION: AN OPEN-LABEL EXTENSION OF A DOUBLE-BLIND STUDY IN ADULT PATIENTS WITH SCHIZOPHRENIA

Dean Najarian[1], Ibrahim Turkoz[2], Silvana Galderisi[3], Hector F. Lamaison[4], Piotr Zalitacz[5], Suresh Aravind[2], Ute Richarz[6], Ute Richarz*[7]

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Background: Long-acting injectable (LAI) paliperidone palmitate 6-month (PP6M), administered twice yearly, demonstrated non-inferiority to paliperidone palmitate 3-month (PP3M) in preventing relapse in patients with schizophrenia in a phase 3 randomized, double-blind (DB) global study.1 We report results of a 2-year single-arm, open-label extension (OLE) of this study (NCT04072575). The objective of this OLE study was to assess the long-term efficacy and safety of PP6M in patients with schizophrenia.
Methods: Patients who completed the DB study without relapse were enrolled and followed up every 3 months for up to 2 years. Patients received 4 PP6M injections (700/1000 mg eq.) at baseline, 6-month, 12-month, and 18-month visits. Efficacy endpoints included relapse rate, Positive and Negative Syndrome Scale (PANSS) total score, Personal and Social Performance (PSP) score, and Clinical Global Impression-Severity (CGI-S) scale change from baseline. Safety was assessed by treatment-emergent adverse events (TEAEs), physical examinations, and laboratory tests.
Results: Of 178 patients, 154 (86.5%) completed the study. The mean age of patients was 40.4 years and 70.8% were men. The mean duration of PP6M exposure was 682.1 days. Overall, 7/178 (3.9%) patients relapsed between 20 to 703 days after enrolment. Mean (SD) change from baseline to endpoint: PANSS total score, 0.7 (8.22); CGI-S, 0.0 (0.51); PSP Scale, 0.5 (7.47). Overall, 111/178 patients (62.4%) reported ≥1 TEAE; the most common (>10%) TEAEs were headaches (13.5%) and blood prolactin increased (10.7%). A total of 7/24 patients withdrew due to TEAEs, and 8/178 (4.5%) patients experienced serious TEAEs. No deaths were reported during this study.
Discussion: The relapse rate with LAI PP6M, administered twice-yearly, was very low (<4%). Clinical improvements in PANSS, CGI-S, and PSP scales demonstrated in the DB study were maintained during this 2-year OLE study and no new safety concerns were identified.

90. HEARING LOSS IN SCHIZOPHRENIA: FEASIBILITY, RELIABILITY, AND CLINICAL UTILITY OF SHOEBOX AUDIOMETRY

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Background: Hearing loss (HL) is a potentially disabling condition that has a significant impact on psychological, cognitive, and social functioning in older adults. Recent research using age-based epidemiological data suggests a higher prevalence of HL in adults with schizophrenia than expected, calling attention to the need for further investigation. While a

thorough audiometric assessment is the benchmark for diagnosis of HL, multiple barriers may impact access to assessment and treatment. In community settings where traditional clinical audiometry is not available or impractical, the Shoebox portable audiometry system may serve as a valuable alternative. This study assessed for HL in older adults with schizophrenia spectrum disorders and evaluated the feasibility, reliability and clinical utility of the Shoebox tool in community settings.

Methods: Participants ages 50-70 with a schizophrenia spectrum diagnosis were recruited from 4 community-based behavioral health facilities in the New York City metro area. Participants were screened for HL using the Hearing Handicap Inventory for the Elderly Screening Version (HHIE-S) and underwent audiometry with the Shoebox device - the first clinically validated portable iPad audiometer. Equipment includes an iPad with a built-in sound level meter and RadioEar DD450 headphones. Hearing ability was measured for the left and right ear at 500, 1000, 2000, 4000 Hz, and 8000 Hz stimuli. A pure tone average (PTA) was calculated from frequencies 500, 1000, 2000, and 4000 Hz. Hearing threshold (dB) was characterized by the better ear PTA (dB) and HL classified by severity, where ≤25 dB was considered normal. All testing was done in a quiet room with ambient sound <45 dB. Several participants were assessed with Shoebox audiometry a second time to measure reliability.

Results: The mean (SD) age of the sample (N=41) was 59.98 (5.72) years, 63.4% (n = 26) were male, and most self-identified as non-Hispanic/non-Latinx (80.5%, n=33). 97.6% of participants were able to fully complete an audiologic assessment using the Shoebox tool. Completed audiometry assessments (N=40) yielded a mean (SD) audiometric threshold of 24.48 dB (12.66). Of the participants ages 50-59, 30.4% had HL and of the participants ages 60-70, 41.2% had HL. In contrast, 17.1% self-reported any hearing handicap. Pure tone audiometry retest with 11 participants yielded large Pearson's correlation coefficients for left ($r=.96$, $p < 0.01$) and right ($r=.93$, $p < 0.01$) ears indicating high test-retest reliability. Classification of HL severity was highly consistent (Cronbach's alpha =.94) from test to retest.

Discussion: With the aim of improving routine screening and treatment, this study addresses the complex auditory needs of people with schizophrenia in community settings. In this sample of people aged 50 to 70, 29.1% to 41.2% had some hearing difficulty, compared with 13.6% to 26.8% of people aged 45 to 65 in the general population. These results replicate the finding of poorer hearing ability in people diagnosed with schizophrenia, highlighting the need for assessment and treatment in clinical practice. In this study, high test-retest reliability of pure tone audiometry demonstrated the audiometer's relative accuracy in detecting HL in people with schizophrenia while full assessment completion rate >95% indicated the audiometers are not only convenient but also feasible for use in community settings. Further, audiometry assessment yielded clinically useful data not captured by self-report alone. In such environments where audiology services are not readily available, this type of testing is essential for providing appropriate hearing health services to high-risk populations.

91. BEHAVIORAL AND MOLECULAR CHARACTERIZATION OF A NOVEL MOUSE MODEL OF HERV-W ENVELOPE PROTEIN EXPRESSION

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Background: Human endogenous retroviruses (HERVs) are viral genetic elements embedded in the genome throughout evolution that are derived from exogenous retroviruses. Increasing evidence has implicated elevated expression of HERV type W envelope (HERV-W env) in psychotic disorders, including schizophrenia. However, the link between increased HERV-W

env expression and psychotic disorders is mostly based on correlative evidence1. To gain mechanistic insights into the neurobiological disease pathways affected by HERV-W env expression, we generated and characterised a novel mouse model mimicking the transgenic expression of HERV-W env.

Methods: Mice with transgenic HERV-W env expression were generated by inserting the multiple sclerosis-derived retrovirus (MSRV)-pv14env sequence, featuring the HERV-W env open reading frame (ORF) and the 3' long terminal repeat (3'LTR) under the CAG promoter, into the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus. Adult male transgenic (TG) mice and wild-type (WT) littermates were subjected to behavioral and cognitive phenotyping. Next-generation RNA sequencing of hippocampal tissue was used to identify genome-wide transcriptional changes in TG mice relative to WT controls. Ingenuity pathway analysis (IPA) was used to explore the molecular signaling pathways affected by HERV-W env expression. Further post-mortem analyses using western blotting were used to establish methylation levels in the hippocampus. RT-PCR was used to profile the expression of genes involved in epigenetic regulation.

Results: Ubiquitous expression of HERV-W ENV protein was verified in TG mice relative to WT, including brain tissue. Compared to WT controls, TG mice displayed a number of behavioral and cognitive anomalies, including increased locomotor activity, impairments in social recognition memory and novel object recognition, and deficits in prepulse inhibition (PPI) of the acoustic startle reflex. Using a false discovery rate (FDR) threshold of 10% ($q < 0.1$), we found 199 genes dysregulated in the hippocampus of TG mice relative to WT controls. Functional network prediction using IPA further demonstrated that the differentially expressed genes were annotated with the functional nodes "neurodevelopmental disorders" and "schizophrenia", as several of the dysregulated genes have been previously identified as genetic risk variants for schizophrenia and other psychotic disorders, including Ank3, Cacna1a, Cacna1g, Shank1, Shank3, and Setdb1a. Setdb1a encodes a protein of a histone methyltransferase complex that produces methylation of histone H3 at Lys4 (H3K4). Interestingly, we found a decrease in overall methylation levels in 12-day gestation fetuses and young animals, whereas overall methylation was increased in adult TG mice compared to controls. More specifically, H3K4-Dimethylation was decreased in young, and increased in adult TG animals. Expression of epigenetic genes involved in transcriptional activity, such as MEF2c, WDR82, LSD1, KMT2A, and KMT2D, was significantly reduced in adult hippocampal tissue.

Discussion: Our preclinical data provide causal evidence for the role of HERV-W env expression in disrupting behavioral and cognitive functions implicated in schizophrenia. Moreover, our findings demonstrate that the expression of this retroviral element has the capacity to change the brain transcriptome and cause a deregulated expression of genes associated with schizophrenia and other psychiatric disorders with neurodevelopmental components. In particular, the downregulation of SETD1a could explain the abnormal methylation patterns observed in TG animals. Future studies will explore whether the inhibition of the SETD1a counter-acting enzyme LSD1 at a young age can potentially correct the overall methylation changes and the emergence of the behavioral phenotype.

92. SAFETY AND EFFICACY OF KARXT (XANOMELINE–TROSPIUM) IN SCHIZOPHRENIA: RESULTS FROM THE PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER EMERGENT-3 TRIAL

Carol Tamminga*[1], Inder Kaul[2], Sharon Sawchak[2], Andrew C. Miller[2], Stephen K. Brannan[2], Steven M. Paul[2]

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Background: A high unmet medical need exists for more effective, better tolerated treatments for schizophrenia with novel mechanisms of action. All currently approved treatments for schizophrenia have D2 dopamine receptor blocking activity; the efficacy and tolerability limitations of these therapies are well known. KarXT combines the M1/M4 preferring muscarinic receptor agonist xanomeline and the peripherally restricted muscarinic receptor antagonist trospium. KarXT is designed to preserve the beneficial central nervous system effects of xanomeline while mitigating the cholinergic adverse events due to peripheral muscarinic receptor activation. In the 5-week, randomized, double-blind, placebo-controlled EMERGENT-1 (NCT03697252) and EMERGENT-2 (NCT04659161) studies, KarXT demonstrated a statistically significant and clinically meaningful improvement in Positive and Negative Syndrome Scale (PANSS) total score versus placebo starting at week 2, which was maintained at all time points in the study. KarXT also met tested secondary endpoints, demonstrating a significant reduction in both positive and negative symptoms of schizophrenia. KarXT was generally well tolerated in EMERGENT-1 and EMERGENT-2. The most common treatment-emergent adverse events were all mild to moderate in severity and mostly cholinergic in nature. KarXT was not associated with common problematic side effects of currently available antipsychotics, including extrapyramidal/motor symptoms, weight gain, or somnolence/sedation.

Methods: EMERGENT-3 (NCT04738123) is a phase 3, randomized, double-blind, placebo-controlled, multicenter, 5-week trial of KarXT in acutely psychotic individuals with schizophrenia in the inpatient setting. Key inclusion criteria included DSM-5 schizophrenia, age 18-65 years, recent worsening of positive symptoms warranting hospitalization, a PANSS total score 80-120, and a Clinical Global Impression–Severity score of ≥4 (moderately ill). Eligible individuals were randomized 1:1 to KarXT or matched placebo. Dosing of KarXT (mg xanomeline/mg trospium) started at 50 mg/20 mg BID and increased to a maximum of 125 mg/30 mg BID. The primary efficacy endpoint was change from baseline to week 5 in PANSS total score. Secondary endpoints were change from baseline to week 5 in PANSS positive subscale score, PANSS negative subscale score, and PANSS Marder negative factor subscale score vs placebo. Participants completing the EMERGENT-3 study will have the option of rolling over into the long-term, open-label, EMERGENT-4 (NCT04659174) study in which all participants will receive KarXT. All participants who were randomized, received ≥1 dose of study drug, had a baseline PANSS assessment, and had ≥1 postbaseline PANSS assessment will be included in the modified intent-to-treat population and efficacy analysis. All participants receiving ≥1 dose of study drug will be included in the safety population and safety analysis. Analyses will account for multiplicity by using a fixed sequence testing procedure.

Results: A total of 256 individuals at 29 US and Ukraine study sites were enrolled. Study data are being analyzed and will be available at the time of the meeting. Baseline demographics, the results from primary and secondary efficacy outcomes, and the safety and tolerability of KarXT will be presented.

Discussion: KarXT has the potential to be the first in a new class of treatments for individuals with schizophrenia based on muscarinic receptor agonism and a promising alternative to direct dopamine D2 receptor antagonists.

93. LAYER SPECIFIC DENDRITIC SPINE AND PROTEOME ALTERATIONS IN THE PRIMARY AUDITORY CORTEX OF SCHIZOPHRENIA

Daley Favo Auvil[1], Cassandra Happe[1], Zhiyu Sui[1], David Lewis[1], Ying Ding[1], Robert Sweet[1], Matthew MacDonald*[1]

[1]University of Pittsburgh

Background: Reduced cortical layer 3 dendritic spine density has been reproducibly observed in multiple brain areas, including the primary auditory cortex (A1) in schizophrenia (Sz) and is believed to underlie deficits in cortical processing. Dendritic spine plasticity is regulated by synaptic protein networks and a significant number of Sz genetic risk loci are associated with genes that code for postsynaptic proteins. However, dendritic spines have not been systematically investigated in other cortical layers and alterations in the expression of postsynaptic proteins in cortical tissue from patients has not been consistently observed. For example, in a recent study we observed decreased levels of mitochondrial proteins, but not canonical postsynaptic proteins, in primary auditory cortex homogenates from Sz and matched control subjects. Each cortical layer is composed of distinct cell populations with differing connectivity. Here we sought to answer three questions 1: Are dendric spine numbers decreased in A1 layer 5; 2. Are mitochondrial protein alterations ubiquitous across cortical layers, and 3: Are alterations in the expression of canonical postsynaptic proteins in Sz "hiding" in the layers in which dendritic spines are decreased (e.g. layer 3). To answer these questions, we utilized multiple label confocal microscopy to quantify dendritic spine density and size in A1 layer 5 and laser capture microdissection – quantitative mass spectrometry (LCM-MS) to quantify 2,762 proteins in primary auditory cortex layers 3 and 5 from 40 pairs of Sz and matched control subjects in which we had previously assayed A1 layer 3 spines.

Methods: Frozen auditory cortex tissue from 40 pairs of Sz and matched control subjects was obtained from the University of Pittsburgh NeuroBioBank. The left hemisphere was utilized in microscopy studies to assess deep layer 3 spine density and volume. Presumptive spine objects were identified by the colocalization of Spinophilin and F actin, and spine size estimated by F actin volume. The right hemisphere was utilized for LCM-MS. 12 μM thick tissue sections were cut and 4.5E6 μM2 of layer 3 and layer 5 collected by LCM. Tissue from pairs was kept together throughout all processing steps, utilizing a randomized block design. Protein was extracted from each layer, digested with trypsin, and TMT labeled. Pooled TMT labeled peptide digests were quantified on an Eclipse Tribrid Mass Spectrometer utilizing Realtime search and synchronous precursor selection. Database search and TMT reporter ion quantification was conducted with Proteome Discover (FDR < 0.05). Normalization across TMT batches and protein level calculations were done in MSStats and case control comparisons in Limma-Voom. WGCNA was used to reduce dimensionality of the data.

Results: The density of smaller dendritic spines was decreased in A1 layer 5 of Sz subjects compared to unaffected controls ($p = 2.4e-5$). 2762 proteins were quantified with > 60% present call across both layers in all subjects. Of these, 250 differed significantly between Sz and control in layer 3 and 107 differed in layer 5 ($q > 0.05$). Levels of canonical postsynaptic proteins did not differ between Sz and control in either layer. WGCNA identified 16 coregulation modules. Eigenvalues for one module, enriched for mitochondrial proteins, differed between Sz and controls in layer 3 (adjusted $p = 0.035$) but not 5, and were not correlated with spine density. Eigenvalues for a second module, enriched for blood microparticle and acute inflammatory response proteins was increased in Sz subjects in both layers 3 and 5 (adjusted $p = 3e-7$ and $7e-6$) and correlated with small spine density in both layers (adjusted $p = 0.08$ and 0.01).

Discussion: Decreased mitochondrial protein levels are localized to layer 3, suggesting that mitochondrial impairments are not cell autonomous in Sz and maybe downstream of decreased local activity in layer 3. Furthermore, that the expression of canonical postsynaptic proteins was not decreased suggests that these proteins are relocated, not lost, as dendritic spine density decreases in Sz. Finally, that blood microparticle and inflammatory proteins were correlated with spine loss suggests that inflammation drives spine loss in Sz in adults.

Poster Session I

12:00 p.m. – 2:00 p.m.

F1. DAILY MOOD VARIABILITY IN INDIVIDUALS WITH SCHIZOPHRENIA

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Background: This project addresses daily mood variability in individuals with schizophrenia. There has been growing research on trying to capture daily experiences in individuals with schizophrenia (SCZ) and try to understand how mood is being expressed in this population. However, there is little research on seeing whether SCZ mood varies within day to day compared to healthy controls. We will use ecological monetary assessment (EMA) to look at mood variability within day to day. The purpose of the study is to investigate whether individuals with schizophrenia are having more varied mood within day compared to healthy controls, this will help us understand how mood is impacting individuals with schizophrenia daily functioning.

Methods: Included in the study were a total 24 healthy control (HC) participants and 23 people with schizophrenia (SZ). The study design will be a survey- based quantitative data using ecological momentary assessment (EMA). Six signals were sent at random intervals between the time they usually wake up and one hour before the time they usually go to bed for six days. At each timepoint, participants were asked to report on their activity, emotion, and enjoyment, at the present moment, for the past several hours, and their prediction for the next several hours.

Results: To assess whether SZ and HC report differences in daily average mood a hierarchical linear model was conducted. There were three different mood indexes: Positive Average Mood index, Negative Average Mood Index and Internalized Average Mood Index. A hierarchical linear model regression was conducted to test the predictions. Having the mood indexes as a dependent variable and time, diagnosis, age, sex and IQ as covariant. Overall, when we are looking at positive average mood model results it showed no significance $b = 0.04$, $t = 1.40$, $p < .17$. In the negative mood index model the results also showed no significance, $b = -2.55e$, $t = 0.00$, $p < 1.0$. Lastly, results: showed no significance for the internalized average mood model, $b = -9.66e$, $t = 0.00$, $p < 1.0$.

Discussion: Our results show that individuals with SCZ show similar emotional experiences as HC's. There have been confounding results in the literature, these findings are similar to other studies showing no significant differences between mood and healthy controls (Cohen and Minor 2010, Kring and Moran 2008). However, there are other studies indicating that individuals experience more negative mood than HC's (Myin-Germeys, et al., 2000, Cho, et al., 2017). We predicted we would show differences due to having multiple within day mood responses and having more sensitivity capturing that daily mood variability compared to other studies. However, our SCZ sample seems to not show significantly different mood experience to healthy controls. This could be due to the small sample size, not enough differing mood items, not enough observations measured.

F2. PRELIMINARY ANALYSIS OF THE CHAMPION CLOZAPINE TREATMENT CONSULTATION CENTER

Gopal Vyas*[1], Matthew Glassman[1], Ikwunga Wonodi[2], Gloria Reeves[3], Charles M. Richardson[1], Heidi J. Wehring[3], Marie Mackowick[4], Robert W. Buchanan[1], Elaine Weiner[5], Fang Liu[1], AnnMarie Kearns[1], Heather A. Adams[1], Raymond C. Love[6], Sophie Lanzkron[7], Brian Barr[3], Megan Ehret[6], Erica Davis[6], Frederick Nucifora[7], Jared Hunt[1], Emily Bryant[1], Nicole Letvin[6], Nicole Leistikow[3], Sharon Pugh[5], Patricia Ball[1], Julie Kreyenbuhl[3], Deanna L. Kelly[1]

[1]Maryland Psychiatric Research Center, University of Maryland School of Medicine, [2]Sheppard Pratt's Hospital, [3]University of Maryland School of Medicine, [4]Clifton T. Perkins Hospital Center, [5]University of Maryland School of Medicine, Maryland Psychiatric Research Center, Outpatient Research Program, [6]University of Maryland School of Pharmacy, [7]Johns Hopkins School of Medicine

Background: Clozapine is an underused antipsychotic for the treatment of schizophrenia related disorders. Breaking barriers and improving use could be important to improve patient outcomes. 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 which among many benefits included the Athelas Home point of care (POC) device to reduce logistical issues with Absolute Neutrophil Count (ANC) monitoring and a Clozapine Consultation Center (CCC) was created free of charge. Here we present a preliminary analysis of the first 2 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 mentions on all 26 of the educational sessions for those assigned to the educational program. Though not strongly 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 has received a total of 46 requests for consultation from 35 different providers (27 prescribers, 8 non-prescribers). Forty-three were from CHAMPION-ECHO participating sites and three were from providers outside the CHAMPION-ECHO project. Most requests were received via email (91%). Forty-two of the 46 requests resulted in recommendations directly from the CHAMPION team (six) or were triaged for consultation from an expert (36). Most consultation requests received responses from the CHAMPION team within 24 hours (89%). 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 (47%) and via phone (53%).
Discussion: Breaking down barriers to clozapine underuse is important. Improving educational gaps as well as logistical concerns with blood draws and continuity of care are under study with the CHAMPION ECHO project. We have found that assistance with questions and consultations, mainly from prescribers, are an important way to assist with a variety of questions and can be done in a lower cost environment through virtual calls and sharing of consultations.

F3. LINGUISTIC MARKERS OF PSYCHOSIS IN MANDARIN CHINESE: RELATIONS TO THEORY OF MIND

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Background: Disorganized and impoverished language is a key feature of schizophrenia (Sz) but the generalizability of linguistic changes modelled on Indo-European languages remains unknown. Embedded clauses (e.g. 'he is upset' in 'She thinks he is upset') form a specific dimension of interest. Since their content is meta-representational, their production may index well-known theory of mind (ToM) impairments in Sz, creating a link between language and ToM. Here, we aimed to profile selected aspects of grammatical complexity in Mandarin Chinese Sz using spontaneous speech generated as part of a standardized ToM task.
Methods: 51 individuals with Sz and 39 healthy controls described the movements of triangles in the animated triangles task, where triangles are observed to move either randomly or else in an apparently intentional way. Our annotation scheme targeted embedded clauses (both argument and adjunct clauses), Aspect (progressive and completeness), and non-clausal adjuncts (action modifiers, VP-attached adjuncts, and epistemic adverbials).
Results: Both groups produced significantly more embedded argument clauses in the intentional than in the random condition, while the control group produced more such clauses than the Sz group in general. Both groups also produced more Aspect markers in the intentional condition. There was a main effect of reduction in adjuncts at both clausal and non-clausal levels in Sz. Correlational analyses suggested that standardized scores of two ToM tasks were significantly correlated with production of embedded clauses, but not with any other linguistic variables. Moreover, several sparse associations were found between linguistic measures and neuropsychological metrics including verbal working, working memory, motor speed, speech fluency, attention and executive functions, as well as clinical ratings of symptoms.
Discussion: These results document grammatical impoverishment in Sz across several structural domains, for the first time in Chinese. While the evidence supports a relation between specific aspects of grammar and mentalizing, it also suggests that the impoverishment in question is partially independent of a mentalizing difficulty.

F4. BEHAVIORAL APPROACH AND AVOIDANCE IN SCHIZOPHRENIA

Natália Čavojská*[1], Vladimír Ivančík[1], Jakub Januška[1], Alexandra Straková[1], Daniel Dančík[1], Jakub Kraus[1], Jakub Szabó[1], Anton Heretik[1], Vanda Valkučáková[1], Ján Pečeňák[1], Michal Hajdúk[1]

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Background: Interpersonal distance is an important part of nonverbal communication. Physical space between individuals during social interaction describes boundaries of intimacy and has a protective function. Some studies showed that individuals with schizophrenia tend to maintain greater distance during social interaction and greater interpersonal space is often associated with more severe negative symptoms. The present study has two aims: 1) to evaluate preferred distance and pleasantness of approach vs avoidance situation in individuals with schizophrenia, and 2) to evaluate associations of preferred distance and pleasantness with symptom severity.

Methods: The sample consisted of 32 patients (56 % females) diagnosed with schizophrenia (age M = 42.97 and SD = 8.42 years). Participants were asked to perform two versions of the Behavioral Approach Task with the same-sex researcher. During the approach condition, participants were asked to approach the researcher standing 5 m from them and stop at a distance, that is still considered comfortable. In the avoidance condition, the researcher slowly moved toward the participant who had to stop him/her at a comfortable distance. Participants rated how pleasant each condition was. Psychopathology symptoms were measured using the Brief Psychiatric Rating Scale and Community Assessment of Psychic Functioning (CAPE - 42). Wilcoxon's signed-rank test was used to compare distance and pleasantness across conditions. Spearman correlation was used to estimate the strength of associations.

Results: Participants preferred a significantly smaller distance when approaching, compared to being approached by the researcher (avoidance) (1.18 m vs 1.37 m, W = 120, p = .007, r = -.545). Subjective ratings of how comfortable participants felt during each condition significantly differed with the approach version rated as more pleasant than avoidance (W = 216.5, p = .004, r = .711). Patients with more severe negative symptoms measured by BPRS considered the approach condition as less pleasant (r = -.381, p = .032). No other associations with clinician-rated symptoms were found. Using CAPE-42, we found that pleasantness in the approach condition was associated with both positive (r = -.366, p = .039) and negative symptoms (r = -.462, p = .008). In avoidance condition, pleasantness correlated with positive (r = -.497, p = .004), negative (r = -.423, p = .016), and depressive (r = -.458, p = .008) symptoms.

Discussion: Our results showed that symptom severity measured by BPRS was unrelated to objective measures of interpersonal distances in both approach and avoidance conditions. This contradicts previous findings, that both positive and negative symptoms are linked to objective interpersonal distance. Furthermore, we found consistent associations between self-report measures of positive and negative symptoms to perceived pleasantness across approach and avoidance behavior. We suppose that social anhedonia and paranoia might independently add to the feelings of discomfort in social situations. When patients were able to regulate their preferred interpersonal distance, in approach condition, they preferred shorter distances and perceived the situation as more pleasant. Patients being approached led to higher distress in comparison to the condition when the patients initiated social contact. A lack of a control group prohibits the comparison of the preferable distance to healthy controls. However, the data from healthy controls will be collected in the next part of the research project.

F5. EFFECTS OF VISUAL REMEDIATION ON SENSITIVITY TO THE EBBINGHAUS ILLUSION IN PEOPLE WITH SCHIZOPHRENIA

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Background: In the Ebbinghaus illusion, a circle appears smaller when surrounded by larger circles, and larger when surrounded by smaller circles. Compared to healthy and psychiatric controls, patients with schizophrenia (SZ) are more resistant to this illusion, demonstrating superiority in size judgments regarding the target circles compared to other groups. Reduced Ebbinghaus illusion susceptibility in SZ is thought to be related to a deficit in perceptual organization (PO), or the processes that integrate stimulus elements into a coherent whole, leading to reduced integration of outer circles with the inner target circle, and therefore reduced contextual effects during the task. A previous study reported increased context effects after clinical stabilization in patients, but reduced effects in controls over the same 2-week period. Here, we report on effects of visual remediation (VR) on context sensitivity during an Ebbinghaus illusion task in clinically stable SZ patients.

Methods: Patients with SZ (n = 47) were randomly assigned to one of four conditions: cognitive remediation only (CR; the control condition), CR and contour integration training (CR and CIT), CR and contrast sensitivity training (CR and CST), or CIT and CST training. Before training, at baseline (BL), subjects completed a Positive and Negative Symptom Scale (PANSS) interview and an Ebbinghaus illusion task version used in previous SZ studies. In this task, subjects compared the size of two simultaneously presented circles (i.e., they report which is larger, the one on the left or one on the right), first without context (i.e., no surrounding circles), then with context (i.e., with a set of circles surrounding each target circle that could be misleading or helpful for the size comparison). The subjects were tested with the Ebbinghaus illusion task again after 10 VR training sessions (A1), and after 20 sessions (A2).

Results: The Ebbinghaus illusion context effect was operationalized as the relative difference between performance on the task with and without context (i.e., how much task performance was improved by the helpful context and worsened by the misleading context, relative to performance without context). For all VR conditions (CIT and CST, CST and CR, and CIT and CR), Ebbinghaus context effects decreased from BL to A2–these groups became less affected by the irrelevant outer circles and more accurate in size judgements for the inner target circles (linear trend over time $p = .012$; eta squared = .175). Preliminary evidence suggests that the groups receiving VR demonstrated different trajectories than the group receiving CR only (group x linear trend interaction eta squared = .133) Negative correlations between change in context effects over time and BL overall PANSS score ($r(28) = -.417$, $p = .02$), positive symptoms ($r(28) = -.39$, $p = .03$), and excitement symptoms ($r(28) = -.377$, $p = .037$) were found, meaning the most symptomatic subjects showed the smallest improvements in size comparison accuracy over time.

Discussion: These findings demonstrate that repeated exposure to the Ebbinghaus illusion among clinically stable people with schizophrenia is associated with a greater ability to resist effects of irrelevant spatial context, and to perform the task accurately, similar to a prior demonstration in healthy controls. This may reflect improved selective attention to visual targets and reduced processing of irrelevant contextual information. Preliminary evidence suggests that this effect is consistently enhanced by VR, but not by CR, and that the effect is reduced in patients with more symptomology.

F6. PERCEIVING IN TIME OR AHEAD OF TIME: EEG AND BEHAVIOURAL DATA IN CHRONIC PATIENTS WITH SCHIZOPHRENIA

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Background: Synchronizing with the environment, following the flow of events, and being able to fluently interact with the outer world is required to feel immersed in our surroundings. Conversely, the inability to synchronize may explain that individuals with schizophrenia feel disconnected from their surroundings, leading to a fuzzy sense of self. We explored timing in perception to examine this hypothesis.

Methods: Because information processing takes time, being in synchrony with external events requires prediction in time, which includes both automatic and controlled mechanisms, at the level of milliseconds and seconds. We examined automatic mechanisms of temporal prediction based on recent experience: if a visual stimulus occurs at a given millisecond or seconds delay after a first signal, then the same delay is expected on the next occurrence.

Results: In accordance with the literature of the 70s, individuals with schizophrenia are sensitive to the prior time occurrence at the level of seconds (Martin et al., 2017, Sci Rep). Interestingly we observed similar results at the level of milliseconds, showing that at least some automatic time prediction mechanisms are preserved. However, several results from our laboratory suggest that more effortful time prediction at both the level of milliseconds and seconds may allow individuals to better prepare and attend information ahead of time. In a recent study regarding the level of seconds (Chidharom et al. 2021, J Psych Res) checkerboards with different orientations alternated regularly in time and participants had to detect an oddball defined by its longer duration. EEG signals showed a decrease in voltage signing a CNV (contingent negative variation), which is believed to be associated with effortful preparation. In controls the CNV was observed before the usual duration was overtaken, whereas in individuals with schizophrenia the CNV started only once it was overtaken. No physical information signalled this moment, showing that the delay had been automatically processed by patients, but not effortfully anticipated. Interestingly, similar results are observed at the level of milliseconds. In tasks requiring to discriminate between simultaneous vs. asynchronous stimuli, the behavioural results suggest that all participants displace their attention in time and space according to recent experience. However once again controls displace their attention in advance whereas patients do not (unpublished). In addition, EEG results show a specific decrease in oscillatory signals in the alpha range when healthy individuals prepare for an asynchrony, which is absent in individuals with schizophrenia (Marques-Carneiro et al, 2021, Schizophr Bull Open).

Discussion: An explanation for why it is advantageous to attend in advance comes from tapping tasks. It is well known that in those tasks individuals tap slightly in advance of the signal. Once again, we showed that individuals with schizophrenia do not show this behaviour (Wilquin et al, 2018, Front Hum Neurosci). In such a task, tapping in advance helps to perceive a synchrony of the tap with the signal. More generally attending signals in advance may help to subsequently perceive and adjust actions, i.e. to actively and flexibly interact, instead of passively reacting to our environment. The EEG signals, which are typically associated with attention and decision, and were localized in the right frontal cortex, suggest that the ability to prepare slightly in advance is

subtended by cognitive control mechanisms, in connexion with automatic, millisecond prediction mechanisms. If effortful prediction mechanisms do not help individuals with schizophrenia to prepare enough in advance, it may prevent them from interacting efficiently with their environment and may explain their feeling of being out of step from their environment.

F7. BELIEFS ABOUT PERCEPTION IN PATIENTS WITH SCHIZOPHRENIA: RELATIONSHIPS WITH PSYCHOPATHOLOGY AND COGNITION

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Background: Perceptual anomalies are a common feature of schizophrenia spectrum disorders (SSD). Cognitive models have suggested that information-processing disturbances may be responsible for the development and maintenance of perceptual anomalies, with most studies focusing on auditory hallucinations. Yet, although theoretical accounts suggested the role of top-down processes as an important factor in perception, only limited studies focused on these processes in schizophrenia. Moreover, to the best of our knowledge, there are no studies investigating how subjective knowledge about perception may be related to the perceptual experiences of people diagnosed with schizophrenia. The aim of the presented study was to investigate the relationships between different meta-cognitive beliefs about perception and psychopathology and cognitive functions related to perceptual anomalies.

Methods: We analyzed data from a sample of in- and outpatients diagnosed with SSD (N = 89, aged 18–45). The exclusion criteria were age over 45, intellectual disability, history of neurological disorders, hearing impairments, alcohol dependence, and unstable state. Patients were assessed with standardized clinical interviews for symptom severity. Psychotic Rating Symptom Scales (PSYRATS) interview was conducted to assess hallucinatory experiences. Then, The Beliefs about Perception Questionnaire (BaPQ) was assessed. We developed BaPQ to measure attitudes and metacognitive beliefs towards perceptual experiences in greater detail and consists of seven subscales: top-down influence (TDI), blurred boundaries (BB), normalization (N), perceptual self-consciousness (SC), need to control perception (NC), lack of perceptual confidence (LC), and lack of acceptance (LA). Three cognitive processes have been investigated: source monitoring (Action memory task), cognitive inhibition (Go/NoGo task), and top-down processes (False perception task). Spearman correlation coefficients were used for the statistical analysis to determine the associations of measured variables and self-reported hallucinations measured by the Positive and Negative Symptoms Scale (PANSS). Holm correction for multiple comparisons was implemented in correlation analysis.

Results: Hallucinations presence measured by PSYRATS was positively correlated with BAPQ total score and normalization (N), need to control perception (NC), lack of perceptual confidence, and lack of acceptance (LA) subscales. BAPQ subscales were associated with positive symptoms and general psychopathology measured by PANSS. On the other hand, there was no significant correlation between BAPQ and negative subscale in PANSS. Moreover, the need to control perception (NC) and lack of perceptual confidence (LC) were negatively associated with hit rates and positively with response bias in the false perception task. Source monitoring errors were positively associated with blurred boundaries (BB), perceptual self-consciousness (SC), and the

need to control perception (NC). Whereas, negatively with lack of acceptance (LA). False alarms in Go/NoGo task were associated only with the perceptual self-consciousness subscale.
Discussion: Our preliminary findings suggest that beliefs about perception may be an important factor related to perceptual anomalies. Importantly, given the fact that beliefs about perception were not related to negative symptoms severity, these set of beliefs may be specifically related to positive symptoms and to hallucinations in particular. At the same time, beliefs about perception may play a role in cognitive processes related to perceptual anomalies. To conclude, meta-cognitive beliefs about perception may be a promising factor in fostering our understanding of perceptual anomalies in schizophrenia.

F8. IMPAIRED TIME PRODUCTION AND FUNCTIONAL CONNECTIVITY OF THE CORTICO-STRIATAL MOTOR PATHWAY IN PATIENTS WITH TREATMENT-RESISTANT SCHIZOPHRENIA

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Background: Patients with schizophrenia often exhibit impaired time-sensory processing in combination with generalized cognitive dysfunction. Neural circuits including the striatum, supplementary motor area (SMA), cerebellum, and prefrontal cortex play an integral role in time production. However, the pathological basis for impaired time processing in schizophrenia has not yet been fully elucidated. In addition, about 30% of patients with schizophrenia do not respond to antipsychotic medications and are considered to be treatment-resistant schizophrenia (TRS), and it suggests that TRS has a different neural basis compared with non-TRS. In addition, the relationship between treatment resistance and time-processing disorder has not yet been sufficiently understood. Therefore, the objective of this study was to investigate the impairment of time processing in patients with schizophrenia, particularly in relation to treatment resistance. We hypothesized that time-processing ability may be more impaired in patients with TRS than in patients with non-TRS.
Methods: The present study was performed at Komagino Hospital in Japan. Fifty-five patients with schizophrenia (29 non-TRS and 26 TRS) and 30 healthy controls (HCs) participated in this study. All participants were age- and sex-matched. Time production abilities were assessed by tapping on the auditory stimuli using the Harvard Beat Assessment Test (H-BAT). Functional connectivities were calculated from 3-tesla resting-state functional Magnetic Resonance Imaging (MRI) data. We computed the region of interest (ROI) to ROI connectivities using the spearman correlation method. We chose the SMA, the putamen, and the caudate as ROI. For comparing each value, analyses of covariance and post-hoc analyses were performed, controlling for age and sex as covariates.
Results: As for the complex auditory stimuli, the time production ability was lower in the TRS group compared with the HC and non-TRS groups (TRS vs. HCs, $p = 0.05$; TRS vs. non-TRS, $p = 0.01$) while no significant difference was found between the non-TRS and HC groups ($p = 0.97$). In terms of simple auditory stimuli, both the non-TRS and TRS groups had lower performance scores compared with the HC group (non-TRS vs. HCs $p = 0.04$; TRS vs. HCs $p < 0.001$), however there was no significant difference between the non-TRS and TRS groups ($p = 0.65$). On the other

hand, functional connectivity analyses demonstrated that the caudate-SMA connectivity was significantly weaker in patients with TRS than HCs ($p = 0.02$).
Discussion: Our results indicated that patients with TRS had impaired time production, suggesting the potential link between the time production ability and caudate-SMA connectivity. Given that this is an interim analysis, we need to investigate more comprehensively the relationship between time production ability and functional connectivity of the brain in patients with schizophrenia including TRS and non-TRS.

F9. EFFECTS AND MECHANISMS OF ATTENTION TRAINING TECHNIQUE IN PATIENTS WITH SCHIZOPHRENIA WITH AND WITHOUT AUDITORY HALLUCINATIONS – PRELIMINARY FINDINGS

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Background: Attention Training Technique (ATT) is a part of Metacognitive Therapy. However, up to date, it has been researched primarily as a separate therapeutic intervention. Dozens of studies show the effects of ATT on various outcome variables like anxiety, depression, stress levels, and repetitive negative thinking (RNT, i.e. worry, rumination, intrusive thoughts) in both non-clinical and clinical samples. Potential mechanisms of ATT include a change in self-focused attention (i.e. away from threat-oriented self-monitoring), reduction in maladaptive metacognitive beliefs (i.e. "my thoughts are uncontrollable") or enhancement of general attentional functioning. Several case studies show the beneficial effects of ATT on auditory hallucinations in patients with schizophrenia. This study aims to test the effects and mechanisms of ATT in larger samples of schizophrenia patients and a matched control group.
Methods: A randomised, double-blind controlled trial is ongoing. Up to date, 34 patients with schizophrenia and current auditory hallucinations (SH), 55 schizophrenia patients without current auditory hallucinations (SN) and 30 demographically matched healthy controls (HC) were randomised to either receive eight sessions of ATT or sham ATT (placebo control condition) throughout a week. Measurements were conducted before the first and after the last session of ATT. The primary outcomes were measures of RNT (strategies subscale of Cognitive-Attentional Syndrome questionnaire, CAS-1), hallucinations (Revised Hallucinations Scale, RHS) and general psychopathology (Symptoms Checklist 27plus, SCL-27plus). Secondary, mechanistic outcomes were self-focused attention (Self-Consciousness Scale, SCS), metacognitive beliefs (Interpretation of Voices Inventory, IVI, Metacognitions Questionnaire, MCQ-30 and negative metacognitive beliefs subscale from CAS-1), attentional functioning, both self-description (Attention Control Scale, ACS) and auditory attention performance (dichotic listening). Analyses were performed with an ANCOVA, where post-pre differences served as outcome variables and pre-intervention (baseline) measures served as covariates. We analysed the main effects of intervention (ATT vs placebo) in three groups combined and performed planned analyses of the effects of intervention in subgroups.
Results: The study is underway, but preliminary results show that participation in ATT, compared to placebo, significantly reduces RNT in both schizophrenia groups. Also, ATT has a significant

effect on reducing RHS scores in the SH group. We also observed a significant effect of ATT on score improvement in forced right-ear condition in dichotic listening in the SH group. There is also a possibility that ATT affects negative metacognitive beliefs, as measured by CAS-1's subscale. However, there were no significant effects observed for IVI and MCQ-30. Also, there were no significant results regarding SCL-27plus, SCS and ACS.
Discussion: Preliminary results of our study suggest that ATT has beneficial effects for schizophrenia patients, mainly those who currently experience auditory hallucinations, in levels of RNT and severity of auditory hallucinations. The observed outcomes are in line with previous studies showing the effects of ATT in patients with schizophrenia. Possible mechanisms observed are enhancement in auditory attention performance and a decrease in maladaptive metacognitive beliefs. A larger sample is needed to perform suitably powered analyses.

F10. ARE INTIMATE RELATIONSHIP STIGMATISED IN SCHIZOPHRENIA?

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Background: Persons with severe mental illness (SMI) report difficulties in developing and maintaining intimate relationships (IR, Cloutier et al., 2020). Stigma is considered as a barrier to develop IR (Boucher et al., 2016) and one third of persons with diagnosis of schizophrenia report having experienced discrimination in this area (Thornicroft et al., 2009). This study aimed to further identify stereotypes about the IR of persons with schizophrenia in 3 groups: mental health professionals (MHP), health students and the general population. This study also aimed to identify factors associated with stigma.
Methods: A preliminary focus group conducted among persons with SMI identified 9 experienced stereotypes (i.e. beliefs about IR in schizophrenia). On this basis, a questionnaire was then constructed and disseminated online to i) general population (N=144), MHP (N=145) and health students (N=243). Semantic differential scales (Osgood, Suci, and Tannenbaum, 1957) were used and participants rated 3 targets (i.e. "a person with schizophrenia", "general population, i.e. healthy person not diagnosed with schizophrenia", and "myself") on the 9 stereotype scales. Stereotype scores were computed using the difference between "person with schizophrenia" and "general population" ratings. Individual beliefs about mental illness were finally assessed as potential associated factors.
Results: The focus group reported having experienced 9 IR related stereotypes. These were categorized in 5 dimensions: stereotypes about the need for IR (e.g. "persons with SMI do not need IR"), about mental health consequences of IR (e.g. "IR of persons with SMI have negative consequences on their mental health"), about physical attractiveness (e.g. "persons with SMI are unattractive"), about incompetence (e.g. "persons with SMI are not able to engage in couple projects") and about dangerousness (e.g. "persons with SMI are dangerous for their partner"). The 3 groups exhibited stereotypes in all these dimensions, except for the dangerousness dimension that was not significant amongst MHP participants. Regarding the dimension of incompetence, a peculiar contrast was found: MHP were less stigmatizing than health students who were themselves less stigmatizing than the general population. Interestingly, incompetence in IR is the strongest stereotype in the MHP group. Factors such as beliefs in recovery from SMI, beliefs in a

continuum between normal and pathological, and perceived similarities with persons with SMI were negatively associated with stereotype endorsement.

Discussion: The present study identified specific stereotypes regarding IR in schizophrenia, present in the general population but also amongst health students and MHP. These results are in line with previous studies (Valéry and Prouteau, 2021). Stigma may contribute to difficulties in developing IR through i) rejection by potential partners (Boysen et al., 2019), ii) self-stigmatization (Cloutier et al., 2020), iii) lack of support from MHP (White et al., 2021). Regarding this last point, MHP report a lack of knowledge and skills to address needs in this domain, which leads them to avoid this topic (Bonfils et al., 2015). More, the incompetence stereotype, which was found to be the most endorsed stereotype by all the 3 groups, can fuel MHP's paternalizing attitudes and behaviors (Berger-Merom et al., 2021). The training of MHP and health students appear to be a promising solution to reduce stigma and improve practices in this domain (Berger-Merom et al., 2021). It is necessary to support MHP to overcome stigma associated with the IR of persons with SMI, so that appropriate interventions can be introduced and used effectively in routine practice.

F11. ASSESSING COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA USING THE CAMBRIDGE NEUROPSYCHOLOGICAL TEST AUTOMATED BATTERY: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Cognitive impairment is a core feature of Schizophrenia with significant differences observed across domains including working memory, episodic memory, verbal memory, executive function, attention, and social cognition. Cognitive deficits in schizophrenia are observed prior to illness onset, are mainly independent of positive symptoms, and are a strong predictor of functional outcome. The Cambridge Neuropsychological Test Automated Battery (CANTAB) is widely used to assess neurocognitive performance in schizophrenia, however, the comparative magnitude of these differences across tests has not been comprehensively evaluated. Therefore, this study aims to conduct a systematic review and meta-analysis of eight CANTAB tests commonly used to assess cognitive differences in schizophrenia including: Verbal Recognition Memory (VRM), Spatial Working Memory (SWM), Emotion Recognition Task (ERT), Rapid Visual Information Processing (RVP), Multitasking Test (MTT), One Touch Stockings of Cambridge (OTS), Paired Associates Learning (PAL), Reaction Time Task (RTI).

Methods: Using PRISMA guidelines, publications were identified through a systematic search of PubMed and Google Scholar databases. The following search terms were used: 'Cambridge Neuropsychological Test Automated Battery' OR 'CANTAB' and the CANTAB test name (e.g. 'Spatial working memory') OR its acronym ('SWM') and 'schizophrenia' during the period from 1980 to October 2022. These are the inclusion criteria for studies: 1) DSM or ICD criteria used to diagnose schizophrenia 2) Includes a healthy control comparison group 3) Used CANTAB to assess cognition 4) Reported sufficient data to extract Cohen's d (group mean, SD or SE (and N per group) for both patient and control groups 5) Published in peer-reviewed journal. Relevant summary data will be extracted including sample size, means, standard deviations, effect size, any relevant covariates (age, sex, medication, duration of illness, onset of illness, symptom severity).

Studies will be evaluated for eligibility by two independent raters. Data Means, standard deviations and calculated effect sizes derived from the selected papers will then be imported into R for and used in a random-effects meta-analysis using the 'meta' package. The systematic review is registered on PROSPERO.
Results: The electronic search resulted in 9517 articles. 3409 duplicates were removed. A further 4171 articles were removed following the assessment of titles and abstracts. So far, full-text evaluation is being conducted on 251 of the remaining 1837 articles by two independent raters for final inclusion.
Discussion: The findings from this systematic review and meta-analysis will allow for the comprehensive assessment of CANTAB tests for cognitive impairment in schizophrenia. The effect sizes generated for tests will be informative for future research studies and clinical trials using CANTAB to assess cognitive performance in schizophrenia.

F12. DIFFERENCES OF VISUAL STRESS PATTERN IN FIRST-EPISODE SCHIZOPHRENIA AND TREATMENT RESISTANT SCHIZOPHRENIA PATIENTS.

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Background: Despite the presence of acute positive psychotic symptoms in both patients with first-episode schizophrenia (FES) and patients with treatment resistant schizophrenia (TRS), increasing evidence suggested the presence of different neurobiological mechanisms explaining the FES and TRS. The lack of response to the antipsychotic medication with prominent antidopaminergic action of patients with TRS also hinted towards the presence of different neurobiological mechanisms of the two stages of the schizophrenia illness. Visual stress is a sensitivity to visual patterns, particularly stripes, and causing perceptual distortions as well as physical symptoms including headache. It is found to be related to hyperactivation of the visual cortex of the brain and possibly reflecting general cortical excitably. Pattern Glare Test is a standard test to examine the visual stress and people with mood disorders have been found to have elevated visual stress compared with healthy controls. However, there has not been any study to examine the presence of different patterns of visual stress between patients of FES and TRS.
Methods: Fifty-seven healthy controls subjects (HC) and one hundred schizophrenia spectrum patients, in which 51 were treatment-resistant schizophrenia (TRS) prior to the initiation of clozapine or at the early stage of clozapine initiation (clozapine dose <=50mg per day) and 49 first-episode schizophrenias (FES) were recruited. The Pattern Glare Test was presented to subjects one after another in a fixed order from low to high spatial frequencies: 0.3 (low-SF), 2.9(mid-SF) and 9.4 (high-SF) cycles per degree(cpd). The higher the score, the greater the level of visual stress experience. Clinical symptoms were measured with PASNSS and five-factor score of PANSS was used for the analysis. Cognitive function was assessed with digit span, letter-number span and verbal fluency.
Results: A three by two ANCOVA revealed a significant group effects in high-SF level(9.4cpd) [(F(4,308) =2.96, p=.020)] with age as a covariate (p=.029), where FES had a greater experience of visual stress (mean = 1.06±1.21) than TRS (mean = .49±.78). However, no other differences were observed when compared against HC (mean =.89±1.28) and no significant group differences

were found in low-SF and mid-SF. Mann-Whitney U test found no significant difference in PANSS positive 5-factor score between TRS and FES. A significant association was shown in FES between pattern glare mid-SF and PANSS anxiety and depression factor (r=.326, p=.022) but no significant associations were found between all three level of pattern glare and the 5 factors of PANSS in TRS. A trend significant relationship between verbal fluency and pattern glare mid-SF (p=.50) was found in patients with TRS but no significant relationship of the cognitive function measured and pattern glare in patients with FES.
Discussion: A significant group effect of high-SF pattern glare, specifically between patients of FES and TRS where patients with FES had higher level reflecting a much higher visual cortical excitability in FES than that of the TRS patients. This might be a simple behavioural indicator of the neurobiological differences between the two different stages of the illness. The differential relationship between symptoms and cognitive functions to the pattern glare in the two illness populations further suggest the possible presence of different mechanisms to the symptoms at the different stages of the illness. Further longitudinal study will be required to examine the effect of clozapine treatment.

F13. CORRELATES OF AUDITORY HALLUCINATIONS IN SCHIZOPHRENIA SPECTRUM DISORDERS

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Background: Auditory hallucinations (AH) are one of the cardinal symptoms of schizophrenia spectrum disorders (SSD), with up to 80% of patients with schizophrenia reporting AH at some point in their lifetime. Most recent cognitive models of AH stress the role of source monitoring, top-down processes, and attentional processes. However, research combining these processes is limited. Therefore, we aimed to investigate the role of source monitoring bias, top-down processes, and attentional control in hallucinations in patients with SSD.
Methods: We analyzed data from a sample of in- and outpatients diagnosed with SSD (N = 89, aged 18–45) with no history of neurological disorders, hearing impairments, alcohol dependence, or intellectual disability. All patients were in a stable state during the assessment. Patients were assessed with standardized clinical interviews for symptom severity. Then, participants completed a battery of cognitive tasks assessing source monitoring (Action Memory Task), top-down processes (False Perception Task), and attentional control (auditory Go/NoGo task). Spearman correlation coefficients were used for the statistical analysis to determine the associations between experimental results and the Positive and Negative Symptoms Scale (PANSS). Holm correction for multiple comparisons was implemented in correlation analysis. A hierarchical regression analysis with the hallucination scores as the outcome variable was applied.
Results: Hallucination presence was positively associated with response bias measures (a tendency towards responding yes or no on the task) in the False Perception Task. Correlations between self-reported hallucinations and remaining cognitive tasks did not reach significance. On the other hand, source monitoring errors correlated positively with response bias measures in the False Perception Task and negatively with the hit rate (the rate of correct identifications of audible words). Correlations with PANSS scores showed a positive relationship between the total score in PANSS and source monitoring bias as well as false alarms (the number of incorrect responses on the task) in the Go/NoGo task. Negative symptoms correlated negatively with the hit rate in the

False Perception Task and positively with false alarms in the Go/NoGo task. Hierarchical regression analysis showed that only response bias in the False Perception Task significantly predicted self-reported hallucinations. However, the relationship was opposite from the expected. **Discussion:** These preliminary findings suggest that the current models do not give a sufficient explanation for clinical hallucinations at the level of cognitive processes. These resultsindicate that investigated cognitive models might not be necessarily specific to hallucinations only but to general symptoms of schizophrenia spectrum disorders. Further research is needed to confirm these findings.

F14. COGNITIVE DYSFUNCTION IN THE CONTINUUM OF PSYCHOSIS: EPIDEMIOLOGIC EVIDENCE FROM QATAR

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Background: A large body of literature supports cognitive deficits in patients with severe mental illness including schizophrenia. However, less is known about cognitive deficits in otherwise healthy participants with schizotypal traits. Schizotypy is a psychosis phenotype that is shown to precede and interact with environmental stressors to precipitate subthreshold psychotic symptoms, which may lead to psychosis. We hypothesized that higher schizotypy scores would be associated with worse overall cognitive function.

Methods: Data collection was completed as part of a pilot for the World Mental Health Qatar study. A probability-based sample (N=349) representative of Qatar's Arab adults in the general population was recruited and surveyed face-to-face in participants' homes in May 2019. The Montreal Cognitive Assessment (MoCA), a brief screening instrument for mild cognitive impairment was administered to assess participant's overall cognitive performance using a maximum score of 30 points including executive functions, visuospatial abilities, short-term memory, language, attention, working memory, and temporal and spatial orientation. A shortened version of the Schizotypal Personality Questionnaire (45 items) was also administered and a composite score was computed. The most recent version of the Composite International Diagnostic Interview (CIDI 5.0, version 3.3) was administered to assess for the presence of depressive and anxiety diagnoses and ensure that they were not causing an impact beyond schizotypy. Basic sociodemographic information was collected. The entire questionnaire was programmed and administered in Arabic, electronically captured and anonymously stored using highly secure password protected server. Descriptive statistics and linear regression models were fit to data and weighted analysis to account for sample design was conducted in STATA version 16 using significance level of 0.05.

Results: 349 out of 1076 eligible participants completed the survey interviews including the MOCA and the SPQ. Approximately, half of the sample were females (48.6%). The age of the participants ranged from 19 to 74 years with mean age of 38 (SD = 11). The mean education in years was 13 (SD = 5). The mean MoCA score was 23 (SD = 3) and mean SPQ score was 89 (SD = 21). There was negative correlation between overall MoCA and SPQ scores, $r(347) = -.13$, $p = .026$. The coefficient for regression model with SPQ as the only predictor of MoCA score was not statistically significant $R2 = .02$, $F(1, 288) = 2.92$, $\beta = -.020$, $p = .088$. After adjusting for education years ($\beta = .179$, $p < .001$), age ($\beta = -.042$, $p = .074$) and female gender ($\beta = -.716$, $p = .109$), the SPQ coefficient was statistically significant $R2=0.13$, $F(4, 285) = 4.64$, $\beta = -.022$, $p = .021$). After

adjusting for any mood or anxiety disorders (β = -.407, p = .448), the SPQ coefficient was borderline statistically significant (β = -.020, p = .046). We tested two-way interactions between SPQ and education years (β =.004, p =.008), and between age and years of education (β =.008, p =.034), on MoCA scores. In addition, the main effects of SPQ (β = -.065, p = .001), age (β = -.139, p = .008), and education years (β = -.439, p = .006) were all statistically significant. This model explained the largest amount of variance in the data (R2 = 0.17 , F(7, 288) = 5.78, p < .001). The SPQ score was not significantly associated with visuospatial executive task score or the total memory score of the MoCA in any of the models that we ran.

Discussion: Our findings support that higher schizotypy scores in otherwise healthy subjects was related to reduced overall cognitive performance. Lower MoCA scores in those with higher education and in younger age may be related to higher schizotypy in the general population. This may have important implications for screening and intervention in those at higher risk for psychosis.

F15. COGNITION AND AUDITORY HALLUCINATIONS: A SYSTEMATIC REVIEW

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Background: Auditory hallucinations (AH) are a key component of psychosis and can lead to significant distress for affected individuals. Several cognitive mechanisms have been proposed for AHs, including aberrations in perception, memory, inhibition, and language processes. However, empirical results lending to each of these cognitive domains are inconsistent. The extent to which the literature pertains specifically to AHs, as opposed to broader diagnostic profiles and/ or cross-modality hallucination experiences, also requires clarification. A systematic review is needed to better understand if/ how these cognitive functions support aetiological models of AH, in the context of schizophrenia spectrum diagnoses.

Methods: A protocol was developed in line with the PRISMA-P guidelines, and pre-registered with Prospero (CRD42020148907). A comprehensive search of the Web of Science, PubMed and Scopus databases was conducted to identify records published in English between 1980 to the present. Following the removal of duplicates, 22,391 records were screened against the following criteria: i) group design empirical investigation, ii) participant group(s) with a psychiatric diagnosis, iii) absence of organic syndromes and substance dependence, iv) objective behavioural measure(s) of cognition, v) AH presence/ severity confirmed via valid assessment or clinical judgement, and vi) relationship between cognition and AH presence/ severity examined. Studies were assigned quality ratings, developed from the Newcastle-Ottawa Scale, to determine the appropriateness of methodological processes.

Results: Data was extracted from 90 retained studies and tabulated to reflect key emerging cognitive domains. The number of studies reporting any significant data points indicative of an association between AHs presence/ severity and relevant cognitive processes are as follows: decreased sensory detection ability (13 of 23), increased imagery and/ or sensory expectation bias (5 of 11), decreased source monitoring accuracy (16 of 27), decreased general memory accuracy (11 of 29), decreased hemispheric lateralisation for language processing (3 of 6), decreased

language production efficiency (3 of 7), decreased inhibition capacity (4 of 8), decreased attention capacity (4 of 11), and decreased emotion processing accuracy (3 of 7). The strength and pattern of findings across each of these key cognitive domains will be discussed in further detail (note: manuscript pending completion).

Discussion: Given that each of these cognitive processes have been cited as possible mechanisms for AHs and have thus formed the basis of several theoretical models (e.g., inner speech misattribution, intrusive memories, salience/ expectation bias, attention hypervigilance), it is important to highlight our mixed findings. In addition, many studies were omitted based on employing a general hallucination (i.e., not specific to the auditory modality) and/ or psychosis measure, despite offering aims and inferences specific to AHs. Furthermore, while many studies investigated the presence of clinical AHs with reference to a healthy control group, the decision was made to omit these specific data points from the synthesis, with the view that this contrast cannot effectively isolate AHs from the broader clinical presentation of the patient group. The above methodological issues significantly reduced the amount of data available for synthesis, and thus highlights a gap within the literature between the extent of theoretical claims made about the role of cognition in AHs, and the body of rigorous empirical evidence supporting such claims. Implications for future research and proposed aetiological models of AHs will be offered if permissible.

F16. IS EGO-DISTURBANCE ASSOCIATED WITH ABERRANT SALIENCE?

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Background: The aberrant salience hypothesis (Kapur, 2003) is a dominant pathophysiological hypothesis of schizophrenia, which postulates that a hyper-dopaminergic state in the midbrain-striatum causes heightened attribution of salience to ordinary stimuli, leading to the formation of delusion and hallucination. Symptoms such as made experience are classified as delusion in English and American psychiatric tradition, while they are considered ego-disturbance in German psychiatry and have been studied as the alteration of a sense of agency and/or sense of self. One important question is whether ego disturbance is associated with aberrant salience. In this study, we used questionnaires of aberrant salience and ego disturbance and investigated their association.

Methods: We recruited 47 patients with schizophrenia and performed the Aberrant Salience Inventory (ASI: Cicero et al, 2010) and the Embodied Sense of Self scale (ESSS: Asai et al, 2016) for the assessments of aberrant salience and ego-disturbance, respectively. ASI consists of 29 items and five subscales (increased significance, senses sharpening, impending understanding, heightened emotionality, and heightened cognition), while ESSS consists of 25 items and three subscales (sense of ownership, narrative self, and sense of agency). We investigated the Pearson partial correlation between five ASI subscales and three ESSS subscales, and ASI and ESSS total scores. Age and sex were used as control variables. The statistical threshold was $p<0.0031=0.05/16$. This study design was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine. After receiving a complete description of the study, all participants provided written informed consent.

Results: The sense of agency subscale of ESSS was significantly and positively correlated with the heightened emotionality subscale of ASI ($r=0.503$, $p<0.001$), and the sense of ownership

subscale of ESSS with increased significance ($r=0.494$, $p<0.001$) and heightened emotionality ($r=0.482$, $P<0.001$) subscales of ASI. The total score of ESSS and ASI was also significantly and positively correlated ($r=0.447$, $p=0.003$).
Discussion: We confirmed the association between ego disturbance and aberrant salience in schizophrenia. The sense of ownership subscale of ESSS is considered to assess passive/perceptual experience, i.e. the input level of information, and compatible with the concept of aberrant salience attribution to perceptual stimuli. On the other hand, the sense of agency subscale is considered to assess active bodily output, and the association between this subscale and ASI may indicate that the aberrant salience is also associated with the output level of experience.

F17. EFFORT-BASED DECISION MAKING IN SCHIZOTYPY AND ITS RELATIONSHIP WITH AMOTIVATION AND PSYCHOSOCIAL FUNCTIONING

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Background: Suboptimal effort-based decision-making with reduced willingness to expend effort for high-probability/high-value reward is observed in schizophrenia patients and is related to diminished motivation but is understudied in schizotypy.
Methods: This study recruited 40 schizotypy individuals and 40 demographically-matched healthy controls, based on the Schizotypal Personality Questionnaire-Brief (SPQ-B) score (top and bottom 10% SPQ-B scores, respectively), from 2400 young people aged 15-24 years participating a population-based mental health survey in Hong Kong and examined effort allocation using the Effort Expenditure for Reward Task (EEfRT). Negative / amotivation symptoms and psychosocial functioning were assessed by the Brief Negative Symptom Scale (BNSS) and the Social Functioning and Occupational Assessment Scale (SOFAS), respectively. Schizotypy individuals were further categorized into high-amotivation and low-amotivation groups based on a median-split of BNSS amotivation domain score.
Results: Our results showed no main group effect (in either two or three-group comparison) on effort task performance. Three-group comparison analyses on selected EEfRT performance indices revealed that high-amotivation schizotypy individuals displayed significantly less increase in effortful options from low-value to high-value reward (reward-difference score) and from low-probability/low-value to high-probability/high-value reward (probability/reward difference score) than low-amotivation individuals and controls. Correlation analyses demonstrated trend-wise significance between BNSS amotivation domain score and several EEfRT performance indices in schizotypy group. Schizotypy individuals with poorer psychosocial functioning tended to exhibit smaller probability/reward difference score relative to other two groups.
Discussion: Overall, our findings indicate subtle effort allocation abnormalities in schizotypy individuals with high levels of diminished motivation and suggest the link between laboratory-based effort-cost measures and real-world functional outcome.

F18. INTROSPECTIVE ACCURACY AND CONFIDENCE ACROSS THE PSYCHOSIS SPECTRUM: INFLUENCE OF SLEEP QUALITY

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Background: People across the psychosis spectrum have impairments in their perceptions of their abilities (introspective accuracy [IA]) and tend to be overconfident while completing tasks. Research suggests that depression may be related to IA and confidence, but findings are mixed. Examining sleep as a determinant of IA and confidence may help explain these mixed findings. Our preliminary work suggests that sleep may not be directly linked to IA for multi-modal emotion recognition, but rather may be related to confidence. It is currently unclear how these relationships may extend to facial emotion recognition or if sleep quality may moderate relationships between depression and IA and confidence. This study aimed to extend findings from our previous work and examine relationships between sleep quality, depression, IA, and confidence in diagnostic groups across the psychosis spectrum.

Methods: Participants (schizophrenia n=34, schizoaffective n=55, bipolar disorder with psychotic features n=78) completed a facial emotion recognition task and indicated for each item whether they thought they answered correctly (perceived score) and their confidence in their answer. IA was calculated as the difference between perceived and actual performance. Participants self-reported their sleep quality. Depression was determined from a clinical interview.

Results: Across the sample, IA was associated with higher confidence ($r=.40$, $p<.001$). In the schizophrenia group, lower confidence was associated with higher daytime tiredness ($r=-.37$, $p=.03$), and underestimation of abilities was associated with poorer sleep quality ($r=-.43$, $p=.01$), longer sleep latency ($r=-.38$, $p=.03$), shorter sleep duration ($r=-.36$, $p=.03$), increased sleep disturbances ($r=-.35$, $p=.04$), and overall poorer sleep ($r=-.36$, $p=.04$). In the bipolar group, increased use of sleep medication was associated with lower confidence ($r=-.24$, $p=.04$) and underestimation of abilities ($r=-.26$, $p=.02$). In contrast, in the schizoaffective group, higher confidence was associated with increased sleep disturbances ($r=.33$, $p=.01$), and overestimation of abilities was associated with increased sleep latency ($r=.33$, $p=.02$). Diagnostic groups did not differ on perceived or actual task scores, confidence about task performance, or IA difference scores. The bipolar group reported increased sleep disturbances ($F=4.55$, $p=.01$) and poorer subjective sleep quality ($F=4.42$, $p=.01$) compared to the schizophrenia group; groups did not differ on other sleep scores. Across the sample, sleep quality significantly moderated the relationship between depression and confidence ($R2 = .05$, $F(3,163)= 2.88$, $p=.04$) such that for those with poor sleep quality, elevated depression was associated with higher confidence, while for those with better sleep quality, elevated depression was associated with lower confidence. Sleep quality did not moderate the relationship between depression and IA.

Discussion: Extending prior work, differential relationships between sleep quality, confidence, and IA emerged across diagnostic groups. Despite moderate correlations between IA and confidence, results suggest that sleep, and the interaction between sleep and depression, may differentially impact these different forms of self-evaluation. Our moderation findings regarding better sleep are consistent with existing literature on depressive realism, but the findings regarding poor sleep quality are more difficult to interpret and require further research. Overall, our findings suggest that sleep quality may be important for understanding both IA and confidence, particularly when completing a facial emotion recognition task.

F19. REGULATORY T CELLS IN SCHIZOPHRENIA PATIENTS WITH POSITIVE ANTI-GLIADIN ANTIBODY (AGA) TITERS CORRELATE NEGATIVELY WITH AGA IGG LEVELS AND WITH NEGATIVE SYMPTOMS

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Background: Immune dysfunction has increasingly been identified as a part of the pathogenic process in schizophrenia. In about a third of schizophrenia pts, there is an elevation of anti-gliadin IgG antibodies (AGA-IgG) associated with increased levels of TNF-α, IL-1, and kynurenine – all markers of pro-inflammation. There are few studies assessing markers of anti-inflammation in this AGA-IgG positive subgroup of schizophrenia. We have previously shown that regulatory T cells (Tregs, defined in this study as CD3+CD4+CD25+Foxp3+) are increased and correlate with decreased negative symptoms in schizophrenia. In this current analysis, we aimed to evaluate this relationship within the subgroup of schizophrenia patients known to have an immune response to AGA.

Methods: The study was a cross-sectional study conducted at the Maryland Psychiatric Research Center (MPRC) in Catonsville, MD. In total, 17 Healthy Controls (HC) and 26 patients with a DSM-IV-TR or DSM-5 diagnosis of schizophrenia or a schizophrenia related disorder were ultimately included, for which we collected regulatory T cell measurements and AGA-IgG levels. Negative psychiatric symptoms were evaluated utilizing the Scale for the Assessment of Negative Symptoms (SANS). Peripheral Blood mononuclear Cells isolated from whole blood were stained with CD3, CD4, CD8, CD25, CD45RA and Foxp3 prior to flow cytometric analysis. AGA-IgG was measured using ELISA and cutoff for positive AGA-IgG titer was set to greater than or equal to 20 U. Datasets were analyzed for normality utilizing the Kolmogorov-Smirnov test. Pearson's correlation coefficients were utilized for correlations between Tregs and antibody levels and Spearman's Rank Correlation utilized for correlations in non-normal distributions. Cutoff for positive AGA-IgG titer was set to greater than or equal to 20 U.

Results: In schizophrenia patients with positive AGA-IgG titer, there was a negative correlation between Tregs and AGA-IgG levels which was not evident in HC with a positive titer($R = -0.62$, $p = 0.03$* vs. $R = -0.47$, $p = 0.15$) nor in schizophrenia patients with a negative AGA-IgG titer ($R = -0.15$, $p = 0.61$). In schizophrenia patients with positive AGA-IgG titer, but not in schizophrenia patients with a negative (or equivocal) AGA-IgG titer, there is a negative correlation between Tregs and SANS Total ($R = -0.58$, $p = 0.04$* vs. $R = -0.13$, $p = 0.66$). Finally, schizophrenia patients with positive AGA-IgG titer, but not schizophrenia patients with a negative AGA-IgG, had a negative correlation between Tregs and SANS alogia (Spearman Rank's Correlation $rs = -0.64$, $p = 0.03$* vs. $rs = -0.37$, $p = 0.19$).

Discussion: To our knowledge, this is the first investigation into the role of Tregs in an AGA positive schizophrenia cohort. Tregs appear to be negatively correlated with AGA-IgG titers, SANS Total, and SANS Alogia. Notably, this correlation between Tregs, total AGA-IgG titer, and negative symptomology was not similarly present in the negative AGA group. While this sample

size is relatively small, these findings are certainly suggestive of potential protective roles of Tregs in this gluten-sensitive cohort of patients with schizophrenia.

F20. MOMENT-TO-MOMENT AFFECTIVE DYNAMICS IN SCHIZOPHRENIA AND BIPOLAR DISORDER: AN EXPERIENCE SAMPLING STUDY

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Background: Affective dynamics consist of dimensions such as valence, intensity, variability, instability, and reactivity to stress. Although affective abnormality is proposed to be a transdiagnostic risk factor, little evidence has specified the similarities and differences in patterns of these dynamics across disorders. This is especially important for severe mental disorders such as schizophrenia and bipolar disorder, where affective disturbances are common, complex, and persisting, and have been suggested as targets for treatment. As schizophrenia and bipolar disorder largely share both genetic predisposition and biological mechanisms, we expect extensive overlap between these disorders and similar differences as compared to healthy volunteers.
Using experience sampling methodology (ESM), an ecologically valid method that captures subjective experiences in the flow of daily life, the present study aimed to compare individuals with schizophrenia and bipolar disorder to healthy controls across parameters of affective dynamics.

Methods: The sample consisted of patients with schizophrenia (n= 46), patients with bipolar disorders (n= 46), and healthy controls (n= 46). Diagnoses were assessed with the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (SCID). Age- and gender-matched healthy controls who reported no psychiatric diagnoses (confirmed by the SCID) were recruited.
In addition to clinical rating scales, all participants were required to fill out an ESM assessment on a mobile phone app. The questionnaire was repeated at ten random times per day for six days. The ESM items consisted of momentary positive affect ('PA': happy, relaxed, contented) and negative affect ('NA': irritated, low, anxious), as well as event-related stress. Only participants who completed one-third or more ESM questionnaires were included in data analysis.

Intensity levels of momentary PA and NA were computed by averaging the three respective items per timepoint. Affective instability of momentary affects were calculated using the adjusted squared successive differences (ASSD) and probabilities of acute change (PAC). Variability was represented by the within-person standard deviation of PA or NA respectively. Affective reactivity to stress was calculated as the within-moment association between affect and event-related stress for PA and NA separately. Differences in these indexes between patients and controls, and between the two patient groups were tested either using multi-level modelling or Mann–Whitney U tests.

Results: Compared to controls, patients (schizophrenia and bipolar disorder groups combined) had significantly more intense momentary NA (B= 0.37, p= .046, d= 0.17), and reduced within-person variability of PA (U= 1484, p= .004, r= 0.30) and PAC in PA (B= -0.65, p= .020, OR= 0.52). When the patient groups were not combined, the schizophrenia group had higher intensity

of NA (B= 0.51, p= .018, d= 0.20), and reduced within-person variability of PA (U= 694, p= .004, r= 0.34) and PAC in PA (B= -0.77, p= .021, OR= 0.46) than controls. There were no significant differences in any affect indexes between the two patient groups.
Discussion: As hypothesized, the two patient groups shared similarities in affective dynamics, which were distinct from healthy individuals. While patients (especially those with schizophrenia) had more intense negative affect, they presented lower moment-to-moment fluctuations in positive affect than controls, which may suggest that patients are less likely to have their affect changing in response to happenings in daily life. Findings are discussed in relation to patients' engagement in activities, symptom profiles, and treatment implications.

F21. UPDATING ITS TEMPORAL PREDICTION IN A MOTOR TASK: LACK OF FLEXIBILITY IN INDIVIDUALS AT HIGH RISK OF PSYCHOTIC CONVERSION

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Background: Alterations in time experience and bodily self are found to be related in psychosis and could serve as a predictive marker in high risk (HR) individuals. To objectify these disorders, we explore how the passage of time can be used to anticipate the occurrence of predictable stimuli. To do so, we use a well-known paradigm: the variable fore period paradigm, during which a signal is followed at variable delays by a target. In neurotypicals, the more the participant waits for the target, the faster he reacts to it. This is called the 'hazard function' (HF) and is altered in patients with disorders of the self. Since previous results suggest that HR individuals may be impaired in the most automatic aspects of temporal prediction, we additionally measure sequential effects (SE). SE are used to explore how participants are automatically influenced by what happened on the previous trial (trial N-1) to build their temporal prediction for the current trial (trial N). We have developed a motor task in which we use the tactile modality, given the importance of tactile information and motor action in the disturbances of bodily self. We test whether impairment in temporal prediction abilities in a motor task using the tactile modality, related to alteration of bodily self, could serve as a marker for the risk of psychotic conversion.
Methods: Participants are asked to perform arm movements inside a box in response to tactile stimuli. A first tactile signal indicates they can start their movement in a straight line. After a short or long delay, a second tactile signal indicates they have to stop their movement as soon as possible. Then, participants have to return to their starting position, thus they repeat the same movement at each trial. We were interested in the stop latency, i.e., the RT of our participants. We also collect the exact moment when participants start to slow down their trajectory in anticipation of the stop signal. Regarding this slowing down, we were interested in two cases: a slowing down in anticipation of the short stop (prediction 1), and a slowing down in anticipation of the long stop (prediction 2). The results presented are preliminary and were obtained on young neurotypicals and HR individuals with a genetic risk of developing SZ or bipolar disorder.
Results: On all the indicators we observed, HR individuals were slower than neurotypicals. We found a HF on the RT of our participants: they stop faster after a long delay than after a short one. We also found SE: the trial N performances were influenced by the delay at trial N-1. SE are present in both groups on their RT: participants stop their movement slowlier on a short trial N if it is preceded by a long vs. short trial N-1, i.e., they are slowlier when the target occurs earlier than

expected. When the target occurs at a long delay, the latency of prediction 2 in HR individuals is more variable between trials when the delay on trial N-1 is short vs. long, i.e., when the prediction needs to be adjusted because the target did not occur at a short delay as expected. This effect was not observed in neurotypicals.

Discussion: Our protocol allows us to acquire usual and more innovative markers of temporal prediction, and especially indexes of prediction during the action itself (the slowing down of the trajectory). HR individuals are slower than neurotypicals which is consistent with the literature. In HR individuals, unlike in neurotypicals, the latency of the prediction 2 was variable between trials when the temporal prediction had to be adjusted during the trial. This could suggest that HR individuals are less flexible than neurotypicals when adjusting their prediction online, even though the presence of SE shows that temporal prediction errors have been detected.

F22. THE OROPHARYNGEAL MICROBIOME IN INDIVIDUALS WITH SCHIZOPHRENIA AND OTHER SERIOUS MENTAL ILLNESSES

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Faith

Background: The biology of schizophrenia is not fully understood; environmental factors such as inflammation as well as genetic factors are likely involved in the etiology of the disorder. It is now well-established that microbes in the gastrointestinal track, collectively termed the microbiome, have an effect on systemic inflammation and brain functioning through a set of bi-directional pathways. While most studies of the human microbiome focus on fecal samples, the oropharynx also has a microbiome which can modulate systemic inflammation and contribute to a brain disorder such as schizophrenia. The composition of the oropharyngeal microbiome can be repeatedly assessed through oral swabs involving minimal discomfort. To date, only limited studies have been performed examining the role of the oropharyngeal microbiome in schizophrenia and the association between the oral and the intestinal microbiome within the same individuals.

Methods: We obtained 565 samples from 175 individuals including 27 persons with schizophrenia, 51 with bipolar disorder, 80 with major depression, and 17 without any current or past psychiatric disorder. The samples included 216 throat swab samples, 213 cheek swab samples, and 136 stool samples. Each individual also provided a blood sample which was used for the measurement of immune markers and antibodies to infectious agents. DNA was extracted from the swabs and amplified using primers directed at conserved regions in DNA encoding the 16s ribosomal gene. The amplified sequences were matched to bacterial genomes through the use of QIIME2 software and available databases. The distributions of the organisms were compared using diversity measures and principal component analyses. The levels of individual taxa were compared in terms of diagnostic groups using mixed effects models employing age, gender, race, tobacco use, and BMI as covariates.

Results: There was a significant correlation between the microbiome of the throat and the cheek (R=.235 95% CI .128, .343, p=.0001). There was no significant correlation between the throat or the cheek and the stool microbiome. The diagnostic groups differed in terms of several diversity measures. In analyses of individual taxa, the largest difference among diagnostic groups was found for the genus Rothia and the pathogenic species Rothia mucilaginosa which is capable of causing brain infections This species was increased in individuals with schizophrenia in cheek

samples (coef=232.7, 95% CI 110.4, 355.0, p<.002) and throat samples (coef=171.7, 95% CI 43.5, 299.9. p<.009). Conversely, individuals with schizophrenia had decreases in non-pathogenic bacteria such as members of the genera Neisseria and Hemophilus. Tobacco smoking was the covariate with the greatest effect on oropharyngeal taxa levels. There were relatively few diagnosis-associated differences in the stool microbiome.
Discussion: The oropharyngeal microbiome shows substantial variation among diagnostic groups. Analysis of the oropharyngeal microbiome should be included in studies directed at the characterization of the microbiome in individuals with schizophrenia and other psychiatric disorders.

F23. AUDITORY AND VISUAL HALLUCINATIONS ASSOCIATED WITH MODALITY-SPECIFIC PRIOR-WEIGHTING

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Background: Auditory and visual hallucinations are among the most debilitating symptoms of psychotic disorders. Although up to 84% of individuals report having hallucinations in both sensory modalities, many only experience unimodal hallucinations. Recent work has framed hallucination development within a predictive processing framework, positing that hallucinations arise due to over-reliance on perceptual expectations (priors), relative to incoming sensory information. However, most research in this area has been focused on auditory hallucinations, and it is thus unclear whether prior-reliance drives hallucinations in other sensory modalities or whether prior-reliance is modality specific.
Methods: To determine whether the processes driving hallucinations are modality-specific, we employed a Pavlovian auditory conditioned hallucinations (ACH) task, which previously extracted mechanisms of prior-reliance and related them to severity of auditory hallucinations. We additionally administered a novel visual conditioned hallucinations (VCH) task. 857 participants from a heterogeneous group of individuals reporting a wide spectrum of uni- and multi-modal hallucinogenic experiences completed both tasks online. We used task behavior to fit parameters of a hierarchical gaussian filter (HGF) model corresponding to latent states of prior-reliance, learning, and belief-updating.
Results: Our results are consistent with previous reports on the ACH task, demonstrating that hallucination frequency correlates with susceptibility to conditioned hallucinations, and that this relationship is explained by overweighting priors. In addition, participants' performance on both tasks were found to be differentially explained by the sensory modality of hallucinations, suggesting that prior-reliance is modality-specific.
Discussion: New versions of the HGF accounting for processes across sensory modalities were compared to disentangle whether behavior was driven by modality-specific or general prior weighting. Taken together, our results indicate that hallucination susceptibility may reflect neural processes unique to sensory modality, with implications for hallucination development and creation of effective circuit-specific treatments.

F24. LONGITUDINAL INFERENCE OF MULTISCALE MARKERS IN PSYCHOTIC DISORDERS

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Background: Multiscale neuroscience conceptualizes psychiatric disorders, such as psychosis, as the result of alterations within and across multiple scales, spanning genetics, brain, symptoms, and functional outcome. A better understanding of mental illness can be acquired by studying these complex cross-scale interactions via multiscale research. Here, we apply this approach in the service of creating a novel disease progression model of psychosis, which describes how changes at the level of the brain result in poor functional outcomes through several cognitive and clinical symptoms. We hypothesize that in such a multiscale model, psychosis progresses from hippocampal-cortical dysconnectivity to impaired episodic memory and social cognition, resulting in higher negative symptoms and, ultimately, poor functional outcome. We further hypothesize that such multiscale marker development is only apparent in a cognitively impaired subtype of patients, while a second patient subtype shows normal-range performance on these multiscale markers.

Methods: To address the temporal and phenotypic properties of the proposed model, we implemented Subtype and Stage Inference (SuStaIn), a recently developed machine-learning technique. SuStaIn simultaneously integrates the methodologies of disease progression modeling and clustering to infer longitudinal multiscale trajectories from cross-sectional data. We extracted imaging, cognitive, and clinical data of 163 patients and 117 non-clinical controls from two datasets of first-episode and multi-episode psychosis. As a measure of hippocampal-cortical connectivity we used the graph-theoretical participation coefficient, derived from T1- and T2-weighted hippocampal volumes computed through MAGeT brain and cortical thickness via CIVET. The patient data of bilateral hippocampal-cortical connectivity, episodic memory, social cognition, negative symptoms and functional outcome were used as the multiscale marker input for z-score SuStaIn.

Results: Three patient subtypes were identified through 10-fold cross-validation, with Subtype 0 showing normal-range performance on the multiscale markers. From the two subtypes which showed impairments, patients in Subtype 1 had significantly deteriorated episodic memory, social cognition, functional outcome and higher negative symptoms (all $p < .001$) in comparison to Subtype 0. Patients in Subtype 2 showed significantly higher hippocampal-cortical dysconnectivity than Subtype 0 (both $p < .001$). In terms of disease progression, Subtype 1 progressed from impairments in episodic memory to social cognition, hippocampal-cortical dysconnectivity, negative symptoms and functional outcome. Subtype 2 progressed similarly, yet, left hippocampal-cortical dysconnectivity deteriorated simultaneously with social cognition.

Discussion: Our results provide evidence for distinguishable multiscale psychosis subtypes characterized by distinct profiles of impairment across the markers of the proposed model. While episodic memory is central in early disease progression, hippocampal-cortical dysconnectivity based on morphometric features may not be the neural correlate driving its deterioration. Measuring connectivity within targeted memory networks and through the integration of multiple

neuroimaging modalities may help identify additional biomarkers of episodic memory and disentangle their contribution to functional outcomes of psychosis. The inclusion of genetic markers may further improve predictions of functional outcome in multiscale models. Finally, algorithms which do not assume linear disease progression might additionally allow to better account for intra-individual marker fluctuations.

F25. PSYCHOSIS AND TRAUMA – MEASUREMENTS OF BLOOD-BASED EXOSOMAL BIOMARKERS FROM BRAIN ORIGINS: PRELIMINARY RESULTS

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Background: Psychological trauma is a well-known environmental risk factor for psychosis. Neuroinflammation is a phenomenon commonly observed in both psychosis pathophysiology and trauma response. Still, the mechanisms underlying these associations, and how trauma history interact with the immune function in psychosis remain misunderstood. Recently, growing interest has aroused on brain-derived exosomes, which are inflammatory cargo that cross the blood-brain barrier to reach the bloodstream, where they release inflammatory regulators. Being easily accessible through blood analysis, these brain-derived exosomes are a powerful tool to identify non-invasive biomarkers specific to brain alterations. The aims of the study are to evaluate the association between inflammatory markers from brain-derived exosomes and: (1) severity of psychotic symptoms; and (2) history of traumatic events.
Methods: 50 healthy individuals and 50 patients with first episode psychosis will be recruited. Patients will be divided on a with or without trauma history basis. Patients will be evaluated twice at a six-month interval. Sociodemographic information, psychiatric and treatment history, symptomatology severity and trauma history will be collected at each visit, in addition to blood samples for assessment of brain-derived exosomes.
Results: Recruitment is ongoing and available preliminary results are going to be presented.
Discussion: Using a non-invasive and innovative approach, this study presents a unique opportunity for longitudinal assessment of inflammatory markers that are specific to brain changes in association to psychosis pathophysiology. Considering the effect of past trauma, this multifactorial study is a critical step towards a more accurate diagnosis and treatment of psychosis.

F26. REVIEW OF THE TAAR1 AGONIST ULOTARONT: PART I - FROM DISCOVERY TO CLINIC

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Background: Trace amine-associated receptors (TAARs) are a family of G-protein-coupled receptors (GPCRs) first identified in 2001. TAAR1, expressed both peripherally and in multiple brain regions, has emerged as a promising therapeutic target for several neuropsychiatric disorders due to its ability to modulate monoaminergic and glutamatergic neurotransmission. Ulotaront is the first investigational agent in this class to complete Phase 2 clinical trials. Here we provide a brief review of the discovery of ulotaront and the preclinical research suggesting its efficacy in schizophrenia, leading to the first clinical trial resulting in FDA designation of ulotaront as a Breakthrough Therapy.

Methods: Candidate compounds were screened using a high-throughput, mouse-behavior phenotyping platform (SmartCube®) in combination with in vitro anti-target screening designed to identify compounds exhibiting antipsychotic-like activity in the absence of dopamine (D2) and serotonin (5-HT2A) receptor activity.

Ulotaront was identified and subsequently studied in established preclinical models of schizophrenia and tested against several panels of known molecular targets (ion channels, GPCRs, and enzymes). Follow-up studies, including in vitro and in vivo electrophysiology recordings, as well as PET imaging, were conducted to elucidate the underlying mechanism of action. In addition, a battery of studies was conducted in rats to evaluate whether ulotaront produces behavioural changes suggestive of human abuse potential.

Results: The anti-target approach was designed to identify drug candidates that worked in animal models of schizophrenia without the D2/5-HT2A blockade characteristic of the currently available antipsychotic class of drugs. This high-throughput, mouse-behavior phenotyping methodology identified ulotaront as a novel drug candidate. In vivo, ulotaront demonstrated efficacy in preclinical models of schizophrenia, including phencyclidine (PCP)-induced hyperactivity, prepulse inhibition of the acoustic startle response, and subchronic PCP-induced deficits in social interaction. Although not fully elucidated, the mechanism is thought to be largely mediated by agonism at TAAR1 and 5-HT1A receptors. This was further corroborated with whole cell patch clamp recordings, demonstrating inhibition of dorsal raphe nucleus and ventral tegmental area neuronal firing via 5-HT1A and TAAR1 receptors. Pre-treatment with ulotaront has been shown to counteract MK-801-induced pre-pulse inhibition in wild type mice, but the effect is not observed in TAAR1-knockout mice. Furthermore, ulotaront attenuated the ketamine-induced increase in striatal dopamine synthesis capacity, suggesting that it may modulate presynaptic dopamine dysfunction, hypothesized to contribute to the pathophysiology of schizophrenia. The results of a standard preclinical abuse liability battery suggest that ulotaront is not likely to pose a risk for abuse in humans and may even have potential therapeutic utility as a treatment of substance use disorders.

Discussion: Findings from in vitro and in vivo studies have identified ulotaront as a TAAR1 agonist with robust antipsychotic-like activity in rodent models. Ulotaront's unique target profile led to its designation as a member of the new "-taront" class of TAAR1 agonists, distinct from the approved D2/5-HT2A class of antipsychotics. A companion poster will summarize the broad-spectrum efficacy, tolerability, and safety features of ulotaront based on initial clinical trials in patients with schizophrenia.

F27. CLINICAL APPLICABILITY OF VOCAL MARKERS OF SCHIZOPHRENIA: ASSESSING THE GENERALIZABILITY OF MACHINE LEARNING MODELS

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Background: Machine learning (ML) approaches are a promising venue for identifying vocal markers of neuropsychiatric disorders, such as schizophrenia. While recent studies have shown that voice-based ML models can reliably predict diagnosis and clinical symptoms of schizophrenia, it is unclear to what extent such ML markers generalize to new speech samples collected in varying contexts and languages. Indeed, we need to identify which patterns of features are invariant across languages, and thus more robustly related to the psychopathology of the disorder; further, we need to assess whether and to what extent vocal markers can be applied to under-represented and under-resourced languages. The assessment of generalization performance of ML voice-based models is thus crucial for testing their clinical applicability. In this research, we systematically assessed the generalizability of ML models across contexts and languages relying on a large cross-linguistic dataset of audio recordings of patients with schizophrenia and controls.

Methods: We trained ML models of vocal markers of schizophrenia on a large cross-linguistic dataset of audio recordings of 231 patients with schizophrenia and 238 matched controls (>4.000 recordings in Danish, German, Mandarin and Japanese). We developed a rigorous pipeline to minimize overfitting. We tested the generalizability of the ML models on: (i) different participants, speaking the same language (hold-out test set); (ii) different participants, speaking a different language. Finally, we compared the predictive performance of: (i) models tested on a single language (e.g., Danish) (ii) MoE models, i.e., ensemble of models (experts) trained on a single language whose predictions are combined using a weighted sum (iii) multi-language models trained on multiple languages (e.g., Danish and German).

Results: Model performance was comparable to state-of-the-art findings (F1 ~ 70%-80%) when trained and tested on participants speaking the same language (out-of-sample performance). Crucially, however, the ML models did not generalize well - showing a substantial decrease of performance (close to chance, F1 ~ 40%-55%) - when trained in a language and tested on new languages (e.g., trained on Danish and tested on German). MoE and multi-language models showed a better increase of performance (F1 ~ 55%-60%), but still far from the needs of clinical applicability.

Discussion: Our results show that the cross-linguistic generalizability of ML models of vocal markers of schizophrenia is very limited. This is an issue if our first goal is to translate these vocal markers into effective clinical applications and apply them to support the assessment and treatment of schizophrenia especially in under-represented and under-resourced contexts. We argue that more emphasis needs to be placed on collecting large open cross-linguistic datasets to test the

generalizability of voice-based ML models and explore more in depth the clinical applicability and adaptability of multi-lingual models to target under-resourced languages.

F28. UNDERREPRESENTED GROUPS' ATTITUDES, BELIEFS, AND KNOWLEDGE ABOUT BIOMARKERS AND SCHIZOPHRENIA

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Background: Biomarkers hold considerable promise for personalized medicine, in terms of risk prediction, disease staging, and tailoring treatments. Even though schizophrenia affects all racial/ethnic groups, there is a relative dearth of genetic and biomarker research that includes historically underrepresented (e.g., Black/African Americans, American Indian/Alaskan Native and Latinx) groups. Greater representation of ethnic and ancestral diversity in genetic and biomarker research is a scientific and ethical imperative. The purpose of this investigation was to explore attitudes, beliefs, and knowledge about biomarkers and schizophrenia. It is part of the UBIGR Participation Study (Gooding and Gleason, co-PIs), a concerted effort to ascertain the perspectives and needs of minoritized groups to help facilitate greater inclusion in and benefit from future schizophrenia research.

Methods: We surveyed nearly 1600 adult participants recruited from the community at large (58%) as well as through targeted crowdsourcing (42%). The questionnaire, administered online via Qualtrics, included items ascertaining demographic characteristics as well as participants' views on serious mental illness, schizophrenia, and genetic testing. Respondents' attitudes about research were examined using the Research Attitudes Questionnaire (RAQ-7; Rubright et al.,2011). To place their responses in context, participants were also asked about their health behaviors (e.g., cancer screenings) and attitudes towards safety practices (e.g. wearing helmets, vaccinations).

Results: The sample included participants who self-identified as: Non-Hispanic white (NHW, n=725), Black/African American (AA, n=599), Latinx (LTX, n=149), and American Indian/Alaska Native (AI/AN, n=120). Most were middle-aged (Mean age = 44.31 ± 12.4). There were significant group differences in terms of attitudes and knowledge about schizophrenia, attitudes about research, and relative willingness vs. reluctance to engage in biomarker research. Examination of the total RAQ-7 scores revealed that the distributions were dissimilar across the groups, $x2(3) = 34.37$, $p = 0.000$. Post hoc analyses revealed that the AA group expressed significantly less positive attitudes regarding research, as evidenced by lower total mean RAQ scores, than the other three ethnic groups. AA participants expressed less willingness to engage in biomarker research for schizophrenia than NHWs, with a significantly smaller proportion agreeing that they would be willing to undergo biomarker testing for schizophrenia [$x2(6)=41.19$, $p < 0.00001$] or mental illness in general [$x2(6)=31,04$, $p = 0.00003$]. Post hoc tests revealed that the AAs responded significantly differently from NHW and LTX groups but not from the AI/AN group, whereas the NHW group responded significantly differently from the AA and AI/AN group but not significantly different from the LTX group.

Discussion: These data have implications for future recruitment efforts and can be used to help modify scientists' approaches to research with participants historically excluded from biomarker research. The results suggest avenues to tailor education, as well as the need for more trust- and

alliance-building with historically under-included populations. Findings point toward the need for outreach and engagement programs to occur prior to attempting genetic research recruitment. Altogether tailored engagement would provide a path to build inclusive clinical trials for schizophrenia biomarkers.

F29. POSTER WITHDRAWN

F30. ASSOCIATIONS BETWEEN PERSISTENT DISTRESSING PSYCHOTIC-LIKE EXPERIENCES WITH CHANGES IN COGNITIVE AND NEURAL METRICS

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Background: Psychotic-like experiences (PLEs), including perceptual abnormalities and mild delusional thoughts, are relatively common in school-age children. Persistence and distress are factors that distinguish more clinically significant PLEs. Research on other forms of psychosis spectrum symptoms indicates that worsening symptoms over time are associated with worsening cognitive performance and greater impairments in neural metrics over time. Analyses examined whether longitudinal changes in cognition and global structural neural metrics predict persistent distressing PLEs using three waves of unique longitudinal Adolescent Brain Cognitive Development Study data (ages 9-13).

Methods: Multigroup univariate latent growth models examined associations between three waves of cognitive and neural metrics with three PLE groups: persistent distressing PLEs (n=279), transient distressing PLEs (n=374), and low distressing PLEs (n=1209). Multigroup latent change score models examined associations between two waves of neural metrics with PLE groups. Cognitive metrics included NIH toolbox tests measured at all three time points and neural metrics included global structural indices of thickness, surface area, and volume.

Results: Results indicate that for a test of inhibitory control and a test of processing speed, only the persistent distressing group showed decreasing performance over time. For neural metrics, for cortical volume, which normatively decreases across the course of adolescence, the persistent distressing PLEs group was the only group that failed to show this normative pattern and did not display lower cortical volume at wave 2 compared to baseline. In contrast, the persistent PLEs group was the only group to show lower subcortical volume at wave 2 compared to baseline, with the transient distressing PLEs and low PLEs groups not showing significant change in subcortical volume over time.

Discussion: Conclusion: Our findings provide evidence that only the persistent distressing PLEs group showed consistent evidence of impaired cognitive and neural metrics over time. Analyses demonstrated evidence that impairments over time in executive functioning may be broadly associated with clinically significant PLEs. Longitudinal impairments in processing speed and neural volume may represent unique features of persistent distressing PLEs in middle childhood/early adolescence. Results indicate that middle childhood/early adolescent PLEs show worsening cognitive and neural metrics that parallel findings from indices of severe mental illness, including psychotic disorders.

F31. RELATIONSHIP BETWEEN INTERPERSONAL TRAUMA AND SOCIAL SKILLS IN ADOLESCENTS AT FAMILIAL HIGH-RISK FOR PSYCHOSIS

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Background: Experiencing trauma perpetrated by other people may have particularly harmful effects on future social relationships. Broadly, studies have found a relationship between exposure to interpersonal trauma and impaired social skills across psychiatric illnesses, including psychotic disorders. However, our understanding of exposure to interpersonal trauma and social skills in those at familial high-risk (FHR) for psychotic disorders is not well known. This is of relevance given that FHR individuals, relative to peers, experience more trauma and impaired social skills and social problem behaviors. The present study seeks to examine differences in exposure to interpersonal trauma and relationships between exposure and current social skills and problems in adolescents at FHR for psychotic disorders, relative to their peers. It was hypothesized that FHR adolescents, compared to controls, will 1) experience more interpersonal trauma, but not non-interpersonal trauma, and 2) experience a stronger relationship between interpersonal trauma and current social problem behaviors and social skills.

Methods: A sample of adolescents (n = 53; 19 FHR; 24 Control) aged 13-19 years (M = 16.2, SD = 1.9) completed self-report measures including the Social Skills Improvement System (SSIS) and Childhood Traumatic Events Scale (CTES), which provided ratings of social skills and problem behaviors, as well as type and severity of childhood trauma. Group differences in trauma types (interpersonal and non-interpersonal) were examined with independent samples t-tests. Regressions examined whether group membership and trauma (number of incidents and overall severity) were associated with social skill outcomes; specifically, social problem behaviors and social skills.

Results: The FHR group reported more exposure to interpersonal trauma, but not non-interpersonal trauma, relative to controls, $t(22) = -4.07$, $d = 1.36$, $p = .001$. The FHR group, relative to controls, also experienced a stronger relation of interpersonal traumatic incidents with current social problem behaviors. Specifically, for the FHR group, the number of traumatic incidents ($\beta = .384$, $p = .025$) and overall childhood trauma severity ($\beta = .471$, $p = .003$) predicted social problem behaviors.

Discussion: These data contribute to ongoing work suggesting those at FHR for psychotic disorders experience more exposure to trauma but offer unique specificity. Interpersonal trauma in particular may be impacted in this group. Furthermore, these data offer novel findings suggesting that exposure to interpersonal trauma is related to current social skills and problem behaviors. Results have clinical implications for adolescents at risk for psychosis, suggesting the importance of a trauma-informed approach for future social skill and functioning interventions. Additionally, these data could help clarify contributors to and/or consequences of social deficits in those at genetic risk for psychosis, as well as risk for future mental health disorders.

F32. CONSEQUENCES OF ANTIPSYCHOTIC INDUCED HYPERPROLACTINEMIA ON GROWTH AND PUBERTAL DEVELOPMENT

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Background: Knowledge is lacking regarding the consequences of antipsychotic induced hyperprolactinemia on height and pubertal development in children and adolescents. Prolactinoma induced hyperprolactinemia, which are typically more severe but for a shorter duration than antipsychotic induced hyperprolactinemia, can induce delayed pubertal development if not treated. However, the effect of antipsychotic induced hyperprolactinemia on growth- and sex hormones as well as height and pubertal development in children and adolescents are not well studied. This is the case, even though 28-69 % of children and adolescents who are treated with antipsychotics experience hyperprolactinemia. In this study, we aim to investigate whether antipsychotic induced hyperprolactinemia is associated to disturbances in height and pubertal development.
Methods: In this retrospective cohort study, we are studying a population of children and adolescents aged 7-18, who are treated with antipsychotics. We are currently including patients and the aim is to include a population of 385 patients. Patients with a somatic illness or state causing either hyperprolactinemia or interfering with sex hormones (e.g. sex change, breastfeeding, pregnancy) are excluded. Using medical record data on half-yearly serum-prolactin measurements, area under the curve for prolactin exposure during antipsychotic treatment will be investigated for association with height development and current Tanner stage measured during a medical examination. Confounders such as parental height, psychiatric and somatic comorbidities and treatment with other medications will be taken into account and adjusted for.
Results: Preliminary data will be presented at the conference.
Discussion: Current guidelines on how antipsychotic induced hyperprolactinemia should be handled are contradicting and largely based on consensus, in lack of a solid evidence base, especially regarding children and adolescent. This study aims to provide some of the knowledge regarding antipsychotic induced hyperprolactinemia with a focus on consequences for height and pubertal development in a population of children and adolescents. If no association exists, suboptimal treatment may be avoided. On the contrary, if an association exists, this may warrant an increased focus in guidelines on consequences for growth and pubertal development, so this may be taken into account when choosing antipsychotic treatment.

F33. EARLY LIFE ADVERSITY PREDICTS PSYCHOTIC-LIKE EXPERIENCES IN ADOLESCENT GIRLS: EVIDENCE FROM A LONGITUDINAL ANALYSIS

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Background: While psychotic-like experiences seem relatively common in the general population, the trajectories through which young people develop them remain poorly understood. Early life adversities (ELA), capturing negative and stressful experiences in childhood, have been consistently associated with the onset of psychosis later in life. Furthermore, ELA may represent a more severe risk factor for the onset of psychopathology in females. Yet, it is unclear when sex-specific associations between ELA and psychotic-like experiences emerge. Here, we investigated the early relationship between ELA, sex, and the onset of psychotic-like experiences in young adolescents.
Methods: We evaluated a total of n=230 school adolescents (mean age=12.4 years SD=1; 54% female) at baseline and again n=90 of them (66.7% female; mean age=13.7 years SD=0.9) after one year. We evaluated ELA with the Childhood Experience of Care and Abuse (CECA) and psychotic experiences using the Community Assessment of Psychic Experiences (CAPE). We estimated cumulative exposure to individual-level and area-level adversity, and a weighted score reflecting frequency and perceived distress of psychotic experiences. We used two regression models: first, to investigate the effects of ELA and sex on psychotic-like experiences at baseline (model 1) and second, to investigate whether baseline ELA and sex predicted psychotic-like experiences at follow-up, whilst controlling for baseline psychotic-like experiences (model 2).
Results: At baseline, females experienced less cumulative ELA (mean score=2.4 SD=1.6) than males (mean score=2.6, SD=1.7), but more psychotic-like experiences (mean score=0.2 SD=0.3 vs mean score=0.11 SD=0.2 respectively). Model 1 significantly explained variance in baseline psychotic-like experiences (adjusted $R2=0.11$, $p<.001$). There were significant main effects of ELA ($F(227)=0.05$, $p<.001$) and sex ($F(227)=0.1$, $p=.004$) on baseline psychotic-like experiences, and adding the interaction between ELA and sex did not improve model fit ($p=.19$). At follow-up, females consistently reported more psychotic-like experiences (mean score=0.22 SD=0.4) than males (mean score=0.06 SD=0.15). Model 2 explained variance in psychotic-like experiences at follow-up (adjusted $R2=0.33$, $p<.001$), and revealed a significant interaction between ELA and sex ($F(85)=0.11$, $p=.009$), whilst controlling for baseline psychotic-like experiences. Post-hoc exploration revealed a significant association between baseline ELA and psychotic-like experiences a year later in females ($F(55)=0.09$, $p=.007$), but not in males ($F(27)=0.02$, $p=.382$).
Discussion: At baseline, cumulative exposure to ELA and female sex were independent risk factors for psychotic-like experiences. In females, but not in males, baseline ELA predicted psychotic-like experiences a year later, independently of baseline psychotic-like experiences. This suggests that the heightened sensitivity to ELA in females develops early in life. Girls who enter puberty relatively early may be particularly vulnerable to psychopathology, and early onset puberty might interact with ELA to increase the vulnerability to psychotic-like experiences. Indeed, our ongoing work will investigate puberty-related effects in the larger sample. Still, this preliminary evidence points to the heightened vulnerability of girls exposed to ELA, who may benefit from early intervention to ameliorate the possible sequelae of these events.

F34. A META-ANALYTIC INVESTIGATION OF METACOGNITIVE THERAPIES FOR SCHIZOPHRENIA-SPECTRUM ILLNESS

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Background: The number of controlled studies of metacognitive therapy for schizophrenia-spectrum illness has grown substantially over the past 10 years. While recent meta-analyses have evaluated specific forms of metacognitive therapy (i.e., metacognitive training [MCT] for psychosis), or have focused on specific domains of outcome (i.e., insight, or cognitive bias), no recent meta-analysis has evaluated different forms of metacognitive therapy (e.g., metacognitive reflection and insight therapy [MERIT] and MCT) in the literature together across a broad range of outcome measures.
Methods: The meta-analysis was pre-registered on PROSPERO (CRD42022318713). Electronic databases were searched up to June 2022 using variants of the key words: "metacognitive therapy", "clinical trials", and "schizophrenia". Articles were included if they met the following criteria: (1) were published between 1980 (year of publication of DSM-III) and June, 2022, (2) study included at least 70% people with schizophrenia/schizoaffective disorder, delusional disorder, psychotic disorder not otherwise specified, or schizophreniform disorder; (3) study provided focused training on knowledge and feelings around cognitions as an intervention; (4) study measured at least one symptom or index of cognitive bias; (5) study included a control group. Data were extracted by 4 authors with strong reliability (>90%). Symptom, bias, function and other relevant outcomes were assessed with random effects models.
Results: This search produced 45 unique controlled trials from over 20 countries that met all inclusion criteria for the study. Preliminary meta-analytic results revealed that metacognitive therapy produced significant small-to-moderate size effects on positive symptoms (g=.31; 95% CI: .18/.44) and delusions (g=.35; 95% CI: .12/.58).
Discussion: Preliminary results support the application of metacognitive therapies for reducing positive symptoms generally and delusions more specifically in schizophrenia-spectrum illness. The implications of these findings for further refinement of existing meta-cognitive therapies will be discussed.

F35. PREVALENCE OF PROMINENT NEGATIVE SYMPTOMS USING DIFFERENT CRITERIA FOR CLINICAL STABILITY

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Background: Negative symptoms are an important source of disability in people with schizophrenia but Identifying patients with negative symptoms for clinical trials has several challenges. To focus on primary negative symptoms, clinical stability needs to coincide with the presence of negative symptoms. For defining clinical stability, one strategy has been to select patients based on the absence of agitated or disruptive behavior. In a series of treatment studies targeting negative symptoms, participants were selected for the presence of negative symptoms, accompanied by scores ≤ 4 on PANSS items related to agitation (P4 Excitement, P6 Suspiciousness/persecution, P7 Hostility, G8 Uncooperativeness, and G14 Poor impulse control). These patients were found to have very low levels of total positive symptoms despite no direct consideration of these symptoms during selection. This study examines the prevalence and convergence of different definitions of clinical stability with negative symptoms in a large, aggregated sample of outpatients with schizophrenia. It is critical to understand if clinical criteria

used to enter participants into treatment trials are reflective of the realities of typical patients seen in everyday practice.

Methods: 867 outpatients with schizophrenia participated in this study, with their data coming from four different NIMH funded studies. All participants were evaluated with the PANSS, as well as an array of other assessments including everyday functioning. We examined the proportion of patients who met different clinical criteria for symptom stability as well as the presence of negative symptoms. We used the previous criteria for agitation-based stability and compared that to the prevalence of clinical stability based on having scores ≤ 4 on PANSS items related to psychosis (P1 Delusions, P2 Conceptual Disorganization, P3 Hallucinations, P6 Suspiciousness, and G9 Unusual thought content). The negative symptoms severity criterion using the original PANSS negative symptoms subscale was > 20.

Results: The sample was racially and ethnically diverse (45% black; 22% Latinx), with 44% females. 82% of the participants met the agitation-based stability criteria and 40% met the psychosis-based stability criteria. 22% met the negative symptoms criteria. 17% met the combined agitation and negative symptoms criteria, while 10% met the combined psychosis and negative symptoms criteria. 100% of the cases who met the psychosis based stability criteria also met the agitation-based criteria. Participants who met the agitation and negative symptoms criteria had significantly ($p<.001$, $d=.33$) more impairments in in everyday social functioning rated by high contact informants but not work or everyday activities. PANSS reduced emotional experience scores were also considerably higher in those who met the combined criteria ($p<.001$; $d=1.59$).

Discussion: Selection criteria applied in previous negative symptoms clinical trials identifies about 20% of ambulatory participants with schizophrenia. This proportion of cases suggests that there is a meaningful subgroup of participants who are both clinically stable and have congoing negative symptoms. Selecting for clinical stability based on agitation may reduce rater bias, but still yields a sample with reduced positive symptoms overall. Participants selected with these combined criteria manifest the expected profile of relatively specific social deficits, with no differential impairments in aspects of everyday functioning that are more strongly linked to cognitive impairments.

F36. PATIENT-REPORTED OUTCOME MEASURES IN BIPOLAR DISORDER DEPRESSION; A RANDOMIZED CONTROLLED TRIAL COMPARING ELECTROCONVULSIVE THERAPY WITH ALGORITHM BASED TREATMENT AS USUAL.

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Background: Electroconvulsive therapy (ECT) is a treatment alternative for severe or treatment resistant bipolar disorder (BD) depression. Concerns regarding memory problems are limiting its use.

There is a need for more information with emphasis on how patients experience ECT to optimize informed treatment decisions.

Methods: 73 inpatients with severe treatment resistant BD depression in Norway were included in this multicentre randomized controlled trial. Patients were randomized to either ECT or algorithm based pharmacological treatment (APT). Weekly assessments were performed during the six week treatment period, and again at six months follow up. Clinician-rated assessments included the Montgomery and Asberg Depression Rating Scale (MADRS) and Clinical Global Impression – Improvement (CGI-I). Short-term Results: showed that ECT was significantly more effective compared to APT (previously published). Further, the following patient rated outcome measures (PROMs) were used; the Patient Global Impression – Improvement (PGI-I) and the Everyday Memory Questionnaire-28 questions version (EMQ).
Both the CGI-I and PGI-I are Likert-scales ranging from 1 Very much improved/ Very much better respectively, through to 7 Very much worse.

The EMQ has a maximum score of 252 and a minimum score of 28, with higher scores signifying greater memory problems. The EMQ was applied at three time points, before treatment, immediately after treatment, and at six months follow-up.

In the preliminary analyses, we compared scores between the two groups using independent t-tests. Further, we plan longitudinal analyses with linear mixed effects models.

Results: A varying number of patients are included in the analyses, as patients switching groups or otherwise violating the protocol were excluded from further analysis. 66 patients entered the treatment (ECT N=36, APT N=30), 44 completed treatment (ECT N=23, APT N=21) and 39 met for 6 months follow up (ECT N=20, APT N=19).
Before treatment, mean score on the MADRS was 39.5 and 37.6 in the ECT- and APT group respectively (p 0.272).

Preliminary results indicate a greater self−rated improvement in patients treated with ECT compared to APT from week 3 (PGI-I, 2.5 vs 3.2, p = 0.017), or week 5 (observer−rated) (CGI-I, 2.0 vs 2.8, p = 0.001). However, this group difference was transient, and no longer present at 6 months follow up on either CGI-I or PGI-I (2.4 vs 1.9, p = 0.444 and 2.1 vs 1.6, p = 0.131 respectively).

There was no statistically significant difference between the groups on the EMQ, but the ECT group had consistently numerically lower scores at all three time points (118.5 vs 125.8, p = 0.519, 107.1 vs 116.7, p = 0.409, and 87.3 vs 103.5, p = 0.278 respectively).

Further results from the longitudinal analysis will be presented at the congress.

Discussion: PROMs as assessed in this study showed that patients who received ECT reported greater improvement compared with APT during the acute treatment period. Contrary to what may be common belief, we did not find that patients in the ECT group reported more memory problems compared with APT.
This information will add to the knowledge base patients utilize when making informed treatment choices regarding their severe mental illness.

F37. INFLUENCE OF CANNABIS ON THE RISK OF TRANSITION IN YOUNG PEOPLE AT ULTRA-HIGH RISK OF PSYCHOSIS (ICAAR STUDY): A LONGITUDINAL STUDY

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Background: There is evidence of an association between exposure to cannabis and the emergence of schizophrenia. However, little is known about longitudinal effects of cannabis exposure and the influence of genetic factors and neurodevelopment on the transition to psychosis. We designed a study on the Influence of Cannabis in Adolescents and Adults at Risk mental state (ICAAR) in order to fulfil these gaps.

Methods: 312 individuals characterised as Ultra-High Risk (UHR, n=170), First Episode Psychosis (FEP, n=54) and non-at-risk Help-Seeking Controls (HSC, n=88) were included in ICAAR using the Comprehensive Assessment of At Risk Mental States (CAARMS). Participants responded to questionnaires of cannabis consumption, neurodevelopment at baseline and after 6- and 12-months follow-ups, and a blood sample was collected for genetic assessment. We compared the three groups at baseline and UHR versus HSC according to whether they had converted to psychosis or not at follow-up. We examined the influence of cannabis, neurodevelopment and genetic factors in the conversion to psychosis using univariate comparisons.

Results: The three groups did not present sociodemographic or non-psychotic clinical characteristics differences. At baseline, future converters UHR (n=42) consumed significantly more cannabis compared to non-converters UHR (n=62). They also experienced more anxiety, time contraction or expansion, impression of change in self and visual hallucinations related to cannabis consumption compared to non-converters. Converters also showed more neurodevelopmental features compared to non-converters. We found no association between conversion and polygenic risk scores of schizophrenia.

Discussion: This prospective study is the first to consider the influence of cannabis in the progression of psychotic illness, associated with neurodevelopment and genetic measures. It shows that, while there are no major differences in cannabis consumption between groups, the data at baseline can predict future converters to psychosis, and this appears to be associated with neurodevelopmental features. These results strongly support the emphasis to limit cannabis consumption in UHR.

F38. EFFICACY AND SAFETY OF ICLEPERTIN (BI 425809) IN PATIENTS WITH SCHIZOPHRENIA: CONNEX, A PHASE III RANDOMISED CONTROLLED TRIAL PROGRAM

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Background: Cognitive impairment is a major determinant of poor functional outcome in schizophrenia and no pharmacological treatments are currently available. Iclepertin (BI 425809), an inhibitor of glycine transporter-1, enhances glutamate N-methyl-D-aspartate receptor signalling in the brain by increasing synaptic levels of its co-agonist glycine (1). The Phase III CONNEX program aims to confirm the efficacy, safety and tolerability of iclepertin in improving cognition and functioning across a large cohort of patients with schizophrenia.

Methods: The CONNEX program consists of 3 replicate randomised, double-blind, placebo-controlled parallel trials in patients diagnosed with schizophrenia (NCT04846868, NCT04846881, NCT04860830). 586 patients are being recruited from 32 countries and randomised 1:1 to receive iclepertin 10 mg, or placebo daily over 26-weeks. The primary efficacy endpoint is change from baseline (CFB) in overall composite T-score of the Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery. The key secondary efficacy endpoints are CFB in total score on the Schizophrenia Cognition Rating Scale and CFB in the adjusted total time in the Virtual Reality Functional Capacity Assessment Tool. Long-term safety and tolerability data will be collected in an open-label safety extension study (CONNEX-X; NCT05211947).

Results: The studies are currently recruiting (first patients enrolled Aug–Sept 2021), with completion expected in Q2 2024. An overview will be provided of the current study status, including information relating to screening failures, and data collection experiences.

Discussion: To date, most large industry-sponsored studies testing compounds for cognitive deficits have failed to show proof-of-clinical-concept. Demonstration of efficacy in this Phase III program would establish iclepertin as the first efficacious medication to address cognitive impairments and daily functioning associated with schizophrenia.

F39. EVENAMIDE, AS AN ADD-ON TO ANTIPSYCHOTICS, BENEFITS PATIENTS WITH TREATMENT-RESISTANT SCHIZOPHRENIA: 1-YEAR INTERIM RESULTS FROM THE FIRST 100 PATIENTS IN AN ONGOING INTERNATIONAL RANDOMIZED STUDY

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Background: Treatment resistant schizophrenia (TRS) develops in ~30% of patients in about 5 years from starting treatment with antipsychotics (APs), resulting in increased morbidity, suicidality, and mortality [1]. Findings from neurochemistry, neuro-metabolism, and functional imaging in TRS patients indicate abnormalities in glutamatergic neurotransmission [2] rather than excess of dopamine synthesis [3, 4], suggesting the need to add a drug that attenuates glutamate release. Evenamide, a selective inhibitor of voltage-gated sodium channels, is devoid of biological activity at >130 CNS targets, normalizes glutamate release without affecting basal levels, and demonstrated benefits in animal models of psychosis as monotherapy and as an add on to APs (including clozapine), reversing deficits produced by amphetamine, scopolamine, phencyclidine, or ketamine. Combination of ineffective doses of evenamide and other APs, including clozapine,

is associated with similar benefits, suggesting synergies in mechanisms that may benefit poor responder patients to current APs. Study 014 and its extension, Study 015, were designed to evaluate the long-term safety, tolerability and preliminary efficacy of evenamide given orally at 3 fixed doses (7.5, 15 and 30 mg bid) in patients with TRS [5] not responding to a stable therapeutic dose of an AP. Assessment of efficacy was based on changes from baseline on the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression – Severity and Change (CGI-S/C), while tolerability was assessed based on all safety measures.

Methods: Study 014 is a 6-week, randomized, rater-blinded, international study with completers continuing assigned doses for an additional 46 weeks in Study 015. Patients were initially randomized to 7.5 or 15 mg bid; the Independent Safety Monitoring Board (ISMB) allowed randomization to 30 mg bid after reviewing safety data from the first 50 patients. Subsequently, the 7.5 mg bid dose group was discontinued, and patients were randomized 1:3 to doses of 15 mg bid and 30 mg bid, respectively, to achieve an approximately equal number of patients assigned to each of the three treatment groups. At baseline, patients were moderately to severely ill (CGI-S of 4 to 6), with a PANSS total score of 70-90 and predominant positive symptoms (score of 4 or more on at least 2 core symptoms and a PANSS Positive total score ≥ 20), along with functional deficits (GAF ≤ 50). Efficacy ratings were performed by a psychiatrist blinded to the evenamide dose. Data were analyzed as a single evenamide group, using descriptive statistics to assess changes from baseline to endpoint (Week 52).

Results: A total of 161 patients were randomly assigned to treatment in Study 014, with a minimum of 50 in each of the 3 treatment groups. Interim, group-blinded, 52-week results for safety and efficacy (PANSS and CGI-S/C) for the first 100 patients (including 6 on 30 mg bid) will be presented. All safety and efficacy data for patients randomized to 7.5, 15, and 30 mg bid were pooled in a single group to maintain the blind in the study. Disposition data collected to date in patients who have completed their participation in Study 014 demonstrate a low rate of dropouts (5.0%), with a high proportion (94%) of patients who completed 6 weeks of treatment continuing in Study 015.

Discussion: This trial is an extension of Study 014, the first international trial of a drug acting on the glutamate system as an add-on to a single typical or atypical AP in patients with TRS. If positive, the results of this study would support the safety and efficacy of long-term administration of evenamide as add-on to APs in TRS patients.

F40. THE EFFICACY OF LUMATEPERONE 42 MG IN THE TREATMENT OF SCHIZOPHRENIA: A POOLED ANALYSIS OF PHASE 2 AND 3 RANDOMIZED CONTROLLED TRIALS

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Background: Lumateperone is an FDA-approved antipsychotic to treat schizophrenia and depressive episodes associated with bipolar I or bipolar II disorder as monotherapy and as adjunctive therapy with lithium or valproate. Lumateperone has a unique mechanism of action that simultaneously modulates serotonin, dopamine, and glutamate neurotransmission. Lumateperone was evaluated in 3 randomized, double-blind, placebo-controlled studies in patients with acute exacerbation of schizophrenia. In 2 of the studies, lumateperone 42 mg (ITI-007 [lumateperone

tosylate] 60 mg) met the primary endpoint, significant reduction vs placebo in the Positive and Negative Syndrome Scale (PANSS) Total score. In 1 study, no significant difference between lumateperone 42 mg vs placebo was seen; however, the magnitude of improvement in PANSS Total score was similar to that seen in the 2 positive studies. In all 3 studies, lumateperone was well tolerated. This pooled analysis of the 2 positive studies evaluated the efficacy of lumateperone 42 mg in the treatment of schizophrenia.

Methods: Data were pooled from the 2 positive studies for analysis. The primary efficacy endpoint in the pooled analysis was change from baseline to Day 28 in PANSS Total score. Secondary assessments included change from baseline in PANSS subscale scores (Positive Subscale [PS], Negative Subscale [NS], General Psychopathology Subscale [GPS], derived Prosocial Factor [PF]) and Clinical Global Impressions–Severity (CGI-S) score. Additional secondary endpoints were percent of patients meeting various PANSS response criteria (20%, 30%, and 40% PANSS improvement). Analysis of PANSS Total and subscale scores, and CGI-S score was conducted via a mixed model for repeated measures; PANSS response rates were analyzed using Fisher's exact test.

Results: The intent-to-treat population comprised 520 patients (placebo, 221; lumateperone 42 mg, 224; risperidone 4 mg, 75). Lumateperone 42 mg significantly reduced PANSS Total score compared with placebo (least squares mean difference versus placebo [LSMD]= −4.76, P=.001) with efficacy similar to risperidone 4 mg (LSMD= −4.97, P=.014). Lumateperone 42 mg also showed significant efficacy vs placebo across 3 of the 4 PANSS subscales analyzed (PS, LSMD= −1.71, P<.001; NS, LSMD= −0.76, P=.098; GPS, LSMD= −2.04, P=.009; PF, LSMD= −1.47, P<.001) and on the CGI-S (LSMD= −0.29, P<.001). Lumateperone 42 mg was associated with significantly higher PANSS response rates than placebo for each criterion level (20% improvement, 37% vs 50%, P=.010; 30% improvement, 24% vs 38%, P=.002; 40% improvement, 15% vs 25%, P=.010). Negative results from the third study did not impact the ability of lumateperone 42 mg to significantly separate from placebo when the 3 studies were pooled.

Discussion: In this pooled analysis in adult patients with acute exacerbation of schizophrenia, lumateperone 42 mg significantly improved symptoms of schizophrenia. Clinically meaningful improvement on PANSS total score and various subscales, and greater PANSS response rates suggest that lumateperone 42 mg has broad efficacy across schizophrenia symptoms.

F41. THE IMPACT OF SCI-PANSS INTERVIEW DURATION ON THE DATA QUALITY

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Background: The use of the Structured Clinical interview for the Positive and Negative Syndrome Scale (SCI-PANSS) has become standard practice in clinical trials as part of the effort to enhance reliability and validity through standardization. The duration of clinical interview, however, may vary considerably, even when the structed interview guide is utilized. While some of the variability may be explained by the severity of psychotic symptoms in an individual patient, interviews that are too long or too short may raise concerns about rater performance and may impact the accuracy of ratings.

In this study we examined whether assessments that are durational outliers (either too short or too long) result in higher rates of scoring discrepancies and/or are deemed to not meet assessment

quality expectations when reviewed by a team of highly trained and calibrated independent clinicians.

Methods: We aggregated and analyzed the data from several large multinational, multicenter studies of patients with schizophrenia, including 7,000 interviews conducted with 1,795 subjects. PANSS assessments were stratified into three groups based on the duration: expected (20-60 minutes), too short (<20 minutes), and too long (>60 minutes.) The cut-off was established based on the theorical and conceptual framework, as well as general experience with the use of the interview. Interviews conducted by site raters were independently reviewed via audiovisual recording. Both site raters and independent reviewers underwent a rigorous qualification and certification process prior to being added to studies. ANOVA statistics were calculated to compare scoring discrepancy rates, and number of item score discrepancies, as well as quality and scoring failure rates across the three duration groups.

Results: One-way ANOVAs comparing the duration groups revealed significantly worse performance in the too long duration group versus the expected duration for discrepancy rates ($df = 2$, $F = 18.36$, $p < .01$) and significantly higher quality failures in too short duration group than expected duration ($df = 2$, $F = 19.16$, $p < .01$). While there were no statistically significant differences among the groups for item discrepancies and score failure, the too long duration had more both item discrepancies and score failures compared to the other two groups.

Discussion: Results indicate that unusually long duration PANSS interviews are associated with significant increases in scoring discrepancies and unusually short duration PANSS interviews are significantly associated an increased administration errors. Unusually long PANSS administration times were also associated with slight increase in both scoring and administration errors. Additional analyses will be conducted to evaluate the magnitude of total score difference between site raters and independent reviewers to further investigate the score discrepancy rates and conduct a qualitative analysis to identify the reasons for quality failure for unusually short administration.

F42. POPULATION PHARMACOKINETIC MODELING OF TOTAL ACTIVE MOIETY EXPOSURE FOLLOWING DOSES OF TV-46000, A LONG-ACTING SUBCUTANEOUS ANTIPSYCHOTIC INJECTION

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Background: TV-46000 is a long-acting subcutaneous antipsychotic (LASCA) injection with flexible dosing either once monthly or once every two months. Population pharmacokinetic (PopPK) modeling was used to characterize the pharmacokinetics (PK) of the parent drug, risperidone and the active metabolite, 9-OH risperidone, and to describe the time course of total active moiety (risperidone + 9-OH risperidone, TAM) exposure compared to oral risperidone dose regimens, and to evaluate the potential covariate effects on the TAM exposure following TV-46000 in patients with schizophrenia.

Methods: The PopPK model included rich phase 1 PK data and sparse phase 3 PK data. A sequential parent-metabolite PopPK model was developed using nonlinear mixed effect modeling software (NONMEM). Covariate selection was performed using the likelihood ratio test with forward addition followed by backward elimination. Potential effects of intrinsic and extrinsic

factors were evaluated on clearance (CL) and rate constants for fast (KA1) and slow (KA2) absorption. The intrinsic factors included demographics, concomitant medications, and disease status. Extrinsic factors included injection site, rubbing injection site, vial or prefilled syringe presentation, injection volume [dose]. The PopPK model calculated TAM exposure metrics at steady-state (AUC,ss, Ctrough,ss, and Cmax,ss) in comparison to TAM exposures following oral risperidone doses.

Results: PK of risperidone was best described by 1-compartment model, with double first-order absorption route (1 fast and 1 slow) and first-order elimination. KA1 decreased with increased injection volume (more pronounced with subtherapeutic doses, 12.5mg and 25mg). The balance between the KA1 and KA2 absorption rates shifted toward KA2 with increased body mass index (BMI). Administration to the arm was associated with a higher KA1 than injection in the abdomen. Although injection site was a significant covariate in the parent model, no impact was observed on the overall steady-state TV-46000 exposure, as CL was similar for both sites. PK of 9-OH risperidone was best described by a 1-compartment model with first-order input from the risperidone compartment and first-order elimination. There were no statistically significant or clinically relevant covariate effects on the PK of 9-OH risperidone. Overall, TAM exposure (AUCss) was not affected by covariates (injection volume, BMI, and injection site). Simulations of TAM concentrations following TV-46000 administration across all doses and dose regimens were within the range of TAM exposure (Ctrough,ss to Cmax,ss) of the approved doses of oral risperidone (1-16 mg/day).

Discussion: While injection volume [dose], BMI and injection site were identified as statistically significant covariates affecting the double first-order absorption route of risperidone, overall TAM exposure (AUC,ss) was not affected by the identified covariates and there were no clinically relevant effects.

F43. COMPUTATIONAL MODELLING REVEALS ALTERED PERCEPTUAL-DECISION STRATEGIES AND LESS EFFICIENT METACOGNITION IN PATIENTS WITH PSYCHOTIC DISORDERS

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Background: Every day we face numerous noisy perceptual decisions, which we rarely have full certainty about. For example, in a crowded metro station, we may have to decide quickly if a voice we heard was a friend calling our name. Bayesian inference and predictive coding provide theoretical frameworks for explaining how humans constantly aim to optimize their perceptual efficiency based on internal predictions and feedback. Metacognitive evaluation, especially confidence, is one way of internally surveying one's own decision accuracy. Both perceptual and metacognitive decisions are based on the accumulation of sensory evidence towards bounds. In psychotic disorders, both perceptual and metacognitive accuracy are believed to be suboptimal. However, little is known if metacognition is selectively impaired in perceptual decisions and how such impairment relates to hallucination and delusion proneness.

Methods: We assessed patients with psychotic disorders admitted to a psychiatry ward (F2x.x diagnoses; N(clinical)=14; M(age)=35.6; female=6) and healthy controls (N(healthy)=33; M(age)=24.8; female=25). All patients received antipsychotic medication. An auditory detection

task presented participants with sounds at low vs. high levels of noise and asked them to report if they perceived a voice in the noise (50% of all trials contained a voice sample) and their confidence in the decision's accuracy. Individual hallucination and delusion proneness scores were obtained from the LSHS-R and PDI instruments. Our analyses focused on hierarchical modelling of perceptual decisions and metacognitive efficiency. Particularly, drift diffusion models mechanistically characterize factors underlying response times in rapid binary perceptual decisions.

Results: Modelling results show decreased perceptual decision accuracy on voice-present trials and for patients. This group's overall worse accuracy co-occurs with overall higher confidence, which was also expressed in their generally lowered metacognitive efficiency. Patient status also interacted with delusion proneness as in accuracy increased most with higher delusion proneness. Patients' median perceptual response times (RTs) were generally slower and also depended on experimental factors (e.g., slower RTs for voice-absent trials). In general, increasing delusion proneness resulted in slower RTs across all participants. Hallucination and delusion proneness both interacted with patient status and predicted RTs but in opposite ways. While patients' RTs expedited more with increasing hallucination scores, their RTs slowed more with increasing delusion scores. A detailed analysis of RT distributions using accuracy coded data in the drift-diffusion framework revealed that evidence accumulation was overall slower for accurate voice-present than voice-absent trials. Patients exhibited the slowest accumulation for voice-present trials, while no group difference was observed for voice-absent trials. Patients' encoding time of the stimulus evidence was particularly fast in voice-absent trials alongside the largest increases in their decision boundary.

Discussion: Our results demonstrate generally altered perceptual decision-making paired with performance-independent reduced metacognitive abilities in patients. Their decision strategy results in some fast trials, particularly when a voice is absent, but a general strategic shift towards longer evidence accumulation before a response in most trials. In line with expectations, increased delusion proneness leaves these patients to be more cautious in responding and deliberate in their confidence ratings at the expense of higher performance costs.

F44. SYNTHETIC LANGUAGE AS A MARKER OF SCHIZOPHRENIA IN MORPHOLOGICALLY-RICH LANGUAGES: A NEED TO INTEGRATE SYNTHETIC LANGUAGE ASSESSMENT IN NATURAL LANGUAGE PROCESSING?

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Background: Natural Language Processing (NLP), which deals machine interpreting human language, is emerging as a potential tool for measuring thought, language and communication impairment in schizophrenia (Sz). Given the vastness of any natural human language preprocessing of text is done in several ways with the intention of decreasing the computational requirement. Among others stemming and lemmatization are preprocessing methods that essentially reduce any given word to their root/dictionary, thereby they reduce the inflectional or rather synthetic language features like inflectional morphemes – which are suffixes and prefixes expressed for grammatical functions or attributes to derive the root words in deriving semantic coherence and related speech metrics. Dravidian languages like Kannada are derivationally and

morphologically rich with higher and more complex inflectional and agglutinative words (two or more words are joined together whilst being expressed). We aim to evaluate the importance of these words in differentiating schizophrenia (Sz) from healthy controls that can be potentially missed in the preprocessing for NLP.
Methods: Four-minute speech samples of six Sz and six healthy controls (HCs) were collected by presenting two images of the Indian version of the Thematic apperception test. The speech samples were recorded in the language of kannada, on a portable audio recorder and was later transcribed to text. Two native Kannada speakers consensually quantified the inflectional and agglutinative words. Standard texts "Kannada Ratnakosha" and "Sankshipta Kannada Nighantu" books were used as references in identifying the root words and inflectional morphemes. The Chi-square test was applied to assess the proportion of inflectional and agglutinative words used by Sz compared to HCs
Results: There was a significantly higher proportion of usage of inflectional words (53% vs 47%, $x2=3.85$, $p=0.049$) as well as agglutinative words (20% vs 13%, $x2=11.35$, $p<0.001$) in the speech by patients with schizophrenia compared to healthy controls
Discussion: In this preliminary study, the usage of morphologically complex words was seen in patients with Sz in comparison to HC. Understanding the pattern of these synthetic languages may form an important marker to identify the linguistic disturbances in schizophrenia. A high proportion of inflectional and agglutinative words seen in the Kannada language emphasizes the need for evaluating these morphemes rather than removing them in NLP-based linguistic analysis.

F45. QUALITY OF LIFE AMONG VOICES HEARERS IS ASSOCIATED WITH CONTROL OVER THEIR VOICES AND THEIR ABILITY TO UPDATE THEIR BELIEFS ABOUT THE WORLD: A DATA-DRIVEN APPROACH

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Background: Auditory-verbal hallucinations (AVH) are a core symptom of psychosis spectrum disorders. By the time most patients present with symptoms, the prognosis is highly variable but overall associated with significantly increased lifetime morbidity and mortality. Because of this, significant efforts have been made in recent years to intervene early in the process, when treatment is most impactful. Unfortunately, symptoms like AVH have both poor sensitivity and specificity in predicting who will go on to develop psychosis, as the prevalence of these perceptual abnormalities in the general population is estimated to be as high as 10-15%. Complicating matters further, AVH lead to highly variable degrees of distress, dysfunction, and decreased quality of life across the population. Unfortunately, the determinants of this variance are largely unknown, despite their significant promise toward helping improve voice-hearers' functioning. This study sought to better understand these determinants by exploring the relationship between quality-of-life patterns in help-seeking (HS) and non-help-seeking (NHS) individuals experiencing AVH utilizing a novel, powerful data-driven framework.
Methods: A subsample of 181 help-seeking voice-hearers (HS) 232 non-help-seeking voice-hearers (NHS), and healthy volunteers (n= 146) were selected from the ongoing Yale COPE Project. Sparse partial least squares (SPLS) analysis was employed to detect multivariate

associations between quality-of-life measures and self-reported information on sociodemographic features, depressivity, personality traits, traumatic events, delusional tendencies, hallucinatory traits, and religiousness/spirituality, as well as behavioral performance on the auditory conditioned hallucinations (CH) task, which has been shown to be sensitive to hallucination state and reflective of perceptual states driving hallucinations using computational modeling.
Results: The first extracted latent variable on SPLS analysis linked decreased quality of life to survey and questionnaire variables that measured depressed mood and other symptoms of depression. Intriguingly, the second latent variable linked better social and family relationships, higher functioning in daily life, and sexual drive with the ability to control AVH, in addition to multiple task-derived computational parameters corresponding to perceptual belief updating and confidence in perceptual judgments.
Discussion: These results suggest that lower quality of life in all participants is most highly associated with depressive symptoms, the next most significant factor in voice-hearers is having control over AVH, along with a robust ability to update one's beliefs about the world.

F46. SIPS GENERAL PSYCHOPATHOLOGICAL SYMPTOMS PREDICTION USING MACHINE LEARNING METHODS

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Background: At Risk Mental State (ARMS) criteria depend on scores on the Structured Interview for Symptoms Instruments Psychotics (SIPS - Intermittent Psychotic Symptoms) specially based on positive psychopathological symptoms. This study aimed to predict general psychopathological symptoms from SIPS scale using recent machine learning methods applied in facial and head movement features extracted from brief video-recordings.
Methods: 58 ARMS and 69 Control participants were interviewed with the Structured Interview for Prodromal Syndromes while being recorded. Based on video facial landmarks, descriptive statistics and a combination among them, we created 210925 features. The feature selection was based on gradient boosting machines used to select the best 0.05% (110) features. To classify the general psychopathological symptoms (present-absent) several machine learning methods were applied (random machines, extreme gradient boosting, dense multilayer perceptron, random forest, support vector machines and logistic regression) and compared by complementary Brier Score measure (cBS), which denotes the general accuracy of a prediction of a model. Random machines are a new machine learning method based on support vector machines ensemble and recently proposed by the authors. cBS is a strong and rigorous measure to evaluate the accuracy of probabilistic predictions.
Results: Impaired Tolerance to Normal Stress (G4) was successfully predicted with 100-holdout repetition validation method and random machines with 100 replications overlapped the other methods with cBS 75%, F1-score 59% and AUC 58%. Random machines had a superior or equal cBS in 99% compared with XGB, 52% in RF, 100% in DMLP, 73% in SVM, and 99% in LR. Also, RM had a superior or equal in almost 60% compared with the other methods Extreme

gradient boosting was used with 1000 replications, dense multilayer perception with one middle layer with 128 nodes and ReLU activation function, random forest with 1000 trees, support vector machines with rbf kernel function and logistic regression was standard. For Considering Sleep Disturbance (G1), Dysphoric Mood (G2) and Motor Disturbances (G3) all the applied methods had low predictive performance, with low cBS (lower than 60%), F1-Score (near 50%) and AUC (near 50%).

Discussion: The use of random machines indicates a possible path towards the use of facial landmarks to early detect Impaired Tolerance to Normal Stress with video interviews alone, since the proposed predictions were obtained without any clinical or social information. In a sense, the other general psychopathological symptoms (Considering Sleep Disturbance, Dysphoric Mood and Motor Disturbances) were not evident by video recordings, feature selection and by applied machine learning methods.

F47. SEX DIFFERENCES IN SCHIZOPHRENIA: RESULTS FROM A 30-YEAR HEALTH RECORDS REGISTRY

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Background: Sex differences have been described in schizophrenia regarding premorbid trajectory, incidence, symptoms presentation, comorbidity, and outcomes. Given the relatively rare incidence of schizophrenia, large sample and prospective design studies are needed in order to investigate possible differences between sexes and to tailor future interventions. The goal of this study is to investigate sex differences in patients diagnosed with schizophrenia.

Methods: Our cohort study included patients admitted to outpatient care in the Department of Mental health in Ferrara, Italy, from 1991 to 2021. Index date is the date the diagnosis of schizophrenia spectrum disorders (ICD-9: 295.*) was first recorded in their records. Clinical and demographic characteristics were compared between sexes before and after index date. Analyses on predictors of 295.* diagnosis were also performed, yet still to be completed.

Results: A total of 2,439 patients were included, of those 1,191 were women (48.8%). Compared to men, women were on average significantly older at first visit at mental health service (43.7 [SD 15.1] vs 36.8 [SD 13.9] $p<0.05$) and at time of first diagnosis of schizophrenia (47.8 [SD 15.2] vs 40.6 [SD 14.6]; $p< 0.05$) with peak incidence around 47 years old (vs 38, $p<0.05$). Before the index date, 92.3% of women (vs 91.6% of men) were not prescribed drugs. If pharmacological treatment was prescribed, both women and men received mainly oral antipsychotics (80.4% vs 88.6%) or anxiolytics (66.3% vs 76.2%). Antipsychotic long-acting was prescribed more frequently to men than women (37.1% vs 33.7%), as also mood stabilizers (17.1% vs 14.1%). In men, the last diagnosis received before the index date was delusional disorder (27.7%) or personality disorder (24.3%). Women were diagnosed mostly with depression (24%) and delusional disorder (30.1%). The interval between first admission to mental health service and index date was not statistically different between the sexes. After the index date, both sexes were treated mainly with oral antipsychotic (90.3% and 86.1%), but long-acting were most frequently prescribed to men (46.5% vs 36.3%; $p<0.05$), as well as clozapine (13.2% vs 9.4%). Mood stabilizers were more prescribed to women (24.3% vs 21.1%; $p<0.05$), as well as antidepressants (50.1% vs 35.5%; $p<0.05$), and

anxiolytics/hypnotics (75.9% vs 73.3%; p<0.05). After the index date, women were hospitalized more frequently than men but less frequently had involuntary admissions (10.1% vs 13.6%).
Discussion: Our 30-year-long record registry confirms that sex differences exist in clinical and demographic characteristics of individuals diagnosed with schizophrenia spectrum disorders. These Results: outpoint the necessity to implement a tailored sex-approach in early detection programs for psychosis.

F48. COMPUTATIONAL MECHANISMS OF BELIEF UPDATING IN RELATION TO PSYCHOTIC-LIKE EXPERIENCES

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Background: Psychotic-like experiences (PLE) possibly result from altered weighting of prior beliefs and new evidence in the belief updating process. However, it is unclear whether overweighting of prior belief or of new evidence is the underlying mechanism of PLEs or whether this varies depending on the level of environmental and belief uncertainty. This led us to investigate the uncertainty-related dynamics of belief updating in relation to PLEs using an online study design.
Methods: We collected self-report questionnaires of PLE in a large online sample (n = 300) which performed a dynamic belief updating task (Nassar et al., 2010, 2012). This task requires participants to establish and dynamically update their belief about a helicopter's location. Optimal behavior is achieved by adjusting the learning speed to belief uncertainty and the probability of environmental change points. We adopted a previously established normative learning model (Nassar et al., 2010, 2016), which allowed us to examine the relationship of PLE and adherence to specific model parameters. Using factor analyses, we followed up these results by delineating the subcomponents of PLE that showed a specific relationship with altered learning parameters. Lastly, to test specificity of our results we investigated associations with other psychiatric traits.
Results: We found that PLE was linked to lower accuracy in tracking the helicopter's location ($\beta = 0.35$, $t(70596) = 5.15$, $p < .001$) and to a smaller increase of belief precision across observations after a change point ($\beta = -0.23$, $t(70596) = -34.38$, $p < .001$). Computational modelling suggested that PLEs were associated with heightened adherence to the estimated probability of large environmental change points ($\beta = 1.011$ $p = .008$). Yet, PLE was not related to faster, but to instead to slower belief updating upon when change points were likely ($\beta = -.071$, $t(5787) = -2.59$, $p = .01$). On the other hand, PLE was related to faster updating when the environment was stable ($\beta = .043$, $t(53633) = 4.99$, $p < .001$). The relationship between altered belief updating and sub-components of PLE was strongest with regard to "Aberrant salience" and "Delusional ideation and auditory alteration", and not related to other psychiatric constructs like anxiety, obsessive-compulsiveness, apathy or alcohol use.
Discussion: Our results suggest that PLEs are related to altered temporal dynamics of belief updating. Increased learning speed during stability may lead to instable beliefs and a heightened sense of uncertainty. On the other hand, lower learning speed after meaningful environmental changes may result in rigid beliefs, as seen in delusions. These findings corroborate the notion that the process of balancing prior belief and new evidence as a function of uncertainty is altered in

PLE. The present study fosters a deeper understanding of inferential mechanisms underlying PLEs. Future research should investigate if the findings hold in clinical populations.

F49. INVESTIGATING THE PHENOMENOLOGY AND MECHANISMS OF FORMAL THOUGHT DISORDER IN A LARGE, TRANSDIAGNOSTIC SAMPLE

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Background: Formal thought disorder (FTD) is considered a hallmark feature of psychosis: it is prevalent and has considerable implications on prognosis and functional impairments. However, due to the covert nature of thoughts, FTD is usually diagnosed based on a person's speech. Thus, it is unclear whether incoherent speech in FTD results from disorganized thinking rather than impairment in the executive regulation of the overt expression of occasional thought slippages. Furthermore, conceptualizing FTD based on the relatively extreme clinical prototype found in schizophrenia might miss milder, or covert forms of the same core process (e.g., covert disorganized thinking). We conducted a large transdiagnostic study (N = 1000), combining computational modeling and natural language processing (NLP) to investigate the interactions between thought and speech disorganization in psychosis and psychiatry in general.

Methods: Exploratory factor analysis was used to characterize dimensions of self-reported FTD in the general population. To examine which of the resulting dimensions are characterized by objectively atypical discourse, participants were asked to generate free narratives, which were analyzed using NLP methods measuring atypicality and disorganization. Finally, we asked participants to produce single words associations. We used a recently developed computational model to examine whether atypical associations are caused by disorganized thinking rather than abnormal executive regulation of speech.

Results: We found three psychiatric dimensions explicitly measuring abnormality in language and communication: Eccentricity ("I use long and unusual words to say simple things"), Disorganized Speech ("I use too many words to say simple things"), and Reduced Speech ("My speech gets suddenly blocked"). Only self-reported Eccentricity predicted objective abnormalities in language: the production of atypical ($r = -0.17$, $p < .001$) and internally incoherent ($r = -0.15$, $p < .001$) narratives, as well as atypical associations ($r = -0.16$, $p < .001$). Computational modeling explained these atypical associations as reflecting disorganized thinking ($r = -0.10$, $p = .002$) rather than aberrant executive control over the expression of thoughts ($r = -0.03$, $p = .36$). No objective alteration in language or thought was found in the other two self-reported FTD dimensions, or other dimensions reflecting psychotic experiences (e.g., Hallucinations, Magical Thinking). The interpersonal nature of the Eccentricity dimension is in line with previous theories highlighting the role of interpersonal difficulties in FTD. Interestingly, whereas other interpersonal dimensions showed alterations in language and thought, these were remarkably distinct from the ones found in Eccentricity. Specifically, Social Anxiety predicted greater typicality in language ($r = 0.20$, $p < .001$), whereas Suspiciousness predicted atypical thinking processes ($r = -0.08$, $p = .01$) that remained covert due to increased filtering ($r = 0.13$, $p < .001$).

Discussion: Our results characterize FTD as a continuous, multi-dimensional phenotype and clarify its mechanisms. Previous studies were equivocal concerning the involvement of semantic and executive impairments in FTD. Whereas these studies were mostly based on correlations

between different tasks, our computational approach elucidated how these processes interact during a single free-association task. This has shown that FTD indeed reflects disorganization of thought. Finally, our findings suggest that different interpersonal symptoms, potentially reflecting distinct mechanisms of coping with social exclusion, have distinct implications on language and thought.

F50. TRAJECTORIES THROUGH SEMANTIC SPACES IN SCHIZOPHRENIA, AND THE RELATIONSHIP TO HIPPOCAMPAL RIPPLE BURSTS

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Background: Symptoms and signs of schizophrenia – from thought disorder to delusions –are thought to reflect an organisation of structured conceptual representations (i.e., cognitive maps) encoding relationships between entities in the world (e.g., semantic association). Schizophrenia is linked to abnormalities in neural processes thought to support such representations, including hippocampal replay and ripple power. Here, we develop a computational assay of semantically-guided conceptual sampling. We then test an hypothesis that people with a diagnosis of schizophrenia (PScz) exhibit abnormalities in associatively-guided cognition, which relate to hippocampal memory reactivation.
Methods: Fifty-two participants (26 PScz [13 unmedicated] and 26 age-, gender-, and IQ-matched non-clinical controls) completed a category and letter word fluency task, followed by a magnetoencephalography (MEG) scan involving a separate associative learning task. We used a pre-trained Natural Language Processing (NLP) model of semantic similarity, coupled to a generative model of word selection, to quantify the degree to which each participant's behaviour was guided by semantic association. Using MEG, we indexed hippocampal ripple power in a post-task rest session.
Results: Word selection was strongly influenced by semantic association in all participants. The strength of this influence was sensitive to task demands (category>letter fluency), and predicted task performance (rho=0.31, P=0.03). In line with our key hypothesis, semantic association strength was reduced in schizophrenia (t=2.82, P=0.01), predicted negative symptoms (rho=-0.42, P=0.03), and correlated with an MEG signature of hippocampal ripple power (β=0.16, P=0.001).
Discussion: Our findings support a hypothesis that some symptoms of schizophrenia may reflect a dysregulation of a fundamental neuro-cognitive process involving structured internal representations of the world (cognitive maps). Future studies that employ concurrent M/EEG recordings in similar semantic sampling tasks are expected to shed light on the neural coding schemes that support such associative cognition, where the latter constitute a promising target for novel therapeutic intervention across a range of psychiatric conditions.

F51. PROBLEM GAMBLING AND PSYCHOTIC DISORDERS: A SCOPING REVIEW

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Background: Problem gambling (PBG) can lead to financial issues, social isolation and mental health problems, including suicide. Our previous study, the only one to date on this issue, suggests that young adults with first-episode psychosis (FEP) are at increased risk of PBG and that the antipsychotic drug aripiprazole may contribute (Corbeil et al., 2021). Yet, no PBG screening tool or treatment have been adapted to this population.
Methods: We used Levac's six-stage methodology for scoping review. 1153 articles from seven databases were screened, and 72 articles were included.
Results: In this presentation, results of a systematic scoping review about the comorbidity between PBG and psychotic disorders will be unveiled, including prevalence data, risk factors, consequences as well as potential treatments and screening tools. In addition to summarizing the extent and nature of research conducted so far on this comorbidity, gaps in the existing literature will be identified. These gaps are currently being addressed through an ongoing multicentre cohort study conducted in 2 FEP clinics (approximately 800 patients). Preliminary results of this study, for which an innovative screening procedure for PBG adapted to people with FEP has been developed, will be presented as well.
Discussion: These findings will help to identify individuals most at risk for PBG and to offer them preventive measures, such as modification of antipsychotic treatment, if the link with aripiprazole use is confirmed. The multicentre study is also the first phase of a larger project (FRQ-SC grant), in which a PBG treatment adapted to people with FEP will be developed, and evaluated, by experts in both fields and patient partners.

F52. THE NIMH RDOC INITIATIVE AND PSYCHOSIS RESEARCH: AN OVERVIEW OF THE GRANT PORTFOLIO AND DISCUSSION OF FUTURE DIRECTIONS

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Background: The U.S. National Institute of Mental Health's Research Domain Criteria (RDoC) initiative has entered its second decade. This presentation will provide an overview of the RDoC portfolio, an update on the status of the initiative, and a discussion of future directions, with an emphasis on research focused on psychosis.
Methods: A semi-quantitative and thematic analysis of the RDoC grant portfolio and recent research literature.
Results: Over 100 grants have been supported under 13 NIMH-issued funding opportunity announcements specifically focused on RDoC and many more RDoC-focused grants have been funded under general funding opportunities.
Discussion: A senior NIMH program officer who focuses on RDoC and psychosis will present the results and be available to engage with attendees' questions and comments about RDoC and NIMH research funding priorities and procedures. Among the RDoC grants focused on psychosis, a broad collection of RDoC constructs are studied using highly innovative methods to delineate various neurobehavioral functions spanning diagnostic groupings and the health-to-illness spectrum. Consistent with RDoC principles and goals, this work is making progress in unpacking the relationships within and across multiple neurocognitive functions, multiple kinds of symptoms,

and multiple neurobiological and genetic measures—compounded by the complexities of intermixed clusters and dimensions. This work is facilitated by the rapidly accelerating use of machine-learning algorithms to identify new multi-system mechanisms and provide individual-level prediction of prognosis, treatment, and outcome. Challenges for the future include incorporating new conceptualizations of phenotypes into clinical and regulatory frameworks.

F53. MEASUREMENT INVARIANCE OF THE REVISED-GREEN PARANOID THOUGHT SCALE ACROSS BLACK AND WHITE AMERICANS

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Background: The Revised-Green Paranoid Thought Scale (R-GPTS; Freeman et al., 2021) is designed to measure paranoia as a dimensional construct expressed throughout the population. Despite the widespread use of the R-GPTS and its original form (GPTS; Green et al., 2008), the psychometric properties of these measures have not been examined across racially diverse respondents. This is of particular interest given that the racial breakdown of samples were not reported in initial validation procedures for either form. Furthermore, numerous investigations have demonstrated heightened self-reported paranoia in Black Americans (e.g., Combs et. al., 2006; Whaley, 2001), though it is unclear whether such elevations in paranoia reflect true differences between groups or may be produced via systematic measurement error. Thus, measurement invariance testing was conducted to examine the construct validity of the R-GPTS across Black and White Americans.

Methods: A total of 921 individuals self-identified as either 'Black/African American' or 'White' were recruited through Amazon's Mechanical Turk (MTurk) using demographic filtering. Of this, the analytic sample consisted of 400 non-Hispanic White and 396 non-Hispanic Black participants who completed the R-GPTS, contained complete demographic data and passed rigorous quality control checks. Participants recruited through the Mturk platform have been demonstrated to be more demographically diverse and more closely representative of the true American population compared to undergraduate participant samples (Buhrmester et. al., 2011).

At the first stage of measurement invariance testing, a multigroup confirmatory factor analysis (CFA) was performed to establish whether a similar factor structure holds between groups of interest (configural invariance testing). Next, this multigroup CFA was rerun with factor loadings in the model constrained to be equivalent between groups, thus allowing group comparisons regarding the strength and manner in which individual items relate to the latent construct of interest (metric invariance testing). Lastly, a multigroup CFA was run with both factor loadings and item intercepts constrained to be equivalent between groups, to examine whether individual items were scaled in a similar manner (scalar invariance testing). These models were compared in a stepwise fashion at each stage of measurement invariance testing (i.e., configural versus metric, metric versus scalar) to examine potential differences in model fit indices produced by the added constraints. Non-invariance was determined by threshold cutoffs of a decrease in ΔCFI less than or equal to 0.05 and an increase in ΔRMSEA less than or equal to 0.015 following Chen (2007). The collective efforts of this measurement invariance testing provide empirical evidence regarding

the validity of the R-GPTS across Black and White Americans. Specifically, whether the R-GPTS maintains a similar structure across groups and if group-mean comparisons may be appropriately drawn.

Results: The results of the present study show full measurement invariance of the R-GPTS across Black and White Americans, providing empirical support that mean score comparisons of the R-GPTS may be appropriately drawn between these groups. Regarding mean group differences, Black participants scored significantly higher on this dimensional measure of self-reported paranoia compared to their White counterparts (mean=20.6±15.9 and mean=13.92±14.48, respectively). Furthermore, race remained a large, statistically significant predictor of R-GPTS total score after accounting for relevant covariates including age, biological sex, and socioeconomic status (β=-0.398, $p< 0.001$).

Discussion: The present study both established the psychometric invariance of a widely used measure of self-reported paranoia (R-GPTS) amongst Black compared to White Americans and found evidence of a heightened paranoia expressed in Black Americans. Such heightened paranoia has been hypothesized to be an adaptive response to the race-based stressors Black Americans experience in their sociocultural environment (e.g., experiences of major discrimination; Grier and Cobbs, 1980; Mosley et al., 2017). These findings suggest that close attention must be paid towards how items indexing paranoia may perform when couched within broader measures capturing psychosis-spectrum phenomenology and risk (e.g., psychotic-like experiences, attenuated psychosis). Investigations of the psychometric performance of psychosis-risk measures are particularly important given evidence that items indexing paranoia may not confer equitable risk or functional outcomes across majority groups and those groups who experience systematic racial marginalization (Wolny et al., 2021; Rouhakhtar et al., 2021). Furthermore, there is high potential for the conflation of adaptive paranoia with psychiatrically meaningful symptomatology in global diagnostic decision-making. To promote racial equity in psychosis-measurement, future research must examine how paranoia functions in relationship to latent constructs intended to capture illness-risk and may influence global diagnostic decision-making.

F54. TEMPORAL ASSOCIATIONS AMONG PARANOIA, NEGATIVE AFFECT, LONELINESS, AND WORRIES ACROSS PARANOIA CONTINUUM

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Background: Paranoia, an unfounded belief that others intend to cause harm, is a typical symptom of schizophrenia spectrum disorders. However, it also spans across other psychiatric diagnoses, showing its transdiagnostic nature. Paranoia can also be present in a healthy population on a subclinical level. Moreover, it has been shown to fluctuate over time, in connection to other factors, such as negative affect, loneliness, or characteristics of the social context. Using the Experience Sampling Method (ESM) it is possible to observe these changes in real time, over a period of several days. This method is well suited for studying paranoia in daily life. It also allows for analyzing temporal relationships that provide stronger evidence for potential causal interpretations. The current study aims to examine the temporal associations of momentary

paranoia, negative affect, loneliness, and worries in a sample with varying degrees of paranoia severity.
Methods: The current sample consisted of 63 individuals (67% females) with a mean age of M = 33.13, SD = 11.3. Out of these, 37 were stable outpatients diagnosed with schizophrenia spectrum disorders (N = 15), depression (N = 16), or bipolar disorder (N = 5) and 26 were healthy controls. They received an ESM questionnaire through a smartphone notification ten times per day at random times, over a six-day period. Momentary paranoia was computed as a mean of three items. Similarly, negative affect was computed as a mean of four items. Loneliness and worries were each measured by one item. All items were rated on a 7-point Likert scale. Two network models were computed. First, a contemporaneous model with associations between the variables within the same time point. To account for the time-dependent changes, this was followed by a temporal model, representing lagged associations between the nodes during measurements at t and t +1.
Results: The overall paranoia level was relatively low (M = 1.64, SD = 0.87). The contemporaneous model revealed significant associations among all studied variables, except for the absent connection between worry and loneliness. Negative affect was most strongly connected to other nodes. In the temporal network model, the strongest connections were found for nodes predicting themselves in time (autoregression). This was especially apparent for paranoia and negative affect. Furthermore, paranoia was the only significant predictor of all other nodes in the temporal network. Higher paranoia preceded worries, negative affect, as well as loneliness at the next time point, but not vice versa.
Discussion: Momentary paranoia is an important symptom shaping daily emotional experiences. Elevated paranoia led to increased feelings of loneliness, negative affect, and more intense worries later on. Contrary to the expectations, we did not observe an opposite direction of effect, meaning neither of the other factors temporally predicted subsequent paranoia. Our sample was generally very mildly paranoid. Therefore, in individuals with more severe paranoia (persecutory delusions), other patterns of temporal associations might emerge. Taken together, our results show paranoia is more likely a cause of negative affect, worries, and loneliness, rather than their consequence.

F55. SOCIAL INTERACTIONS AND PERCEPTION OF THESE INTERACTIONS IN INDIVIDUALS WITH SCHIZOPHRENIA

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Background: Individuals with schizophrenia have lower social skills compared to healthy controls. This leads to difficulties in real–world social interactions and together with negative symptoms adds to wide–range impairment in real – world functioning. The goal of the study is to examine social skills in unstructured social interaction and to investigate how specific aspects of social skill problems are linked to symptom domains in individuals with schizophrenia. The secondary aim is to analyze differences in the perception of social interaction from patient's and researcher’s perspective.
Methods: The sample consisted of 32 patients with schizophrenia spectrum disorders (56 % female, mean age M = 42.97, SD = 8.42). Social skills were measured by Conversation Probe, a performance–based measure. Symptoms were measured by Brief Psychiatric Rating Scale. Participants were instructed to have a 3-minute unstructured conversation (meeting a classmate at

a language course) with a research assistant. Interactions were videotaped and later rated by an independent rater on several domains (fluency, clarity, affect, overall social skills, etc.). Both the participant and the research assistant completed an 8-item Subject Impressions Questionnaire to measure the perception of the given social situation. Spearman correlation coefficients were used to determine relationships strength between symptoms, social skills domains, and perceptions of social interaction. Wilcoxon signed-rank tests were used to compare patients and conversation partners in perception of social interaction.
Results: Overall social skills domains were linked to the negative symptoms ($rs = -.466$, $p < .01$). This relationship was driven mainly by associations to flat affect during interaction ($rs = -.613$, $p < .001$) and lack of involvement ($rs = -.533$, $p < .01$). Positive symptoms were associated only with lower quality of interaction content ($rs = -.389$, $p < .05$). We found significant differences between patients and their conversation partners (research assistants) in perception of social interaction in dimension of closeness ($W = 20.00$, $p < .001$), where patients felt closer to their partners than vice versa. Patients also found the conversation significantly more enjoyable ($W = 59.00$, $p = .001$) than conversation partners. Patients with more severe depression/anxiety perceived to be more under pressure ($rs = .495$, $p < .001$). In terms of social interaction judgements and social skills, patients who found the conversation more enjoyable, were also speaking more ($rs = .503$, $p < .01$). Consequently, conversation partners felt closer to patients, who were talking more smoothly with partners ($rs = .649$, $p < .001$), had higher overall social skills ($rs = .580$, $p < .001$) and when patients were discussing multiple topics in a more natural way ($rs = .563$, $p < .001$).
Discussion: Based on our results we found that deficits in social skills in schizophrenia are predominantly associated with the severity of negative symptoms. We also found evidence of the abberant perception of social interaction in patients with schizophrenia. More specifically, patients perceived interaction as more pleasant and enjoyable than their interaction counterpart. This difference might signal an aberrant introspective accuracy about one's own performance in social interactions, that in turn might add to observed interpersonal functioning difficulties.

F56. EXPLORING HOW CHILDHOOD TRAUMA RELATES TO THE PRESENCE AND EXPERIENCE OF DELUSIONS: A MEDIATION ANALYSIS

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Background: Research into the relationship between childhood trauma and delusional experiences is growing. The intensity of the delusional experience is not just in the number of unusual beliefs endorsed, but also in the degree of distress, preoccupation and conviction associated with these unusual beliefs. This study thus sought to (i) examine associations between childhood trauma and aspects of the delusion experience, and (ii) clarify potential pathways by which trauma may be linked to the experience of delusions by examining mediating factors for these relationships. Noting the incidence of delusional experiences outside of clinical diagnoses, and the expected mechanistic similarities, this study additionally adopted the continuum approach to study these experiences across the spectrum of clinical to non-clinical individuals.
Methods: Individuals aged 18 years and above (with and without psychiatric diagnoses) completed an online Qualtrics survey consisting of the Peters' Delusion Inventory (PDI), Aberrant Salience Inventory (ASI), Brief Core Schema Scale (BCSS), Creative Experiences Questionnaire

(CEQ), Depression, Anxiety and Stress Scale (DASS-21), Penn State Worry Questionnaire (PSWQ), Rosenberg Self-Esteem Scale (RSES), Rotter's Locus of Control (RLOC) and Childhood Trauma Questionnaire – Short Form (CTQSF). Basic demographic information (e.g. age, sex, religion) were also collected. Four PDI variables were extracted to reflect endorsement of delusional occurrences (PDI-E), as well as their levels of distress (PDI-D), preoccupation (PDI-P) and conviction (PDI-C). Only respondents who endorsed at least one item on the PDI were included in the analyses (404 out of 517).
Results: Mediation analyses using the PROCESS macro in SPSS revealed that childhood trauma was significantly associated with the endorsement, distress, preoccupation and conviction of delusions (p=.01-.03). Notably, fantasy proneness, as measured by the CEQ, significantly mediated the relationships between childhood trauma and all four PDI variables. Negative self-schemas and self-esteem levels also significantly mediated the relationship between childhood trauma and PDI-D specifically. No other mediating factors were identified.
Discussion: The findings suggest that childhood trauma may be linked to delusional experiences through contributing to the development of fantastical thinking, a disposition towards vivid mental imagery and memories, and an overactive creative imagination – all components of fantasy proneness. The contributions of trauma to negative views of the self also influence degrees of distress over these delusions. These associations help to clarify the mechanisms that may lead to how delusions are experienced. They also critically provide potential avenues of remediation to reduce the severity or incidence of delusional experiences through methods such as psychological therapies.

F57. EMERGENCE OF DELUSIONS AND HALLUCINATIONS IN HIGH-RISK AND FIRST-EPISODE SAMPLES

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Background: The positive symptoms of psychosis–hallucinations and delusions–are frequently studied in tandem. However, emerging evidence implicates distinct and potentially opposing cognitive and computational mechanisms driving susceptibility toward these two symptoms. Interrogation of the timing of hallucination and delusion emergence may help disentangle the independence of their respective mechanisms.
Methods: We examined the timing of emergence of hallucinations and delusions in two large clinical high risk (CHR) samples (NAPLS2, N = 720 ; NAPLS3, N = 699) and one large first-episode psychosis (FEP) sample (McGill Prevention and Early Intervention for Psychosis (PEPP), N = 695). Data were derived prospectively and retrospectively, using the Structured Interview for Psychosis-Risk Syndromes (SIPS), Circumstances of Onset of Symptoms and Relapse Schedule (CORS), and the Topography of Psychotic Episode (TOPE).
Results: A similar pattern emerged across all three cohorts, wherein a majority of individuals reported the emergence of delusional ideation prior to emergence of hallucinations (57.0%, 57.9%,

and 61.7%, respectively). In addition, delusions were more stably present over time, while hallucinations were more volatile. Lastly, recurrence of symptoms after remission recapitulated individual patterns of initial symptom emergence.
Discussion: Together, results support a new understanding of positive symptom emergence in which hallucinations emerge after, and perhaps as a compensatory response to, delusion formation. This pattern is consistent with a secondary account of hallucinogenesis, and may help to reconcile seemingly opposed computational theories of hallucination and delusion susceptibility.

F58. HOW CAN EARLY INTERVENTION SERVICES ADDRESS HOMELESS YOUTH'S COMPLEX NEEDS? EQIIP SOL'S 10-YEAR EXPERIENCE IN MONTREAL

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Background: In 2012, a specialized intensive outreach intervention team (EQIIP SOL) for homeless youth with substance use disorders (SUD) and first episode psychosis (FEP) was created within an early intervention service in Montreal. This 3-year program combines social interventions to exit homelessness and evidence-based interventions for FEP.
Methods: This 3-years longitudinal study includes all homeless youth (18-30) with first episode psychosis admitted to EQIIP SOL from February 2012 to June 2022. The primary outcome was stable housing, defined as an autonomous or supervised accommodation where the participant has been for at least a month and wishes to stay for at least 6 months. The secondary outcomes were illness severity (CGI), general functioning (GAF, SOFAS), alcohol and substance use (AUS, DUS). All outcomes were assessed at baseline and at 1, 3, 6, 9, 12, 15, 18, 24 and 36 months. Repeated measures ANOVA and Cochran's Q test followed by post-hoc analysis were used to investigate if outcomes improved significantly over time. A generalized mixed model was used to analyze each patient housing stability at all 10 follow-up times points. To correct for within individual measures correlation, a random intercept and a random slope for time were employed. Baseline independent variables were tested with univariate regression with a threshold ≤ 0.1 to qualify for the multivariate model.
Results: Of the 226 patients admitted to EQIIP SOL 82.3% were male, 91.2% single, 61.7% did not complete high school. Mean age at baseline was 22.7 year. Overall, 75.7% went through childhood adverse experiences, including neglect 55.7%, physical 41.23%, psychological 41.8%, sexual abuse 19.3%, and placement in foster care 42.3%. Baseline unemployment rate was 86.7%, with 61.9% of patients depending on government aid and 22.6% having no income. Two patients died during follow-up (suicide and overdose). Globally, 77.4% reached housing stability over the 3-years. Post-hoc analysis indicated a sharped rise in housing stability during the first six months, plateauing after nine months. CGI ($F(5.13, 420.69) = 48.48$, $p < 0.0001$), SOFAS ($F(5.3, 439.60) = 58.25$, $p < 0.0001$) and GAF ($F(4.86, 430.23) = 63.21$, $p < 0.0001$) improved concurrently, mainly during the first nine months, with subsequent milder progression. Alcohol ($Q=13.674$, $p=0.003$), cannabis ($Q=10.645$, $p < 0.0001$) and stimulants ($Q=8.4$, $p < 0.05$) use disorders improved over time as well. Post hoc analysis showed different patterns for each substance: cannabis use decreased significantly in the first year ($p < 0.05$), while alcohol and stimulant (cocaine and/or amphetamine) use disorders took two ($p < 0.05$) and three years ($p < 0.05$) respectively for a significant improvement to be observed. In the multivariate generalized mixed

model, the number of months elapsed since baseline was associated with an increase in housing stability (OR: 1.42 (1.31;1.55)). Patients suffering from stimulant use disorder had less chance to attain housing stability (OR: 0.52 (0.28-0.96)), as well as patients with history of chronic homelessness lasting more than 12 months (OR: 0.36 (0.15;0.83)).

Discussion: EQIIP SOL experience suggests that an intensive assertive community treatment offering housing support and integrated care to homeless youth with FEP and SUD results in a rapid increase in housing stability, closely followed by clinical and functional outcomes improvement. Although all SUD decrease over time, since psychostimulants use disorder seems to take more time to decrease and reduces the likelihood of attaining housing stability, further research should examine the mechanism behind this impact so specific interventions can be developed.

F59. USE OF LONGACTING ANTIPSYCHOTIC INJECTABLES IN PENNSYLVANIA FIRST-EPISODE PROGRAMS

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Background: For many years long-acting injectable antipsychotics (LAI) were mainly used for persons with chronic psychotic disorders who experienced inadequate adherence with the goal of stabilization rather than recovery. Over the past 15 years, advances in second-generation antipsychotics and vehicle administration have led to more widespread and earlier use of LAIs. We examine the naturalistic use of LAIs compared to oral antipsychotics (OAP) across 14 PA CSC programs in association with participant demographics, clinical symptoms, functioning and treatment retention.

Methods: All PA FEP sites collect demographic, clinical and functional data at admission and every 6 months to evaluate programmatic CSC efforts. Data are submitted to HeadsUp, the FEP coordinating center, at the University of Pennsylvania. We compared the use of LAIs versus OAP and no antipsychotic medications at admission to CSC and at 6-month and 12-month intervals (including premature discharges) on demographic and clinical variables. Medication group assignment was based on being on LAI or OAP at 6 and 12 months.

Results: At intake, persons on LAI vs. OAP differ in age, gender, ethnicity, age at onset, duration of illness, past hospitalizations/hospital days. Over 12 months, there were no differences in clinical or functional improvement between OAP and LAI groups.

Discussion: About 30% of persons with FEP who are followed over 12 months are maintained on LAIs.

Treatment with LAIs is associated with similar clinical and functional improvement compared to OAP. LAIs offer an important pharmacological medication intervention in clinical care for young persons with FEP.

F60. THE ROLE OF GEOGRAPHY AND DISTANCE ON PHYSICIAN FOLLOW-UP AFTER HOSPITALIZATION WITH A DIAGNOSIS OF A SCHIZOPHRENIA SPECTRUM DISORDER: A RETROSPECTIVE POPULATION-BASED COHORT STUDY IN ONTARIO, CANADA

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Background: Timely follow-up after hospitalization for a schizophrenia spectrum disorder (SSD) is an important quality indicator. We examined the proportion of individuals who received physician follow-up within 7 and 30 days post-discharge by health region and estimated the effect of distance between a person's residence and discharging hospital on follow-up.
Methods: We created a retrospective population-based cohort of incident hospitalizations with a discharge diagnosis of a SSD between 01/01/2012 and 30/03/2019. The proportion of follow-up with a psychiatrist and family physician within 7 and 30 days were calculated for each region. The effect of distance between a person's residence and discharging hospital on follow-up was estimated using adjusted multilevel logistic regression models.
Results: We identified 6,382 incident hospitalizations for an SSD. Only 14.2% and 49.2% of people received follow-up care with a psychiatrist within 7 and 30 days of discharge, respectively, and these proportions varied between regions. Although distance from hospital was not associated with follow-up within 7 days of discharge, increasing distance was associated with lower odds of follow-up with a psychiatrist within 30 days.
Discussion: Post-discharge follow-up is poor across the province. Geospatial factors may impact post-discharge care and should be considered in further evaluation of quality of care in this clinical population.

F61. BUILDING AN EPINET HUB LEARNING HEALTH SYSTEM: IMPLEMENTATION LESSONS AND PRELIMINARY FINDINGS OF AC-EPINET

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Background: The National Institute of Mental Health (NIMH) initiated the Early Psychosis Intervention Network (EPINET) in 2019 to advance a learning healthcare system (LHS) for first-episode psychosis (FEP). LHSs seek to integrate best practice care, quality improvement and discovery-oriented research. EPINET funds a national data coordination center and eight reginal hubs, which include more than 100 Coordinated Specialty Clinics (CSCs) for FEP. The Academic-Community EPINET (AC-EPINET) joined this national initiative in 2020 and is comprised of six academically affiliated CSCs. This presentation will describe AC-EPINET implementation, lessons learned, and preliminary outcomes.
Methods: Collection of data elements from EPINET's consensus Common Assessment Battery (CAB) was successfully operationalized at five of the original AC-EPINET sites. Attending to the importance of building a culture of learning and quality improvement, bi-weekly meetings of site

PIs, a site inclusive assessment and implementation work group, and regular virtual site visits by hub staff were initiated. This work was designed to address concerns ranging from data security to the impact of data collection procedures on clinical workflows. An informatics workflow that included the use of REDCap (Research Data Capture) and a purpose-built platform HONE (Health Outcomes, Network and Education) were integrated and used to deliver analysis and visualizations of outcomes. Preliminary CAB data examined thus far include acute care visits (hospitalization and emergency visits), as well as social and occupational functioning. Demographic and acute care visit data was collected by treating clinicians who also used collateral from caregivers and medical record review. Social and occupational functioning was measured via the MIRECC GAF with ratings conducted by CSC team members, after training and certification.

Results: 414 baseline and 264 six-month follow-up CAB assessments have been completed. The enrolled sample included a preponderance of males (69.6%), as well as Caucasian (45%) and Black (45%) participants. The three primary DSM diagnoses in this sample included schizophrenia (35%), unspecified schizophrenia and other psychotic disorders (25%), and schizoaffective disorder, bipolar type (10%). The Median duration of untreated psychosis (DUP), or time between symptom onset and admission to a CSC within AC-EPINET, was 7.55 (IQR = 19.9) months. Preliminary median test analysis suggested DUP differed between sites ($X2(4) = 12.22$, $p = .02$). Between baseline assessment (6-months prior to enrollment) and the 6-month follow-up assessment, the percentage of both acute psychiatric hospitalizations (44.4% to 13.3%) and ER visits (16% to 4.5%) decreased. This was accompanied by improvements in social functioning: the average MIRECC GAF score improved (62.5, SD = 17.1 to 68.1, SD = 14.3), and the occupational functioning sub-scale improved (53.8, SD = 24.2 to 60.9, SD = 21.4).

Discussion: AC-EPINET has implemented a LHS, embracing a culture of shared learning and incorporating the EPINET common assessment battery within the workflows of five academically affiliated CSCs. Preliminary data suggest salutary trends in patient outcomes. Further examination of between site difference and opportunities for learning, updated data on outcomes, ongoing and future quality improvement projects, and integration with an active research project will be presented and contextualized with implications for the national EPINET effort.

F62. CARIPRAZINE AS A TREATMENT FOR NEGATIVE PSYCHOTIC SYMPTOMS IN FIRST-EPISODE PSYCHOSIS: CASE SERIES

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Background: Negative psychotic symptoms are among the most disabling features of schizophrenia and are strongly associated with relatively poor clinical and functional outcomes. However, there are no effective treatments for negative symptoms, and this represents a major unmet clinical need. Recent research has shown that negative symptoms are already present in many patients at illness onset. There is evidence that cariprazine, a dopamine D3/D2 potent partial agonist, may improve negative symptoms in patients with chronic schizophrenia. However, its utility in treating negative symptoms in the early stage of the disorder is unclear.

Methods: We examined the clinical information of patients with first-episode psychosis (FEP) who were presenting with negative symptoms, including treatment response, based on rigorous clinical assessments and close observations by highly experienced EIS consultants. The sample

comprised five men and one woman, with a mean age of 29.5 ± 5.5 years (range 24–37 years). The mean dosage of cariprazine administered was 2.5 ± 0.77 mg/d (range 1.5–3 mg/d), with a time to response of 4.5 ± 2.3 weeks (range 1–8 weeks).
Results: There was a clinically meaningful improvement in negative symptoms in four cases in which cariprazine was used as a monotherapy, and in one case when it was given as an adjunct to lurasidone. In one case, cariprazine had to be discontinued shortly after the start of treatment, because of a dystonic reaction.
Discussion: The cases described in this series provide the first indication that cariprazine may be effective in the treatment of negative symptoms in FEP.

F63. THE ROLE OF AEROBIC EXERCISE QUANTITY AND INTENSITY IN COGNITIVE IMPROVEMENT AFTER A FIRST SCHIZOPHRENIA EPISODE

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Background: Recent evidence suggests that aerobic exercise can have beneficial effects for cognitive deficits in schizophrenia (Firth et al., 2017). One recent study indicates that the addition of aerobic exercise to systematic cognitive training can significantly enhance the impact of cognitive training on cognition and work/school functioning after a first schizophrenia episode (Nuechterlein et al., 2022). Whether the intensity of aerobic exercise is a factor in producing cognitive gains needs additional study, as this would impact successful implementation of an exercise program for individuals with schizophrenia.
Methods: In a randomized controlled trial with first-episode patients with schizophrenia, we are contrasting six months of Cognitive Training and Exercise (CT and E) with Cognitive Training and a didactic Healthy Living Group (CT) alone. The computerized cognitive training using Posit Science BrainHQ programs was provided to all participants, four hours/week for six months. The CT and E group (n = 45) also participated in interval training aerobic exercises, with a goal of completing 150 minutes/week. Two of the aerobic exercise sessions were held as a group led by a certified fitness trainer, while the other two were to be completed individually. Intensity of exercise was titrated individually with a heart rate monitor, targeting 50-80% of heart rate reserve. Cognitive gain was measured by repeated measurement with the MATRICS Consensus Cognitive Battery (MCCB). Achieved quantity and intensity of exercise was measured by the total number of minutes in the targeted heart rate zone and the average heart rate during exercise.
Results: Within the CT and E group, the total minutes in the target heart rate zone was significantly predictive of the magnitude of overall cognitive gain at 3 months (Overall Cognitive Composite of the MCCB; $r = 0.35$, $p < .04$) and tended to show a similar relationship at 6 months ($r = .21$, NS). Among the cognitive domains measured by the MCCB, this relationship was clearest for Attention/Vigilance ($r = 0.44$, $p < .01$, at 3 months; $r = 0.47$, $p < .01$, at 6 months). Average heart rate during exercise sessions was not significantly predictive of cognitive gains. Cumulative total time in the target heart rate zone was clearly related to the number of exercise sessions completed ($r = 0.47$, $p < .001$) but was a more sensitive predictor of cognitive gain.
Discussion: As more evidence is available regarding the benefits of exercise for cognitive improvement in schizophrenia, perhaps particularly in combination with systematic cognitive

training, the characteristics of exercise that predict amount of cognitive gain become important to clarify. Results from this study with patients after a first episode of schizophrenia suggest that the total quantity of exercise in the aerobic heart rate zone is a factor in achieving meaningful cognitive improvement. The absolute intensity of exercise, at least as indexed by the average heart rate during exercise, appears less critical. Thus, designing exercise programs that maximize sustained engagement in exercise in the aerobic heart rate zone should aid cognitive results.

F64. ACCEPTABILITY, SATISFACTION, AND USE OF THINKAPP: A MOBILE-APP INTERVENTION FOR YOUNG PEOPLE WITH FIRST EPISODE PSYCHOSIS

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Background: Technology-based interventions, including Internet-based interventions, mobile-based interventions, health applications, social media interventions, and any interventions based on technological devices, have shown effectiveness in neurocognition, functioning and social cognition for patients with psychosis (Morales-Pillado et al., 2022). Technology-based interventions contribute to a more flexible, accessible, feasible, adapted and immediate use of interventions for people with psychosis (Alvarez-Jimenez et al., 2014; Berry et al., 2016) with the security of being evidence based (Firth et al., 2016).

Mobile-app interventions for psychosis can improve clinical and social outcomes and are acceptable and viable (Alvarez-Jimenez et al., 2014). They have been associated with treatment and medication adherence (Firth et al., 2016), symptom reduction, self-efficacy (Ben-Zeev et al., 2014, 2018), improving auditory hallucinations, depressive symptoms and functioning (Schlosser et al., 2018).

In addition, young patients with First Episode Psychosis (FEP) have interest on online interventions, including mobile-app interventions, are positive towards using digital technologies for mental health and have high rates of mobile ownership (Bonet et al., 2018; Torous et al., 2014, 2016). Thus, young patients with FEP may be willing and able to use mobile phones for engaging in early mental health interventions (Firth and Torous, 2015). However, high attrition rates have been demonstrated (Alvarez-Jimenez et al., 2014).

Little is known about the acceptability, satisfaction and use of mobile-based interventions in patients with FEP, being better known in the case of patients with psychosis. (Bonet et al., 2017).

The objective of the study is to describe the acceptability, satisfaction and use of a mobile app–based intervention (Thinkapp) in young people with first episode psychosis, as a complement to their usual treatment.

Methods: We included 26 patients with FEP, aged 14-30, recruited from Gregorio Marañón Hospital, Ramón y Cajal Hospital, San Joan de Déu Hospital and AMAFE Foundation in Spain. Patients received treatment as usual plus a psychological-based intervention through the mobile app called ThinkApp which has five modules: psychoeducation, symptom recognition and relapse prevention, problem solving, mindfulness, and social skills. ThinkApp was delivered during 12 weeks and patients could access daily. The use of the intervention was assessed by the number of times each participant logged into ThinkApp and each module and the number of times participants viewed videos, listened to audios, answered questionnaires, and wrote in the Social Skills and Problem solving module. Additionally, after 12 weeks using ThinkApp, participants were asked what they thought of ThinkApp, whether they found it useful, whether other people would use the app, and how satisfied they were with it.

Results: This study showed that 92% of the 26 participants included in ThinkApp logged into the app over the 12 weeks and 77% of the participants used the 5 modules. The most visited module was the Psychoeducation module with 88% of participants using it. It was a module for individual use and had psychoeducational audiovisual information created for this study with 12 videos, which were viewed by 46% of the participants. It was followed by Mindfulness module, whose objective was to reduce anxiety and improved the feeling of control. It consisted of recordings with focused attention exercises that explained the technique. Eighty eight percent of the participants used this module, but only 46% used the recordings.

The least used module has been the Symptom recognition and relapse prevention module visited by the 84% participants. The Symptom recognition and relapse prevention module was for individual use. Its objective is to help patients to identify the warning signs that indicate a relapse, improved disease awareness and adherence to treatment. It consisted of a questionnaire related to the disease or treatment answered by 42,3% of the participants at least one time and gave the possibility of setting alerts to answer the questionnaire and schedule your appointments.

In the case of the 2 modules that require interaction with the other participants (Problem solving module and Social skills module), both of them were used by 84% of the participants, but only a 15% of the participants shared posts in the Social Skills module.

Attending the access of ThinkApp intervention, 85% of the participants that used ThinkApp answered they were satisfied with the app, 78% of the participants that used Thinkapp answered that the app had been useful or very useful for them, and 100% of the participants answered that it could be useful for other people with FEP.

Discussion: Our results are consistent with other studies that showed that patients with psychosis perceived mobile-based interventions as positive, satisfactory and useful in a percentage higher than 70% (Alvarez-Jimenez et al., 2014; Bonet et al., 2017).

The Psychoeducation module was the most used, so it can be effective in mobile-based interventions to include clear and attractive information about FEP that can benefit patients. (Alvarez-Jimenez et al., 2014).

F65. STRATEGIES FOR ENGAGING PATIENTS AND FAMILIES AS EQUAL PARTNERS IN MENTAL HEALTH RESEARCH: A FOCUS ON IMPROVING EARLY PSYCHOSIS INTERVENTION CARE FOR YOUTH AND EMERGING ADULTS

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Background: NAVIGATE is a recovery-oriented, manualized model of Early Psychosis Intervention (EPI) care that aims to improve youth and emerging adults (YEA) suffering from a first episode of psychosis (FEP) by offering four pillars of care: (1) medication management; (2) individual resiliency training; (3) supported employment and education; and (4) family education. Our project is currently evaluating the implementation, fidelity, sustainability, and individual-level symptomatology and functioning outcomes for YEA receiving NAVIGATE. Our unique project also meaningfully engages patients and family members with lived experiences of FEP as equal research partners. According to Canada's Strategy for Patient-Oriented Research (SPOR), involving patients and families in healthcare research ensures that studies focus on patient-identified priorities, ultimately leading to improved individual- and system-level outcomes. Our study provides a distinctive strategy for carrying out patient-oriented mental health research predicated on SPOR's guiding principles of inclusiveness, support, mutual respect, and co-building.

Methods: At the start of our project, we formally established a Youth Advisory Committee (YAC) and Family Advisory Committee (FAC). YEA are eligible to join the YAC if they are between 14 and 35 years of age with lived experiences of FEP and are towards the end or have completed an Ontario-based EPI program. Similarly, family members are eligible to join the FAC if they have a loved one between 14 and 35 years of age who have past or current symptoms of psychosis. We continuously recruit advisors through outreach initiatives across Ontario EPI clinics. Each committee meets virtually once per month to guide recruitment strategies, assessment and treatment protocols, outcome measures, and the interpretation and dissemination of findings. We measure advisors' perception of study engagement using the modified Public Patient Engagement Evaluation Tool (PPEET) self-report. We administer the PPEET to YAC members every 3 months and FAC members monthly as recommended by participating advisors. Mean scores and percentage of favourable responses were calculated for Year 1 (March 2020 – February 2021) and Year 2 (March 2021 to February 2022). Year 3 (March 2022 to February 2023) scores will be calculated and compared to Year 1 and 2 scores.

Results: The YAC consists of six diverse individuals across Ontario with unique lived experiences. The FAC consists of one sibling and eight parents who have a loved one with lived experience of FEP. Across the 11 items of PPEET rated on a scale of 1 to 5, mean scores of perceived engagement and satisfaction increased from 4.3 to 4.7 for YAC members and from 4.2 to 4.5 for FAC members from Year 1 to Year 2. Mean scores improved notably for two items: (1) feeling as if their views could be expressed freely (4.5 to 5 for YAC and 4.3 to 4.6 for FAC); and (2) feeling as if they make a difference and their contribution matters (4.5 to 4.9 for YAC and 3.9 to 4.3 for FAC). Based on the increase in mean scores from Year 1 to Year 2, we hypothesize that mean scores from Year 2 to Year 3 will also increase. Year 3 scores and specific advisory-led contributions to our study will be discussed.

Discussion: Our project is designed to improve the delivery of recovery-oriented, evidence-based EPI care by meaningfully engaging youth and family members with first-hand FEP experiences. NAVIGATE is a holistic approach to EPI care that supports recovery of the mind, body, and soul, a major healthcare priority emphasized by our YAC and FAC. Establishing advisory governances at the beginning of this project has provided incredible valuable in developing and carrying out all research objectives while empowering our youth and family advisors to be leaders of change. We

regularly consult with our advisors to advance our current strategies for implementing and executing patient-oriented research to ensure involvement remains collaborative, genuine, and impactful.

F66. RURAL-URBAN STATUS AND SOCIODEMOGRAPHIC FACTORS ASSOCIATED WITH DURATION OF UNTREATED PSYCHOSIS: A MENTAL HEALTH ELECTRONIC CLINICAL RECORDS ANALYSIS IN THE EAST OF ENGLAND, UK.

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Background: The influence of rurality on the duration of untreated psychosis (DUP) in first-episode psychosis (FEP) is poorly understood. We investigated (a) whether FEP patients differ by rural-urban status; (b) whether DUP differs by sociodemographic and rural-urban status, and (c) the relationship between the mode of onset of psychosis and sociodemographic and rural-urban status.

Methods: We used the Cambridgeshire and Peterborough NHS Foundation Trust Research Database (CPFTRD) to identify all persons presenting with a first episode psychosis (ICD F20-29 codes) who presented to an early intervention for psychosis service in CPFT between 2013 and 2015. We performed chi. square/fisher exact, t and Kruskal Wallis tests to assess the relationships between the study outcomes and the independent variables.

Results: One hundred and fifty-five FEP patients were identified, with a mean age of 23.4 (sd, 5.3) years. The median DUP was 129.0 (IQR: 27.5 -524.0) days. In rural areas, FEP patients were more likely to live with family compared with those living alone (84.8% vs 8.9%, respectively, $p<0.001$), and they were more likely to be employed compared with those who were unemployed (47.8% vs 26.1% respectively, $p<0.001$). A longer DUP was observed among patients with an insidious onset of psychosis compared with those with an acute onset (619.5 (IQR: 333.5- 945.0) vs 17.0 (IQR: 8.0 -30.5 days respectively, $p<0.0001$)). There was no evidence of rural-urban differences in DUP. An acute mode of onset was associated with employment status (employed: 47.3% vs unemployed: 29.1%, $P=0.02$). In the patients with an acute onset of psychosis, those who lived alone differed statistically from those living with family/relatives (5.4% vs 96%, respectively, $p=0.04$).

Discussion: Our results suggest that the mode of onset of psychosis is an important indicator of treatment delay. Sociodemographic variations in FEP exist in rural populations, and our findings are comparable to those observed in urban settings. Our findings provide vital information for service planning and delivery.

F67. INTERNALIZED STIGMA AS A PREDICTOR OF TREATMENT RESPONSE AFTER COGNITIVE BEHAVIOR THERAPY FOR SOCIAL ANXIETY IN FIRST-EPISODE PSYCHOSIS

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Background: Social anxiety is highly prevalent in first-episode psychosis (FEP) and has been associated with poor prognosis and significant social disability. Symptoms of social anxiety have

been found to persist in FEP patients even after remission of psychotic symptoms which highlights the importance of understanding how treatments can be optimized to reduce these symptoms. As only a few randomized controlled trials (RCTs) have examined how Cognitive-Behavior Therapy (CBT) can reduce social anxiety in FEP, the mechanisms underlying treatment response remain understudied. Internalized stigma is a known contributor to the development and maintenance of social anxiety in psychosis and has been both targeted and improved in previous clinical trials for psychosis. However, research has not yet investigated how improved internalized stigma may underlie social anxiety outcomes after treatment in early psychosis. The aim of this study is to determine whether changes in internalized after a manualized group CBT predicts a positive change in social anxiety in FEP.

Methods: Secondary analyses were performed on an RCT which recruited 96 FEP patients with social anxiety from five sites in Montreal. Participants were randomized to either a 13-week group CBT adapted for social anxiety or cognitive remediation (CR) as an active control.

Results: Preliminary results of hierarchal linear regressions revealed that changes in internalized stigma from pre- to post-treatment significantly predicted 30% of the change in social anxiety after CBT. Such an association was not observed after CR.

Discussion: Improvements in social anxiety in FEP can be attributed to the specific effects of CBT on reducing internalized stigma, over nonspecific factors. This implies that internalized stigma would be an important intervention target in future research and clinical practice in the context of aiming to alleviate social anxiety symptoms in FEP.

F68. IMPROVING DELIVERY OF EARLY PSYCHOSIS INTERVENTION PROGRAMS: CAN IMPLEMENTING A STRUCTURED MODEL OF CARE INCREASE QUALITY?

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Background: NAVIGATE is an evidence-based, structured model of Early Psychosis Intervention (EPI) that emphasizes systematic delivery of medical and psychosocial interventions by an interdisciplinary team. In Ontario, Canada, EPI is a priority service with about 50 programs currently delivering EPI across the province. Past sector fidelity assessments demonstrated good program compliance with EPI model standards in many areas but some variability in delivery, including for psychosocial treatments. The present study aimed to improve the quality and consistency of care by implementing NAVIGATE in six geographically diverse Ontario EPI programs, serving approximately 300 patients with psychotic disorders annually. We evaluated the effect of implementing NAVIGATE on fidelity to the EPI model standards.

Methods: The study used a multicentre effectiveness-implementation design, with fidelity as a primary outcome. Fidelity was assessed using the FEPS-FS (Addington et al, 2020), with 31 items rated on a scale from 1 (not implemented) to 5 (fully implemented). A rating of 4 was defined as good performance. Study sites received a baseline assessment during 2019 prior to implementation of NAVIGATE (T1) and a second assessment 20 months later after most clients had at least one year of exposure to the model (T2). The second assessment occurred during 2020-21 when COVID-19 was exerting a major impact on health care delivery. At each site, staff interviews, administrative data and client chart data were collected and reviewed by trained assessors to make

the fidelity ratings. For reporting, items were grouped into five domains (team practice, access and continuity, assessment and care planning, pharmacotherapy and psychosocial treatments). Mean T1 and T2 fidelity scores were calculated at the item, domain and total scale levels for the entire sample. The percentage of items reaching good fidelity (rating of 4 or more) was calculated.
Results: Of 31 FEPS-FS items, two measured practices that could not be implemented during COVID (required in-vivo community contacts) and were excluded from calculations. The mean fidelity score for the 29 included items increased from 3.82 to 4.05. At the domain level, mean ratings increased for team practice (4.14 to 4.45) and psychosocial treatments (2.79 to 3.77). Within these domains, mean item ratings increased for multidisciplinary team (4.00 to 4.67) and psychiatrist caseload (1.83 to 3.00) (team practice domain), and for family support (2.33 to 3.50), supported employment (1.00 to 2.17) and supported education (1.00 to 4.33) (psychosocial treatment domain). Despite improvements, mean item ratings did not reach good performance for 38% of items at T1 and 28% at T2. Persistently lower items included CBT, supported employment and early intervention (prior inpatient admissions).
Discussion: The NAVIGATE model was expected to improve practice in a number of areas including delivery of psychosocial treatments and team function. Despite being implemented during turbulent times, study programs were able to sustain and improve EPI practice in these and other areas. However, gaps in fidelity for some practices persisted. Despite a small study sample, our findings suggest that this manualized multicomponent model can be implemented with benefit. Continued effort is needed to identify challenges and support ongoing program improvement in model delivery.

F69. PEER EXPERIENCES AMONG YOUTH AT CLINICAL-HIGH RISK FOR DEVELOPING PSYCHOSIS: "STIGMA IMPACTS BEING PART OF THE SOCIAL FABRIC"

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Background: Adolescence is a period when peer relationships are increasingly important and tied to identity development. Disconnection from social contacts including loss of friendship and isolation is a common experience among youth in the early stages of psychosis. This can happen for a number of reasons including experiences of perceived and experienced stigma, and increased symptoms. Less research has focused exclusively on the experiences of peer relationships among youth at clinical high risk for developing psychosis (CHR-p). The following secondary analysis qualitative study explored peer experiences (supportive, unsupportive) among youth at CHR-p, and how these experiences impacted (positive, negative, mixed) how they see themselves.
Methods: The current study was part of a larger longitudinal study examining the impact of "psychosis risk" identification among youth accessing clinical high-risk for psychosis programs in the USA between the years 2012-2015. Qualitative baseline data from CHR-p individuals collected from three sites (Beth Israel Deaconess Medical Center/Harvard Medical School (Boston, MA),

Maine Medical Center (Portland, ME), and New York State Psychiatric Institute (New York, NY) was utilized. Youth were included in the sample if they spoke about peer experiences in the open-ended qualitative portion of the study. Example questions included: "Since being told that you are at-risk for or developing a [mental illness], have you had other experiences of how other people treat you, both positive and negative?" Three analysts, including student and peer researchers, engaged in thematic analysis, utilizing open coding, memo writing, and constant comparison, that led to the development of a codebook. Strategies for rigor included multiple coders, peer debriefing, and audit trails.

Results: The sample was comprised of 113 youth between the ages 12-29 across the three sites. Mean (SD) for age was 18.7 (4.2), with 62% male, 66% White, 12% Black, 12% Interracial, 4% Asian, 3% Central/South American, 2% First Nation. Peers included friends, peers with lived experience, peers at work, peers at school, online peers, and significant others. Fifty-one percent of the sample spoke about receiving support from peers that came in the forms of emotional and instrumental support. Forty-eight percent of the youth spoke about not receiving support from peers. Instead, they discussed experiences such as being treated differently and dismissed by their peers, peers distancing themselves from the youth, as well as experiences of stigma and discrimination. When discussing the impact of these experiences, 34% of the youth spoke about a positive impact, including positive changes in life, connection through shared lived experiences, and positive emotions. One youth stated, "Some people are either going through the same thing or want to know more so they can help... It makes me feel good." Forty-four percent of the youth spoke about the negative impact of these experiences including negative emotions and self-image, social isolation, disconnection, and internalized stigma. One youth said, "I've lost a lot of self-confidence...people think about me differently - weird, annoying, too many problems."

Discussion: Peer experiences were both supportive and unsupportive, which impacted how the youth at CHR-p viewed themselves. Investments in peer involvement and leadership in early intervention in psychosis services has been found to improve symptoms and well-being, and decrease internalized stigma. Future research should explore the role of peer support for youth at CHR-p in increasing positive outcomes, and in buffering stigma experiences.

F70. IMPROVING TREATMENT OUTCOMES FOR YOUTH AND EMERGING ADULTS WITH A FIRST EPISODE OF PSYCHOSIS: EVALUATING THE EFFECTIVENESS OF NAVIGATE

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Background: While early psychosis intervention (EPI) services have grown in recent years, programs struggle to deliver consistent, coordinated, recovery-based care for youth and emerging adults. These challenges exist across Canada, as well as internationally. 'NAVIGATE' is an evidence-based, manualized model of coordinated EPI care that aims to improve the day-to-day functioning of youth and emerging adults suffering from a first episode of psychosis (FEP) by incorporating four pillars of care: (1) medication management; (2) individual resiliency training; (3) supported employment and education; and (4) family education. In this multi-site

implementation study, we sought to investigate longitudinal patient-level functioning and symptom outcomes of youth participants receiving NAVIGATE.

Methods: We recruited 100 participants between the ages of 14 and 35 years old across six geographically diverse EPI programs in Ontario, Canada who meet criteria for a DSM-diagnosis psychotic disorder. Participants were eligible if they had been in their EPI program for under two years. Trained interviewers complete comprehensive assessments at baseline, and every six months over two years. Outcome measures included of the Quality of Life Scale (QLS), the Social and Occupational Functioning Assessment Score (SOFAS), the World Health Organization Disability Assessment Schedule 2.0 (WHODAS), as well as the Brief Psychiatric Rating Scale (BPRS) and the Patient Health Questionnaire (PHQ-9) to evaluate symptom change. Change in outcome measures over the first 12 months was evaluated using linear mixed models.

Results: To date, 64 participants enrolled in this study have reached their 12-month assessment time-point. Participants had a mean age of 22.8 years, and 42% were female. Over the first 12 months of NAVIGATE treatment, participants exhibited a significant improvement in QLS scores ($F(82.2,2) = 13.129$, $p<.001$), and a significant improvement in SOFAS score ($F(53.9,1) = 47.890$, $p<.001$). There was also a trend for improvement in overall symptoms as measured by the BPRS ($F(87.6,2) = 2.802$, $p=.066$). There were no significant changes over time in WHODAS scores, nor in PHQ-9 scores.

Discussion: Coordinated specialty care for early psychosis with the NAVIGATE treatment program seeks to enhance the delivery of comprehensive evidence-based care to improve recovery outcomes for individuals experience a first episode of psychosis. Preliminary findings on the effectiveness of NAVIGATE on early psychosis outcomes in Ontario, Canada, suggest that youth and emerging adults receiving NAVIGATE exhibit significant improvements in functioning over the first year of treatment. These results are in line with findings from other jurisdictions on the functional outcome benefits of NAVIGATE for early psychosis treatment. Through this ongoing study, continued evaluation of outcomes over the full two years of treatment will offer further evidence on the effectiveness of NAVIGATE on outcomes, and inform opportunities for EPI service design to provide comprehensive evidence-based care to enhance outcomes for individuals experiencing early psychosis.

F71. TARGETING RACIAL TRAUMA and STIGMA-BASED STRESSORS IN EARLY-STAGE PSYCHOSIS SERVICES: COMMUNITY-BASED PARTICIPATORY RESEARCH TO DEVELOP A PROVIDER EDUCATION PROGRAM

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Background: Upwards of 50-70% of youth from minoritized groups in the United States report experiencing racial discrimination (e.g., Anglin et al., 2014), and racism and other stigma-based stressors are common worries among individuals at clinical high risk for, or in the early stages of (e.g., first-episode), psychosis (Nagendra et al., 2022; Saleem et al., 2014). Furthermore, experiences of racial discrimination and other race-based stressors, collectively known as racial trauma, are associated with distressing psychotic experiences (Anglin et al., 2014) as well as conversion to psychosis among individuals at-risk (Stowkowy et al., 2016). Despite this knowledge, significant racial and ethnic inequities exist within early-stage psychosis programs (Jones et al., 2021), such that youth from minoritized groups may not consistently receive

culturally sensitive care or achieve comparable treatment outcomes to White youth. Thus, the purpose of this grant-funded project is to develop and test an education program for early-stage psychosis providers focused on racial trauma and stigma. The goals of this project are to enhance providers' abilities to provide culturally responsive services and, subsequently, improve patients' treatment engagement and outcomes.

Methods: We first conducted a narrative review of Community-Based Participatory Research (CBPR) in early-stage psychosis work to understand best practices and knowledge gaps. This project is then being conducted in two phases. In phase 1, we co-developed a recorded provider education program (~30 minutes) focused on racial trauma and other stigma-based stressors. Aligned with a CBPR framework, this program was co-developed by the first author and three youth who have lived experience of psychosis. This program was developed over six months via weekly meetings and brainstorming sessions. In phase 2, we will pilot the program with N = 50 North American early-stage psychosis providers (mental health professionals) between January – April 2023. We will have three time-points (pre-test, immediate-post-test, 3-month follow-up) to better understand providers' knowledge and comfort around racial trauma and stigma, as well as any changes in their clinical work as a result of watching the education program (e.g., use of assessment tools or treatment strategies, perceived stronger therapeutic relationship with minoritized patients, etc.).

Results: CBPR work in the early-stage psychosis area is in its infancy but holds tremendous promise for the development of user-friendly services and the meaningful involvement of service users in the research process. For phase 1, the main topics of the education program include: intersection of psychosis and race, intersectionality and anti-racism, person-centered treatment, racial awareness, assessment and treatment strategies for racial trauma and stigma-based stressors, and a conclusion with resources. Resources and the full training video will also be hosted on a dedicated website. Accomplishments, insights, challenges, and suggestions for CBPR work in early-stage psychosis will be shared. Phase 2 data will be collected in January 2023, and at least baseline and immediate-post-test data will be available for presentation at the SIRS 2023 Annual Congress. We anticipate that the program will be feasible and acceptable to providers, and that providers will experience a positive impact on their services.

Discussion: Culture and psychosis are deeply intertwined, and racial trauma and stigma are strongly associated with psychosis-spectrum experiences. Thus, there have been specific calls for the development of provider education programming in early-stage psychosis services to better assess and treat racial trauma and other stigma-based stressors, especially since most mental health providers report never receiving formal training in these areas. Our project aimed to fill this gap by (1) collaboratively developing a provider education program on racial trauma and other stigma-based stressors, and (2) conducting a pilot test of its feasibility and acceptability. To date, CBPR work appears to be a feasible and essential method in early-stage psychosis work, which allows diverse voices to be centered and key content to be integrated into early-stage psychosis programming. The voices of youth with lived mental health experience are rarely heard, particularly in early-stage psychosis work, and this work represents a small step toward a more inclusive field.

References

Anglin, D. M., Lighty, Q., Greenspoon, M., and Ellman, L. M. (2014). Racial discrimination is associated with distressing subthreshold positive psychotic symptoms among US urban ethnic minority young adults. Social psychiatry and psychiatric epidemiology

Saleem, M. M., Stowkowy, J., Cadenhead, K. S., Cannon, T. D., Cornblatt, B. A., McGlashan, T. H., ... and Addington, J. (2014). Perceived discrimination in those at clinical high risk for psychosis. Early intervention in psychiatry

Stowkowy, J., Liu, L., Cadenhead, K. S., Cannon, T. D., Cornblatt, B. A., McGlashan, T. H., ... and Addington, J. (2016). Early traumatic experiences, perceived discrimination and conversion to psychosis in those at clinical high risk for psychosis. Social psychiatry and psychiatric epidemiology

F72. DO STRESS AND EARLY ADVERSITY IMPACT THE PATHWAYS BETWEEN NEURODEVELOPMENT AND EXECUTIVE FUNCTIONS IN PATIENTS AT ULTRA HIGH RISK OF PSYCHOSIS?

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Background: Schizophrenia (SZ) is a neurodevelopmental disorder characterised by cognitive impairments – in particular executive functions – and is aggravated by risk factors, such as stress or early adversity. Associations between neurodevelopmental deficits and executive dysfunction have been proposed in the temporal spectrum of schizophrenia but remain relatively unknown. Our objective was to explore the relationship between neurodevelopment deficits and executive dysfunctions and the potential effect played by stress and early adversity in patients at ultra-high-risk of developing psychosis (UHR), a temporal window of opportunity for schizophrenia prevention.

Methods: Neurological soft signs (NSS), previous and recent social functioning, flexibility, reasoning and planification tests, Childhood Trauma Questionnaire (CTQ), State Trait Anxiety Inventory (STAI) were assessed in 116 subjects (75 UHR, 24 SZ and 17 healthy controls (HC)). We performed moderation and mediation model analyses using composite Z-scores.

Results: In the UHR group, regression analyses showed an association between previous social functioning and flexibility and reasoning scores ($p = 0.006$ and $p = 0.02$ respectively), whereas in the SZ group, associations between current social functioning / autistic traits and flexibility scores ($p = 0.04$) and between NSS and reasoning scores ($p = 0.001$) were found. Interestingly, mediation and moderation models on CTQ and STAI effects on these relationships were not significant.

Discussion: These findings show that neurodevelopmental impairments and executive functions are differently associated within the temporal spectrum of schizophrenia, and these associations do not appear to be mediated or moderated by stress or early adversity factors.

F73. EFFECTS OF MUSIC BEAT ON MOVEMENT SPEED IN PEOPLE WITH PSYCHOTIC-LIKE EXPERIENCES: A RANDOMIZED CONTROLLED PILOT TRIAL

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Background: Early intervention is one of current priorities in psychiatric services. Increasing research attention has been drawn to the general population with psychotic-like experiences (PLEs), who has higher likelihood of developing psychotic diseases afterwards than do people without PLEs. Movement abnormalities have been reported to be risk factors of transition to full-blown psychosis in individuals at clinical high risk of the psychotic onset. It is noteworthy that people with PLEs have been found to exhibit movement abnormalities, such as movement slowness. In addition, movement problems extensively limit the ability to study in school, work, and socialize for people with PLEs. It is of clinical meaning to develop early intervention for tackling movement problems in this population. Earlier research has shown that rhythmic auditory stimulation is effective in inducing faster movements or even improving movement speed in patients with psychosis or people with PLEs. Given that music with rhythm is common in daily life and an interesting therapeutic medium, this study was to examine effects of music beat on movement speed in people with PLEs.

Methods: A total of 13 people with PLEs were screened out through the use of the 16-item Prodromal Questionnaire and the 15-item Community Assessment of Psychic Experiences. They were randomly allocated either to the group receiving upper-limb movement training (picking up beans from different bowls to the main bowl) with the aid of music beat (n=6), or to the group receiving the same movement training without the aid of music beat (n=7). The training lasted for 21 days with a daily basis and 40 minutes per day. For people receiving the aid of music beat, we provided piano music “Sign of The Times” with three gradually faster tempi. People in this group were required to match the movement tempo of picking up each bean to the music beat. For people receiving no aid of music beat, they were required to execute movements as quickly as possible during the training. At pretest and posttest, this study used the motion analysis system to calculate the kinematic variable, normalized movement time (nMT), which objectively and sensitively represented movement speed. In addition, the Extrapyramidal Symptom Rating Scale was also used to assess severity of movement slowness. This study also recruited 13 age- and gender-matched healthy controls, who did not have PLEs, to provide reference data of movements. Healthy controls only received baseline measurement and did not receive movement training.

Results: The independent sample t test showed that people with PLEs had larger nMT and thus slower movements than did healthy controls ($p < .001$). In addition, the analysis of covariance was used to control for possible influences of age, the gender ratio, education, cognition, scores of the 16-item Prodromal Questionnaire and the 15-item Community Assessment of Psychic Experiences, and pretest nMT. The results showed that people with PLEs receiving music beat had smaller nMT and thus faster movements than did people with PLEs receiving no aid of music beat ($p = .035$). No significant results were found for differences between people with PLEs and healthy

controls (p = 0.651) and for effects of music beat (p = .070) when scores of the Extrapyramidal Symptom Rating Scale were used.
Discussion: These pilot data supported that music beat may be effective in improving movement speed in people with PLEs. This study is one of pioneering studies that develop early intervention programs to address movement abnormalities, which are early signs of worsening psychosis progress, in the early stage of psychosis continuum. Future large-scale research is needed to increase generalizability of study results.

F74. FUNCTIONAL CONNECTIVITY-BASED SIGNATURES OF PERCEPTUAL DISTURBANCES IN INDIVIDUALS AT CLINICAL HIGH-RISK FOR PSYCHOSIS: A MULTIVARIATE PATTERN ANALYSIS

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Background: Perceptual abnormalities are a hallmark feature of schizophrenia, experienced by 40-62% of patients, and is predictive of later development of psychosis in those at clinical high risk for psychosis (CHR-P). However, this domain has received little attention due to its phenomenological nature – in contrast to cognition. While numerous studies have shown aberrations in static and dynamic connectivity in CHR-P, particularly in the salience and default mode network regions involved in sensory, motor, attention, and cognitive functions, few studies have investigated the predictive ability of resting-state network connectivity in identifying perceptual abnormalities at the individual-level in CHR-P.
Methods: Structural and functional MRI were acquired from 49 CHR-P (mean [SD] age = 23.57 [5.29], 45% male) on a GE MR750 3T scanner at Columbia University and on a 3T Siemens Skyra scanner (Erlangen, Germany) at the ISMMS. To enhance reproducibility, resting-state networks were defined using the templates developed by Gordon and colleagues, and comprised of 12 networks including dorsolateral and ventromedial somatomotor, visual, and auditory networks. For multivariate pattern analysis, we used the NeuroMiner software (v1.0) to classify CHR-P with or without perceptual disturbances (SIPS-P4) based on within- and between-network connectivity of the Gordon atlas using a Support Vector Machine algorithm with 5-fold cross-validation. Feature selection included identifying principal components that cumulatively explained 80% of the variance and scaling these components from 0-1. Statistical significance of the observed classification performance of our model was identified through permutation analysis by randomly shuffling the labels 1000 times. We then calculated the significance of the observed out-of-training balanced accuracy (BAC) as the number of events where the permuted out-of-training BAC was higher or equal to the observed BAC divided by the number of permutations performed.
Results: The algorithm identified CHR-P with perceptual dysfunctions with a BAC of 69.9% (Sensitivity = 76.7%; Specificity = 63.2%; p = 0.02). Between-network connectivity of the RetrosplenialTemporal network with 1) FrontoParietal, 2) ventrolateral somatomotor, 3) auditory, and 4) default networks and within-network connectivity of the ventrolateral somatomotor network were the variables most frequently chosen by the algorithm to generate decisions.
Discussion: We identified an accurate and meaningful neurosignature associated with perceptual disturbances in CHR-P. The retrosplenial cortex was identified as a core region of connectivity in

identifying individuals with perceptual aberrations and has been shown to be involved in generating (both real and imagined) perspectives of the external world. These findings suggest the retrosplenial cortex may play a key role in the perceptual abnormalities experienced in individuals with psychosis spectrum disorders and may serve as an important target for interventions.

F75. A COMPARISION OF LANGUAGE-NETWORK FUNCTIONAL CONNECTIVITY IN FORMAL THOUGHT DISORDER AND PRIMARY APHASIA

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Background: Formal Thought Disorder (FTD) is a positive symptom of schizophrenia (SZ) characterized by conceptual disorganization and incoherence of speech. As with other conditions affecting speech such as aphasia, these are the result of specific neurological changes. While these disorders have been compared in terms of language presentations, specific neurological similarities and differences between FTD and disorders with similar linguistic presentations such as primary progressive aphasia (PPA) have been less well-studied, despite being a potential avenue for better understanding the neurology underlying disordered language in both these conditions.

Methods: Resting-state functional Magnetic Resonance Imaging (rs-fMRI) images from the Tracking Outcomes in Psychosis (TOPSY) study at Western University were produced from scans of first-episode psychosis patients participating in the Prevention and Early Intervention Program for Psychoses (PEPP) at the London Health Sciences Centre. Images from 51 patients and 31 healthy controls were used to create topographic brain-connectivity maps. The groups were also evaluated for the presence of FTD clinically and via analysis of their speech, from which the Analytic Thinking Index (ATI), a measure of conceptual disorganization via analysis of linguistic style, was calculated for each. Specific seed regions previously shown to center intrinsic connectivity networks involved in language abnormalities in PPA, as well as a seed region shown to have reduced connectivity in FTD patients, were selected and functional connectivity (FC) analyses were performed to assess for group differences and the effect of ATI.

Results: Decreased FC was seen in patients compared to controls between the left posterior-Inferior Temporal Gyrus (ITG) and a cluster including parts of the right ITG and Inferior Occipital Gyrus. When controlling for ATI, this was maintained, and decreased FC was additionally seen in patients between the left posterior-ITG and a cluster in the right Postcentral Gyrus. When controlling for the effects of group, FC correlated negatively with ATI between the left anterior-Medial Temporal Gyrus (MTG) and a cluster located in the dorsolateral Superior Frontal Gyrus, and between the right anterior MTG and a cluster including parts of the right Cuneus, Superior Parietal Gyrus and Precuneus.

Discussion: Our results showed SZ patients had decreased FC in a network linked to language abnormalities in PPA which is involved in top-down control of semantic processing. The altered connectivity seen in this network may contribute to the verbal memory deficits seen in both conditions. We also found SZ patients had decreased FC from the center of this PPA-linked network to an area outside of it, which may contribute to aberrant saliency determination involved in auditory hallucinations in SZ.

Similarly, we found FC correlated negatively with conceptual disorganization as measured by ATI between an area centering a semantic-processing network linked to language abnormalities in PPA and an external area, which may play a role in providing increased inhibitory control needed to compensate for conceptual disorganization. We also found FC correlating negatively with conceptual disorganization between the same location in the opposite hemisphere and a location linked to selective attention, which may result from a need for increased control of semantic processing in FTD.

F76. TABLET-BASED ASSESSMENT OF MANUAL DEXTERITY TO IDENTIFY FIRST EPISODE PSYCHOSIS.

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Background: Neurological symptoms can inform on degree of neurodevelopmental load in psychiatric disease and may be useful for early detection of psychosis. Aim: to study whether tablet-based measures of manual dexterity can provide behavioral markers for discrimination of first-episode psychosis (FEP), and to describe potential differences in cortical excitability/inhibition parameters.

Methods: Method: to assess the differential impact of neurodevelopmental loads in psychotic diseases, behavioral and neurophysiological testing was undertaken in 20 persons diagnosed with FEP, 20 persons with (stabilized) schizophrenia (SCZ), 20 persons with autism spectrum disorder (ASD), and 20 healthy controls. Five tablet-tasks assessed different motor and cognitive functions: Finger Recognition for effector (finger) selection and mental rotation, Rhythm Tapping for temporal control, Sequence Tapping for control of motor sequences, Multi Finger Tapping for finger individuation, and Line Tracking for visuomotor precision and attentional modulation. Clinical neurological soft signs (NSS) and medication were also assessed. Cortical excitability and inhibition, as well as cerebellar brain inhibition, were evaluated with transcranial magnetic stimulation.

Results: FEP patients showed slower reaction times and higher errors in Finger Recognition, and increased variability in Rhythmic finger Tapping. Using ROC-curves, rhythm tapping performance alone was sufficient to show enhanced discrimination of FEP patients vs. controls (75% sensitivity and 90% specificity) compared to clinical NSS (95% sensitivity and 22% specificity). Rhythm Tapping performance also allowed discrimination between FEP and ASD/SCZ patients. To improve the discrimination of FEP patients; all dexterity variables were included in a Random Forest analysis which showed 100% sensitivity and 85% specificity in discriminating FEP from the control, SCZ, and ASD g. Cortical excitability was not different among the group, but the FEP group had reduced cortical inhibition compared to control, ASD and SCZ groups.

Discussion: Conclusion: Easy-to-use tablet-based measures of manual dexterity are promising behavioral markers for the detection of FEP. Reduced cortical inhibition in FEP may represent a key mechanism related to early psychosis development.

F77. GREATER OVERESTIMATION OF SOCIAL FUNCTIONING IN PERSONS AT CLINICAL HIGH-RISK FOR PSYCHOSIS THAN IN MAJOR DEPRESSIVE DISORDER AND COMMUNITY CONTROLS

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Background: In people experiencing psychosis, poor insight is associated with similar outcomes as those with Major Depressive Disorder (MDD), such as poor social functioning, and more prominent negative symptoms; however, they differ in that greater insight is associated with less depression.
Introspective bias (IB) is an insight framework utilizing standardized objective ratings adjusted for self-assessment. Underestimation is defined as self-ratings below that of a rater, while overestimation is defined as self-ratings above that of a rater.

Poor social functioning and negative and depressive symptoms are common in individuals at clinical high risk for psychosis (CHR); therefore, understanding insight in CHR is needed.

The first aim of this study was to compare clinical and functional outcomes between under and overestimators. We hypothesized that overestimators would have greater negative symptoms, poorer social functioning, and less depression.

The second aim was to compare the proportions of under and overestimators in individuals with MDD, CHR, and controls. We hypothesized that CHR would have more overestimators, MDD would have more underestimators, and controls would have equal proportions.

The third aim was to compare outcomes for individuals with MDD, CHR, and controls, covarying for IB. We hypothesized that CHR would have less depression than MDD but more than controls. CHR and MDD would have greater negative symptoms than controls but would not differ from each other. CHR would have the poorest social functioning, followed by MDD, then controls.

Methods: Participants were recruited as part of the Multisite Assessment of Psychosis-risk Study with persons at CHR (n=28), with Major Depressive Disorder (MDD; n=66), and community controls with no current or history of mental illness (n=32). There were no differences in age ($p = .53$), race ($p = .09$), ethnicity ($p = .30$), or gender ($p = .44$) between groups.
Participants completed the self-report scales for social functioning (Social Functioning Scale – Psychosis Risk) and depression (Center for Epidemiologic Studies Depression Scale). Semi-structured interviews were conducted to assess CHR status (Structured Interview for Psychosis Risk Syndromes), psychiatric diagnoses (Structured Clinical Interview for DSM-5), and interviewer-rated social functioning (Global Functioning Scale: Social). IB was the standardized difference between interviewer-rated and self-rated social functioning, with the former as the anchor. We used both dimensional and categorical (overestimators below zero, underestimators above) operationalizations.

Results: Overestimators had greater negative symptoms (p =.04), poorer other-rated social functioning (p < .001), and greater self-rated social functioning (p < .001). Overestimators and underestimators did not differ in depression (p =.53).
There was a greater proportion of underestimators among controls (p < .001), CHR had more overestimators (p = .02), and MDD had no difference (p = .81). Estimated marginal means covarying for IB as a dimensional construct showed that CHR and MDD had worse depression than controls, CHR had greater negative symptoms than controls, and CHR had worse social functioning than MDD, who had worse social functioning than controls (p's < .001 - .025).

Discussion: IB did not show evidence of accounting for group differences, which suggests it is not driving these outcomes. Given the mediating relationship between social stigma and insight in other research on people with psychosis, such relationships with an IB for social functioning should be explored. Extrospective bias for social functioning, or that of raters, could be used as a frame to study insight emphasizing the individual as the expert in their own experience.

F78. ADVERSE CHILDHOOD EXPERIENCES, POSITIVE PSYCHOTIC SYMPTOMS, AND THE ROLE OF COGNITIVE REAPPRAISAL

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Background: There is a well-documented association between adverse childhood experiences and elevated rates of psychosis (Morgan and Gayer-Anderson, 2016). Less clear, however, is the relationship between ACEs and specific types of psychotic symptoms. A recent systematic review found mixed support for associations between ACEs and delusions, hallucinations, thought disorder, paranoia, and negative symptoms (Grindey and Bradshaw, 2022). While the strongest support appeared between ACEs and positive symptoms, results were varied, and did not include individuals at clinical high risk (CHR) for psychosis. It is unclear whether associations between ACEs and positive symptoms hold in CHR individuals. Clarifying this relationship has implications for early identification and intervention.
Difficulties in emotion regulation have also been considered a factor in the maintenance of positive symptoms. Cognitive reappraisal is an adaptive emotion regulation strategy that involves attempting to change the meaning or importance of an event. The cognitive model of positive symptoms posits that negative affect and cognitive biases contribute to a delusional interpretation of anomalous events (Garety et al., 2001). Individuals with psychosis have demonstrated less frequent cognitive reappraisal in relation to controls (Ludwig et al., 2019).

In this study we aimed to elucidate the relationship between ACEs and positive symptoms of psychosis and the role of cognitive reappraisal in CHR individuals. We hypothesized that ACEs would be positively correlated with positive symptoms. In line with the cognitive model of positive symptoms, we expected cognitive reappraisal to buffer this association, such that more frequent use of cognitive reappraisal would diminish the relationship between ACEs and positive symptoms.

Methods: The present study included English-speaking participants aged 18+ identified as being at clinical high risk (CHR) (N = 32, 53.1% female, M age = 25.59). Participants completed a questionnaire of Adverse Childhood Experiences (ACEs; Dube et al., 2001), as well as the

Emotion Regulation Questionnaire (ERQ; Gross and John, 2003). Participants also completed a semi-structured interview including a section of the Structured Interview for Prodromal Symptoms (SIPS; McGlashan et al., 2001) to assess for CHR status and measure positive symptoms. A moderated regression was conducted to test the role of cognitive reappraisal in the relationship between ACES and positive symptoms of psychosis. Analyses were conducted using SPSS 28.
Results: Participants were mostly black (56.3%) and college graduates (79.3%), all between the ages of 20 and 35. We found a significant, moderate correlation between ACEs and positive symptoms of psychosis ($r = .48$, $p = .006$). Moderation analysis then probed whether cognitive reappraisal moderates the relationship between ACEs and positive symptoms. results indicated that the interaction between ACEs and cognitive reappraisal was not significant ($b = .98$, $SE = .65$ $p > .05$), meaning that cognitive reappraisal did not appear to significantly impact the relationship between ACEs and positive symptoms of psychosis.
Discussion: This study provides further support for the relationship between ACEs and specific symptoms of psychosis; however, it did not support cognitive reappraisal strategies as a moderator. Emotion regulation strategies are a target of evidence-based interventions for psychosis and have been shown to enhance treatment engagement (Spidel et al., 2018). Various considerations regarding these findings will be discussed. This research supports the need for trauma-informed care and early assessment of ACEs in clinical practice.

F79. THE CHANGES IN HIPPOCAMPAL VOLUME AFTER INITIAL ANTIPSYCHOTIC MEDICATIONS WERE DIFFERENT BETWEEN YOUNGER AND OLDER FIRST-EPISODE SCHIZOPHRENIA PATIENTS

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Background: Hippocampus is involved in the pathological process of schizophrenia, and its volume alterations after initial antipsychotic treatment are reported in first-episode schizophrenia (FES). However, whether they interact with age is still unclear.
Methods: The present study included 120 medication naïve FES patients (age range 15-) and 110 matched healthy controls (HC). Patients took MRI scans before and after weeks of antipsychotic treatment, while HC took MRI scans at baseline. Volumes of hippocampus and subfields were measured by FreeSurfer 7. Liner mixed models (LMM) and repeated measures analysis of variance (RM-ANOVA) were mainly used for statistical analyses.
Results: The volume of the hippocampus and subfields were comparable between FES and HC before treatment. LMM showed a significant main effect of time($\beta=62.486$,$t= 2.571$, $p=0.011$), as well as a significant age-by-timepoint interaction effect ($\beta=-1.964$,$t= -2.048$, $p=0.043$) on the left hippocampal volume in FES. Implying that the left hippocampus atrophied from pre- to post-treatment as age in baseline decreased. While PANSS score decreased from pre to post-treatment as age increased, for a significant main effect of time($\beta=19.691$, $t= 4.057$, $p < 0.001$), and a significant age by timepoint interaction effect ($\beta=0.419$, $t=2.185$, $p=0.031$). To further analyze the longitudinal change, the whole sample was divided into two subgroups by age 24. RM-ANOVA revealed a significant group-by-time interaction for the left whole hippocampus ($F= 5.395$, $p = 0.022$, $\eta^2=0.046$), and post hoc ANOVA exhibited a significant volume decrease in the left whole

hippocampus (F= 10.291, p = 0.002, η^2=0.085) among the younger FES. On the subfield level, the interaction effects existed in left granule cells in the molecular layer of the dentate gyrus (GC-ML-DG) (F=8.499, p = 0.044, η^2=0.071, FDR corrected) and left cornu ammonis 4 (CA4) (F=8.231, p = 0.028, η^2=0.069, FDR corrected), and significant volume decrease also exhibited in the left GC-ML-DG (F= 14.484, p ＜0.001, η^2=0.115) and left CA4 (F=12.648, p =0.001, η^2=0.102) of the younger FES (age＜24 y, n=60) after antipsychotic medications. However, older FES (age ≥24 y, n=60) showed insignificant longitudinal change, though the pre-treatment left hippocampus was smaller than matched HC. The difference in longitudinal changes of volume in the two subgroups still existed after controlling their respective baseline volumes. Exploratory analyses revealed a partial correlation between negative score reduction rate and volume decrease in left GC-ML-DG (pre-post) (r=-0.275, p = 0.045) among older FES controlling for age, sex, education years, duration of untreated psychosis, chlorpromazine equivalents and intracranial volume.
Discussion: The smaller left whole hippocampus in older FES pre-treatment was in line with the mainstream findings and reflected the hippocampal injury in the early stage of schizophrenia.
The severe longitudinal hippocampal atrophy in the younger FES could be a reflection that the immature hippocampus is more vulnerable in the psychotic attack stage and more sensitive to being affected by the toxic effects of antipsychotics. While the unshrink hippocampal volume in the older FES may possibly reflect the neuroprotective effect of atypical antipsychotics.

The antipsychotic treatment in the acute stage failed to improve hippocampal atrophy of FES, while the correlation between the volume shrinkage and negative symptom reduction in the older FES may suggest that the preservation of hippocampal volume is beneficial to the prognosis.

Our findings suggest that age affects the hippocampal volume changes after initial antipsychotics of FES, with the younger showing a more pronounced volume reduction in the left hippocampus.

F80. DEVIATIONS IN WHITE MATTER MICROSTRUCTURE VARY IN LOCATION ACROSS INDIVIDUALS AT CLINICAL HIGH RISK FOR PSYCHOSIS

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Background: White matter alterations are commonly found in young people at clinical high risk for psychosis (CHR). However, it's not clear how locations of white matter abnormalities differ

across individuals at CHR or whether overall number or severity of abnormalities relate to different CHR outcomes.
Methods: Multi-shell diffusion weighted 3T-MRI was collected from 123 CHR participants (26 developed psychosis; CHR-P, 97 did not; CHP-NP) and 86 healthy control (HC) participants. All participants were aged 14-25 and were recruited from the Shanghai At-Risk for Psychosis Program (SHARP). White matter microstructure alterations were evaluated using free-water imaging, which separately quantifies cellular changes with fractional anisotropy of tissue (FAt) and extracellular changes with the fraction of free-water (FW). Individual deviations, i.e., absolute z-scores > 1.96, in FAt and FW were determined using sex-specific normative models across age constructed for 46 white matter tracts. ANCOVAs covarying for age, sex, and motion were used to test group differences in location-independent derived measures. These included number of deviations, the largest z-score (severity), the average z-score, and the standard deviation of z-scores across tracts.
Results: 120 out of 123 (97.6%) CHR participants had at least one FAt or FW deviation compared to 75 out of 86 (87%) HC. However, the location of deviations did not overlap across more than 18% of CHR participants or 8% of HC. Irrespective of location, CHR participants had a larger number of negative FAt ($F=7.2$, $p=0.008$) and positive FW deviations ($F=9.2$, $p=0.003$), greater severity (FAt: $F=16.3$, $p<0.005$; FW: $F=14.3$, $p<0.005$) and standard deviation (FAt: $F=9.3$, $p=0.003$; FW: $F=14.3$, $p<0.005$) compared to HC. CHR-P participants had lower FW severity ($F=4.4$, $p=0.04$) compared to CHR-NP participants.
Discussion: White matter deviations are prevalent but vary in location across CHR, potentially reflecting important neurobiological heterogeneity in the CHR population. Location-independent measures differentiated CHR from HC, providing support for a consistent overall burden of alterations across the brain. Our results capture inter-individual differences in deviation location, suggesting lower FAt (more negative deviations) and higher FW (more positive deviations) in CHR participants compared to HC, which is consistent with the findings in previous group-based CHR and schizophrenia studies. Location-independent measures also differentiated CHR-P from CHR-NP, although mechanisms driving this finding are not clear yet. Further investigating location heterogeneity, in addition to variations in location-independent measures, could therefore provide clearer insight into diverging CHR outcomes.

F81. PSYCHOTIC EXPERIENCES IN THE GENERAL POPULATION: AN EXPLORATION OF CUMULATIVE EFFECTS ON MENTAL HEALTH OUTCOMES

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Background: Transdiagnostic models have hypothesized that mental disorders may have an early shared pathway where observed signs and symptoms may evolve into a range of mental health disorders. The general population who report psychotic experiences may represent sub-clinical symptoms and indicate vulnerability in the development of mental health problems. The following study examined the association between psychotic experiences and different mental health outcomes within a large cohort of people living in the community in Lolland-Falster, Denmark.

Methods: Participants were randomly sampled (n=16,137) and invited to complete an adapted version of the screening tool for psychotic experiences (PLIKSi) and a range of validated measures for mental health outcomes including depression, anxiety quality of life and well-being
Results: A total of 965 people (6%) reported they had experienced 1 or more psychotic experiences. People that reported psychotic experiences scored significantly worse on all mental health outcomes (depression, anxiety, well-being, functioning and quality of life) compared to those who did not report psychotic experiences. The greater the number of concurrent psychotic experiences reported, the greater the severity of poor mental health outcomes were reported.
Discussion: There was a clear association between reporting psychotic experiences and poorer mental health outcomes. People reporting concurrent psychotic experiences may be at higher risk of poor mental health outcomes and represent a group that could monitored and provided with mental health care if required. Results indicate the need to conduct further research into the association between psychotic experiences and mental health in order to understand the wider implications for the general population.

F82. PREFRONTAL GLUTAMATE LEVELS ARE POSITIVELY ASSOCIATED WITH COGNITION DURING THE FIRST TWO YEARS OF ILLNESS IN INITIALLY ANTIPSYCHOTIC-NAïVE PATIENTS WITH PSYCHOSIS

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Background: Glutamatergic neurotransmission affects cognition in preclinical models of schizophrenia. In support, we have recently reported a positive association between prefrontal glutamate levels and attention in antipsychotic-naïve patients with first-episode psychosis (FEP) (Bojesen 2021). However, prefrontal glutamate levels may decline due to age and antipsychotic treatment (Meritt 2021, Egerton 2018) and the decline can affect the association with cognition. The aim of this study was to investigate if the association between prefrontal glutamate levels and cognitive function is altered by illness duration and treatment in initially antipsychotic-naïve FEP. Secondly, we tested if prefrontal glutamate levels decrease after two years and if antipsychotic treatment accelerates the glutamatergic decline in FEP.
Methods: We recruited 54 initially antipsychotic-naïve FEP and 55 healthy controls (HC) matched on age, sex and parental socioeconomic status and followed participants up after six weeks (FEP: 43; HC: 50), six months (FEP: 36; HC: 51), and two years (FEP: 40; HC: 44). After baseline examinations, patients were treated with antipsychotic medication according to clinical need. Glutamate levels were assessed with magnetic resonance spectroscopy in a 2*2*2cm3 voxel placed in dorsal anterior cingulate cortex using the PRESS sequence (TR=3000ms, TE=30ms) on a 3T scanner. Glutamate levels were estimated with LCModel and corrected for gray and white matter fraction as well as cerebrospinal fluid. The cognitive domain attention was assessed with

the Cambridge Neuropsychological Test Automated Battery with rapid visual information processing (RVP A' as outcome).
Linear mixed models were used to evaluate the trajectory of both glutamate and attention as well as the association between glutamate levels and attention in the FEP and HC after six weeks, six months and two years follow-up.

Results: Prefrontal glutamate levels:
Glutamate levels were lower in FEP compared with HC (main effect of group: $p=0.035$) and decreased over time in both FEP and HC (main effect of time: $p=0.008$). The decline was not accelerated by antipsychotic treatment in FEP (group*time insignificant: $p=0.41$).

Cognitive function:

FEP performed less well at all assessments on the test of attention (effect of group: $p<0.001$) but both FEP and HC showed better performance at the re-test assessments (effect of time: $p<0.001$). The improvement did not differ in FEP compared with HC (group*time insignificant: $p=0.10$).

The association between prefrontal glutamate levels and cognition during two years:

The relation between attention and glutamate levels differed in FEP compared with HC (group*glutamate: $p=0.027$) due to a more positive association in the FEP group at all follow-up examinations during the first two years of illness. The relation between attention and glutamate levels was not changed during the two years (time*glutamate insignificant: $p=0.72$) and there was not evidence for a different association between prefrontal glutamate and attention over time in the FEP and HC (group*glutamate*time insignificant: $p=0.14$).

Discussion: The results suggest an age-related decrease of prefrontal glutamate levels after two years that is not accelerated by antipsychotic treatment in FEP. There was a more positive association between prefrontal glutamate levels and cognition in FEP compared with HC that did not change during the first two years of illness. The more positive association in FEP might reflect a compensatory mechanism due to lower glutamate levels and may imply glutamate modulating agents as potential cognitive enhancers in patients with first-episode psychosis.

F83. IDENTIFICATION OF SUBTLE VISUAL DYSFUNCTIONS IN RECENT ONSET PSYCHOSIS AND CLINICAL HIGH-RISK STATE USING ENTROPY AND ENERGY FEATURE MAPS.

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Background: The neurobiological underpinnings of subtle visual dysfunctions (VisDys) in patients with a recent onset psychosis (ROP) or at clinical high-risk state for psychosis (CHR) are unclear. A deeper understanding of VisDys in early psychotic states could not only provide useful information for clinical practice, but also advance understanding of the underlying disease perceptual mechanisms that mediate susceptibility to psychosis.
Methods: We investigated the utility of entropy and energy texture features for the identification of VisDys in ROP and CHR, respectively. Entropy measures the complexity of the texture distribution, and its inverse measure is the energy that reflects the regularity and uniformity of the texture distribution. We developed prediction models based on structural MRI data of 135 ROP (64 patients with VisDys) and 134 CHR (71 patients with VisDys) from the Personalised Prognostic Tools for early Psychosis Management (PRONIA) study. The discrimination power of the trained prediction model will be validated in a second sample of 125 ROP (60 patients with VisDys) and 124 CHR (68 patients with VisDys). Fourteen items from the SPI-A were selected to represent different aspects of VisDys, e.g., CHR scored higher for oversensitivity to light and changes in colour vision scores while ROP scored higher for photopsia and captivation by visual details. A clustering analysis will be implemented to identify different patterns of the individualized predicted brain texture map associated with perceptual aspects expressed by SPI-A scores, symptom's clinical severity (BDI, SANS, GAF, PANSS scores) and functional outcome associated with changes in clinical scores. An explainable deep neural network framework is proposed which enhances the identification of VisDys in ROP and CHR patients.
Results: Presence of VisDys in both groups was predicted with classification accuracy >72%. In ROP, using the energy feature map, regions that contributed most to the classification decision of VisDys were amygdala, right putamen, angular gyrus, left parietal cortex, postcentral cortex, precuneus, gyrus rectus, left thalamus, parts of vermis (1_2_3) and occipital lobe. In CHR, using the entropy feature map, cuneus and parts of vermis (8_9) showed positive relevance for correctly classified VisDys. Shared regions were identified for the prediction of VisDys in ROP and CHR using energy and entropy feature maps, respectively. Cerebellar areas, calcarine sulcus left, frontal and temporal lobe, fusiform gyrus, hippocampus, right insula, and lingual left contributed most to the classification decision of VisDys.
Discussion: The proposed method supports a model of the visual system being implicated in core disease mechanisms of psychosis that may potentially contribute to the identification of structural biomarkers for psychosis. We hypothesize that distinct neurobiological patterns of VisDys are associated with the complexity of the microstructural changes in common regions in ROP and CHR patients and behavioral aspects.

F84. ANTHROPOMETRY IN ANTIPSYCHOTIC-NAïVE FIRST-EPISODE PSYCHOSIS PATIENTS: THE ROLE OF ENVIRONMENTAL EARLY LIFE EVENTS IN TWO INDEPENDENT SAMPLES

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Background: Schizophrenia is a complex medical condition associated with an increase in the co-morbidity of medical conditions. Patients with schizophrenia exhibit a reduced life expectancy of about 15 years due to increased morbidity and early mortality. Current literature suggests that the risk of several medical conditions is increased by gestational and perinatal problems. This model has been translated into the mental health realm suggesting that adverse influences during early development might underlie the later development of medical conditions, such as glucose abnormalities in serious mental illness. Different kinds of stressful events, such as infections, placental abnormalities, emotional stress, under-nutrition, or alcohol or tobacco exposure impact the fetus, at different stages of its maturation and development, implying different consequences in the short and long term as epiphenomena.

Winter birth, a historical environmental risk factor associated with schizophrenia in the northern hemisphere is also related to the later development of medical conditions. Indeed, season and month of birth have been correlated with later anthropometric features in childhood in the general population. Birth weight (BW), a surrogate marker of the intra-uterine milieu, behaves as a powerful predictor of anthropometric variables in adulthood, mainly body mass index (BMI) and weight.

In mental health disorders, the association between anthropometric and clinical characteristics has been described: reduced weight and body mass index (BMI) shorter stature in adulthood, or an inverse correlation for height and BMI

Given the above, we evaluated anthropometric variables at onset (height, weight, and BMI) in two different cohorts of antipsychotic-naïve first-episode patients with non-affective psychosis and control subjects and examined the relationship of these variables with two environmental factors such as winter birth and BW while highlighting sex differences if applied. We hypothesized that differences in the anthropometry of naïve subjects shall have an association with prenatal surrogate markers of early-life stress.

Methods: Patients were recruited from two different well-described cohorts, cohort B (Barcelona), patients come from a larger study evaluating the metabolic profile of non-affective psychosis patients at first clinical contact for psychosis. 91 antipsychotic-naïve patients with a first episode of non-affective psychosis and 110 healthy controls were included in the analysis.

In Cohort S (Santander), patients formed part of a larger prospective longitudinal study on first-episode non-affective psychosis, called PAFIP, 644 naïve patients with a first episode of non-affective psychosis and 235 healthy controls were included in the analysis.

When evaluating season of birth, multiple regression analyses (General Linear Model) were performed, being height, weight, or BMI included as the dependent variables, and age, sex, diagnosis (psychosis vs healthy control), and season of birth and the interaction of season of birth by diagnosis included as covariates.

When evaluating BW, multiple regression analyses (General Linear Model) were performed, being height, weight and BMI included as the dependent variables, and age, sex, diagnosis (psychosis vs. healthy control) and weight at birth and the interaction of birth weight by diagnosis included as covariates. Data regarding BW was only available for cohort B. Afterwards, we evaluated the multiple comparisons between groups using the Bonferroni post-hoc test

Results: Our results show that patients were significantly lighter and with a reduced BMI compared with controls, while significantly shorter in cohort S. In cohort B patients also displayed a reduced BW.
Male patients were significantly lighter and with reduced BMI compared with controls. In cohort S shorter heights in patients showed a trend. In cohort B, a reduced BW in patients also showed a trend. Female patients were significantly shorter than controls in both cohorts. Significantly reduced weight and BMI was described for patients in cohort S while a reduced weight for patients showed a trend in cohort B. In both cohorts, females displayed a significant reduced height when born in winter.

Discussion: Our results support a systemic disease concept in which schizophrenia involves not only the brain disorder but also implies the whole body. Interestingly winter birth displayed a reduced height only in females suggesting that events during the 3er trimester might impact heavier in the development of the female body.
Our results underlie the concept of early life stressful events applied to serious mental illnesses, as a surrogate marker, such as BW or season of birth, might impact on the onset of psychiatric diseases and other conditions such as anthropometric values. This approach is in line with the neurodevelopment hypothesis of schizophrenia where early life events affect normal brain maturation but also other developmental processes, like “scars” of early experiences emerging across development. Our approach highlights the need to delve into the neurodevelopmental model of psychosis taking into consideration established models from other areas of research.

F85. GENETICS OF SUICIDE RISK IN SCHIZOPHRENIA: ASSOCIATION OF THE COMPLEMENT COMPONENT C4 GENE

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Background: In Canada, schizophrenia directly affects 1 in 100 people while leaving life-changing effects on even more family members and friends. Suicide is a major cause of death among schizophrenia patients, with approximately 50% attempting and 10% dying from suicide. Despite growing efforts, suicide attempts remain alarmingly high among schizophrenia patients, leading to significant emotional and medical costs for our society. Although genetic components play a significant role in schizophrenia risk, with 79% heritability, the underlying genetic risk factors for suicide are poorly understood in schizophrenia patients. It is suggested that the immune system plays a key role in suicide vulnerability across psychiatric disorders, including schizophrenia. The complement component C4 gene, involved in the innate immune system, has recently been identified to be strongly associated with schizophrenia risk. In addition, preliminary findings also implicated the C4 gene in suicide risk, making it a potential candidate of interest for

studying suicidality in schizophrenia patients. The C4 gene has a complex genetic structure with two distinct variations, C4A and C4B. Both C4A and C4B could be further divided into either long (AL, BL) or short (AS, BS) variants, resulting in four possible forms: C4AL, C4BL, C4AS, and C4BS. It has been reported that the C4AL variant has the highest association with increased schizophrenia risk. The purpose of this research is to investigate the relationship between the C4 gene variants and suicide risk in patients with schizophrenia, and potentially identify a new genetic marker for suicide risk in this group. With C4AL having the highest association with increased schizophrenia risk, it is hypothesized that schizophrenia patients with C4AL will have an increased suicide risk than those without.

Methods: This study includes a sample of N=578 schizophrenia patients (402 males:176 females) from our ongoing study on the genetics of schizophrenia (Toronto Schizophrenia sample). All patients have been diagnosed with schizophrenia or schizoaffective disorder based on the Structured Clinical Interview for DSM-IV Axis (SCID) and have provided blood samples for DNA extractions. The precise C4 gene variant and the number of repeats are determined in three steps: 1- Copy-number assays are used to determine the number of copies of long, and short versions of C4A and C4B; 2-Long-range PCR is performed in subjects with at least one copy of C4S; 3- The presence of either C4AS and/or C4BS is determined by using a custom TaqMan genotyping assay. Data on suicide attempts, suicidal ideation, and suicidal plans are being extracted from the mood disorder module of the SCID, referral notes, and summary of medical records. In addition, data on risk factors for suicide, such as substance use disorder and alcohol use disorder, are also being extracted.

Results: Preliminary analysis has been done on 137 subjects. The analysis did not show any association between any C4 gene variant and suicide attempt/ suicidal ideation (p-value>0.05). In addition, the expected C4A or C4B gene expression did not show a significant association with suicide attempts in this pilot sample (p-value >0.05).

Discussion: This study will be the first of its kind to analyze the association between the complement component C4 gene and suicide risk in schizophrenia patients. Although no association is observed in the preliminary analysis, results from further investigation of our overall sample of subjects will be presented. In addition, a sex-stratified analysis will be conducted to investigate potential sex-specific effects of C4 and suicide risk.

F86. MACHINE LEARNING-BASED APPROACH FOR IDENTIFYING PATIENTS WITH SCHIZOPHRENIA FROM THEIR VOICES

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[1]CRIM

Background: Some studies have suggested developing ML-based approaches using NLP and SP techniques to analyze vocal and textual data obtained from patients' interviews can be helpful in identifying patients with schizophrenia [4 - 6]. On the other hand, it has been verified that monolog speech collected during language tasks can be helpful in detecting language impairments or language disorders associated with neurodegenerative or mental disorders. One well-known language task is the picture description task, particularly the Cookie Theft Picture, which clinicians have used to detect language impairments in patients with dementia [8].

Methods: Our approach is based on ML algorithms and NLP and SP techniques. The NLP and SP techniques will be used to extract vocal and language features from verbal and textual datasets

obtained from patients while describing the Cookie Theft Picture. Examples of linguistic features are lexical diversity, the total number of words, and syntactic, semantic, and pragmatic parts.
Examples of acoustic features are Voice Activity-related Features (VAF) or Prosodic Features (PF). We will use feature selection methods such as Variance Threshold (VT) or Minimal Redundancy Maximal Relevance Criterion (mRMR) to select informative features to train ML algorithms.

Results: We have created a textual dataset of patients with Schizophrenia from examples that have been discussed in multiple articles [1-3]. The textual samples have been labeled as the language of patients with tangential speech (N=10) and incoherent speech (N=5). Using the tree-based feature selection method features (N=7) from the set of linguistic features including lexical (N=5), syntactic (N=8) and semantic-based features (N=2; incoherence and tangentiality metrics) have been selected and used to train ET classifiers. The ET classifier could classify these with an accuracy rate of 70% (+/- 0.43) with an F1 score of 62% (+/- 0.54).
Based on the above results we expect our ML-based approach can be correct in classifying patients with Schizophrenia from those with other mental disorders.

Discussion: Our ultimate goal is to develop a trustworthy AI system for Schizophrenia that could be integrated into healthcare settings. To do so, we have suggested collecting vocal data using a standardized language task. We believe using our suggested approach can provide vocal data sets that could be useful to identify quantitative language markers, e.g., and ambiguous pronoun usage of language disorders in Schizophrenia. Furthermore, collecting verbal data using such standardized methods could help develop AI systems that distinguish patients with different mental disorders from each other.

F87. USE OF OUTPATIENT AND INPATIENT SERVICES BY INDIVIDUALS WITH PSYCHOTIC DISORDERS IN PERU: NATIONAL RESULTS BASED ON ADMINISTRATIVE DATA

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Background: Psychotic disorders are considered serious mental illnesses whose treatment often require consistent outpatient follow-up or services, as well as inpatient services in case of illness exacerbation. Despite this, many persons with psychosis have difficulties accessing appropriate mental healthcare, particularly in non-high-income contexts. To face this problem, in 2012, Peru implemented a community-based model of mental healthcare that seeks to increase access to mental health services via community mental health centers in the primary and secondary levels of the health system throughout the country. Many new community mental health centers have opened since 2015. However, little attention has been paid to measure their use by clients, which is vital to evaluate the implementation of health system interventions. In this study, we evaluated the feasibility of an administrative database to provide information on the use of mental health services by individuals with psychosis. The specific objectives were to determine what percentage of care and hospitalizations for mental health diagnoses are for psychotic disorders and to determine at what level of the health care system these services are provided.
Methods: We analyzed the utilization of outpatient and hospitalization services by individuals diagnosed with schizophrenia spectrum disorders (ICD-10: F20) in Peru in 2018. The data comes

from the records available on the website of the National Superintendence of Health (SUSALUD), open data, which contains information from the entire national health system. For each care episode in the national health system, the platform registers information on the year and month of the use of outpatient or hospitalization services, the region, province and district where the health service was provided, as well as the age, and sex of the service user. Diagnosis is coded according to the International Classification of Diseases version 10. We conducted descriptive analysis using Stata v. 14.

Results: At a national level, in 2018, the healthcare system in Peru registered a total of 52,100,000 care episodes and 2,064,132 hospitalizations throughout the country. Of these, 1,078,073 (2.1%) care episodes and 14, 419 (0.7%) hospitalizations were due to mental disorders. Psychotic disorders accounted for 105,747 care episodes and 3668 hospitalizations, that is, 9.8% and 25.4% of the total number of care episodes and hospitalizations for mental disorders, respectively. More males (54.3%) than females (45.7%) required medical care, but more females (51%) than males (49%) were hospitalized. Only 5.1% and 23.6% of care episodes and 1.4% and 31.1% of hospitalizations occurred in the first and second level of the healthcare system, respectively.

Discussion: Around one of ten medical care episodes and one quarter of hospitalizations for mental disorders in Peru are accounted for by persons with psychotic disorder diagnoses. Also, the majority of mental healthcare provision is still provided in the third level of the health system, despite the spread of and push towards use of new community mental health centers at the primary and secondary levels, suggesting that more needs to be done to enhance use of community services and reduce use of hospital-based services. The administrative database was feasible to understand the nationwide utilization of healthcare services by people with psychotic disorders. We believe that administrative data may be used to measure implementation outcomes (i.e., reach) and investigate service utilization patterns. Prospective administrative data can also provide us with information on the penetration of the community mental health model in the national health system of Peru.

F88. ASSESSING THE COMPARATIVE EFFECTIVENESS OF SECOND-GENERATION ANTIPSYCHOTICS LONG-ACTING INJECTABLES IN SCHIZOPHRENIA

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Background: Schizophrenia is a debilitating mental disorder associated with increased disability and higher mortality compared to the general population. Use of second-generation antipsychotics long-acting injectables (SGA LAI) have demonstrated reduced relapse and readmission rates compared to oral antipsychotics and have improved tolerability compared to first generation LAI. Comparisons among four common SGA LAI (aripiprazole, olanzapine, paliperidone, and risperidone) have been limited to reviews and network meta-analysis. Our primary objective was to compare time to schizophrenia-related hospitalization or all-cause death among the LAIs aripiprazole, olanzapine, paliperidone, and risperidone.

Methods: We used Optum's Clinformatics Data Mart, which is an administrative claims dataset between January 2011 and June 2021. Patients aged ≥18 years who had claims for a SGA LAI were identified using Healthcare Common Procedure Coding System codes. The first day of SGAI LAI for each patient served as the index date. We then restricted our sample to those with 180 days

of continuous enrollment pre-index to 1) ensure incident use of SGA LAI by excluding those with recorded prior use, 2) ensure a diagnosis of schizophrenia with 1 inpatient or 2 outpatient claims with schizophrenia disorders in the primary diagnosis position, and 3) exclude patients with a diagnosis of bipolar disorder. An intent-to-treat design was used. Independent variables included demographics, comorbidities, baseline healthcare utilization, geographic region, and index year. To control for potential imbalance of independent variables, inverse probability of treatment weights were applied. Upon applying the propensity score weights to the four treatment arms, we applied Cox proportional-hazards (PH) models to the primary and secondary outcomes.
Results: Our sample consisted of 128 patients who initiated treatment with aripiprazole, 251 with risperidone, 508 with paliperidone, and 72 with olanzapine. Average age of patients who started treatment with aripiprazole were youngest (40.62, standard deviation [SD]=16.77) followed by paliperidone (43.90, SD=16.42), risperidone (47.44, SD=16.55), and olanzapine (52.72, SD=17.42). After applying propensity score weights, time to schizophrenia-related hospitalization were significantly shorter for patients on risperidone (hazard ratio [HR]=1.52, 95% CI: 1.12-2.06) and olanzapine (HR=3.39, 95% CI: 1.91-6.01) compared to paliperidone, while patients who initiated aripiprazole did not have significant differences in time to schizophrenia-related hospitalization compared to paliperidone (HR=0.94, 95% CI: 0.61-1.45). Patients who had pre-existing hypertension also resulted in a shorter time to schizophrenia-related hospitalization (HR=1.53, 95% CI: 1.05-2.24).
Discussion: Patients who initiated aripiprazole and paliperidone as a LAI resulted in longer times to a schizophrenia-related hospitalization compared to olanzapine and risperidone. Future studies in other administrative claims databases or in electronic health records will further inform these comparisons.

F89. POSTER WITHDRAWN

F90. EXAMINING THE EMPLOYMENT STATUS OF PEOPLE LIVING WITH SCHIZOPHRENIA AND RELATED PSYCHOSES FROM AN INTERSECTIONAL PERSPECTIVE

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Background: Discrimination in employment based on age, sex and ethnicity is well documented in the general population and seems to persist despite social and legal programs aimed at reducing these inequalities. From an intersectionality perspective, living with a mental illness and belonging to a marginalized group (e.g., based on age, sex, or ethnicity) may result in discriminatory experiences that are greater than the sum of its parts, leading to under-representation on the labor market. The intersectionality framework proposes that individual characteristics and social positions not only add on to each other, but also interact between themselves. While 70-90% of individuals living with schizophrenia and related psychoses remain unemployed, about 80% of them report desiring and being able to work. Their under-representation on the labor market could

therefore be the result of the interaction between multiple factors, including experiences of discrimination based on individual characteristics and social positions. In this study, we aimed to extend previous research by examining the interactive relationships between individual characteristics, social positions and employment status in patients with schizophrenia and related psychoses.

Methods: A total of 973 participants were included in this report, wherein secondary data analysis was performed. Some participants were in treatment for a first episode of psychosis (FEP) at the Prevention and Early Intervention for Psychosis Program (PEPP-Montréal) and others had experienced multiple episodes of psychosis (MEP) and took part in two other studies conducted at the Douglas Mental Health University Institute, in Canada. Data on employment status, individual characteristics (i.e., sex, age, psychiatric diagnosis) and social position (i.e., education level and socioeconomic status), as well as positive and negative symptom severity (using the Scale for the Assessment of Positive Symptoms and the Scale for the Assessment of Negative symptoms) at baseline were used for analyses. Simple and multiple regression were performed to identify independent predictors of employment status. Chi-squared Automatic Interaction Detection (CHAID) analyses were also performed to identify homogeneous subgroups of participants based on individual characteristics and social positions, that were statistically predictive of employment status.

Results: In simple regression analysis, age, education, as well as positive and negative symptom severity were independent significant predictors of employment status. In multiple regression analysis, a significant 2-way interaction between age and symptom severity was observed. CHAID analyses indicated that unemployment rate was highest for a homogeneous subgroup comprised of older (35-45 years old) participants living with high negative symptom severity.

Discussion: Individual characteristics, including age and negative symptom severity, seem to not only have additive effects, but also interact with each other to partially explain employment status. Future studies investigating potential perceived discriminative experiences in employment based on individual characteristics of people living with schizophrenia and related psychoses could shed further light on their under-representation on the labor market.

F91. EVALUATING THE MEASUREMENT STRUCTURE AND CORRELATES OF THE PRIME SCREEN AMONG BLACK AND WHITE COLLEGE STUDENTS

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Background: Self-report measures of attenuated psychosis (AP) and subclinical psychosis experiences (PEs) contribute to the understanding of psychosis across the severity spectrum and may aid in identification and prevention efforts. Screening tools are an important part of these efforts, facilitating broader scale prevention efforts. Current measures, however, are limited by high false positive rates and lack of accuracy. Psychosocial factors are theorized to impact psychometric properties of AP/PE self-report instruments. Where differences exist, systematic biases may exist that differentially impact measurement validity, particularly for marginalized racial identity groups. Factor analytic techniques and evaluation of criterion validity in diverse samples of community participants reporting on a continuum of AP/PEs may aid in detection of measure biases, yet research in this area is limited to date. Building on previous work, the current

study evaluated the factor structure and criterion validity of the Prime Screen, a commonly used measure of AP/PEs, in Black and White college students.
Methods: In a sample (N = 308) of Black and White college students between the ages of 18-31 years old (M=20.67), we performed confirmatory then exploratory factor analysis of the Prime Screen. Multiple logistic regression models were estimated separately for each race group, with measures of psychopathology, functioning, discrimination, community violence, and spirituality predicting identified factor scores.
Results: Exploratory factor analysis in Black and White participant samples generated differential factor models, indicating presence of configural variance for some items in the Prime Screen measure. A cross-sample two-factor model was generated from items showing configural invariance for Black and White participants, with factor one reflecting "positive symptoms" and factor two "magical thinking." Within this adapted tool, item responses across racial identity group were not uniformly related to other measures of pathology and psychosocial or contextual variables. Although items loading onto the first factor ("positive symptoms") showed equivalent associations with a concurrent measures of AP/PE for both Black and White participants, Prime Screen items loading onto the second factor ("magical thinking") showed stronger associations with concurrent measures of AP/PE in the White racialized identity group ($t[173] = 5.46$, $p < .001$, $f2 = 0.17$) as compared to their Black peers ($t[85] = 2.75$, $p = .01$, $f2 = 0.09$). Most notably, spirituality was associated with magical thinking Prime Screen item scores for Black participants ($t[85] = 2.35$, $p = .02$, $f2 = 0.06$), with this effect present at a trend level/small effect size among Black participants for items loading onto factor one ("positive symptoms;" $t[85] = 1.81$, $p = .07$, $f2 = 0.04$).
Discussion: Results indicate the need for further work to develop and validate the Prime Screen, highlight limitations of this commonly used measure of AP/PEs for use in diverse populations, and provide some future directions for measure revision.

F92. COURSE AND FACTORS ASSOCIATED WITH SUICIDAL THOUGHTS AND BEHAVIORS IN PERSONS WITH FIRST-EPISODE PSYCHOSIS: A CROSS-CULTURAL COMPARISON IN INDIA AND CANADA

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Background: Multiple studies conducted in high-income countries (HICs) have reported a high risk of suicide among persons with a first episode of psychosis (FEP) compared to the general population, with the risk being up to 18 times higher. Given that most studies have been conducted in HICs, it remains unknown whether the Results: from studies in HICs can be generalized to FEP patients in low- and middle-income countries (LMICs). We aimed to compare the course and factors associated with suicidal thoughts and behaviors in persons with FEP treated in Montreal, Canada and Chennai, India.
Methods: Patients received similarly structured early intervention services for psychosis for two years at both sites. Suicidal thoughts and behaviors were measured seven times during follow-up

with the suicide item of the Calgary depression scale for schizophrenia. The two-year evolution of suicidal thoughts and behaviors was compared by site with generalised estimating equations. A hurdle model (binomial generalized linear model and a gamma distribution model) was performed by site including known risk factors for suicide in FEP or in the general LMICs population.
Results: A total of 333 patients with FEP were included in the study; 168 in Chennai, India and 165 in Montreal, Canada. While three women died in Chennai in the first four months of follow-up compared to none in Montreal, the rates of suicidal thoughts and behaviors prior to entry into early intervention services and at admission were significantly higher in Montreal than in Chennai. In Montreal, 25.6% and 19.5% of patients with FEP reported suicidal ideation or suicide attempts prior to service entry, respectively, whereas these rates were 10.7% and 10.1% in Chennai. At admission, 22.5% of patients in Montreal reported frequent or occasional suicidal ideation, 8.8% had a suicidal plan, and 7.5% had attempted suicide compared with 11.9%, 6.5%, and 3.6%, respectively, in Chennai. A significant decrease in suicidal thoughts and behaviors was observed across contexts. While depressive symptoms and previous suicide attempts were associated with the presence or severity of suicidal thoughts and behaviors across contexts, other factors, such as past suicidal ideation and relationship status, were differentially associated by site. For example, among FEP patients who reported suicidal ideation or behaviors at admission, married persons were at greater risk of engaging in more severe suicidal behaviors in Chennai and the opposite was observed in Montreal (although the latter association was close to significance with a p-value of 0.053).
Discussion: Results suggest that the period following admission to early intervention services for psychosis is crucial as suicide risk is at its peak across contexts, although the rates of suicidal ideation and suicide attempts appear to be higher in HICs. Prevalence and factors associated with suicidal risk in FEP appear to vary according to context. Further studies are needed to better understand the influence of sociocultural and political-economic context on suicide among persons with FEP and therefore guide suicide prevention strategies.

F93. ACCESS TO PUBLIC MENTAL HEALTHCARE IN BRAZIL IN SCHIZOPHRENIA: TRENDS FROM 2010 TO 2020

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Background: The Brazilian public health system provides universal health coverage through the Unified Health System (SUS). The implementation of community health care and the deinstitutionalization program reduced the number of psychiatric hospitalizations in exchange for increased community-based care, namely the CAPS (Centers for Psychosocial Care) and Family Health Strategy (FHS).
Methods: We conducted an ecological study of time series, costs and geographic distribution of factors related to the access to treatment of schizophrenia and related disorders during the years 2010-2020 in the five Brazilian geographical regions.
Data on hospitalizations were extracted from the SUS database and socioeconomic indicators were extracted from databases of the National Demographic Census carried out in 2010 by the Brazilian Institute of Geography and Statistics (IBGE).

Results: From 2010 to 2020 the hospitalization rate for schizophrenia decreased by 43.7%, from 517/million inhabitants to 291/million, mainly due to the decrease in the number of beds. In 2010 there were 30,360 beds in psychiatric hospitals and 13,888 in 2020. In addition, in 2020 there were 1886 psychiatric beds in general hospitals. The beds are more concentrated in the Southeast and South regions. The mean length of stay decreased from 62.8 to 25.3 days. The federal spending on hospitalizations decreased from BRL 283,538 735 in 2010 to
BRL 105,720 638 in 2020. The amount spent in 2010, adjusted for inflation, would correspond today to BRL 500,953.954 97, which corresponds to a decrease of 79%. In USD (PPP rate) there was a decrease from USD 204,311 048 to USD 44,702 172. Meanwhile, the coverage of CAPS achieved 12.9 CAPS/million inhabitants and the FHS coverage increased to a national average of 100%. In 2021, the federal spending with the CAPS was BRL 1,234 308 138.

In a multiple linear regression model, there was a correlation between the total spending and the GBP per capita, illiteracy rate, and FHS coverage ($R2=0.66$; $p<0.0001$).

The number of psychiatric hospitalizations in the private system is very low, with little impact on the total population, as in Brazil only 15% have health insurance. The psychiatric hospitalization rate (any diagnosis, not only schizophrenia) was 0.4% in 2020.

Federal spending on mental healthcare increased substantially in the decade, but not in schizophrenia.

Discussion: The hospitalizations for schizophrenia dramatically decreased and the hospital beds were replaced by community healthcare, following the example of other countries. However, this change was probably not enough to compensate for the loss of psychiatric beds when they are necessary, particularly in the North region of Brazil.
Although federal spending on mental health increased, the CAPS and FHS offer treatment for other mental conditions more prevalent than schizophrenia, such as depression and alcohol and substance abuse. In addition, the FHS, as a primary care service, provides treatment for conditions such as hypertension and diabetes.

Considering that many people with schizophrenia still do not have regular treatment, they probably do not have access to hospitalization when they have a psychotic break. It is urgent to know the extension of the gap in the treatment of schizophrenia to offer a treatment that meets the needs of this population, both in quantity and quality.

F94. FOOD INSECURITY AND WHITE MATTER DEVELOPMENT IN CHILDREN AND ADOLESCENTS: AN ABCD STUDY

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Background: A significant body of evidence indicates that social determinants of health are risk factors for the development of psychiatric disorders, including schizophrenia. Food insecurity is a growing public health concern in the United States, with approximately 14.8% of households suffering from food insecurity and 7% of those being affected food insecurity being children. Prior

studies show that children suffering from food insecurity are disproportionately likely to experience persistent symptoms of depression, anxiety, attentional difficulties, and substance use problems. It is also likely that inconsistent access to diet-derived nutrients is detrimental during critical periods of brain development, particularly for the brain's white matter, which is actively maturing during late childhood. However, to date there are no neuroimaging studies aiming to investigate whether food insecurity influences white matter development. In this study, we utilize extant demographic and diffusion magnetic resonance imaging (dMRI) data from the Adolescent Brain and Cognitive Development (ABCD 4.0) study to evaluate the extent to which food insecurity impacts white matter health in children and adolescents aged 9 to 11 years.

Methods: Food security status was defined by a "yes" response on item "demo_fam_exp1_v2" in the Parental Demographic Survey administered at the baseline visit. Propensity score matching was used to construct comparable groups of children with reported food insecurity (FI) matched with respect to age, sex, parental income, parental education, intelligence quotient, and site, to children without reported food insecurity (noFI). DMRI data for those subjects included in the above groups were pre-processed and harmonized across the 21 ABCD imaging sites. Whole-brain two tensor tractography was performed and an unsupervised fiber clustering atlas (white matter analysis) was applied. Average fractional anisotropy (FA) for 49 tracts was extracted for each participant. Linear regression was carried out with average FA for each tract as the dependent variable, food security status as the independent variable and age, sex, parental income, parental education, intelligence quotient, and site included as covariates. Corrections for multiple comparisons were achieved using a Bonferroni-corrected threshold ($p < 0.001$). To assess effect size, Cohen's d was also calculated. Our final sample consisted of 310 children with reported FI and 285 matched children with no reported FI.

Results: Significant reductions ($p > 0.001$) in FA were found in 7 white matter tracts in the FI group compared to the noFI group: Corpus Callosum Section 5 (Cohen's d = 0.29); Corpus Callosum Section 6 (Cohen's d = 0.28); Left Inferior Longitudinal Fasciculus Left (Cohen's d = 0.29); Right Inferior Longitudinal Fasciculus (Cohen's d = 0.34); Left Middle Longitudinal Fasciculus (Cohen's d = 0.25); Right Middle Longitudinal Fasciculus (Cohen's d = 0.26), and the Left Striato-Parietal tract (Cohen's d = 0.25).

Discussion: To our knowledge, this is the first study to show an association between food insecurity and white matter microstructure in children. We observe small, but significant, reductions in the FA in 7 white tracts in children with reported food insecurity compared to matched peers. We would like to note that important considerations, such as race, ethnicity, body mass index, diet, and stress, are not included in the present analysis but will be vital to examine in our future work. Given the developmental nature of schizophrenia, policies that aim to address food insecurity, particularly in childhood, may help attenuate or eliminate that risk for future difficulties with mental health.

F95. THE IMPACT OF NON-MEDICAL CANNABIS LEGALIZATION AND COMMERCIALIZATION ON THE FREQUENCY AND HEALTH SERVICE USE FOR PSYCHOTIC DISORDERS

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Background: Cannabis has been implicated as a causal factor in the onset and persistence of psychotic disorders. Canada legalized the non-medical use of cannabis in October 2018, and there is concern that any increases in cannabis use following legalization may have consequences for the frequency and health services utilization for psychotic disorders at the population level. This presentation will review findings from a series of population-based studies focused on: (i) changes in the incidence and health service use for psychotic disorders during a post-legalization period with strict limits on cannabis retailers and product types; (ii) the impact of cannabis retailer proximity on service use for psychotic disorders; and (iii) the impacts of widespread cannabis commercialization, which removed market restrictions, on emergency department (ED) visits for psychotic disorders.

Methods: We used population-based health administrative data from the province of Ontario (Canada) over the period January 2014 to September 2021. We identified all contacts with health services with a psychosis-related diagnostic code, as well as first presentations to services for psychotic disorders. Our observation window included the initial post-legalization phase, which was a period of limited retail outlets and restrictions on product types, as well as a subsequent commercialization phase where restrictions were lifted and there was widespread availability of cannabis retailers and high potency products. We analyzed these data using multivariable Poisson regression models and interrupted time-series designs.

Results: We found no evidence of temporal changes in overall health service use or incident cases of psychotic disorders during the period of market restriction. However, the retailers that were permitted to open during this period were differentially located in areas with higher pre-legalization rates of service use for psychotic disorders. Living in close proximity to a cannabis retailer was associated with a higher risk of outpatient visits (IRR=1.16, 95%CI=1.15,1.18), ED visits (IRR=1.26, 95%CI=1.19,1.33), and hospitalizations (IRR=1.16, 95%CI=1.15,1.18) for non-affective psychotic disorder, even after adjustment for baseline service use. We also found evidence of stronger effects of retailer proximity among people with first presentations for psychotic disorders, relative to prevalent cases. The subsequent commercialization phase was associated with an immediate increase in rates of ED visits for cannabis-induced psychosis (IRR 1·30, 95% CI 1·02-1·66), with larger increases for youth above (IRR 1·63, 1·27-2·08, ages 19-24) versus below (IRR 0·73 95%CI 0·42-1·28 ages, 15-18) the legal age of purchase.

Discussion: Our findings suggest that the initial period of non-medical cannabis legalization with tight market restrictions was not associated with an increase in health service use or the frequency of psychotic disorders overall. However, people living in close proximity to one of the few available retailers had higher rates of service use for psychotic disorders. In contrast, cannabis commercialization increased presentations for cannabis-induced psychosis, particularly for youth above the legal age of purchase. Taken together, these findings suggest that adherence to a strict public health framework, with restrictions on the availability of cannabis retailers and high potency products, may help to mitigate cannabis-related harms.

F96. CUB AND SUSHI MULTIPLE DOMAINS (CSMD) 1 AND 2 GENE EXPRESSION IN POSTMORTEM FRONTAL CORTEX IN SCHIZOPHRENIA: RELATIONSHIP WITH SYNAPTIC DENSITY

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Background: The complement system is a key effector of innate immunity, mediating elimination of pathogens and debris. It is now known that complement also participates in synaptic pruning and refinement, opsonizing synapses for elimination via microglial phagocytosis. While mounting evidence implicates dysregulation of the complement system in schizophrenia, the underlying biological mechanisms remain to be elucidated. The proteins CUB and sushi multiple domains (CSMD) 1 and 2 play a role in the regulation of the complement system, with CSMD1 reported to inhibit complement activation via degradation of C3b and C4b. Furthermore, both CSMD1 and CSMD2 are enriched at synaptic sites, and contribute to neural circuit development. Notably, genetic variations in human CSMD1 and CSMD2 genes have been associated with SCZ risk. While expression of CSMD1 is lower in peripheral blood in SCZ relative to controls, it is not yet clear whether CSMD1 and CSMD2 expression is similarly altered in brain tissue in this disorder. As such, the aim of this study was to compare CSMD1 and CSMD2 mRNA expression in frontal cortex in schizophrenia and control subjects, and explore the relationship between CSMD1, CSMD2 and synaptic density.
Methods: mRNA expression of CSMD1 and CSMD2 was quantified in postmortem frontal cortex in individuals with SCZ (n = 35), bipolar disorder (n = 34), and matched controls (n = 35) using quantitative PCR. Levels of the pre-synaptic marker SNAP-25 were quantified in the same samples by ELISA.
Results: In frontal cortex, gene expression of CSMD1 did not differ between groups, however, CSMD2 levels were significantly lower in the SCZ group relative to the control group. Correlational analyses revealed a significant association between CSMD1 gene expression and levels of SNAP-25 protein, but no relationship between CSMD2 expression and synaptic density.
Discussion: Our results are consistent with a role for CSMD1 and CSMD2 in the etiology and pathophysiology of SCZ. Additional research is needed to explore the temporal course of complement dysregulation in SCZ, downstream impacts on brain circuits, and relationship with clinical phenotypes.

F97. DISTINCT NEUROMETABOLIC PROFILES ACROSS VARIOUS STAGES OF SCHIZOPHRENIA

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Background: Previous studies have suggested the involvement of abnormal glutamate metabolism in the pathophysiology of psychosis. However, little is known about the specificity of the metabolite changes to glutamate alone, or if the glutamatergic excess or deficit reflects a generalized metabolic profile associated with different stages of psychosis.

Methods: In this study, we used magnetic resonance spectroscopy (MRS) data to identify metabolic clusters in individuals with psychosis. MRS data were collected from four different sites across three stages of illness (clinical-high-risk, first-episode psychosis and chronic schizophrenia), with a total of 488 individuals (healthy controls = 146). Across all samples, we have derived MRS spectra and concentrations of glutamate, glutamate+glutamine, myo-inositol, choline compounds, N-acetyl aspartate, and glutathione from the anterior cingulate cortex. We then used K-means clustering (in the NbClust package in R) to identify neurometabolic clusters.
Results: Leveraging the variance in healthy controls, two neurometabolic profiles were identified, across the prodromal, first-episode and chronic stages of schizophrenia. One profile showed high levels of neurometabolite while the other showed overall lower levels of all neurometabolite, with an exception for myo-inositol and choline. Compared to healthy people, those at a clinical high-risk stage are more likely to be classified in the high-neurometabolite group. In the first-episode stage, patients are more likely to be categorized in the low-neurometabolite group. Interestingly, in the chronic stage, patients are more likely to belong to the high-neurometabolite group, similar to clinical-high-risk patients, but there was more variability in the distribution of established schizophrenia across the 2 neurometabolite groups.
Discussion: Our findings suggest that distinct metabolic profiles, characterized by different levels of glutamate, are evident across different stages of schizophrenia. Different neurometabolite profiles may be associated with different symptom domains in psychosis and further research is needed to confirm these findings and explore the potential underlying mechanisms.

F98. ABNORMAL CHOLINERGIC SYSTEM IN THE BRAIN OF INDIVIDUALS WITH SCHIZOPHRENIA: A SYSTEMATIC REVIEW

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Background: Post-mortem, neuroimaging, pharmacological, and genetic studies have suggested that the cholinergic system in the brain is altered in schizophrenia. An improved understanding of the cholinergic dysregulations associated with schizophrenia and its symptoms can inform on the development of treatments. However, a systematic review summarizing the evidence from the broad literature in human studies has not been published to date.
Methods: Here, we systematically reviewed the literature on experimental quantitative data of the cholinergic system expressed in the brain of individuals with schizophrenia, compared to healthy controls or individuals with non-psychotic psychiatric conditions. The current study followed the PRISMA guidelines, with 2 independent raters conducting the title and abstract screening, full-text review, data extraction, and risk of bias assessment. Disagreements were resolved through discussion until consensus was reached. Inclusion criteria for studies encompass using a validated, direct experimental measure of a brain cholinergic component; target population with schizophrenia or schizoaffective disorder; healthy control or non-psychotic psychiatric comparison group. Exclusion criteria include review articles; animal studies; genetic studies without expression/mRNA data. Searches were performed in Embase and Medline. 2900 articles were initially identified, and 65 studies met eligibility criteria.

Results: Of these 65 studies, 59 were post-mortem studies and 6 were neuroimaging studies. Of the post-mortem studies, 29 concerned muscarinic receptor protein, mRNA expression, and/or coupling; 15 assessed nicotinic receptor protein and/or mRNA expression. 9 reported on histological components such as cholinergic neuronal counts and cytoarchitecture of cholinergic nuclei; and 6 investigated cholinergic enzymes. To note, 45 of the 59 post-mortem studies (more than 75%) indicated a dysregulation in components of the cholinergic system in schizophrenia. Of the neuroimaging studies, 5 assessed nicotinic receptors, and one investigated non-specifically muscarinic receptors. Five out of the 6 neuroimaging studies found significant differences in the cholinergic system, and all but one reported significant associations with symptoms.
Discussion: Overall, we conclude that the current empirical evidence supports the presence of changes in the cholinergic system in the brain of individuals living with schizophrenia. Better elucidating the neurobiology implicated in schizophrenia is important to provide a rationale for the continued development of treatments targeting the cholinergic system. Gaps in knowledge include the lack of in vivo studies targeting specific subtypes of muscarinic receptors as well as cholinergic innervation; the relatively small sample sizes in many reports; the lack of cholinergic markers for the different stages of the disease; and the difficulty in disentangling medication from illness effects.

F99. REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS) TREATMENT REDUCES VARIABILITY IN BRAIN FUNCTION IN SCHIZOPHRENIA: DATA FROM A DOUBLE-BLIND, RANDOMIZED, SHAM-CONTROLLED TRIAL

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Background: Cognitive impairments, particularly deficits in working memory (WM), are a core feature of schizophrenia and predict functional outcome. Recent evidence suggests that repetitive transcranial magnetic stimulation (rTMS) to the dorsolateral prefrontal cortex (DLPFC) in schizophrenia improves WM. We conducted a four-week randomized, controlled trial (RCT) and recently reported rTMS-induced increases in DLPFC thickness. We performed a secondary analysis of changes in WM task-evoked brain activity.
Methods: We randomized 81 participants (18-59 yrs.) with schizophrenia/schizoaffective disorder to 20 sessions of active (20Hz) or sham rTMS administered bilaterally to DLPFC. Participants completed an fMRI letter sequence N-back task pre- and post-treatment. Data with acceptable performance and motion were available from 42 participants (active/sham: n=19/23). WM-evoked activity during 3-back vs. 1-back tasks was contrasted. Mean beta weights were extracted from an 8mm-ROI around the rTMS coordinates to investigate local rTMS effects. The average correlational distance in brain activity pattern from each participant to all participants within the same group quantified individual variability in spatial activation pattern (lower distance indicating a more typical activity pattern). Performance in neurocognitive domains was assessed via the MATRICS battery.
Results: We observed an increase in task-evoked left DLPFC activity in the active group (mean (SD) change: 0.20±0.32) but not in the sham group (-0.05±0.38) and the difference between the

two groups was significant (F(1,36)=5.83, p=0.04). Although whole-brain activation patterns were similar in the two groups, active rTMS reduced the individual variability in activation pattern (mean (SD) change: 0.074±0.05), while sham rTMS did not (0.005±0.06) and the difference was significant (F(1,36)=32.57, p<0.0001). Reduction in individual variability was associated with improved attention (F(1,16)=14.82, p=0.0014).
Discussion: Our results suggest rTMS effects occur by reducing individual variability of brain function. Future studies need to confirm and expand these results.

F100. THE ASSOCIATION BETWEEN TDCS RELATED CHANGES IN REGIONAL CEREBRAL BLOOD FLOW AND IMPROVED ILLNESS AWARENESS IN SCHIZOPHRENIA

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Background: Impaired illness awareness (IIA) occurs in up to 98% of patients with schizophrenia and leads to negative clinical outcomes. Previous functional MRI studies suggest that IIA may be related to interhemispheric imbalance in the posterior parietal area (PPA). Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation that applies a weak current passed between anodal and cathodal electrodes placed on the scalp. Recent studies support the potential value of tDCS to improve IIA in schizophrenia. Arterial spin labeling (ASL) is a brain imaging technique that provides an absolute measure of regional cerebral blood flow (CBF). We investigated the effect of tDCS on regional CBF and changes in IIA.
Methods: A total of 19 participants with schizophrenia with moderate-to-severe IIA were randomized to receive either bilateral PPA active (n=11) or sham (n=8) 2mA tDCS for 20 sessions. IIA was measured using the VAGUS, Self-report (VAGUS-SR). Regional CBF underneath the electrodes was measured using pseudo-continuous ASL (pCASL) pre- and post-tDCS and extracted using REX toolbox.
Results: The mean age was 43.4 (SD=13.6) and 21% were female. The baseline mean VAGUS-SR score was 4.7/10 (SD=2.2). Regional increases in CBF with 20 sessions of bilateral tDCS of the PPA in the active treatment group were associated with improved IIA when controlling for baseline illness severity (p<0.05).
Discussion: The results indicate that increases in regional CBF beneath the anode with bilateral PPA tDCS may represent a neuroimaging biomarker of treatment associated improvements in IIA.

F101. CORTICAL NETWORK DISRUPTION IN SCHIZOPHRENIA

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Background: A variety of changes in neural architecture and function accompanies schizophrenia, the nature of which is still an active subject of research. Current models based on fMRI and diffusion weighted imaging (DWI) describe a remodeling of the cortical architecture, suggesting cortical dysconnectivity as a possible explanation for schizophrenia symptoms. Many of these models derive from graph theory analysis, a mathematical framework used to describe networks. One model proposes that central cortical nodes are highly susceptible to damage due to their extensive connectivity. As the disease progresses, the brain may reroute itself to bypass these hubs. This model predicts a shift in connectivity strength toward peripheral regions of the cortex. Here, we test this hypothesis through a network analysis of the structural connectivity network.
Methods: N=40 first episode psychosis (FEP) patients and N=30 healthy controls were recruited from an established cohort enrolled in the Prevention and Early Intervention Program for Psychoses (PEPP) in London, Ontario. DWI tractograms were created using an MRTrix pipeline and translated to a non-directional association matrix weighted using the fractional anisotropy of the diffusion signal. We calculated the hubness of each node using a composite hubness measurement based on various graph theory metrics. This hubness was compared with edge weight variation and disruption. We also identified disrupted edges using the Network-Based Statistic (NBS) and correlated the probability of disruption with node hubness.
Results: The hubs identified were broadly similar to those found by previous reports. Hub identity remained stable across disease conditions. Consistent with prior studies, we observed disruption of connectivity in FEP, but not to the extent previously observed. Interestingly, this disruption did not correlate with node hubness. Instead, edges connected to low hub nodes showed greater inter-group variability. Higher hubness was associated with greater edge stability. The relatively few edges with significant disruption as measured by NBS had no correlation with node hubness.
Discussion: Although we reproduced the generally observed disruption of connectivity in schizophrenia, we did not observe a predilection toward disruption among high hubness nodes. Instead, edges connected to peripheral, low hubness nodes, showed greater variability of strength. This may indicate a robustness in the brain's core network not previously observed. Longitudinal data will be needed to confirm if this stability persists into the later stages of the disease.

F102. INCREASED RESTING-STATE PERFUSION IN MOTOR AND FRONTO-LIMBIC AREAS IS LINKED TO DIMINISHED EXPRESSION OF EMOTION AND SPEECH IN SCHIZOPHRENIA PATIENTS

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Background: Negative symptoms (NS) are a core component of schizophrenia, hampering treatment compliance and leading to social withdrawal and poor functional outcome. NS consist of five consensus domains which previous work suggests to be mapped in two distinct dimensions: (1) Diminished expression (DE) including blunted affect and alogia, (2) motivation and pleasure (MAP) including anhedonia, asociality and avolition. Although partly distinct neural correlates have been proposed for each dimension, no study to date has investigated whole-brain perfusion across the two distinct dimensions, as well as, the five consensus domains of NS. Here, we focus

on associations between whole-brain resting-state perfusion (rCBF) and symptoms of DE and MAP including underlying consensus domains.
Methods: To test the effect of NS on rCBF we applied structural and functional MRI using a pseudo continuous arterial spin labeling (pCASL) sequence in a sample of 47 schizophrenia patients (mean age = 38 years, 59% male). We assessed NS in patients using the Clinical Assessment Interview for Negative Symptoms (CAINS). We calculated mean values for the two dimensions (DE and MAP), as well as, the five consensus domains in accordance to the most recent guidelines. We applied multiple regression analyses to test associations between NS and rCBF correcting for age, motion parameters, antipsychotic medication, positive symptoms, duration of illness and years of education. A threshold of p (FWE) < .05 was applied to correct for multiple comparisons.
Results: Our results showed that DE was linked to increased perfusion in the cerebellum extending to the left lingual gyrus (kE = 955; p (FWE) < .001) and supplementary motor area (kE = 417; p (FWE) = .024). In contrast, we observed no associations between rCBF and MAP. When examining the five consensus domains of NS separately, we observed that blunted affect was linked to increased rCBF in the cerebellum and right fusiform gyrus (kE = 879; p (FWE) = .001). Furthermore, alogia was positively associated with perfusion in a cluster including left inferior and middle frontal gyrus and bilateral SMA (kE = 3741; p (FWE) < .001), the anterior cingulate cortex (kE = 1329; p (FWE) < .001), right (kE = 376; p (FWE) = .033) and left (kE = 346; p (FWE) = .044) precentral gyrus and two clusters within the bilateral (kE = 449; p (FWE) = .017) and right cerebellum (kE = 1336; p (FWE) < .001). Additionally, alogia was linked to increased rCBF in the right cuneus (kE = 601; p (FWE) = .005), the left inferior parietal lobe (kE = 612; p (FWE) = .004) and the right cerebrum including rolandic operculum and heschl gyrus (kE = 869; p (FWE) = .001), as well as the superior temporal gyrus, insula, head of the caudate, putamen and nucleus accumbens (kE = 1196; p (FWE) < .001). Conversely, no rCBF associations with anhedonia, asociality and avolition were observed.
Discussion: Overall, we observed altered rCBF in schizophrenia patients with DE of emotion and speech. Our results suggest distinguishable associations between rCBF and NS dimensions highlighting the central role of the motor and frontal-limbic areas in the expression of emotion and speech.

F103. ANHEDONIA IN SCHIZOPHRENIA: THE NEURAL CORRELATES OF MOTIVATION AND EMOTIONAL EXPERIENCE TO HUMOR AND MONETARY REWARDS

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Background: Studies on anhedonia in schizophrenia have shown that people with schizophrenia experience in-the-moment pleasure similar to that of healthy subjects but show deficits in anticipatory pleasure. In functional magnetic resonance imaging (fMRI) studies, anhedonia in schizophrenia have shown that patients show brain activation in emotion-related regions similar to that of healthy control. Previous studies have integrated the temporal experience of emotion with reward processing and found that people with schizophrenia show intact in-the-moment

pleasure ("liking") but impaired anticipatory pleasure ("wanting"). While monetary rewards have been widely used, few studies have directly examined social and nonsocial rewards. The aim of the present study is to examine the neural processing underlying the anticipation ("wanting") and consumption ("liking") of humor rewards in people with schizophrenia. We sought to investigate (1) whether people with schizophrenia show patterns of emotion-related activation during social and nonsocial reward consummation that are similar to those of controls, (2) the differences between schizophrenia and controls during social and nonsocial reward anticipation, (3) the different neural correlates of "humor comprehension" for people with schizophrenia and controls, and (4) the relationship between emotion-related neural activation and clinical symptoms of schizophrenia.

Methods: Participants included 17 patients diagnosed with schizophrenia and 17 healthy controls. Symptom assessments included the Positive and Negative Syndrome Scale (PANSS) and the Scale for the Assessment of Negative Symptoms (SANS). The study used an adapted monetary incentive delay (MID) task, including three types of rewards: monetary, humor and non-reward. Images were acquired on a Siemens 3T scanner. After preprocessing, two separate models were analyzed for the anticipation and consummatory phases in the first-level analysis. In the group analysis, the parameter for each participant was entered into a 2 × 3 flexible factorial model, including a between-group factor (schizophrenia and control) and a within-subject factor (monetary, humor and non-reward). A region of interest (ROI) analysis was performed for a specific a priori hypothesis. Four anatomical regions, including the nucleus accumbens (NAc), midbrain, dorsolateral prefrontal cortex (dlPFC) and orbitofrontal cortex (OFC) were selected for reward anticipation. The amygdala, midbrain, inferior frontal gyrus (IFG), and middle temporal gyrus (MTG) were selected for the processing of reward consumption.

Results: During reward anticipation phase, Group comparisons revealed a significantly greater increase in BOLD responses in the bilateral NAc, midbrain, right OFC and right dlPFC for monetary rewards in healthy controls compared with schizophrenics. In reward consumption phase, there were no significant group differences in the IFG, MTG, midbrain and amygdala when receiving monetary rewards. During the consumption of humor rewards, the between-group contrasts did not differ in the midbrain and amygdala. However, compared to normal controls, people with schizophrenia showed lower activation in the IFG and MTG. In addition, within-group analyses conducted separately in the patient and control groups found significant activation in the midbrain and amygdala. Correlations between clinical measures and related brain activity revealed that significant negative correlations were found between right midbrain activation and scores on the Avolition-Apathy and Anhedonia-Asociality subscales of SANS scale.

Discussion: This study used humor as a social reward to investigate the neural mechanisms underlying motivational and emotional processing in people with schizophrenia. The main findings of this study were: 1) in the presence of humor rewards, the amygdala and midbrain activity of schizophrenia patients was similar to that of healthy controls; 2) midbrain activity elicited in persons with schizophrenia by humor rewards correlated negatively with a clinical measure of schizophrenia symptoms (SANS scores), especially with scores on the avolition-apathy subscale; 3) during monetary anticipation, people with schizophrenia displayed less NAc, midbrain, OFC and dlPFC activation than controls; and 4) during humor consumption, people with schizophrenia showed less IFG and MTG activation than controls, even though there were no group differences in ratings of humor understanding. Our results indicate that the in-the-moment experience of pleasure is relatively intact but that the ability to anticipate future events may be impaired for both monetary and humor rewards in people with schizophrenia. Specifically, patients

have the basic ability to understand and appreciate humor despite dysfunction in brain areas related to social cognition. We speculate that schizophrenia patients have the basic ability to understand and appreciate humor but are sometimes hindered in their responses owing to deficits in social cognition. Our findings contribute to both the clinical assessment of anhedonia and to an understanding of the neurological basis of potential treatments for schizophrenia.

F104. FUNCTIONAL CONNECTIVITY HETEROGENEITY IN PSYCHOSIS: DIMENSIONAL PREDICTORS OF INDIVIDUAL VARIABILITY DURING REST AND TASK FMRI

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Background: Individuals with schizophrenia spectrum disorders (SSD) often demonstrate social cognitive impairments, associated with poor functional outcomes. Neurobiological heterogeneity in SSD has made understanding such deficits difficult; case-control comparisons in social cognitive neural circuits have yielded variable and inconsistent results. While heterogeneity in SSD has posed challenges, it can be leveraged as an opportunity to discover how variations in brain function relate to behavior. We examined the relationship between behavioral data and individual variability of functional connectivity at rest as well as during an emotional-processing task.

Methods: Neuroimaging and behavioral data (social cognitive tests and MATRICS cognitive battery) were analyzed for 193 individuals with SSD and 155 controls (total n=348). Functional connectivity was evaluated for both resting state and task functional magnetic resonance imaging (fMRI) data. Background connectivity analysis was used for the task data, which involved removing the modelled stimulus-evoked response and correlating residual activation over time across regions of interest. Individual variability in functional connectivity patterns was quantified through correlational distance of fMRI functional connectivity between participants; the mean correlational distance from one participant to all others was defined as a whole-brain 'variability score'. High mean correlational distance implied a greater level of 'idiosyncratic' variability; i.e. more divergent from the common group pattern. Hierarchical regressions were performed to determine potential predictors of individual variability. Post-hoc permutation tests were run to specifically examine within- and between-network functional connectivity variability in poor versus good cognitive performers independent of diagnostic category.

Results: Direct group comparisons of mean correlational distance between SSD and controls revealed diagnostic differences in variability for rest ($t = 3.87$, $p = 0.00013$) and task ($t = 2.92$, $p = 0.0037$). However, these diagnostic differences were not present in the hierarchical regression incorporating additional covariates. Instead, variability was related to social cognitive (mentalizing) scores for the emotional-processing task ($\beta = -0.0048$, $p = 0.011$), and neurocognitive (reasoning) scores for resting state ($\beta = -0.00015$, $p = 0.049$). Individuals with lower social cognitive mentalizing scores displayed greater variability specifically in default mode, frontoparietal and ventral multimodal within-network connectivity.

Discussion: Apparent diagnostic differences between SSD and controls were driven by differences in cognitive abilities, suggesting cognitive differences across groups could masquerade as diagnostic effects when not properly controlled for. Examining connectivity during a social cognitive task state allowed for better delineation of the relationship between variability and related social cognitive functions. Our results suggest that widespread increased within-network variability may be compensatory in individuals with lower mentalizing scores and may represent reduced functional efficacy and aberrant connectivity. Further validation of the variability underlying brain-behavior relationships could guide targeted treatment development for those exhibiting social cognitive deficits, and future studies should consider individualized patterns of variability during task and rest to optimize individualized treatment.

F105. EXTERNAL SPEECH PROCESSING AND AUDITORY VERBAL HALLUCINATIONS: A SYSTEMATIC REVIEW OF FUNCTIONAL NEUROIMAGING STUDIES AND THEIR CLINICAL IMPLICATIONS

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Background: It has been documented that individuals who hear auditory verbal hallucinations (AVH) exhibit diminished capabilities in processing external speech. While functional neuroimaging studies have attempted to characterise the cortical regions and networks facilitating these deficits in a bid to understand AVH, considerable methodological heterogeneity has prevented a neurobiological consensus being reached. This ultimately hinders the accessibility of this information to the end-users of this research, such as the healthcare professionals associated with voice-hearers.

Methods: The current systematic review investigated the neurobiological underpinnings of external speech processing deficits in voice-hearers in 38 studies published between January 1990 to June 2020.

Results: AVH-specific deviations in the activity and lateralisation of the temporal auditory regions were apparent when passively listening to speech sounds, words and sentences. Namely, decreased activity of the left superior temporal gyrus, decreased connectivity between the primary auditory cortex homologues, and increased activity of the left supramarginal gyrus, were observed in both clinical and non-clinical voice-hearers relative to non-voice hearers with the same diagnosis. Studies investigating network-level interactions also suggest that increased coupling of auditory regions to a wider network, including components of the auditory, language processing, cerebellar, limbic and default mode networks, may underlie speech processing deficits in clinical voice-hearers.

Discussion: Poor study quality and a lack of replicable results plague the literature, limiting the conclusions that were able to be drawn in the current review. Overall, the field lacks suitable samples, with most studies drawing from small, poorly characterised participant pools. Most detrimental was the lack of inclusion of a comparable non-voice hearing clinical group in many clinically-based studies. When a non-voice hearing group was included, several studies reported

non-significant differences in AVH symptomology between these groups. Finally, a considerable proportion of studies characterised their AVH population based on overall positive symptomology instead of AVH-specific scores on standardised clinical assessments.
A detailed list of recommendations has been provided to improve the quality of future research on this topic. Pertinently, these involve numerous recommendations around inter-laboratory coherence in methodological design and AVH classification, alongside directions for future behavioural paradigms and neuroimaging approaches. Through these improvements to study protocols, the involvement of cortical regions and networks in AVH-related speech processing deficits will be further elucidated. This may increase our understanding of the involvement of these regions and networks in the experience of voice-hearing. These methodological adaptations may additionally aid in our understanding of the real-life challenges that voice-hearers experience during spoken or social communication, which may have benefits for psychiatric intervention.

In response to the systematic review, an advisory piece was composed. During this, key findings form the empirical research into external speech processing deficits in voice-hearers was presented with the intention of informing healthcare professionals. In addition, the advisory piece provides a broad set of recommendations on how to adapt speech when conversing with individuals who hear voices. It is the view that through a better understanding of the speech processing deficits faced by individuals who hear voices, more effective communication with such patients can be had.

F106. RELATIONSHIP BETWEEN INDIVIDUAL VARIABILITY AND SOCIAL COGNITION AS MEASURED BY FRACTIONAL AMPLITUDE OF LOW FREQUENCY FLUCTUATION IN A TRANSDIAGNOSTIC GROUP OF SCHIZOPHRENIA AND AUTISM SPECTRUM DISORDERS

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Background: Social cognition is a core impairment in schizophrenia spectrum disorders (SSD) and autism spectrum disorders (ASD). Studies have investigated functional abnormalities of social cognitive networks in individuals with SSD and ASD, however, inconsistencies among findings represent a challenge in understanding the neurobiology of these disorders. In this study, fractional amplitude of low-frequency fluctuation (fALFF), a localized measure of signal power representing the amplitude of change over time, was performed to explore local activity in SSD and ASD at the group level, inter-individual variability, and the relationship with social cognition.
Methods: Resting state functional magnetic resonance imaging (rsfMRI) and social cognitive scores were extracted from a harmonized dataset consisting of 175 control participants, 59 individuals with ASD, and 206 individuals with SSD (total n = 440). fALFF was defined as signal power within two frequency ranges, slow-4 (0.027 – 0.073 Hz) and slow-5 (0.01 – 0.027 Hz), which are both normalized by the power in the remaining frequency spectrum. Social cognition was defined by a 'mentalizing' factor score derived from multiple tests related to higher-order social processing, such as theory of mind (Oliver et al., 2018). Permutation analysis of linear

models were employed to investigate the relationship of fALFF values (separately for slow-4 and slow-5) across the cortex with diagnostic groups, mentalizing scores, and the interaction between them. Further, individual variability was quantified via distance of fALFF maps between participants; average distance of one participant to all others defined a 'variability score.' Higher variability indicated a less typical spatial pattern of fALFF at the individual level.
Results: Lower slow-4 and slow-5 fALFF in visual and motor regions were found in both SSD and ASD groups compared to controls. SSD also showed differences from controls in insula and medial prefrontal cortex. No significant differences were observed between SSD and ASD. There was a widespread association between slow-4 and slow-5 fALFF values with mentalizing scores, but no interaction with mentalizing and diagnostic groups. Further, greater individual variability in slow-4 and slow-5 fALFF maps were significantly negatively associated with mentalizing scores ($p < 0.0001$).
Discussion: Our results show a common diagnostic pattern of fALFF reductions in ASD and SSD in primary cortices, indicating common disruptions in low level regions of the brain. While SSD did show differences in a broader range of cortex, suggesting more widespread impairments, the overlap and lack of significant differences between SSD and ASD suggest common neurobiological mechanisms. A general increase in fALFF was also associated with better social cognition, and deviations from a 'typical' fluctuation pattern resulted in poorer social cognitive performance, regardless of diagnosis. Cumulatively, this suggests that altered dynamics in fALFF may play a key role in the neurophysiology of social cognition, but the social cognitive deficits observed in ASD and SSD share a common pattern with poor performers in the control group.

F107. THE ROLE OF THE INFERIOR PARIETAL CORTEX IN PERSONAL SPACE REGULATION ACROSS PSYCHOSIS AND HEALTHY POPULATIONS: TASK-BASED AND RESTING-STATE FMRI FINDINGS

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Background: The regulation and representation of personal space, which is the space near the body into which others cannot intrude without eliciting discomfort, is one common form of non-verbal social communication. Based on neurophysiological studies conducted in non-human primates, a frontoparietal-subcortical network of areas has been identified that responds to the intrusion of others into this space. Several previous studies have reported personal space abnormalities in clinical populations, including in those with serious mental illnesses. However, correlations between social functioning impairments and personal space characteristics have been observed in both clinical and healthy subjects. Here we investigated the neural basis of these relationships by measuring personal space and the responses of brain areas involved in personal space regulation in individuals with and without diagnoses of psychotic disorders.
Methods: 3T fMRI data were collected for 37 individuals with non-affective or affective psychotic disorders (mean age: 26.8 yrs.; 26 males) and 60 demographically-matched control subjects (mean age: 25.9 yrs.; 39 males) while they viewed 3D images of faces which appeared to move towards or away from the subject. Personal space network regions-of-interest were defined independently using group results from a previous study and a striatal network atlas based on functional connectivity. Personal space size and permeability (boundary flexibility) were measured using the classic Stop Distance paradigm.

Results: The psychosis group demonstrated a significantly larger personal space ($p = 0.005$) and were less tolerant to personal space intrusions ($p = 0.006$) compared to the control group. Within the personal space network, responses of the inferior parietal cortex (IPC), but not of the other ROIs, was significantly correlated with personal space size in the full sample ($r = -0.26$; $p = 0.011$) and in the psychosis ($r = -0.35$; $p = 0.031$) but not the control group ($r = -0.19$; $p = 0.139$). In the psychosis group, personal space size correlated with IPC-ventral striatal connectivity ($r = 0.35$; $p = 0.034$), whereas in the control group, personal space size correlated with IPC-amygdala connectivity ($r = 0.43$; $p < 0.001$). Lastly, BOLD activity only within the IPC region varied systematically over time as participants viewed faces intruding upon or withdrawing from them throughout the 16 second blocks, non-linearly increasing or decreasing respectively.
Discussion: While personal space is enlarged on average in individuals with psychotic disorders and variation in inferior parietal cortex function may play a role in this enlargement, these findings also suggest that distinct neural pathways in psychotic and non-psychotic individuals, between the inferior parietal cortex and the ventral striatum versus amygdala, respectively, contribute to variation in personal space-related behaviors. Understanding such brain-behavior relationships may lead to the development of objective treatment targets for novel interventions aiming to treat social dysfunction in psychotic illness.

F108. TDCS-INDUCED MODULATION OF FACE EMOTION PROCESSING DEFICITS IN SCHIZOPHRENIA

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Background: Impaired face emotion recognition (FER) is a core feature of schizophrenia (Sz) which has been linked to atypical neuronal activity within visual cortex. In the visual system, FER depends upon coordinated functioning of subcortical and cortical regions including the pulvinar nucleus of the thalamus and motion-sensitive cortical regions (MT+) for processing of moving facial features. Abnormal processing of basic motion features (e.g., direction, velocity) is also consistently observed in patients with Sz and has been associated with FER deficits. In this ongoing study, we use personalized transcranial direct current stimulation (tDCS) delivered to MT+ in combination with behavioral measures of motion perception and FER, and concurrent EEG recordings and fMRI to evaluate effects on both behavior and associated EEG and fMRI activation patterns. Based upon prior work by us and others, we predicted that cathodal stimulation targeting MT+ would have the greatest beneficial effects on FER and motion perception.
Methods: Participants were 9 patients (mean age 37 years) meeting DSM-IV criteria for Sz. For tDCS, MxN stimulation was combined with realistic head modeling to generate a personalized model per subject that maximized current flow within MT+. Subjects participated in 3 tDCS/EEG sessions separated by at least 1 wk., followed by a single tDCS/fMRI session. tDCS/EEG sessions consisted of either sham (30sec ramp-up/ramp-down condition), cathodal or anodal stimulation. For the tDCS/fMRI session we used sequential sham and cathodal stimulation. Behavioral measures of coherent motion detection were determined using random dot kinematograms (RDK) at pre-set coherent motion levels (20-25%). Dynamic emotional faces were used to assess FER accuracy. Behavioral variables were collected pre, during and post-stimulation during EEG sessions. For fMRI the same stimuli used in the RDK and FER tasks were delivered passively.

Lastly, EEG data was analyzed in the time-frequency domain where, in healthy controls, we've observed prominent activations within alpha- and theta-frequency ranges in response to RDK stimuli.
Results: We observed the predicted increase in the theta evoked power response to RDK stimuli during cathodal stimulation that was significant even in this small sample size ($t=3.45$, $p=.011$). Moreover, the increase correlated with improved motion sensitivity, which, in turn, correlated with improved FER ($p<.05$). In contrast, we observed decreases during and after anodal stimulation that were not significant in this sample size. We also evaluated tDCS effects on fMRI activations during motion and FER processing. Consistent with the EEG findings, we observed enhancement of the fMRI response in the cathodal vs. sham stimulation condition to both RDK and FER stimuli. For motion stimuli significant enhancements were observed within MT+ ($t=3.14p<.01$) and early visual regions ($t=2.31p<.05$). Additionally, we observed correlations between changes in MT+ activation and behavioral improvement ($p=.03$). For face stimuli we observed a numeric increase in superior temporal sulcus activation that was not significant in this sample size ($p=.08$).
Discussion: The ability to recognize and respond to the emotional content of faces is crucial for social cognition and is impaired in SZ. The findings thus far from this study are consistent with previous work and support the hypothesis that deficits in motion processing contribute to social cognition impairment in Sz and support the feasibility of using combined tDCS/EEG/fMRI to evaluate the mechanisms underlying early sensory contributions to cognitive impairment in Sz.

F109. CLOZAPINE DEMETHYLATION ASSOCIATED WITH ASTROCYTE ACTIVITY AND SCHIZOPHRENIA SYMPTOMOLOGY IN TREATMENT-RESPONSIVE, BUT NOT TREATMENT-RESISTANT, PATIENTS WITH SCHIZOPHRENIA: A PROTON MAGNETIC RESONANCE SPECTROSCOPY STUDY.

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Background: Treatment-resistant schizophrenia (TRS) is found in ~30% of the schizophrenia population and is characterized by persistent positive symptoms despite adequate antipsychotic treatment. Clozapine is the only antipsychotic approved for the treatment of TRS, showing clinical efficacy in 30-60% of TRS patients (i.e., clozapine-responders; ClzR+), while the remaining 40-70% are left with no pharmacological recourse for improvement (i.e, clozapine-resistant; ClzR-). The mechanisms underlying clozapine's efficacy in TRS remain unknown, however, growing in vitro evidence suggests clozapine may attenuate glutamatergic dysregulations observed in patients with TRS, by modulating astrocyte's activity in glutamate's biochemical cycle. In this study, we examine clozapine-treated patients with TRS, and compare astrocyte activity biomarkers in association with clinical symptomology, and clozapine demethylation between ClzR+ and ClzR-.
Methods: Using 3T proton-magnetic resonance spectroscopy (3T1H-MRS), we quantified levels of myo-Inositol, biomarker of astrocyte activity, in the dorsal-anterior cingulate cortex (dACC), left-dorsolateral prefrontal cortex (left-DLPFC) and left-striatum of 138 participants (ClzR-=29;

ClzR+=30; treatment responders=30; controls=49). Plasma levels of clozapine, and its main metabolite norclozapine, were assessed 11-12 hours after last clozapine dose to assess clozapine demethylation, and measures for symptom severity (i.e., PANSS) and cognitive impairment (i.e., MMSE) were undertaken.

Results: Elevations of myo-Inositol were observed in the dACC of all schizophrenia groups versus controls ($F=11.321$, $p<0.001$, $\eta 2=0.202$). Higher clozapine demethylation was associated with lower myo-Inositol levels in the dACC($r=0.500$,$p=0.006$) and left-DLPFC($r=0.647$,$p<0.001$), as well as reduced positive symptom severity ($r=0.536$,$p=0.003$) in ClzR+, but not ClzR-.

Discussion: Our study indicates possible clozapine-astrocyte interactions in response to clozapine efficacy in ClzR+, but not ClzR-. These results come in support of growing in vitro evidence showing clozapine-mediated astrocyte modulation, and recent stem-cell research on astrocytic distinctions between TRS. A longitudinal study with multimodal biomarkers of astrocyte activity on antipsychotic-free patients with schizophrenia is underway to elucidate these possible astrocytic differences.

F110. TARGETING GABAERGIC DYSFUNCTION IN SCHIZOPHRENIA: POTASSIUM CHANNEL MODULATION (KV3.1/3.2) AS TREATMENT TARGETS IN SCHIZOPHRENIA - IMAGING AND ELECTROPHYSIOLOGICAL BIOMARKER FINDINGS FROM A FIRST IN PATIENT STUDY

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Background: The pathophysiology of schizophrenia involves abnormal reward processing, thought to be secondary to altered striatal and dopaminergic function. Imaging studies in people with the disorder find abnormalities in striatal dopamine synthesis capacity and striatal hypoactivation in response to reward-related cues, when compared with healthy controls. In addition, electrophysiological studies in schizophrenia, find evidence of cortical excitation-inhibition mismatch due to alerted glutamatergic and GABAergic neurotransmission, which may have downstream effects on striatal control. GABAergic interneurons are also thought to modulate both glutamatergic and dopamine neuron activity. GABAergic neuron firing rates, in turn, are related to voltage-gated potassium 3.1 (Kv3.1) and 3.2 (Kv3.2) channels functioning, suggesting that targeting Kv3.1/3.2 could augment striatal reward circuits and offer novel treatments in schizophrenia.

This presentation documents three experiments which tested the effects of a novel compound AUT00206, which targets voltage-gated potassium 3.1 (Kv3.1) and 3.2 (Kv3.2) channels expressed on GABAergic parvalbumin-containing neurons, on imaging and electrophysiological biomarkers in people with schizophrenia.

Methods: The first study measured the effect of AUT00206 on pre-synaptic dopamine synthesis capacity as measured by FDOPA Positron Emission Tomography (PET) in people with

schizophrenia. The second used a functional magnetic resonance spectroscopy (fMRI) paradigm, the monetary incentive delay task (MID), to measure bold signal activation during reward anticipation in people with schizophrenia, before and during treatment with AUT00206. The final study tested the effects of AUT00206 on resting state gamma-band electroencephalography (EEG) in people with schizophrenia.
Results: AUT00206 had no significant effect on dopamine synthesis capacity, however, there was a significant correlation between reduction in Kicer and reduction in symptoms in the AUT00206 group ($r = 0.58$, $p = 0.03$). This was not observed in the placebo group ($r = -0.15$, $p = 0.75$), although the placebo group may have been underpowered to detect an effect.
We found a significant inverse relationship at baseline between symptom severity and the anticipation-related neural activation in the right associative striatum ($r = -0.461$, $p = 0.035$). Following treatment with AUT00206, there was a significant increase in reward-anticipation related activation in the left associative striatum ($t13 = 4.23$, peak-level $p(FWE)<0.05$)), but no significant effect in the ventral striatum. This provides preliminary evidence that the Kv3.1/3.2 potassium channel modulator, AUT00206, may address reward-related striatal abnormalities in schizophrenia.

We found a significant positive correlation between frontal resting gamma (35-45Hz) power ($n=22$, $r = 0.613$, $p < 0.002$) and Positive and Negative Syndrome Scale (PANSS) positive symptom severity. We also found a significant reduction in frontal gamma power ($t13 = 3.635$, $p = 0.003$) from baseline in patients who received AUT00206. This provides initial evidence that the Kv3.1/3.2 potassium channel modulator, AUT00206, may address gamma oscillation abnormalities in schizophrenia.

Discussion: Taken together these three studies suggest that AUT00206, a Kv3.1/3.2 channel modulator engages with pathophysiological mechanisms linked to schizophrenia and may reverse some of abnormalities seen in the reward system and in the excitation-inhibition balance in the disorder. Further large-scale studies are required to confirm this effect.

F111. POSTER WITHDRAWN

F112. LATENT GROWTH MODELING OF THE EFFICACY OF ROLUPERIDONE ON NEGATIVE SYMPTOMS AND SOCIAL FUNCTIONING

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Background: Negative symptoms remain a therapeutic challenge in the care of people with schizophrenia. Roluperidone is a 5-hydroxytryptamine 2A (5-HT2A) and a sigma-2 receptor antagonist with added affinity for α1A-adrenergic receptors. The current study uses latent growth modeling to 1) examine the efficacy of roluperidone for negative symptoms and social functioning in the Phase 2b and Phase 3 trials of roluperidone; and 2) illuminate the trajectories of change in negative symptoms and social functioning during both trials.
Methods: The Phase 2b (N=244) and Phase 3 (N=513) RCTs enrolled patients with predominantly negative symptoms in schizophrenia to receive 1 of 2 roluperidone doses, 32 mg/day or 64 mg/day,

or placebo for 12 weeks. In Phase 2b, patients were recruited from 36 sites and 6 European countries. The Phase 3 trial recruited from 60 sites and 8 countries including the United States. Patients completed assessments of psychopathology, safety, and tolerability throughout the study. The current analyses focus on negative symptoms drawn from the Positive and Negative Syndrome Scale (PANSS) Negative Symptoms Factor Score (NSFS); and social functioning measured with the Personal and Social Performance (PSP) scale. Assessments were completed at baseline, Week 2, Week 4, Week 8, and Week 12 (endpoint). Growth curve models were fitted to the data sequentially. First, the most appropriate model of change was determined by fitting intercept only, linear, and then quadratic models to the data. Next, external variables including treatment group, age, sex, country, were evaluated as predictors of the longitudinal change function. The goodness-of-fit of the estimated growth models was adjudged using the comparative fit index (CFI) ≥ 0.95, Root Mean Square Error of Approximation (RMSEA) ≤ 0.08, and Standardized Root Mean Square Residual (SRMR) ≤ 0.08. Indices of relative fit including the Akaike information criteria (AIC), Bayesian information criteria (BIC), and sample-size adjusted BIC (SSA-BIC) were used to compare competing models. The change model with lowest information criteria estimate was selected as the preferred model.

Results: In the Phase 2b and Phase 3 data, only the quadratic model produced CFI, RMSEA, and SRMR values that consistently met thresholds for good-fit for both negative symptoms and social functioning. In both trials, information criteria indices heavily favored the quadratic model of change over the intercept only and linear models. The addition of external variables further improved the absolute fit of the quadratic model. In Phase 2b trial, treatment was a significant predictor of improved negative symptoms (slope=-0.269, $p<0.001$) but its effect on non-linear change was not significant ($q=0.156$, $p=0.134$). treatment drove reductions in both the PANSS emotional expression (EXP) (slope = -0.289, $p<0.001$) and motivation and pleasure (MAP) items (slope = -0.168, $p<0.05$).

In Phase 3 trial, treatment was a significant predictor of reductions in negative symptoms (slope= -0.148, $p<0.05$) but not non-linear change ($q=0.123$, $p=0.064$). There were domain-specific effects on linear (slope= -0.236, $p<0.0001$) and non-linear ($q=0.207$, $p<0.001$) change in MAP items. Treatment group was associated with linear (slope= -0.167, $p <0.001$) and non-linear quadratic ($q =0.206$, $p<0.01$) change in social functioning.

Discussion: Roluperidone is associated with reductions in negative symptoms and improvements in social functioning. There are latent trajectories in roluperidone response when negative symptoms and social function are examined. Treatment response was more rapid and ubiquitous in the Phase 2b than the Phase 3 trial. Latent variable models are adaptable to studying repeated measures data when collected longitudinally at fixed time points.

F113. CANNABIDIOL FOR TREATMENT OF NON-AFFECTIVE PSYCHOSIS AND CANNABIS USE: A STUDY DESIGN FOR A RANDOMIZED CLINICAL TRIAL

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Background: Cannabis use is an important risk factor for development of psychosis and further transition to schizophrenia. The prevalence of patients with psychosis and comorbid cannabis use (dual diagnosis) is rising, and it has been reported that 19-57% of patients with first-episode psychosis use cannabis. Patients with dual diagnosis are more likely to be admitted to the hospital, to be hospitalized for longer time periods, to require compulsory admission and to be prescribed several different antipsychotic medications suggesting an increased risk of treatment failure.
People with comorbid substance use disorder are usually excluded from clinical trials which has led to a scarcity of evidence regarding the efficacy of antipsychotics in patients with dual diagnosis. Thus, no approved specialized pharmacological treatment option exists for this group of patients, leaving them to best practice treatment.

Cannabidiol (CBD), a constituent of the Cannabis Sativa plant, has potential both as an antipsychotic and as a cannabis substituting agent. CBD works through the endocannabinoid system, which is of importance to the homeostasis throughout the body.

CBD has in two pilot studies shown significant effect om psychotic symptoms, both as an add on therapy and in a head-to-head study.

The aim of this study is to evaluate the efficacy of cannabidiol versus a first-choice second-generation antipsychotic (risperidone) in patients with psychosis and a lifetime use of cannabis.

Methods: The study is a phase II randomized, double-blinded, parallel-group, active-comparator clinical trial. We plan to include 64 patients aged between 18 and 45 years with a diagnosis of psychosis and a current or former (lifetime) use of cannabis, and currently not treated with any antipsychotic. The recruitment will include both in- and outpatient clinics in Denmark. The participants will be randomized to seven weeks of treatment with either cannabidiol 600 mg (300 mg BID) or risperidone 4 mg (2 mg BID). Participants will undergo clinical assessment after 1, 3, 5 and 7 weeks, telephone assessment the weeks in between and a safety visit two weeks after end of treatment. The primary outcome is psychotic symptom severity on the PANSS positive subscale. The secondary outcomes include cessation of cannabis use for those with a current use of cannabis at baseline (self-reported) and frequency and quantity of cannabis use (self-reported), global illness severity (CGI-S and CGI-I), psychosocial functioning (PSP), subjective well-being (SWN-S), cognition (BACS), sleep (polysomnography), circadian rhythmicity (actigraphy), and metabolomics.
Results: No results design poster.
Discussion: There is a lack of knowledge on the treatment of patients with dual diagnosis since research so far has focused on patients with psychosis without comorbid substance use disorder. The study is the first to investigate if CBD has a role in the treatment of patients with psychosis and a lifetime use of cannabis.The results of this trial can potentially contribute with a new treatment paradigm for patients suffering from dual diagnosis.

F114. META-REGRESSION OF ADJUNCTIVE TREATMENT TRIALS FOR NEGATIVE SYMPTOMS IN SCHIZOPHRENIA

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Background: Negative symptoms of schizophrenia typically persist despite treatment with best available medications for schizophrenia. Clinical studies have evaluated the effects of multiple potential add-on classes of medication, but no approved compounds are yet available. Moreover, interpretation of adjunctive studies may be affected by placebo responses, which have recently been shown to correlate with sample size and site number in monotherapy trials of schizophrenia. Here, we performed a meta-analysis and meta-regression of adjunctive treatment studies for negative symptoms of schizophrenia across all mechanisms with a sufficient number of clinical trials.

Methods: We conducted a literature search of adjunctive treatment studies for which both single- and multi-center studies were available. We identified 156 trials across 7 mechanisms of action (MOA). Meta-analysis and meta-regression analyses were conducted with sample size as a covariate.

Results: Significant effects were observed for 5-HT3R antagonists (d=1.03. p=.01); estrogen modulators (d=.42, p<.001); anti-inflammatories (d=.40, p=.01); NMDAR modulators (d=.34, p<.001); anti-depressants (d=.33, p<.001); and alpha-7 nicotinic agonists (d=.10, p=.02), whereas non-significant results were obtained for DA modulators (d=.14, p=.1) and AChE inhibitors (d=.17, p=.38). Across MOA, the magnitude of the placebo response scaled with sample size to a greater extent than treatment response, leading to a significant reduction in trial effect size with sample size (p<.001). Significant results were obtained preferentially with sample sizes in the range of 30 to 150 individuals.

Discussion: These results highlight the potential efficacy of specific add-on mechanisms and encourages further clinical development. In addition, the results highlight the importance of considering the differential sample size effects on the placebo vs. treatment response when designing adjunctive clinical trials in schizophrenia.

F115. THE LONGITUDINAL EFFECT OF AMISULPRIDE ON STRIATAL DOPAMINE SYNTHESIS CAPACITY IN FIRST-EPISODE PSYCHOSIS

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Background: Antipsychotic drugs are known to be effective treatment for majority of first episode psychosis (FEP), yet its longitudinal effect is less investigated. While dopamine hypothesis is suggested as leading neurobiological mechanism underlying psychotic disorders, and all antipsychotic drug is dopamine antagonist, an effect of specific antipsychotic drug on dopamine synthesis capacity is unclear. To prospectively observe the change striatal dopamine capacity during 1-year amisulpride treatment and to develop predicting model of treatment-responsiveness based on observed neurobiological changes in FEP patients.

Methods: Twenty seven antipsychotic-naive FEP patients, aged 19 or more and less than 45, were enrolled, along with 31 age- and sex-matched healthy controls. Striatal dopamine activity was assessed as kicer value using [18F]DOPA PET, before initiating treatment and after 6 weeks and 1 year of amisulpride treatment. Healthy controls also underwent PET scans according to the

corresponding schedule of the patients. Patients were clinically assessed regularly with Positive and Negative Symptom scale (PANSS) and Clinical Global Impression-severity scale (CGI-S). Treatment response, defined as 20% or more decrease in PANSS total score from baseline, was assessed at 6 weeks after amisulpride treatment.
Results: There were no significant difference in demographic characteristics between FEP patients and healthy controls. Mean PANSS total score of FEP patients at baseline, 6-week and 1-year follow-up were 67.8, 47.8, and 40.0, respectively. All patients showed treatment response after 6-week treatment of amisulpride, while 2 patients had worsening of psychotic symptom and 1 patient had switched to another antipsychotic drug due to adverse effect, afterwards. The change in kicer value over time significantly differed between FEP patients and healthy controls.
Discussion: There were no significant difference in demographic characteristics between FEP patients and healthy controls. Mean PANSS total score of FEP patients at baseline, 6-week and 1-year follow-up were 67.8, 47.8, and 40.0, respectively. All patients showed treatment response after 6-week treatment of amisulpride, while 2 patients had worsening of psychotic symptom and 1 patient had switched to another antipsychotic drug due to adverse effect, afterwards. The change in kicer value over time significantly differed between FEP patients and healthy controls.

F116. THE IMPACT OF EXTRAPYRAMIDAL SYMPTOMS ON SUBJECTIVE WELL-BEING IN FIRST EPISODE SCHIZOPHRENIA PATIENTS STARTING TREATMENT WITH AMISULPRIDE

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Background: The Optimization of Treatment and Management of Schizophrenia in Europe (OPTiMiSE) trial included first-episode schizophrenia patients and was intended to optimise current antipsychotic treatment strategies in schizophrenia. In this post-hoc analysis, we examined frequencies of antipsychotic-induced extrapyramidal symptoms (EPS) in the first 4 weeks of amisulpride treatment and their relationship to subjective well-being.
Methods: EPS were rated with the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale and subjective well-being was assessed by the Subjective Well-being under Neuroleptics short form (SWN-K). Ratings were done at baseline and week 4 of antipsychotic treatment. A correlation analysis of subjective well-being and EPS at baseline and week 4 was performed.
Results: Baseline frequencies of OPTiMiSE's sample (n=473) of EPS were: akathisia (7.4%), followed by rigidity (7.2%), tremor (6.1%), hypokinesia/akinesia (4.9%), dystonia (4.2%), and hyperkinesia (1.1%). The rate of every single EPS increased significantly from baseline to week 4. Again, akathisia was reported most frequently (16.3%), followed by rigidity (12.3%), tremor (11.3 %), hypokinesia/akinesia (9.3%), dystonia (6.8 %), and hyperkinesia (3.8%). The SWN-K total score at baseline was 82.5±17.5, and increased significantly to week 4 (88.8±15.8, $p<.001$). The correlation analysis of EPS and subjective well-being revealed no significant association between any EPS and the SWN-K total score at baseline, whereas at week 4 every single EPS, apart from hyperkinesia, was significantly negatively correlated with the SWN-K total score.
Discussion: The considerable rates of EPS in first-episode schizophrenia patients at baseline are in line with the literature. They seem to have no influence on the patients' subjective well-being at baseline. However, the increasing scores of EPS in our sample after 4 weeks of treatment with

amisulpride, led to a significant negative association with subjective well-being. Further prospective studies of similar nature are needed to confirm these post hoc findings.

F117. DYSGLYCEMIA AND CLINICAL IMPROVEMENT IN PATIENTS WITH SCHIZOPHRENIA TREATED WITH ANTIPSYCHOTICS: A SYSTEMATIC REVIEW

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Background: Antipsychotics are the cornerstone of treatment for schizophrenia; however, their use is associated with several metabolic consequences including weight gain, dyslipidemia, and dysglycemia. Previous research suggests that a 'metabolic threshold', which delineates a relationship between antipsychotic efficacy and metabolic burden, may exist with respect to both weight gain and dyslipidemia. Therefore, the aim of this exploratory review is to determine whether a similar relationship between dysglycemia and clinical improvement exists among patients with schizophrenia.

Methods: To accomplish this, we conducted a systematic search in MEDLINE, EMBASE, PsychINFO, CINAHL, CENTRAL, and Scopus from inception to June 2022. Longitudinal studies that directly examined the relationship between changes in glucose parameters and psychopathology among patients with schizophrenia treated with antipsychotics were included. Findings were synthesized qualitatively according to symptom domain, antipsychotic type, patient treatment status, study duration, and study quality.

Results: Our search identified 11 studies that compared changes in parameters of glucose metabolism and psychopathology over time. In most cases, we found that increased levels of glucose parameters following treatment were associated with clinical improvement. This provides evidence for a metabolic threshold for antipsychotics related to glucose homeostasis. However, independence from weight gain and alterations in lipid parameters remains to be conclusively shown. In addition, further research is needed to determine how factors such as illness duration, cumulative antipsychotic exposure, and treatment resistance may impact the relation.

Discussion: This review supports a need for additional work aimed at exploring the validity of a glucose-psychopathology relation to improve our understanding of antipsychotic side effects in relation to mechanism of action. Subsequent findings can then be used to inform treatment planning, side effect management, and overall patient care.

F118. ALTERED DOPAMINERGIC MARKERS IN THE SUB-CHRONIC PHENCYCLIDINE MODEL MAY CONTRIBUTE TO IMPAIRED ANTIPSYCHOTIC RESPONSE TO AMPHETAMINE-INDUCED LOCOMOTOR ACTIVITY

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Background: The sub-chronic phencyclidine (scPCP) model is a well-established model of relevance to cognitive impairment associated with schizophrenia. Dysregulation of the dopamine system, particularly in the striatum is a key player in both the pathophysiology and treatment of schizophrenia. Our lab, and others have evidenced robust behavioural and molecular changes in

the scPCP model. However, there has been a lack of focus, or conflicting results on the function of dopamine within the scPCP model. An assumption of the scPCP model is its ability to contribute to prefrontal cortex dysfunction via hypodopaminergia. As a bidirectional relationship between prefrontal cortex hypodopaminergia and subcortical hyperdopaminergia has been reported, the scPCP model may increase dopamine in subcortical regions. Animal studies looking at the efficacy of antipsychotics in the ability to reverse locomotor activity (LMA) and treat positive symptoms are often completed in naïve, vehicle animals who do not display potential pathology of relevance to schizophrenia. Therefore, further characterisation and adaptation of the scPCP model will help to aide our understanding of schizophrenia and make it a better tool in identifying new treatments. The aims of this study were to 1. Assess a proxy for positive symptoms, and the ability to reverse them. We measured the behavioural locomotor activity effect of pre-treating scPCP animals with an acute dose of haloperidol or clozapine followed by an acute challenge of amphetamine; and 2. Identify whether scPCP animals display an altered dopaminergic system compared to controls through post-mortem analysis.

Methods: Female Lister-Hooded rats were dosed with either vehicle (0.9% saline) or PCP (2mg/kg i.p.) bi-daily for 7 days. Following a 7-day washout period, rats underwent novel object recognition (NOR) testing to confirm a cognitive deficit in the scPCP rats. Animals were pre-treated with vehicle, haloperidol (0.05mg/kg s.c.) or clozapine (5mg/kg s.c.), followed by an acute dose of vehicle or amphetamine (0.75mg/kg i.p.) and their LMA was recorded (n=10 per group). Following completion of behavioural experiments, brains were taken for post-mortem analysis (n=10 per sub-chronic group); dopaminergic and GABAergic markers, specifically dopamine transporter (DAT), tyrosine hydroxylase (TH), dopamine receptor 2 (D2R), parvalbumin (PV), and GAD67 were measured in the striatum using simple western analysis and ELISA. The area under the curve (AUC) for the LMA were analysed using a two-way ANOVA followed by Tukey's multiple comparisons test. NOR and post-mortem data were analysed by student's t-tests.

Results: In the NOR test, there was a significant reduction in the DI in scPCP animals ($p<0.001$), evidencing a cognitive deficit. All animals displayed similar levels of baseline LMA. Acute haloperidol and clozapine treatment significantly reduced amphetamine-induced LMA in scVehicle rats ($p<0.0001$). By contrast clozapine ($p<0.0001$), but not haloperidol, reduced amphetamine-induced LMA to the same extent in scPCP rats. Simple western analysis showed that scPCP rats had increased levels of TH ($p<0.01$), reduced levels of DAT ($p<0.01$) and GAD67 ($p<0.01$), and no change in PV levels in the striatum relative to vehicle controls; an ELISA showed no change in D2R levels in the striatum.

Discussion: The atypical antipsychotic clozapine, used in treatment-resistant schizophrenia, was able to reduce amphetamine-induced LMA in both scVehicle and scPCP animals. However, haloperidol, a typical antipsychotic was not able to reduce the amphetamine LMA in scPCP animals suggesting they may have an altered dopaminergic system. Post-mortem analysis supports this hypothesis, with alterations in both DAT and TH in the striatum. This scPCP model presents itself as a model that may have relevant behavioural and molecular markers to those seen in treatment-resistant schizophrenia. Further studies, looking at the response of other antipsychotics, PET imaging, and post-mortem markers are ongoing to elucidate the underlying mechanism of the observed haloperidol response. The scPCP model may be useful in testing novel compounds to treat positive symptoms, as well as cognitive symptoms.

F119. CHANGES IN CORTICOSTRIATAL CONNECTIVITY AND STRIATAL TISSUE IRON ASSOCIATED WITH EFFICACY OF CLOZAPINE FOR TREATMENT-RESISTANT SCHIZOPHRENIA

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Background: Numerous studies demonstrate the superiority of clozapine (CLZ) for the treatment of persistent psychotic symptoms that are characteristic of treatment-refractory schizophrenia (TRS). However, the neural and molecular mechanisms underlying CLZ's unique efficacy remain unknown. Prior studies have linked increased corticostriatal functional connectivity as a marker of response to non-CLZ, dopamine (DA) D2-receptor-blocking antipsychotic drugs. It remains unknown whether this connectivity finding also relates to CLZ's unique efficacy. Secondly, whether a response to CLZ is associated with changes in striatal DA functioning is also unknown. Here, we examined response to CLZ in relation to the following: (1) change in corticostriatal functional connectivity; and (2) change in a magnetic resonance-based measure of striatal tissue iron (R2'), which demonstrates utility as a proxy measure for components of the DA system.
Methods: A cohort of 22 participants with TRS underwent scanning while starting CLZ and after 12 weeks of CLZ treatment. Symptoms were assessed with the Brief Psychiatric Rating Scale (BPRS) We used both cortical and striatal regions of interest to examine changes in corticostriatal interactions in top-down and bottom-up analyses in relation to CLZ response (% reduction of psychosis items of the BPRS). Secondly, we derived a measure of R2' from multi-echo turbo spin echo and multi-echo gradient echo sequences. Striatal R2’ was analyzed in relation to CLZ response.
Results: In both top-down ad bottom-up analyses, we observed an increase in corticostriatal connectivity between the dorsal caudate and regions of the frontoparietal network that corresponded with response to CLZ ($P < 0.05$, corrected). We observed no significant changes in striatal R2' across CLZ treatment.
Discussion: These results indicate that changes in corticostriatal networks underlie CLZ response without gross shifts in striatal R2'. Our results provide novel mechanistic insight into response to CLZ treatment.

F120. THE PHARMACOLOGICAL PROFILE AND THE RELATIONSHIP BETWEEN PDE10A ENZYME OCCUPANCY AND PRECLINICAL EFFICACY FOR MK-8189, A NOVEL PDE10A INHIBITOR

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Background: Phosphodiesterase 10A (PDE10A) is a member of the cyclic nucleotide phosphodiesterase family that functions to metabolically inactivate both cAMP and cGMP. PDE10A is predominately expressed in the brain with high levels concentrated in medium spiny neurons of the striatum. Evidence generated in preclinical models supports the hypothesis that PDE10A inhibition may be a novel therapeutic target for the treatment of schizophrenia. Here we

present the preclinical pharmacological profile of MK-8189, a novel PDE10A inhibitor. In addition, we characterize the relationship between PDE10A enzyme occupancy and efficacy in rodent and non-human primate behavioral models to establish PDE10A occupancy targets for clinical studies with MK-8189.

Methods: In vitro functional activity of MK-8189 against PDE10A and other PDE enzyme families was evaluated using a fluorescence polarization assay measuring hydrolysis of cyclic nucleotides. The ability of MK-8189 to inhibit PDE10A in vivo was determined by measuring changes of cGMP and phosphorylation of the AMPA receptor subunit GluR1 (Ser845) in the striatum of rats. A novel PDE10A selective radioligand, [3H]MK-8193, was used to determine PDE10A occupancy of MK-8189 in the rat striatum. Preclinical in vivo positron emission tomography (PET) occupancy studies were also carried out in rhesus monkey. MK-8189 was dosed as an IV bolus + infusion 30 min prior to IV injection of [11C]MK-8193 in order to achieve near steady-state plasma levels of MK-8189 during the PET scan. MK-8189 was tested in three assays (attenuation of psychomotor activity, conditioned avoidance responding, and pre-pulse inhibition) predictive of antipsychotic effects in the clinic.

Results: In vitro assays demonstrated that MK-8189 is a potent, competitive inhibitor of the human PDE10A enzyme (Ki = 0.029 nM). MK-8189 is a highly selective against PDE10A with greater than 500,000-fold selectivity over the other PDE enzyme families (PDEs1 – 11). MK-8189 also has a promising in vitro safety profile against ion channels (Iks, Cav1.2 and Nav1.5 > 30 μM, and hERG Ikr IC50 = 33 μM). Transporter studies indicate high potential for CNS penetration, with MK-8189 having high passive permeability and not being a substrate of human and monkey P-gp (B-A / A-B ratio of < 2). The ability of MK-8189 to inhibit PDE10A in vivo was determined by measuring changes of cGMP in the striatum of rats. Administration of MK-8189 (0.3 – 3.0 mg/kg, p.o.) dose-dependently increased cGMP in the striatum of rats. MK-8189 signaling in the striatum was further characterized by measuring phosphorylation of the AMPA receptor subunit GluR1 at Ser845. MK-8189 produced a dose-dependent increase in GluR1 phosphorylation. Target engagement was further examined by measuring MK-8189 occupancy in the rat striatum with [3H]MK-8193. Ex vivo occupancy studies revealed that a plasma concentration of 52 nM yielded ~50% occupancy of PDE10A in the rat striatum. Occupancy studies were also carried out in rhesus monkey with MK-8189 to examine the utility of [11C]MK-8193 to establish a drug plasma level/ PDE10A enzyme occupancy relationship. These studies determined that a plasma concentration of 200 nM yielded ~50% occupancy of the enzyme in the rhesus monkey striatum. Preclinical efficacy was examined in rodent models that are thought to predict antipsychotic activity of test compounds. MK-8189 (0.25 – 0.75 mg/kg, p.o.) produced a dose-dependent decrease in the MK-801 (non-competitive NMDA receptor antagonist) locomotor response at plasma exposures that corresponded to ~25 – 50% PDE10A occupancy. The antipsychotic potential of MK-8189 was further examined in the conditioned avoidance responding (CAR) assay. MK-8189 (0.125 – 0.5 mg/kg, p.o.) dose-dependently decreased avoidance and the threshold for full efficacy in the CAR assay was achieved between the 0.375 and 0.50 mg/kg doses that correspond to occupancies of ~ 48% and 75%, respectively. MK-8189 also significantly reversed an MK-801-induced deficit in pre-pulse inhibition. Doses ranging from 0.25 - 0.5 mg/kg produced statistically significant reversal of MK-801, similar to the magnitude observed with clinically relevant doses of antipsychotics. Plasma levels indicated that these effects were observed at PDE10A occupancies of ~47% and higher.

Discussion: MK-8189 is a potent and selective PDE10A inhibitor with excellent pharmaceutical properties. MK-8189 inhibited PDE10A in vivo and produced robust activation of the striatum as

measured by cAMP and pGluR1 signaling. A novel PDE10A PET tracer (MK-8193) was used to establish a drug plasma level/ PDE10A enzyme occupancy relationship in both rat and rhesus monkey. These data were used to determine the PDE10A occupancy range required to achieve efficacy in preclinical models of antipsychotic behaviors. These studies suggested that a minimum level of ~30% PDE10A occupancy was required to produce an efficacy signal in some assays, however, full antipsychotic-like activity across assays required >50% PDE10A occupancy.

F121. PRO-COGNITIVE EFFECTS OF INTRAVENOUS ERYTHROPOIETIN IN PATIENTS WITH SCHIZOPHRENIA

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Background: Patients with schizophrenia (PSZ) report impairments across several cognitive domains impacting considerably their functional outcome. Disturbed neurogenesis, synaptogenesis and neural plasticity have been implicated in the pathophysiology of cognitive impairment associated with schizophrenia (CIAS). Recent findings imply that drugs primarily promoting neural plasticity rather than modulating receptor function directly have greatest therapeutic potential. However, thus far, effective treatment options represent an unmet need. In this regard, treatment with erythropoietin (EPO) constitutes a promising approach. EPO is characterized by pleiotropic effects including promotion of neural plasticity and blood-brain-barrier integrity as well as reduction of inflammatory processes. Importantly, these effects appear to be accompanied by improvements of cognitive performance in PSZ. Here, we present cases of five patients suffering from CIAS who were treated with EPO.
Methods: We initiated EPO treatment trials in five patients (P1-P5, m=3) suffering from CIAS. Illness duration ranged between 2-14 years. Patients did not report any severe positive or negative symptoms at the time of treatment initiation. Patients received intravenous EPO infusions (50000 IE) diluted with 250 ml 0.9 % saline. This was conducted weekly over a period of 15 weeks which included three placebo infusions (single-blinded). We assessed cognitive performance using the MATRICS Consensus Cognitive Battery (MCCB). The MCCB allows a brief assessment of key cognitive domains impaired in PSZ including attention, working memory, and speed of processing. MCCB was performed at baseline, once after the last placebo administration, once between two EPO administration visits and once after the last EPO infusion. In addition, each patient performed a visuospatial working memory task. This consisted of four Gabor patch stimuli with differing orientations while two out of four flickered. Additionally, either a predictive or a non-predictive cue was displayed. Patients had to indicate by button press a change of orientation. The visuospatial working memory task was performed at baseline and after the last infusion. Moreover, each visit encompassed physical examination, routine laboratory testing, documentation of concomitant medication and monitoring of adverse drug reactions (ADRs). Bloodletting of 200-300 ml blood was performed in cases the hematocrit exceeded a threshold of 50 %. In addition, patients were required to follow a low-iron diet to reduce thrombosis risk.
Results: Patients did not report any unexpected ADRs. MCCB composite T score and our findings from the visuospatial working memory task yielded improved cognitive performance across

several domains including attention, working memory and speed of processing in each patient except P2. Patient's global psychopathology remained stable during treatment (except P2). Our patients and their families confirmed improved cognitive performance in daily life.
Discussion: Overall, our findings are in line with previous reports demonstrating improved cognitive performance mediated by EPO. Importantly, although EPO results in ameliorated cognitive functioning, it does not counteract the impact of psychopathological phenomena inherent in schizophrenia which is reflected by our findings in P2. Nonetheless, EPO constitutes a promising approach to mitigate cognitive deficits in several patient groups allowing to improve functional outcome. Hence, further efforts to establish optimal administration protocols and to promote a widespread use should be supported.

F122. A VIRTUAL REALITY ADAPTATION OF A STRATEGY FOR SEMANTIC ASSOCIATION MEMORY (SESAME) MODULE: AN INITIAL FEASIBILITY AND EFFICACY STUDY

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Background: Schizophrenia is associated with deficits in the memorization of semantically related verbal information. Strategy for Semantic Association Memory training (SESAME) represents a promising cognitive remediation program in improving semantic encoding strategies for verbal memory. Virtual reality (VR) has been proposed as a novel tool to increase the transfer of learned skills during cognitive training to everyday life by providing participants with an immersive experience with high ecological validity. The present study aims to examine the initial feasibility and efficacy of an adapted module of SESAME delivered using VR technology.
Methods: Thus far, a total of 24 individuals with schizophrenia or schizoaffective disorders have completed this study. Participants were randomized to either a verbal memory training module informed by SESAME training principles using VR, or an active control condition. In the training condition, a coach provided training on semantic encoding strategies while participants had to remember restaurant orders with increasing levels of difficulty. In the control condition, participants were asked to complete visuospatial puzzles in VR with increasing levels of difficulty. A VR experience and cybersickness questionnaire were administered following the completion of the VR program to assess feasibility and acceptability. Trial 1 of the Hopkins Verbal Learning Test-Revised (HVLT-R) was administered pre- and post-intervention to assess initial efficacy of the VR training on the use of semantic clustering.
Results: Feasibility and acceptability are demonstrated by limited or no simulation sickness symptoms reported following VR immersion, along with high levels of enjoyment reported following participation. Preliminary results show that mean number of semantic clusters used pre-intervention generally increased for those randomized to the VR condition following intervention ($t(10) = 1.58$, $p = 0.146$) but remained stable for those in the active control condition ($t(12) = 0.47$, $p = 0.650$).
Discussion: Despite our relatively small sample size, these preliminary results trending towards significance suggest that the short VR module intervention is feasible and may be clinically effective in improving the use of semantic clustering. The single VR intervention was, by design,

short in duration, and therefore a longer program of intervention, over multiple sessions, may prove to be more beneficial in improving verbal memory functioning among this population. Nevertheless, our findings provide support for increased integration of VR-based cognitive remediation into clinical care for individuals with psychotic-spectrum disorders, especially those experiencing persistent cognitive deficits. Future research is also needed to investigate whether VR is associated with improved transfer of learned cognitive skills into everyday life.

F123. REMOTE ADMINISTRATION OF CIRCUITS IN YOUTH WITH RECENT-ONSET PSYCHOTIC DISORDERS: AN ACCEPTABILITY AND FEASIBILITY PILOT TRIAL

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Background: Psychotic disorders in youth have major consequences on the achievement of several milestones such as attending an educational program or starting a career. The main objective of this study was to evaluate the feasibility and acceptability of online administration of cognitive remediation (CR) in young adults followed in early intervention for psychosis programs and involved in a supported education program.
Methods: This is a quasi-experimental pre-post design involving a single group (n = 9). A neuropsychological assessment was conducted remotely at pre-treatment, post-treatment as well as 3-month and 1-year post-treatment. Questionnaires regarding different aspects of feasibility and acceptability were administered remotely at the beginning, middle and end of the CR program. CR was delivered using CIRCuiTS, a therapist-supported computerized program designed to improve metacognitive skills and cognition (attention, memory, executive functioning). It includes two to three 30 to 60 minutes sessions per week, for 3 months (maximum 40 sessions).
Results: Four out of nine participants completed the intervention. Others dropped out because of conflicting school schedule (n = 4) and hospitalization (n = 1). Participants did not report any safety (i.e., extreme fatigue or worsening of symptoms) or acceptability issue (i.e., they accepted and enjoyed the sessions and exercises), but some implementation issues were observed, such as the amount and type of resources needed to implement and ability of participants to carry out intervention and activities.
Discussion: Characteristics of both context and participants are important to consider in the analysis of feasibility of remote CR combined with a supported education program.

F124. A DIGITAL HEALTH INNOVATION TO SUPPORT RECOVERY AND PREVENT RELAPSE IN INDIVIDUALS RECEIVING EARLY PSYCHOSIS INTERVENTION SERVICES: RESULTS FROM A PILOT STUDY OF HORYZONS-CANADA

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Background: Access to psychosocial interventions (e.g., peer support, supported education and employment, coping interventions) for individuals receiving treatment for first-episode psychosis (FEP) can help to prevent relapse, optimize recovery, and sustain treatment benefits; however, comprehensive and sustained access to psychosocial services and interventions remains a challenge. Horyzons-Canada (HoryzonsCa) is an innovative digital health intervention that provides peer support, clinical moderation, and psychosocial support to young people receiving treatment for first-episode psychosis (FEP). HoryzonsCa is a Canadian adaptation of the original version developed in Australia and has been piloted in Canada. In this presentation, we will describe the results from the pilot study, especially in terms of acceptability. We will also discuss the potential for using HoryzonsCa as part of the services delivered by early psychosis intervention (EPI) programs and its potential for supporting transitions and discharge from specialized services.
Methods: Single-group, pre-post, mixed methods (QUAL-QUAN convergent) design to assess the feasibility of implementing and evaluating HoryzonsCa. We recruited 20 participants from an EPI program in Montreal, Canada. Participants received access to HoryzonsCa, completed assessments at baseline and 8 weeks, and were invited to participate in focus groups. In this presentation, we will focus on results pertaining to the acceptability of the intervention based on data from questionnaires, website logins, and focus groups.
Results: The majority agreed or strongly agreed that they had a positive experience with HoryzonsCa (85%, 17/20), the platform was easy to use (95%, 19/20), they felt safe using it (90%, 18/20), and would recommend it to other people (90%, 18/20). In terms of peer-to-peer aspects, 45% (9/20) agreed or strongly agreed with the statement that they enjoyed interacting with other HoryzonsCa users. On average, participants logged into the platform 7 times over the 8-week follow-up period (SD = 7, Median = 5, Range = 0-30), and most participants logged into the platform 4 times or more over 8 weeks (65%, 13/20). Nine participants attended focus groups, from which the following themes were identified: (1) Perceiving HoryzonsCa as helpful for recovery; (2) Appreciating core intervention components (e.g., peer networking; therapeutic content; moderation); (3) Perceiving HoryzonsCa as easy to navigate and familiar to use; (4) Being unaware of HoryzonsCa features; and (5) Expressing concerns, suggestions, and future directions for implementation.
Discussion: Overall, participants appreciated HoryzonsCa, expressed positive perceptions regarding its benefits for recovery, and desired to see it grow in scale, accessibility, and functionality. Insights from this study contributed to the planning of a larger study (HoryzonsCa Phase 3), delivered in French and in English by a bilingual moderation team, to a larger age range (18-35), and a larger target sample (100 participants receiving treatment for psychotic disorders across the continuum of care). Overall, this research has contributed knowledge on the implementation, evaluation, and integration of complex digital mental health interventions in programs providing treatment for psychosis.

F125. ICOGCA: AN INNOVATIVE PROTOCOL PROMOTING COGNITIVE HEALTH THROUGH ONLINE INTERVENTIONS FOR PERSONS LIVING WITH A SCHIZOPHRENIA-SPECTRUM DISORDER.

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Background: Cognitive impairments and distortions collectively represent a core feature of schizophrenia-spectrum disorder (SSD) and adversely impact clinical trajectories and functioning. Hence, there is an important need to ameliorate overall cognitive health in SSD to improve outcomes. This is particularly important since the emergence of the COVID-19 pandemic as the situation has led to questions about access to mental health services and opportunities for cognitively stimulating activities. Despite the existence of effective interventions, such as cognitive remediation (CR) and metacognitive training (MCT), there remains a significant research-to-practice gap limiting the implementation of such interventions in diversified mental health settings. The iCogCA study is a national Canadian collaborative effort to implement online psychological interventions with the aim to promote cognitive health in SSD. We will describe the protocol of an entirely online hybrid effectiveness-implementation trial in which the aims are to: 1) determine the clinical effectiveness of virtual CR and MCT and 2) evaluate our implementation strategy involving the virtual delivery of these interventions combined with a digital learning platform (https://e-cog.ca/) to train mental healthcare practitioners (HCP) across multiple care settings.

Methods: Five sites across Canada (Quebec, Ontario, British Columbia) are part of the project. First, HCP from each site will be virtually trained through the E-Cog platform; the certification for a given therapy (CR or MCT) is composed of modules, which cover different aspects of the theory and implementation of cognitive interventions. Second, over a 2.5-year period, participants living with a SSD will be recruited and assessed for clinical symptoms, cognitive performance, and functioning pre- and post-intervention. Regarding the interventions, each site will run four groups annually (2 CR, 2 MCT) amounting to 390-400 participants. The effectiveness will be assessed with a non-randomized concurrent control design in which one intervention (e.g., CR) acts as the active control for the other (e.g., MCT) and vice-versa, on cognitive and clinical outcomes. For implementation strategy, we will assess whether the digital platform represents an effective educational strategy for implementation, the contextual factors influencing the implementation of the two virtual interventions, and sustainability.

Results: A pilot pragmatic trial has been conducted previously at the Montréal site, evaluating three early implementation outcomes: acceptability, feasibility, and engagement. Of the 28 participants attending at least one session, 75% completed more than half of the sessions. All completers reported a positive experience with therapy, 2/3 were not bothered by the remote setting, and 77% trusted the confidentiality of the information shared. Technology did not appear to significantly impede program participation. Therapist-rated levels of engagement were also satisfactory.

Discussion: At least three significant innovations will stem from this project. First, this national effort represents a catalyst for the use of digital technologies to increase the adoption of evidence-based interventions and will provide important results on the effectiveness of virtually-delivered CR and MCT. Second, the results of the implementation component of this study will generate the expertise needed to inform the implementation of similar initiatives. Third, the proposed study will introduce and validate our platform to train and supervise HCP to deliver these interventions, which will then be made accessible to the broader mental health community.

F126. SEX DIFFERENCES IN DEEP BRAIN SHAPE MORPHOMETRY IN PATIENTS WITH SCHIZOPHRENIA – AN ENIGMA CONSORTIUM META-ANALYSIS

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Background: Schizophrenia (SCZ) is characterized by a disconnect from reality that manifests as various clinical and cognitive symptoms, as well as consistent neurobiological abnormalities. However, unique sex-related differences have been observed regarding clinical presentation, such as disease onset and symptom expression, that imply separate brain substrates. The present study characterized deep-brain morphology using shape features to understand whether the neurobiology of schizophrenia varies as a function of sex.

Methods: This study analyzed multi-site archival data from 1,579 male (M) and 836 female (F) participants with SCZ, as well as 1,934 male and 1,828 female healthy controls (CON) from twenty-four cross-sectional study samples from the ENIGMA Schizophrenia Workgroup. Harmonized shape analysis protocols were applied to each site's data independently for bilateral caudate, putamen, globus pallidus, accumbens, amygdala, hippocampus, and thalamus obtained from T1-weighted structural MRI scans. Four separate contrasts covarying for age and intracranial volume were conducted: 1) SCZ-M/CON-M; 2) SCZ-F/CON-F; 3) SCZ-M/SCZ-F; 4) CON-M/CON-F.

Results: For the effect of disease (contrasts 1 and 2), mass univariate meta-analyses revealed more-concave-than-convex shape differences for all structures ($d=-0.49$ to -0.27, SE = 0.03 to 0.10, $p<0.05$) in both male and female SCZ/CON group comparisons. More extensive patterns of deformation were noted in dorsal putamen, pallidum, lateral hippocampus, and ventral putamen for SCZ women, and caudate for SCZ men. Analyses on the effect of sex (contrasts 3 and 4)

revealed more-concave-than-convex shape differences in all regions among female participants compared to males with similar magnitudes in both SCZ and CON contrasts (d=-0.11 to -0.51, SE = 0.03 to 0.09, $p<0.05$). Pattern and extent of deformation of these differences was greater in dorsal, ventral, and lateral aspects of putamen, hippocampus, and thalamus in SCZ-F.
Discussion: Findings are consistent with prior volume-based analyses in SCZ, as well as earlier studies on sex differences in the brain. Shape patterns reveal more extensive abnormalities in SCZ-F relative to SCZ-M, mimicking the pattern in CON-F, that could aid in our understanding of the sex-specific clinical features observed in the illness.

F127. LATITUDE: LONG-ACTING ANTIPSYCHOTIC TREATMENTS IN COMMUNITY TELEPSYCHIATRY: KNOWLEDGE, ATTITUDES, AND PERCEIVED BARRIERS

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Background: The South Carolina Department of Mental Health instituted a Community Telepsychiatry Program (CTP) to increase patient access to mental health practitioners. The need for in-person administration of long-acting injectable (LAI) antipsychotics may add barriers to their use in telepsychiatry, despite the known effectiveness of these agents for schizophrenia. The LATITUDE study assessed knowledge of, attitudes toward, and perceived barriers to using LAI antipsychotics via telepsychiatry.
Methods: LATITUDE used quantitative surveys of CTP providers and qualitative interviews with CTP providers, community mental health center (CMHC) clinicians, patient caregivers, and adults with schizophrenia to gather perceptions regarding LAI antipsychotic use within the telepsychiatry treatment paradigm.
Results: Eleven CTP providers, 10 CMHC clinicians, 3 caregivers, and 15 adults with schizophrenia participated in qualitative interviews between October 2021 and January 2022. Telepsychiatry services were perceived positively overall; barriers included patient hesitancy (59%) and provider perceptions that patients faced technical challenges in accessing telepsychiatry appointments (44%). A hybrid virtual and in-person treatment approach was endorsed by CTP providers (55%), who stated that improvements were needed in support services for administering LAI antipsychotics after virtual appointments. The main reported benefit of LAI antipsychotics was medication compliance (67%); barriers included fear of needles (49%) and treatment side effects (44%).
Discussion: The LATITUDE study findings highlight both barriers and facilitators of telepsychiatry use. Considering the rapid and potentially long-term adoption of telepsychiatry and hybrid care, this information may prove helpful to understanding and implementing best practices that support LAI antipsychotic treatment within the context of community telepsychiatry.

F128. ANALYZING MULTIMORBIDITY IN PEOPLE WITH PSYCHOTIC DISORDER: A NETWORK PERSPECTIVE

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Background: People with psychotic disorders are more likely to have multimorbidity (defined as the co-occurrence of two and more chronic illnesses in the same individual) compared to the general population, which has an important impact in healthcare. Though the prevalence of multimorbidity increases in people with psychosis, it is unclear whether specific chronic illnesses are more likely to influence the development of other ones. Consequently, the objective of the present study was to characterize multimorbidity from a network perspective in people with psychotic disorders.
Methods: Cross-sectional study using data from the Signature Biobank, a database including biological and psychosocial data from patients admitted at the psychiatric emergency department. A total of 18 chronic illnesses, diagnosed by a health professional, was included in the present study. Illnesses were considered chronic if they lasted at least 6 months. To examine the association between the chronic illnesses, network analyses were run. Given data were binary, network analyses were performed using the IsingFit method of estimation and centrality indexes were extracted. Moreover, the network was compared according to sex to investigate whether there could be sex-related differences.
Results: A sample size of 748 participants with psychotic disorders (69% of men, mean age = 39.5 ± 14.1) were included. Among them, 54% of were found to have multimorbidity. The network Results: show that, among the 18 evaluated chronic illnesses, 16 were fully connected to each other's. Only digestive disorders, and stomach ulcer were not associated with any other. Chronic illnesses with the highest centrality strength were stroke, COPD, and bronchitis. Chronic illness with the highest betweenness centrality scores were hypertension (47), cardiopathy (45) and bronchitis (41). When we compared the network structure according to sex, no differences were found either regarding the network invariance test ($M = 0.18$, $p = 1$), in terms of strength ($S = 1.96$, $p = 0.14$), or in expected influence ($C = 0.21$, $p = 0.39$).
Discussion: The network perspective gives us a new possibility to explore the relationship between different chronic illnesses. Our results showed that the most influential chronic illnesses are from the respiratory and cardiovascular systems. Furthermore, our results indicate that sex did not change the different associations.

F129. THE PHARMACODYNAMIC EFFECTS OF TAAR1 AGONIST ULOTARONT ON METABOLIC BIOMARKERS OF GLUCOSE, C-PEPTIDE AND INSULIN FOLLOWING A MEAL IN PATIENTS WITH SCHIZOPHRENIA

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Background: Obesity, dyslipidemia, hypertension, hyperglycemia, and are highly prevalent in schizophrenia due in large part to the propensity of the current class of antipsychotic drugs to contribute to these adverse metabolic effects. Hyperglycemia, diabetes mellitus, dyslipidemia and weight gain are highlighted in the Warnings and Precautions sections of the FDA approved labels for some of the current class of drugs approved for the treatment of schizophrenia. While each antipsychotic drug has its own benefit/risk profile, the adverse metabolic effects associated with many drugs in the current class have been shown to be associated with increased morbidity and mortality risks, and increased public health costs, that inform treatment decisions. Ulotaront is a

trace amine-associated receptor 1 (TAAR1) and serotonin 5-HT1A agonist currently in Phase 3 clinical trials for the treatment of schizophrenia. Recent preclinical evidence has identified TAAR1 as a novel regulator of metabolic control and a promising target for the potential treatment of obesity and type 2 diabetes. Here we evaluated the effects of ulotaront on liquid metabolic biomarkers which were collected in Phase 1 clinical pharmacology studies.

Methods: Metabolic effects of ulotaront were examined in response to a meal following an 8-12 hour fast. In a study to determine the effect of ulotaront on QTc interval (NCT04369391), subjects with a diagnosis of schizophrenia subjects (N=60) were randomized, in a 3-way crossover design with a 5-day washout period between drugs, to receive single doses of ulotaront (150 mg), moxifloxacin (400 mg), and placebo. Separately, in a standard drug-drug interaction study (NCT04865835), utilizing metformin-HCL (850 mg) as a substrate for the organic cation transporter (OCT)-2, subjects with a diagnosis of schizophrenia (N=25) were randomized in a single-blind, 2-way crossover design to receive metformin and single doses of either ulotaront (100 mg) or placebo. In both studies plasma samples were analyzed for C-peptide, insulin, and glucose; and for plasma concentrations of ulotaront.

Results: Following administration of a meal, ulotaront lowered insulin and C-peptide levels compared to placebo, indicating an effect of ulotaront on glycemic control in response to feeding, with large effect sizes (0.8–1.0) on insulin and C-peptide levels. An integrated population PK/PD model jointly described insulin, C-peptide, and glucose change, in response to a meal, as a function of ulotaront plasma concentrations.

Discussion: The effects of ulotaront on metabolic markers, derived from plasma samples collected in the course of clinical pharmacology studies suggest that the beneficial effects observed in animal models may translate to humans. Phase 1 clinical studies are currently ongoing to test the direct effects of ulotaront on metabolic parameters in patients with schizophrenia (NCT05402111, NCT05463770). The healthcare burden of hyperglycemia, diabetes mellitus, dyslipidemia, and weight gain associated with the treatment of schizophrenia utilizing the currently available antipsychotic class of drugs would be reduced if a novel pharmacological class of compounds were available that demonstrated benefit on these metabolic parameters.

F130. THE IMPACT OF PLAYFUL COLLECTIVE PHYSICAL ACTIVITY ON NEGATIVE EMOTIONAL STATES IN SCHIZOPHRENIA: RANDOMIZED CONTROLLED TRIAL

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Background: Physical activity (PA) is recommended to optimize functioning in persons with schizophrenia. However, most of this population gets an average of 120 minutes of exercise per week, and therefore does not meet the official recommendations. It has been proved that PA improves various psychiatric dimensions altered by the disease, such as quality of life, general symptomatology, stress, depression, anxiety, and global and social functioning. In previous studies, most of PA interventions were based on an individual or collective PA practice but without any social interactions between their participants, one of the reasons why our study is based on a multimodal model of rehabilitation, with a playful, and collective approach. Delivering this type of PA intervention to persons living with schizophrenia will lead to a change in lifestyle and thus

could facilitate a long-term autonomous PA practice. We aim to demonstrate the positive effects of a multimodal 6-week PA intervention on depression, anxiety, and stress symptoms in persons with schizophrenia that could lead to functional handicap encountered in this pathology.
Methods: Randomized controlled with patients randomized in two arms being PA group or a control group with no PA. The PA group (n=11; 9.1% women, mean = 37.6 ± 6.4 years old) who continued to receive usual care, participated to a 6-week intervention, 2 hours, twice per week. The PA intervention consisted of routine movement warm-up, resistance, and aerobic task, created collective games by PA professionals and therapeutic education. The control group (n = 14; 28.6% women, mean = 29.5 ± 7.9 years old) were patients receiving usual care on a waiting list. All participants are evaluated before and after the 6-week intervention period with the Depression, Anxiety, and Stress Scale.
Results: Using repeated-measures ANOVA analyses, we observed no significant interaction effects (depression: p=0,77; anxiety: p=0,96; stress: p=0,87) and scores in the Depression, Anxiety and Stress Scale decreased in both groups. The results revealed a time effect in depression (p=0.008) and anxiety (p=0.006), and a group effect in stress (p=0.03).
When we analyzed individual differences for each group and each of the three dimensions of the scale, the rate of subjects moving from a more to a less severe category of symptoms in depression was 45% for the active group, and 38% for the control group; for anxiety, it was 64% for the active group, and 36% for the control group; and for stress, we find 18% for the active group versus 21% for the control group.

Discussion: Results showed no significant improvements in terms of negative emotional states in the active group compared with the control group at the end of the PA intervention. This may be explained by the large differences in individual scores observed on the three dimensions of the scale. However, the evolution of the symptom severity categories was positive for the majority of the active group participants regarding depression and anxiety scores. This demonstrates that participants in the active group were more likely to experience improvements in the severity of depressive and anxiety symptoms following the intervention. To conclude, grouping of subjects could be changed as each participant is his own control ("N of 1"), to reduce analysis bias between groups. Finally, intervention duration should be extended, given in the literature, interventions last between 8 and 12 weeks on average and observe benefits.

F131. 30-YEAR CARDIOVASCULAR RISK IS ELEVATED IN YOUNG ADULTS WITH SCHIZOPHRENIA SPECTRUM DISORDERS AND BIPOLAR DISORDER COMPARED TO THOSE WITHOUT SERIOUS MENTAL ILLNESS

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Background: Cardiovascular disease (CVD) is the leading cause of death in individuals with serious mental illness (SMI), including schizophrenia spectrum disorders (SSD) and bipolar disorder (BD), and contributes to life expectancies shortened by an average of 10-20 years. Emerging evidence suggests that CVD risk also emerges at earlier ages in individuals with SMI compared to those without SMI, with differential risk decreasing with age. Understanding CVD risk and specific modifiable risk factors in young individuals with SMI is critical to inform

appropriate prevention and early intervention services to improve long term health outcomes. This study compares estimates of 30-year CVD risk and specific modifiable CVD risk factors among young adults aged 20-39 with SSD or BD, and non-SMI comparators.

Methods: This cross-sectional study included all patients aged 20-39 years with a primary care visit at 2 large health centers from January 2016 to September 2018. Patients with SSD or BD were identified using ICD-10 diagnosis codes, with ≥2 outpatient or ≥1 inpatient codes in the previous 2 years required for inclusion. The comparator sample included individuals without SMI, depression, or anxiety. Thirty-year CVD risk was calculated using the Framingham 30-year CVD risk score, which considers age, sex, systolic blood pressure, hypertension treatment, body mass index (BMI), diabetes, and current smoking status. Patients were also categorized into one of five 30-year risk groups based on number of uncontrolled risk factors (blood pressure, lipids, diabetes, and smoking status). General and generalized linear models compared Framingham 30-year CVD risk estimates for those with versus those without SSD or BD and evaluated differences in specific CVD risk factors. All results are adjusted for baseline age, sex, race, ethnicity, and insurance type.

Results: A total of 997 individuals with SSD, 3231 with BD and 155,363 non-SMI comparators were included in the analysis. Model-estimated 30-year CVD risk was significantly higher in individuals with SSD and BD compared to those without SMI. SSD was associated with a 34% higher CVD risk (RR=1.34, 95% CI [1.29, 1.39]), and BD with a 30% higher CVD risk (RR=1.30, 95% CI [1.28, 1.33]), compared to those without SMI. The predicted lifetime CVD risk was 11.9% [11.5-12.4%] for patients with SSD and 11.6% [11.3-11.8%] for patients with BD, compared to 8.9% [8.9-8.9%] for patients without SMI. Additionally, 14.8% [12.9-16.8%] of patients with SSD were predicted to be in the highest risk CVD category of ≥ 2 major uncontrolled risk factors compared to 12.1% [11.1-13.1%] of patients with BD and 4.4% [4.3-4.6%] of patients without SMI. SSD and BD were associated with a higher adjusted likelihood of a diabetes diagnosis (1.6% [1.2-2.1%] and 1.3% [1.1-1.7%], respectively) compared to those without SMI (0.5% [0.4-0.5%]). High rates of obesity and smoking contributed to CVD risk in SSD and BD. The mean BMI was 31.1 [30.7-31.6] in the SSD group, compared to 30.5 [30.3 – 30.8] in the BD group and 27.6 [27.6 – 27.7] in the non-SMI group. Additionally, the likelihood of obesity (BMI ≥ 30) was higher in the SSD (45.4 [41.9-49.0%) and BD groups (41.4% [39.6-43.3%]) compared to the non-SMI group (25.1% [27.3-27.8%]). Rates of current smoking were nearly 3 times higher in patients with SSD (34.2% [31.1-37.2%]) and BD (33.4% [31.7-35.1%]) compared to those without SMI (11.9% [11.7-12.1%]).

Discussion: 30-year CVD risk is significantly elevated in young adults with SMI. More effective prevention and control of major CVD risk factors – especially smoking and elevated body mass index – is critical to reduce the burden of premature CVD morbidity and mortality in individuals with SSD and BD.

F132. SECTIONAL ASSOCIATION BETWEEN MULTIMORBIDITY AND SUICIDAL IDEATION IN PEOPLE WITH PSYCHOSIS

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Background: People with psychotic disorders have a higher mortality risk than the general population. While the main unnatural mortality cause is suicide, physical chronic illnesses account for most natural causes. Recently, there have been a found interest in the potential impact of multimorbidity (defined as the accumulation of two or more chronic illnesses) on suicidal ideation. Hence, the aim of the present study was to understand the association between multimorbidity and suicidal ideation in people with psychosis.
Methods: A cross-sectional study based on the Signature Biobank - a database from the Montreal Mental Health University Institute Research Center which includes biological and psychosocial data from patients admitted at the psychiatric emergency department. All adults with psychotic disorders were recruited in exception of those with severe cognitive impairment or intellectual disability. Multimorbidity was defined as the co-occurrence of two or more chronic illnesses. Suicidal ideation was defined as suicidal thoughts during the past year and was evaluated with the PHQ-9. Suicidal risk was measured with the SBQ-R. Psychotic symptoms was evaluated with the psychotic symptoms questionnaire. Health behaviors (tobacco, alcohol and substance use) were evaluated using self-reported questionnaires. In the present study, three different models of logistic regressions were performed: Model 1 included adjustment on age, sex and employment, Model 2 was model 1 + psychotic symptoms, Model 3 was model 2 + health behaviors.
Results: The sample included 748 participants (69% of men, mean age = 39.5 ± 14.1), 54% of which had multimorbidity. In this group, 32% reported suicidal ideations, and 30% were at suicidal risk. Our preliminary results indicate a significant consistent association between multimorbidity and suicidal ideation in this population across all models (M1: OR 2.9, 95% CI [2.14-4.23]; M2: OR 2.60, 95% CI[1.83-3.71]; M3: OR 2.30, 95% CI [1.61-3.31]). Similarly, multimorbidity was associated with suicidal risk across all models (M1: OR 2.6, 95% CI [1.69-4.05]; M2: OR 2.20, 95%CI[1.40-3.48]; M3: OR 1.84, 95% CI[1.14-2.96]). In regard to health behaviors, only alcohol consumption was found to be a significant covariate in both suicidal ideation (M3: OR, 1.04, 95% CI[1.01 – 1.06]) and risk models (M3: OR 1.05, 95% CI[1.02-1.09]). Furthermore, psychotic symptoms were significantly associated with suicidal ideation (M2: OR, 1.35, 95%CI[1.19 - 1.53];M3: OR, 1.33, 95% CI[1.17 – 1.51]) and risk (M2: OR 1.47, 95%CI[1.24-1.74];M3: OR 1.48, 95% CI[1.25-1.76]).
Discussion: Our findings highlighted the importance of investigating multimorbidity as suicidal risk factor in people with psychosis. Future longitudinal studies should assess these associations.

F133. ARE MOTIVATIONAL READINESS AND SERVICE ENGAGEMENT RELEVANT FACTORS IN TREATMENT ADHERENCE FOR COGNITIVE BEHAVIOUR THERAPY FOR PSYCHOSIS (CBTP)?

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Background: High rates of treatment nonadherence in psychosis extend to psychosocial interventions, such as CBTp, with rates ranging from 32% (Alvarez-Jimenez et al., 2009) to 43% (Richardson et al., 2019). Previous research highlights the association between nonadherence to therapeutic treatments and clinical features of psychosis, such as lower insight, greater negative symptoms, and lower functioning. However, less is known about the cognitive and behavioural

factors affecting adherence and whether clients' motivation to engage and actual service engagement behaviours relate to CBTp adherence.
Methods: Participants (N = 55) were outpatients with a schizophrenia spectrum condition presenting at a specialized CBTp service for group-based CBTp. A comprehensive assessment battery consisting of clinician-rated, performance-based, and self-report measures was administered prior to, during, and following the completion of CBTp as part of a larger research study examining mechanisms of change in CBTp. For the present study, a three-item readiness ruler was created to measure the degree to which respondents attributed importance, readiness, and confidence to attending therapy to make changes to their mental health on a 10-point Likert scale. Additionally, a 14-item, clinician-rated Service Engagement Scale (Tait et al., 2002) was administered to case managers of participants to assess four domains of service engagement (availability, collaboration, help-seeking, and treatment adherence), with lower z-scores indicating higher levels of engagement.
Results: Prior to group-based CBTp, motivation to attend therapy was rated uniformly high with respect to its importance (M = 8.29, SD = 2.11), client readiness (M = 7.84, SD = 2.01), and client confidence (M = 7.66, SD = 2.19), with no significant differences reported across the three domains, ps > .05. Similarly, overall service engagement (M = -.37, SD = .86) was perceived to be above normative rates, as were subscales of availability (M = -.15, SD = .85), collaboration (M = -.30, SD = 1.01), help-seeking (M = -.32, SD = .89), and treatment adherence (M = -.38, SD = .72). However, client-rated motivational readiness was unrelated to clinician-rated service engagement, ps > .05. When treatment non-adherence was examined, the rate for disengagement from group-based CBTp, defined as participants lost to post-treatment follow-up, was 36% (n = 20). There were no differences in motivational readiness reported among clients who were adherent or nonadherent to CBTp, ps > .05. However, CBTp-adherent clients were rated significantly higher by their clinicians on availability, $t(50) = 2.47$, $p = .02$, collaboration, $t(50) = 2.60$, $p = .01$, help-seeking, $t(50) = 2.36$, $p = .02$, treatment adherence, $t(50) = 4.28$, $p < .001$, and overall service engagement, $t(50) = 3.45$, $p = 001$, compared to nonadherent clients, ps < .05.
Discussion: Despite high rates of client-reported motivational readiness and clinician-rated service engagement prior to group-based CBTp, only measures of service engagement showed greater associations with completion of CBTp. Given that approximately one-third of clients prematurely disengaged from treatment, there is a need for further exploration of factors involved in CBTp discontinuation. This could inform efforts to help enhance and maintain service engagement for individuals with severe mental illness who are particularly at high risk of treatment nonadherence.

F134. STIGMA BY ASSOCIATION AND SOCIAL ISOLATION IN FAMILY MEMBERS LIVING WITH RELATIVES WITH SERIOUS MENTAL ILLNESS

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Background: Unfair harsh judgment and societal discrimination have been described by family members who have ties to their relatives living with serious mental illness (SMI). This construct, which has been called stigma by association (SBA), has been investigated by only a few studies, using mainly European samples and qualitative methods The paucity of research in this area is attributable partly to the lack of a specific SBA measure, and to challenges associated with recruiting participants for research on this sensitive topic. The current empirical study examines

the deleterious impact of SBA as a critical and underrecognized factor, directly relevant to social isolation challenges faced by family members.
Methods: Building on previous preliminary findings, a newly adapted 9-item self-report questionnaire was constructed to measure SBA among relatives of people with SMI as part of a larger study on stress and resiliency in family members. Our survey included the UCLA Loneliness questionnaire and the MSPSS social support measure. It was administered online to 124 community member participants, who resided in North America, and who were recruited through programs that support people who have relatives living with SMI. Participants lived experiences of SBA, loneliness, and social support were compared between those who resided in the same home with their SMI relative (n = 81) versus those who did not (n = 43).
Results: Those who resided with a relative with SMI reported comparatively higher levels of stigma by association ($t = 3.02$, $p = .004$) using the novel adapted questionnaire measure. Both groups experienced loneliness (moderate levels), but importantly, the co-habiting relatives perceived themselves as more lacking support from friends ($t = -3.03$, $p = .003$) and other family members ($t = -2.57$, $p < .05$), as well as lacking someone special in their lives ($t = -3.16$, $p = .002$).
Discussion: Results provide quantitative data that increase our scientific understanding of SBA and its relation to wellbeing and offer unique insight about the lived experiences of family members of people with SMI. Findings have important potential to inform support services and interventions that decrease SBA in this population. Our discussion considers key public health implications. Most notably, we discuss the theme that family members who actually live with mentally ill relatives experience heightened social isolation that is under-recognized due to public stigma concerns.

F135. A QUALITATIVE STUDY ON THE SUBJECTIVE EXPERIENCE OF SERVICE-RELATED NEED AMONG YOUTH AT RISK FOR PSYCHOSIS.

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Background: Schizophrenia and related psychoses are debilitating conditions that can result in important negative impacts, including difficulties with functioning, lower quality of life, and higher rates of suicide. As a result, research and clinical work has aimed to identify individuals at clinical high risk for psychosis (CHR) and to intervene prior to the development of a first psychotic episode. Specialized CHR services have consequently emerged around the world, with clinical guidelines primarily focused on the goal of preventing a psychotic episode. However, even when such an episode does not occur, the CHR state in itself is associated with clinical and functional difficulties for which care is required. While research has begun to examine the needs of those in a CHR state, there is surprisingly a gap in evidence regarding needs as expressed by these individuals themselves.
Methods: To address this gap, eleven people currently receiving care at a specialized CHR service in Montreal, Canada were interviewed about their needs. Interview questions included: 1) What do you like/dislike about the CHR service?; 2) Can you describe what you need?; and 3) What kind of help and/or support do you need from the treatment team moving forward? All interviews were audio recorded, transcribed verbatim, and thematically analyzed.
Results: First, participants expressed the importance of and need to understand their mental health problems by receiving diagnostic information from their service provider, or learning from peers

who share similar experiences. However, they were often dissatisfied with the diagnostic information they did receive and typically had to rely on their service provider to "normalize" their experiences. Second, participants identified aspects of the CHR service that were useful, not useful, and gaps in available interventions. The flexibility of the clinical team was a benefit of the CHR service, but there remained a tension related to the prioritization of medications over other treatment options. Finally, participants perceived a lack of guided treatment planning as an important service gap, emphasizing their need to feel confident in their care, hopeful, and reassured.

Discussion: This study is among the first to directly ask individuals at CHR what they perceive their service-related needs to be. Through rich accounts of their mental health and service use experiences, we were able to observe a nuanced perspective on such needs; specifically, that they were more about gaining and normalizing an understanding of mental health problems, rather than simply alleviating distressing symptoms through direct interventions (i.e., medications). Important implications regarding CHR treatment planning are highlighted, including the need for more elaborate psychoeducation efforts, access to peer support services, as well as shared and informed care practices.

F136. THE IMPACT OF VIRTUAL CARE ON TRANSITIONS IN MENTAL HEALTH CARE: FROM INPATIENT ADMISSION TO SPMI OUTPATIENT CARE

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Background: The transition from inpatient to outpatient care is a particularly important event given that the period following discharge from inpatient care is a high-risk period for suicide, disengagement, and re-admission. Unfortunately, a number of structural barriers to a smooth inpatient to outpatient transition have been identified. In the context of the COVID-19 pandemic, most outpatient follow-up had to transition to virtual platforms. However, it is unknown if the provision of care virtually has impacted patients' ability or willingness to engage in outpatient care. While some have found that the accessibility of virtual care makes it easier to attend appointments, others have found going virtual to be a barrier due to lack of access to technology and reduced clinician support. It is unclear what the impact of virtual care implementation in the COVID-19 context has had on engagement with outpatient care following an inpatient psychiatric admission.

Methods: A retrospective chart review of individuals admitted to the St. Michael's Hospital inpatient psychiatry ward between January 1, 2019 and December 31, 2020 was conducted to assess the impact of virtual care on the engagement of patients discharged from an inner-city hospital to affiliated community outreach programs. Charts from individuals' inpatient admission as well as the first 3 months of their outpatient care at a St. Michael's based community programs were reviewed (Community Connections, FOCUS, STEPS). Demographic information (age, gender, diagnosis), inpatient visit information (length of stay, discharge destination) and visit information (attendance at initial appointment and at 3-month follow-up) were collected. Descriptive statistics, T-tests, and ANOVAs were used in comparative analyses of outcomes before and after the implementation of virtual care, including attendance at initial appointment and duration of time in outpatient care.

Results: There were a total of 192 discharged patients who were referred to the Community services in this time frame, 129 pre-pandemic and 63 after the pandemic was declared March 11, 2020. Pre-pandemic, 88% of patients attended their initial Community appointment and 80% were still attending appointments 3-months post-discharge. After the pandemic was declared, 90% of patients attended their initial appointment and this persisted at the 3-month mark. There was no statistically significant difference in appointment attendance with the implementation of virtual care at either time point ($X2$ (1, N = 192) = 3.44, p = 0.06).
Discussion: Despite concerns of lack of adequate access to technology or clinical support, SPMI patients from an inner-city hospital, were able to engage in outpatient follow-up after an inpatient admission at equivalent levels with the shift to virtual care during the early stages of the COVID-19 pandemic. These findings suggest that virtual care is a reasonable option for SPMI patients.

F137. THE RELATIONSHIP OF LEVEL-OF-CONTACT WITH MENTAL ILLNESS AND STIGMATIZATION OF VOICE-HEARING EXPERIENCES DEPENDS UPON THE SPECIFIC CONTENTS OF THE VOICE

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Background: Stigmatization of voice-hearing can impair the wellbeing and social functioning of voice-hearers. However, research has shown that stigma reactions can depend upon the specific contents of the voice-hearing experience as well as characteristics of the perceiver (Phalen et al., 2018; 2019). One characteristic that has been shown to broadly affect stigma responses is a person's prior level of contact with mental illness (LOC). This study explored how the relationship between LOC and stigma toward voice-hearing is impacted by the particular content of the voice-hearing experience.
Methods: Participants evaluated vignettes of people described as hearing voices that varied in terms of their valence (positive or negative) and their theme (religious or non-religious). The Level of Contact Report (LOC; Holmes, et al. 1999) was used to measure LOC. Levels of stigma were evaluated by the Social Distance Scale (Link, et al. 1997) and the Perceived Dangerousness Scale (Link, et al. 1987). The sample included 143 students from two Midwestern universities (82.5% female with a mean age of 20).
Results: We fit multilevel models with desired social distance and perceived dangerousness as outcomes. For both models, we included all main effects, two-way, and three-way interactions between LOC, voice valence, and voice theme. For both social distance and perceived dangerousness, replicating Phalen et al. (2018), there were significant main effects for voice theme ($p<.001$) and valence ($p<.001$) and a two-way interaction between theme and valence ($p<.001$). Regarding LOC, for both perceived dangerousness and social distance we found a significant ($p<.05$) two-way interaction between LOC and voice valence, with higher LOC associated more strongly with lower stigma when the voices were negative. For perceived dangerousness, there was also a trend-level ($p=0.05$) three-way interaction between LOC, voice valence, and voice theme. Plotting suggested that the relationship between greater LOC and lower perceived dangerousness was strongest for the vignette condition featuring a non-religious voice saying negative things.

Discussion: We used a multilevel model to examine how the effect of LOC on the stigma of voice-hearing varies according to the content of the voice (negative versus positive; religious versus non-religious). We found that the relationship between LOC and stigma depended upon the specific content of the voice. In fact, there was no main effect for LOC. Instead, LOC related to stigma for voices with negative content, and primarily when those negative voices were non-religious in nature.
Level of contact with mental illness (LOC) has been associated with lower levels of stigma in prior research, but the potential moderating effect of hallucination content was unknown. Our resluts: demonstrate that the relationship between LOC and hallucinations depends upon the specific nature of the voice-hearing experience in question. Future research should explore how familiarity with mental illness may engender understanding of its stressors, but perhaps only for certain kinds of experiences.

F138. CLINICIAN-RATED, PERFORMANCE-BASED, AND SELF-REPORT OUTCOMES IN GROUP-BASED COGNITIVE BEHAVIOUR THERAPY FOR PSYCHOSIS

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Background: Cognitive Behaviour Therapy for psychosis (CBTp) is an evidence-based intervention that can significantly improve clinical and functional outcomes in psychosis spectrum conditions. Only a minority receive this treatment, and guidelines to inform efficient dissemination methods in the healthcare system are lacking. Stepped care service delivery, such as group-based CBTp, has been proposed to address limited accessibility. Research on group CBTp is limited and heterogeneous, necessitating a better understanding of the progress trajectory of clients and timepoints at which maximal treatment benefit occurs. We examined outcomes from group-based CBTp in a naturalistic clinical setting, incorporating outcome measures that might help explain some of the improvements in treatment, taking into account progress trajectory.
Methods: Outpatients with psychosis spectrum diagnoses (N = 45; Male = 63.6%, Mage = 36.11, SDage = 12.31) enrolled in a CBTp service at an urban public hospital completed a standardized assessment battery to capture changes over the course of their participation in a manualized, 16-week CBTp group. Clinician-rated (positive and negative symptoms, functioning), performance-based (neurocognition), and self-report (social anxiety, emotion regulation, internalized stigma, quality of life, perceived recovery) measures were administered prior to and upon completion of treatment. An additional mid-point evaluation was included to glean nuances in clinician-rated psychiatric symptoms and self-report views of personal recovery.
Results: On the clinician-rated Brief Psychiatric Rating Scale, no changes in negative symptoms were identified, whereas positive symptoms significantly reduced across the three time points, $F(1.63, 53.62) = 7.86$, partial eta2 = .19, $p = .002$, notably between pre- ($M = 5.09$, $SE = .86$) and mid- ($M = 3.47$, $SE = .77$) assessment, and reductions were sustained at post-treatment assessment. On the clinician-rated Personal and Social Performance Scale, the total score did not significantly change over time. Significant improvement in global neurocognition as measured by the Brief Cognitive Assessment Tool for Schizophrenia (B-CATS)* was observed from pre- ($M = -1.27$, SD

= .95) to post- (M = -1.02, SD =.96) treatment, t(28) = -2.31, p = .028. Among subtests of the B-CATS, working memory significantly improved (p = .005), whereas verbal fluency and attention/processing speed did not (ps > .05). On self-report measures, significant improvement was found in perceived wellbeing (Quality of Life Enjoyment and Satisfaction Questionnaire*) from pre- (M = -1.35, SD = 1.57) to post- (M = -.59, SD = 1.21) treatment, t(33) = -2.28, p = .029. Reduction from pre- (M = 44.94, SD = 15.12) to post- (M = 41.59, SD = 13.98) treatment was found on the Difficulties with Emotion Regulation Scale (DERS-18), t(33) = 2.11, p = .043. No changes from pre- to post-treatment were observed in self-reported social anxiety, internalized stigma, or personal recovery.
*Results presented in Z-score relative to clinical samples.

Discussion: Individuals presenting for 16 weeks of group-based CBTp improved on clinician-rated, performance-based, and subjective indices of recovery. Early and sustained changes in positive psychotic symptoms provide insight into the timing of improvements in CBTp, and can help inform optimal treatment dosing. An unexpected effect of improved global neurocogition, largely driven by gains in working memory, provides preliminary support for the pro-cognitive effects of CBTp. Findings support the importance of taking a multipronged assessment approach, and further exploration of the timing of treatment gains to capture and improve the full range of CBTp outcomes.

F139. CONSOLIDATION OF EVIDENCE ON LONG-TERM ANTIPSYCHOTIC CONTINUATION OR CESSATION: THE DEVELOPMENT OF A PATIENT DECISION AID – STUDY PROTOCOL

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Background: Despite the effectiveness of antipsychotics for psychotic symptom management, as few as 50% of individuals achieve personal recovery following first-episode psychosis (FEP). The decision of whether to continue antipsychotics or not following minimally 18 months of FEP remission is controversial given the adverse effects of these drugs and the uncertainty surrounding their effectiveness on personal recovery. Most clinical guidelines agree this decision should be made using shared decision-making, which involves making a joint and informed decision in accordance with the patient's preferences. However, shared decision-making is not widely used in psychiatry and decision-making needs of stakeholders surrounding this decision have never been identified. Furthermore, the advantages and disadvantages of each option of this decision have never been synthesized, and no patient decision aid exists to support shared decision-making with the goal of improving personal recovery for people with FEP. The aims of this study protocol is to consolidate the evidence on the decision to continue antipsychotics or not following minimally 18 months of remitted FEP. Specifically: OBJECTIVE [1] Identify the shared decision-making needs of stakeholders surrounding this decision. OBJECTIVE [2] Synthesize the advantages and disadvantages of each option of this decision. OBJECTIVE [3] Develop and pretest a patient decision aid specific to this decision.

Methods: OBJECTIVE [1] To identify unmet needs, a descriptive qualitative study will be conducted with two groups: healthcare professionals working with people living with FEP and people with remitted FEP. A purposeful sampling method will be used, meaning participants with different gender/ethnocultural identities that may influence shared decision-making will be targeted to document the diversity of unmet needs. Recruitment will stop upon reaching thematic saturation, which corresponds to approximately 20 participants per group according to our team's experience with qualitative research. Data will be collected through individual semi-structured interviews using the Ottawa Decision Support Framework and a thematic analysis of the interviews will be conducted using NVivo. OBJECTIVE [2] A systematic review of randomized controlled trials (MEDLINE, Embase, PsycINFO and Cochrane Central) using the Cochrane method to document the possible outcomes (recovery/relapse/adverse drug reactions) of the decision to discontinue AP or not will be conducted. An independent data extraction by two authors, a synthesis of study characteristics using descriptive statistics and a meta-analysis of outcomes of interest will be made.
OBJECTIVE [3] A patient decision aid prototype will be co-developed with a multidisciplinary team (including researchers/clinicians/patients) using the Knowledge and Evaluation Research Unit's method, whose steps are: 1) Observe decision-making in a clinical context (approximately 10X); 2) Systematic review of the different possible outcomes following the decision of interest. This process will be guided by the International Patient Decision Aids Standards and the identified unmet needs in this protocol. An iterative process of clinical testing will follow until the team reaches a consensus that the PtDA is ready for validation.

Results: The study protocol will be presented.
Discussion: This project will consolidate the actual knowledge, provide novel evidence for stakeholders and create a patient decision aid to support clinical practice and shared decision-making regarding the decision to discontinue antipsychotics or not, hoping to promote personal recovery, the most important patient outcome. In line with current clinical guidelines, this review will contribute to enhancing the shared decision-making quality and thus promoting patient empowerment.

F140. LONG-TERM TRAJECTORIES OF MULTIDIMENSIONAL OUTCOME IN PSYCHOSIS FOLLOWING EARLY INTERVENTION IN THE CRITICAL PERIOD: THE PEPP10+ STUDY PROTOCOL

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Background: Early intervention services (EIS) for first episode psychosis (FEP) aim at decreasing clinical symptoms, improving functional outcomes, and reducing long-term disability. A breadth of research has convincingly demonstrated overall better short-term outcomes. However, the assumption that intervening during the critical period could improve long-term trajectories and recovery is yet to be proven. Indeed, recovery trajectories have shown considerable heterogeneity and a significant proportion of patients exhibit functional impairments, despite symptoms remission. As a national leader in EIS development, with a large, representative, and well

characterized sample, PEPP-Montreal is uniquely positioned to conduct a 10+year follow-up study and examine the long-term outcome of FEP in the context of EIS.
This study aims to: 1) identify distinct trajectories of functional and clinical outcomes over a 10+ year follow-up period, 2) characterize the sociodemographic, functional, clinical, cognitive, along with the physical and brain health profiles of each long-term trajectory and 3) test their prognostic value while identifying risk and protective factors of long-term recovery. As a neglected dimension of the long-term outcome of FEP, a special attention will be given to the evolution of physical health (metabolic, respiratory, and cardiovascular) and its impact on recovery trajectories.

Methods: The Prevention and Early Intervention Program for Psychoses (PEPP) is a 2-year, high-fidelity EIS serving a defined catchment area population of 350 000 in Montreal, Canada. Between 2003 and 2018, PEPP-Montreal has provided services to more than 700 previously untreated FEP patients aged 14-35 years old. A comprehensive longitudinal assessment protocol conducted at 0, 1, 2, 3, 6, 9, 12, 18 and 24 months yielded a detailed characterization of patients on multiple dimensions including sociodemographics, functioning, psychopathology and neurocognition, along with physical and brain health. While 50% of the baseline sample is sought to be re-assessed, the range of the follow-up period will be 6 - 20 years with an estimated mean of 12 years. While recruitment is ongoing, a tracking algorithm has been developed to preserve the representativeness of the sample and identify prospective participants from a variety of sources including the Douglas Institute and other mental health facilities along with primary and secondary care services, administrative databases, and the community. Non-clinical participants will also be recruited for comparison purposes on measures of functioning, physical and brain health. In addition to the initial assessment protocol, data linkage with health administrative databases will be requested over the 10+year follow-up period for the complete PEPP cohort along with 3 controls groups (i.e., mental health controls, physical health controls, and EIS nonuser controls). Health administrative databases will provide information on external visits to family physicians, psychiatrists, and other specialists, and information on prescriptions emergency visits, hospitalizations and individual death.
Results: As of today, 350 prospective participants have been traced, of which 100 have been approached and 50 have been recruited.
Discussion: This study represents the most comprehensive investigation of long-term outcome for youth treated in an EIS in North America and will provide fresh new insights to inform the development of individually tailored treatment by improving prediction and clinical utility of different prognostic markers in FEP.

F141. CHALLENGING TREATMENT RESISTANT SCHIZOPHRENIA: AN INTEGRATIVE APPROACH PRELIMINARY STUDY

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Background: As many as one third of patients with shizophrenia spectrum disorders experience treatment resistance. These patients have chronic severe psychotic symptoms and marked impairments in social community functioning. In 2018 we created a specific psychiatric department in Clermont de l'Oise (Hauts de France area, France) focused on Resistant and Ultra Treatment Resistant Schizophrenia (SPR). This department proposed an integrative approach combinated « personalized psychiatry » cares including global assessments (clinical, biological, genetics, neuropsychological, functional and pharmacological), pharmacological interventions (antipsychotics monitoring and clozapine management) and non-pharmacological (specific intensive recovery-oriented psychosocial rehabilitation programs). The aim of this presentation is to show preliminary data regarding a cohort of 30 patients with resistant schizophrenia who have benefited this integrative approach.

Methods: Between 2018 and 2022, we recruited a cohort of 34 patients suffering from resistant schizophrenia according to DSM 5 criteria from the psychiatric departments in Oise area (Hauts De France area, France) using May and Dencker criteria. Several socio-demographical, clinical, cognitive, biological, genetics, pharmacological data were collected for each patient. Then pharamcological treatment were assessed and monitored according to the litterature data regarding treatment/resistant treatment managing, including biological and genetics markers. At the same time, all the patients were assessed using clinical, neuropsychological (neurocognition and social cognition) and functional tools (quantitative and qualitative) in order to create a personalized and contractualized project of rehabilitation with all the care partners (including caregivers) around the patient. This project combines, in an oriented recovery goal, several modules of therapeutic education, cognitive remediation and cognitive behavourial therapy (CBT). The final projet for each patient, despite the severity of the disease, is to live in the community with a good quality of life and well-being.

Results: Among the 34 patients, 8 presented an other psychiatric or neurodevelopmental disorder (alcohol use disorders, intellectual disabilities). 2 were diagnosed with 22q11 syndrome. All the patients present more global cognitive deficits. Regarding pharmacological treatment, we noticed an improvement of clozapine (twice), less classical antipsychotics and benzodiazepines drugs. All the patients have succeed his own integrative rehabilitation program (alone community living for most of them) with no relapse.

Discussion: These preliminary results confirm the importance of an integrative approach for patients suffering from resistant and ultra resistant treatment schizophrenia. Personalized psychiatry is needed including a pharmacological monitoring focusing in a better use of clozapine , a systematic biological and genetical approach (in order to improve medication monitoring) and a specific Resistance rehabilitation program combining cognitive remediation (metacognition, executive functions and social cognition), CBT (persistent negative and positive symptoms, motivational skills), therapeutic education programs (basic needs, autonomy and caregivers) and psychosocial skills in an ecological way. Other studies must be conducted to better understand the pathophysiology of the trajectory to resistance and ultra resistance identifying vulnerability factors of poor prognosis in order to prevent resistance.

F142. THE TRAJECTORIES AND CORRELATES OF TWO NEGATIVE SYMPTOM SUBDOMAINS IN FIRST-EPISODE SCHIZOPHRENIA

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Background: Recent studies suggest a two-factor structure for negative symptoms as assessed by the Positive and Negative Syndrome Scale (PANSS) in schizophrenia, namely experiential and expressive subdomains. Little is known about their clinical correlates and treatment trajectories. We sought to replicate the two factor-analysis derived subdomains for PANSS negative symptoms in schizophrenia and to assess their independent demographic, premorbid and treatment-related characteristics.
Methods: This was a longitudinal study of 106 minimally treated participants with a first episode of a schizophrenia spectrum disorder who received treatment with flupenthixol decanoate 2-weekly injections over two years. Factor analysis was used to characterise the PANSS negative symptom subdomains and linear mixed-effect models for continuous repeated measures were constructed to assess the temporal relations between the negative symptom subdomains and premorbid and treatment related variables.
Results: Factor analysis confirmed a two-factor solution for experiential and expressive subdomains of negative symptoms, although they were strongly correlated. The treatment response trajectories for the two subdomains did not differ significantly, and neither subdomain was significantly associated with our premorbid variables. We found significant main effects for disorganised symptoms and extrapyramidal symptoms on the expressive subdomain, and for disorganised symptoms and depressive symptoms on the experiential subdomain. Post-hoc testing indicated that reductions in HDL-cholesterol levels were associated with less improvement in both expressive and experiential subdomain scores.
Discussion: The two negative symptom subdomains are closely related, have similar premorbid correlates and respond similarly to antipsychotic treatment. Depression affects the experiential subdomain, whereas extrapyramidal symptoms affect the expressive subdomain.

F143. NARRATIVE EXPECTATIONS OF SCHIZOPHRENIA SYMPTOM STABILITY AND CHANGE OVER TIME: IMPACT ON STIGMA, HELPING BEHAVIOUR, AND SOCIALIZATION

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Background: Social support is critical to recovery for individuals with schizophrenia. However, stigma can act as a barrier to forming and maintaining relationships. It is necessary to identify the underlying beliefs which contribute to stigma and subsequent discriminatory behaviours. Our research examined how one's beliefs about improvement or decline of symptoms in schizophrenia are associated with stigmatizing behaviours (e.g., unwillingness to help and/or socialize).
Methods: Participants (N=250) recruited from Amazon Mechanical Turk completed questionnaires regarding beliefs about schizophrenia or a comparison group (depression). Beliefs assessed included those related to symptom changes over time, personal responsibility, blame, and controllability. Participants also rated their willingness to interact (help and/or form a social relationship) with people with schizophrenia and depression.

Results: Participants indicated less willingness to socialize with or help individuals with schizophrenia compared to those with depression. In a multilevel model, we found that these differences were mediated by beliefs about symptom change over time, specifically that individuals with schizophrenia decline over time while those with depression improve. Notably, narrative beliefs about the progression of symptoms accounted for 33% of the variance in differences of willingness to socialize and 23% of the variance in differences of willingness to help. In schizophrenia, narrative beliefs about illness course predicted unique variance above and beyond perceptions of blame, perceived personal responsibility/controllability of the illness, and one's prior exposure to severe mental illness.
Discussion: We examined stigmatizing beliefs and behaviours across two diagnoses (schizophrenia and depression) that typically vary in severity, chronicity, and public perception. Differences in beliefs about the change in schizophrenia and depression symptoms over time are strongly associated with differences in behavioural intentions towards people with these diagnoses. Participants endorsed narratives of decline for schizophrenia, and not depression, which predicted unwillingness to socialize with and help people with schizophrenia. Future research should continue to explore how beliefs about change are associated with stigmatizing behaviours, as well as whether these beliefs can be modified to alleviate stigma towards people with schizophrenia.

F144. FIRST PERSON NARRATIVES OF PSYCHOSIS: A QUALITATIVE COMPARISON OF PSYCHIATRY-ORIENTED AND ACTIVIST-ORIENTED PUBLICATIONS

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Background: The field of psychiatry's orientation to psychosis research and treatment has long centered the perspectives of professionals (clinicians and researchers) rather than those receiving services, in turn fueling tensions between the service user/survivor movement and mainstream psychiatry. Psychiatry has nevertheless made attempts to engage with first person experience: in academic publishing this has prominently included the long-standing Schizophrenia Bulletin First Person Accounts series (cf Woods, 2012). Meanwhile, service user activists and their allies have also organized more grassroots venues for publication and self-expression. Comparing two major publications, one psychiatric and one activist, the current study takes up the question both of curation (what kinds of first person accounts are found in different venues) and of content (how do the themes of different venues differ).
Methods: This study uses qualitative thematic analysis. Data sources are historical accounts of lived experience of psychosis from two sources: Schizophrenia Bulletin (91 first-person narratives) and Madness Network News (45 issues). The narratives from Schizophrenia Bulletin (1979-2019) were published within an academic journal and written for clinicians. Madness Network News (1972-1986) was published by and written for an audience of activists (service users/survivors and allies). Data analysis proceeded in three steps; (1) inductive generation of codes based on a subsample of narratives; (2) development of deductive codes in the following thematic categories: internal processes and emotions, perceptions and actions of others, treatment experiences, outcomes, beneficial approaches; and, (3) thematic analysis across all narratives.
Results: Common across the publications was a strong desire for understanding and connection, at the level of both the self and community. Both publications highlighted the value of supportive

and empathetic connection with peers and the potential value of meaningful and collaborative relationships with professionals. There were also striking differences between the publications. Whereas writers in Schizophrenia Bulletin frequently detailed feelings of helplessness and isolation, writers in Madness Network News described empowerment and sense of community. Narratives from Schizophrenia Bulletin were more likely to use words that denoted an internalization of stigma, shame, and individual responsibility. Writers to Madness Network News were more likely to use language that externalized negative experiences, repositioning them as consequences of societal and clinical judgment and harm rather than an immutable feature of the psychotic experience.

Discussion: Findings illustrate the ways in which venue of publication shapes both the orientation and content of the stories told and underscores the importance and stakes of clinician and trainee engagement with diverse sources in contexts in which first person narratives are used in training or education. In addition, themes speak to the cross-cutting value of community connection, and the ongoing need to address and unpack social and clinical as well as internalized stigma.

F145. DISENTANGLING POSITIVE AND NEGATIVE SYMPTOM PHENOTYPES IN SCHIZOPHRENIA (SZ) AND AUTISM SPECTRUM DISORDER (ASD) SPECTRUM

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Background: Research has revealed an overlap in social communication and interaction skills deficits between autism spectrum disorder (ASD) and schizophrenia (SZ), as they are required for ASD diagnosis and are highly prevalent in SZ with high negative symptoms. Notably, SZ patients with high ASD traits show lower social functioning and cognitive skills compared to patients with lower ASD traits. Although SZ-related positive symptoms have been described as the most reliable distinct phenotypic measure between ASD and SZ, they alone may not be sufficient to capture their distinct clinical phenotype. Trevisan et al. (2019) introduced a new categorization system of ASD symptoms using the Autism Diagnostic Observation Schedule (ADOS) following the same positive-negative symptom conceptual system of the Positive and Negative Syndrome Scale (PANSS). This system lacked disorder specificity of negative symptoms and did not separate experiential and expressive negative symptoms. Research in SZ shows that negative experiential and expressive symptoms have distinct functional correlates, as higher experiential symptoms are related to worse functional outcomes.

This study examined the symptom dimensions in SZ and ASD, specifically negative experiential and expressive symptoms and positive ASD-related and SZ-related symptoms. An exploratory factor analysis (EFA) was applied with these symptom measurements, and we compared their differences between diagnostic groups and their functional relationships.

Methods: Participants were 52 ASD and 48 SZ subjects (age, M = 23.91; SD= 4.10) part of a larger study. Symptom and functioning measures were analyzed. The EFA included 7 items: PANSS positive subscale, ADOS positive subscale, Scale for the Assessment of Negative Symptoms (SANS) negative experiential and expressive subscales and 3 negative symptom factors extracted from the PANSS characterizing experiential and expressive negative symptoms in both

ASD and SZ. For each FA, eigenvalues >1 served as the selection criteria and items with factor loadings of ≥ 0.5 were considered representative of a given factor. Final factors were compared between groups and correlated with measures of social functioning (SFS) and quality of life (QLS)
Results: The EFA revealed 3 independent factors accounting for 71.7% of total variance: F1) Psychotic Positive Symptoms and Negative Experiential Asociality/Amotivation Factor (32.1%); F2) Negative Expressive Deficits (22.47%); F3) ASD Positive Symptoms and Negative Experiential Mannerisms/Avolition factor (17.1%). A one-way ANOVA between groups showed that SZ had significantly higher scores in F1 than ASD ($F(1,89) = 16.1$, $p < 0.001$); and, ASD had significantly higher scores in F3 than the SZ ($F(1,89) = 5.91$, $p = 0.017$). Significant correlations were observed between F1 and SFS (SZ r= -0.38; ASD r= -0.63; both $p<0.05$) and QLS (SZ r= -0.51; ASD= r=-0.72; both $p< 0.001$), and between F2 and QLS (SZ r=-0.38; ASD r= -0.55, both $p<0.05$) in both groups, and between F3 and QLS (r=-0.38; $p<0.05$) in SZ only.
Discussion: This study revealed distinctive functional symptom phenotype patterns in SZ and ASD. While they shared negative expressive deficits, SZ showed larger deficits in Positive Psychotic-related Symptoms and Negative Experiential Symptoms with Asociality/Amotivation; and ASD had larger deficits in ASD-related Positive Symptoms and Negative Experiential Symptoms with Mannerisms/Avolition. Results are important to differential diagnosis and guiding customized clinical interventions.

F146. AUDITORY PREDICTION ERROR SIGNALING IN SCHIZOPHRENIA: ASSOCIATION WITH PSYCHOTIC SYMPTOMS

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Background: Predictive coding is an information processing model that posits iterative comparison between incoming sensory information with expectations, and a discrepancy yields a prediction error signal (PES). Predictive coding may be a useful framework to understand delusions and hallucinations, which have been conceptualized as reflecting an abnormal PES. Mismatch negativity (MMN) is an event-related potential (ERP) hypothesized to reflect auditory PES. MMN is comprised of two components: 1) response to the standard stimulus (expectations about incoming stimuli), and 2) response to the deviant stimulus (deviance detection). By periodically assigning a new standard tone and altering the train length of standards preceding the deviant tone, the roving standard auditory oddball paradigm is optimized to evaluate the two components of MMN and how they are established. We previously reported overall reduced deviance detection in Sz compared to healthy controls (HC). Moreover, consistent with a predictive coding account of psychosis, we observed an abnormal roving MMN response profile among those with current hallucinations. Specifically, MMN amplitude was not modulated by the number of standards that preceded the deviant, indicating that the strength of the PES was not coupled to the objective 'predictability' of stimuli. Here, we aim to replicate and extend these findings. Using roving standard MMN, we predicted diminished response to deviants in Sz compared to HC, reflecting reduced deviance detection. Furthermore, within Sz we predicted an abnormal roving standard MMN response profile among those with current, clinically significant delusions or hallucinations.

Methods: Electroencephalography was recorded from 33 people with Sz and 31 HC during a roving standard MMN task. Deviant tones were presented after 3, 8, or 33 repetitions of standard tones. For Sz, presence of psychosis (i.e., current delusions and/or hallucinations) was assessed using the BPRS (i.e., score > 3 for unusual thought content and/or hallucinations items). Repeated measures ANOVA were used to test for patient-control differences in ERP response to standards and deviants. Within Sz, independent sample t-tests and follow-up paired t-tests were used to compare roving standard MMN response profile, defined as the difference in MMN amplitude for long (i.e., 33 standards or MMN33) minus short (i.e., 3 standards or MMN3) stimulus trains among those with (SzP+, n = 12) and without current psychosis (SzP-, n = 19).
Results: Compared to HC, there was a trend for diminished ERP response to deviants in Sz [$F(1,62) = 2.83$, $p = 0.10$, partial $\eta 2 = .04$]. Response to standards did not significantly differ between Sz and HC [p = .22]. Within Sz, while overall amplitude of MMN did not significantly differ between SzP+ and SzP- [p = .55], modulation of MMN amplitude by train length significantly differed between groups [mean diff. = 1.68, 95%CI: .28, 3.02, $t(29) = 2.19$, $p = .02$, $d = .81$]. For SzPSY-, MMN amplitude was significantly larger and more negative for MMN33 compared MMN3 [mean diff. = 2.47, 95%CI: 1.54, 3.44, $t(18) = 4.83$, $p < .001$, $d = 1.11$]. In contrast, for SzPSY+, MMN amplitude did not significantly differ across conditions [mean diff. = .80, 95%CI: -.11, 1.86, $t(11) = 1.54$, $p = .17$, $d = .44$].
Discussion: In accordance with our previous findings, these data suggest a tendency for reduced deviance detection in Sz. Consistent with a predictive coding account of psychosis, we observed an abnormal MMN response among Sz with current psychosis. Specifically, the strength of the PES was not reliably coupled with the objective predictability of sensory stimuli. This may reflect a state-like predictive coding abnormality that is present during active psychosis.

F147. BODILY MAPS OF TRAUMA IN INDIVIDUALS AT RISK FOR SCHIZOPHRENIA: DEVELOPMENT OF A NEW TOOL TO INVESTIGATE EMBODIED EMOTIONS ASSOCIATED WITH TRAUMA

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Background: Disturbances of the bodily self are one of the core features of schizophrenia. These can include disrupted bodily ownership, self-other distinction, interoception, and embodiment. Trauma has been linked with similar disruptions in the sense of self and with increased risk for psychosis, although the link to self-disturbance is not fully understood. While previous work has linked trauma and psychosis, the possible connection between psychosis and trauma via bodily disturbances has not been fully explored. The goal of the current study was to investigate how these relationships may be linked in the general population.
Methods: We distributed the anonymous online survey utilizing REDcap (n=103; mean age=29.4; 69.9% women). It included the Prodromal Questionaire-16 (PQ-16) to assess psychosis-risk and The Brief Trauma Questionnaire (BTQ) was used to assess trauma and to ascertain those who met the criteria for DSM-5 PTSD. Additionally, The Depression, Anxiety, and Stress Scale (DASS), the Adverse Childhood Experiences (ACE) questionnaire, Benevolent Childhood Experiences (BCE) questionnaire, and Relationship Questionnaire (RQ) were included to assess mental health. Further items for bodily self-disturbance were also included, namely asking about felt- presence experiences and out of body experiences. To examine the embodiment of trauma, we created a

computerized body mapping task by modifying the BTQ. For each item of the BTQ endorsed by the participant, they were presented with body outlines on which they were asked to indicate (via a mouse click) the locations on the body outlines where they experienced sensations or feelings associated with that specific traumatic event. We quantified the body maps of trauma by counting the number of body regions as well as the specific body regions located.

Results: Of the 103 respondents, 88% of participants indicated that they had experienced at least one traumatic event and of these and 75% of participants met the diagnostic criteria for PTSD. Of the 88% who indicated they had experienced at least one traumatic event in their lifetimes, 100% indicated locations of sensations associated with trauma in the body. A mean of 2.25 body parts were associated per traumatic experience item on the BTQ. Those at high risk for psychosis (PQ score > 6) had elevated BTQ scores than those at low risk. Higher PQ was associated with increased counts of body regions associated with the trauma. Increased localization of body parts linked to trauma was associated with higher scores on BTQ, ACE, PQ, PQ distress, DASS, as well as the presence of out of body experiences. There was some evidence for protective impact of benevolent childhood experience on trauma-related psychopathology.

Discussion: Past trauma is associated with bodily sensations. Trauma was associated with psychosis-risk, replicating past research. Moreover, we found an increased embodiment of trauma in those at risk for psychosis. Future research needs to examine types of trauma (e.g., interpersonal vs non interpersonal) in relation to the symptoms of the schizophrenia spectrum conditions such as paranoia and hallucinations to understand the routes to psychosis from traumatic events. Lastly, we observed some evidence for the protective role of positive experience in childhood, which might contribute to resilience.

F148. COGNITIVE, CLINICAL, AND FUNCTIONAL RELATIONSHIP OF OBSESSIVE-COMPULSIVE SYMPTOMS IN THE SCHIZOPHRENIA-SPECTRUM

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Background: Individuals with schizophrenia (SZ) and schizotypal personality disorder (SPD) have varying degrees of cognitive impairment, severity of clinical symptomology, and functional outcome. Obsessive-compulsive symptoms (OCS) are prevalent in the SZ-spectrum and complicate the clinical and cognitive picture. Some research suggests cognitive impairments are compounded in SZ patients with OCS, while other research indicates cognitive function is preserved. Additionally, much of the literature has shown greater symptom severity and functional impairment in SZ patients with OCS. This complex and unresolved cognitive, clinical, and functioning profile in SZ has not been examined in SPD—a personality disorder in the SZ-spectrum. This study is the first to examine OCS across a SZ-spectrum sample and determine the relationship of OCS severity to cognitive, clinical, and functional outcome.

Methods: A sample of 100 participants received rigorous clinical assessments including structured diagnostic interviews (SCID/SIDP): healthy control (HC; n=42), schizotypal personality disorder (SPD; n=28), and schizophrenia (SZ; n=30). All were administered the MATRICS Consensus Cognitive Battery (MCCB) and received assessments of symptom severity and functioning including the Yale Brown Obsessive-Compulsive Scale self-report, Positive and Negative Syndrome Scale, Childhood Trauma Questionnaire, Social Adjustment Scale self-report and Heinrichs Carpenter Quality of Life Scale. Group differences in OCS severity were assessed with a one-way analysis of variance. Pearson correlations were used to assess the relationship between OCS severity and clinical, cognitive, and functioning measures.
Results: A one-way ANOVA revealed group differences on OCS severity ($F(2,97)=19.85$, $p<0.001$). Post-hoc Tukey tests showed greater OCS in SPD and SZ patients than HC ($p<0.001$). SZ and SPD groups did not differ in OCS severity. Among the SZ patients, greater severity of OCS was associated with better attention composite scores ($r(28)=0.45$, $p<0.014$) and continuous performance test-Identical pairs (CPT-IP) scores ($r(28)=-0.41$, $p<0.024$). In contrast, among the SPD group, greater severity of OCS was associated with poorer attention ($r(26)=-0.47$, $p<0.012$) and CPT-IP scores ($r(26)=-0.47$, $p<0.011$). These correlation coefficients differed between the SZ-SPD groups (attention composite ($p=0.007$); CPT-IP ($p=0.0012$)). This pattern was not observed for other MCCB composite scores/tasks. Additionally, among the SZ patients, greater severity of OCS was associated with greater severity of positive symptoms ($r(28)=0.46$, $p<0.01$) and poorer social functioning ($r(28)=0.53$, $p<0.003$), which was not shown in the SPD group. However, within the SPD group, a greater severity of OCS was associated with greater general symptomology ($r(25)=.45$, $p<0.018$) and severity of childhood trauma ($r(26)=0.59$, $p<0.001$). Altogether, more severe OCS was associated with worse quality of life in the combined patient group ($r(56)=-0.27$, $p=.037$).
Discussion: Individuals with SPD and SZ endorsed similar levels of OCS severity which were greater than the HC group. Between-group differences in clinical and cognitive profiles were shown across the SZ-spectrum in association with OCS severity. Notably, greater OCS severity was associated with better attention in the SZ group and poorer attention in the SPD group. These findings underscore the differential relationship of OCS across the SZ-spectrum and suggest treatment decisions should consider cognitive, clinical, and functioning profiles together with OCS severity. Data collection is ongoing and supplemental imaging data may further elucidate the neurobiological underpinnings of these findings.

F149. THE RELATIONSHIP BETWEEN ORAL CONTRACEPTIVES AND ELEVATED BRAIN FREE WATER IN PSYCHOSIS

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Background: Several diffusion MRI (dMRI) studies showed elevations of the free-water (FW) fraction in recent-onset psychosis (ROP) compared with healthy controls (HC). Corroborating evidence from animal studies and blood markers further associated elevated FW in psychosis with inflammatory processes. Some of the FW findings were sex-specific, although inconsistent across studies. A recent meta-analysis tested possible modifiers of FW in psychosis, such as symptom severity and medication. However, the heterogeneity in sex-specific differences remains unexplained.

Here we test a hypothesis that oral contraceptive (OC) intake affects sex-specific FW findings. Recently, studies in healthy individuals demonstrated an association between OC-intake and increased fractional anisotropy and mean diffusivity. Furthermore, OC-intake was associated with increased blood inflammatory markers, which may explain some of the changes in FW. Since individuals with psychosis are less often prescribed OCs than the general population, OC-intake might influence previously described sex-specific group differences. Therefore, we tested the effect of OC-intake on average FW from ROP subjects and HC from the PRONIA (Personalized Prognostic Tools for Early Psychosis Management, www.pronia.eu) multisite study.

Methods: The analyses included N=201 individuals with ROP (85F/116M) and N=284 HCs (164F/120M) between 15-40 years. Females were further categorized based on self-reported OC-intake, yielding N=61 HC females with current OC-intake (HC-OC+), N=103 HC females that never used any contraceptives (HC-OC-), N=7 females with ROP with current OC-intake (ROP-OC+) and N=78 females with ROP that never used any contraceptives (ROP-OC-). DMRI data were pre-processed, site-harmonized, and co-registered to create an average value of FW across the white matter. We performed a two-way analysis of covariance (ANCOVA) to test the effect of group (HC and ROP) and sex interaction on average FW (dependent variable) controlling for age and age2. In females only we performed a second two-way ANCOVA to test the effect of group (HC and ROP) and contraceptive intake (OC+ and OC-) controlling for age and age2. In case of significant interaction or main effects we performed post-hoc Tukey honestly significant difference test corrected for multiple comparisons.

Results: Comparing HC with ROP revealed a significant interaction of group-sex effects on average FW ($F(1,478)=6.13$, $p=.014$). Post-hoc tests showed significantly lower FW in the HC–male group compared to HC-female ($t=-2.82$, $p=.026$), ROP–female ($t=-4.06$, $p<.001$) and ROP-male ($t=-5.36$, $p<.001$) groups. The HC-female group had lower average FW than ROP-male ($t=-2.97$, $p=.016$) but did not differ from ROP-female ($t=1.77$, $p=.289$) groups. The average FW between ROP-females and ROP-males was not significantly different ($t=-0.87$, $p=.821$). In our sample, HC females were more likely to be OC+ (37%) than ROP females (8%), $\chi2(1, N=249)=22.2$, $p<.001$. A separate ANCOVA in females only revealed a significant interaction of group and contraception use on average FW, ($F(1,243)=4.24$, $p=.041$). Post-hoc tests showed that HC-OC- had significantly lower average FW than HC-OC+ ($t=-3.69$, $p=.001$) and ROP-OC- ($t=-3.07$, $p=.011$). The average FW between all other groups did not significantly differ (all $p>.05$).

Discussion: Our results demonstrate sex-specific elevated FW in individuals with recent-onset psychosis with stronger increases in males. However, higher levels of FW in HC females that use OC may have prevented from identifying elevation in FW in females with recent-onset psychosis.

These findings suggest that both psychosis and OC-intake may increase FW levels, highlighting the importance of considering OC-intake as a potential moderator in brain studies.

F150. NEUROTROPHIN LEVELS AND CANNABIS USE INFLUENCE TRANSITION TO MENTAL DISORDERS IN SUBJECTS AT CLINICAL-HIGH RISK FOR PSYCHOSIS (CHR)

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Background: Neurotrophins (NTs) have important functions in neuronal development, synaptogenesis, and response do stress. As such, there is evidence that NT levels are disrupted in schizophrenia. Reductions in brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) are frequently observed in first-episode, neuroleptic naïve, patients when compared to controls. Nevertheless, NT levels also change with cannabis use, the latter being a well-established risk factor for psychosis. Although there are many studies assessing NT levels in several stages of schizophrenia spectrum disorders, very few are available for subjects at clinical high-risk for psychosis (CHR). Also, to the best of our knowledge, a comprehensive NT analysis and its relationship with cannabis use and transition to a mental disorder has not been conducted in this population until now.

Methods: Our sample consisted of 87 CHR and 55 healthy control subjects, all derived from a population-based sample. CHR status was diagnosed with the Structured Interview for Prodromal Syndromes (SIPS), and presence of any psychiatric diagnosis was ruled out with the Structured Clinical Interview for DSM-5 diagnosis (SCID-5). At baseline, blood samples were collected in EDTA-coated tubes and 8h fasting. Samples were centrifuged at 1800g for 15 min at 20°C for plasma separation. The samples were stored at -80°C until further processing. Plasma levels of BDNF, pro-BDNF, pro-NGF, NGF/NGFβ, NT4/5 and NT3 were determined by enzyme linked immunosorbent assay (ELISA) according to manufacturer's instructions. Neurotrophin levels were determined by absorbance in 450 nm, using optical density values based on the standard curve values. Subjects were followed-up for a mean of 2.5 years, and the same baseline instruments were used to diagnose possible psychiatric disorders. SPSS version 25.0 for OS was used for all the analysis except for the path analysis, for which Mplus 8.0 for Mac was used.

Results: There were no statistical differences between sociodemographic and cannabis use variables between CHR subjects and controls. NGF (824.50 vs 756.27, p=0.034), and pro-BDNF levels (1137.35 vs 1019.75, p=0.003) were significantly higher in CHR subjects, while NT-4/5 (517.41 vs. 648.44, p=0.004) was significantly lower in CHR subjects, compared to controls. Results: remained the same when controlled for sex, tobacco and cannabis use. After follow-up, 15 CHR subjects developed a psychiatric disorder. Stepwise backwards logistic regression including sex and tobacco use as covariates, as well as all the NTs measured, showed that lifetime cannabis use and NGF were predictors of transition to mental illness among CHR subjects. After conducting path analysis, final model showed that transition was influenced by lifetime cannabis use and levels of NGF/proNGF. Cannabis use, for its turn, also influenced levels of NGF/proNGF.

Discussion: Our study shows that NTs are dysregulated in CHR states, and that they are related to transition to mental disorders in these subjects. It also suggests an important biological pathway by which cannabis might influence transition. Results have important implications for the

biological underpinning of early stages of psychotic spectrum disorders, as NTs also regulate brain dopaminergic transmission. Further studies are warranted to address the gaps in this possible pathophysiological pathway.

F151. RENAMING SCHIZOPHRENIA: PRELIMINARY DATA FROM A SOUTH AMERICAN COUNTRY

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Background: Currently, the word "schizophrenia" is questioned as the ideal term for this disorder. Both patients and their relatives consider the word harmful, while clinicians and researchers consider its use to be no longer justifiable, being questionable from a conceptual point of view. In line with this position, Asian countries like Japan and South Korea, replaced the name hoping to reduce stigma.
The aim of this study is to explore the opinions of different sectors of Argentinian society regarding the term "schizophrenia", and the possibility of modifying it.

Methods: Participants included those with lived experience of psychosis and other mental illnesses, family members of mental health services users, mental health professionals and the general public. The survey was distributed via mental health facilities, psychiatrists and psychologists' associations, non-Governmental Organizations (NGOs) focused on the treatment of severe mental illnesses, and social media. We explored whether the participants consider the term "schizophrenia" stigmatizing, and if they consider that the name should be changed. Based on previous publications, we proposed nine different terms to replace the current name. Opinions about them were presented on Likert scales from 1 (don't like it at all) to 5 (like it very much).
To describe our findings, measures of central tendency and dispersion were used. In the case of quantitative variables, mean and standard deviations were used. In the case of qualitative variables, they were expressed as a percentage. Statistical analysis was carried out using SPSS Statistics 26.

These results are preliminary data, as we expect to recruit a greater number of participants in each group, in order to have a more representative sample.

Results: Four hundred and seventy-six participants answered the survey: mental health professionals (66.9%), mental health services users (13.8%), family members (9.2%), and general population (9.9%). Most of the participants found the term "schizophrenia" stigmatizing (78.9%). However, only about half (46%) of the participants think the name should be changed. Family members and mental health professionals were the ones who most strongly supported a change of name (48.9% and 47.3%, respectively), while the general public and mental health services users were the ones that gave less support to this change (38.3% and 40.9%, respectively). From the alternative names proposed, "Altered Perception Syndrome" and "Psychosis Spectrum Syndrome" were the most accepted (2.96 ±1.306 and 2.89±1.341, respectively), while the least preffered term was "Disconnectivity Syndrome" (2.06±1.117). In a deeper analysis, based on selective groups, mental health professionals preffered "Psychosis Spectrum Syndrome" (3.02±1.332), while mental health services users, family members and the general population chose "Altered Perception Syndrome" (3.26±1.281; 3.23±1.179; 3.21±1.232, respectively).

Discussion: Our main findings are that most of the participants, regardless of their group, find the word "schizophrenia" stigmatizing. From the proposed names to replace it, the term "Altered Perception Syndrome" had the greatest acceptability by all groups, except by mental health professionals, who preffered "Psychosis Spectrum Syndrome". These results are consistent with previous studies, in which mental health professionals reported using the terms "psychosis" or "psychotic disorders" in replacement of "schizophrenia". The other participants chose a probably more comprehensible name for the general public. Lastly, despite considering the word "schizophrenia" stigmatizing, more than half of the sample answered that it should not be changed. This finding could be due to people being used to this name, but it could also be associated with a belief that changing it will not reduce the stigma.

F152. MANAGEMENT OF DYSLIPIDAEMIA IN INDIVIDUALS WITH SEVERE MENTAL ILLNESS: A POPULATION-BASED STUDY IN THE GREATER COPENHAGEN AREA

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Background: Having severe mental illness (SMI) is associated with increased cardiovascular risk and premature mortality. Dyslipidaemia is a potentially modifiable cardiovascular risk factor, and inadequately managed dyslipidaemia in people with SMI may account for their unfavourable risk profile. Non-acute management of dyslipidaemia traditionally lies in primary care settings with general practitioners (GPs). We assessed management of dyslipidaemia among patients with SMI vs. people without mental illness in a primary care setting.

Methods: Using Danish registers, we identified adult individuals in the Greater Copenhagen Area with SMI (schizophrenia spectrum disorders or bipolar disorder) who had ≥1 GP contact in the year before 2005 and 2015, respectively. Patients with SMI were matched 1:5 on age and sex with a control population without SMI who also had recent contact with their GP. The quality of lipid management was assessed by the occurrence of lipid profile measurements, presence of

dyslipidaemia and redemption of lipid-lowering pharmacotherapy during these two calendar years. Possibly lower lipid management quality in patients with SMI was analysed in multivariable logistic regression models adjusted for age, gender, somatic comorbidities and selected socio-economic indicators.

Results: We identified 7,217 patients with SMI in 2005 (median age 46 [interquartile range (IQR) 34-58]; 48.2% men) and 9,939 patients with SMI in 2015 (median age 43 [IQR 30-56]; 49.6% men). After 10 years, patients with SMI went from having lower odds of lipid profile measurements to having higher odds ratio (OR) of lipid profile measurements compared with controls (OR2005 0.70 [95% confidence interval (CI) 0.65-0.76] vs. OR2015 1.34 [95%CI 1.26-1.41]; P for OR2005 vs OR2015 <0.01). Compared with controls, patients with SMI had higher odds of dyslipidaemia during both years (OR2005 1.43 [95%CI 1.17-1.74] vs. OR2015 1.23 [95%CI 1.11-1.36]; P = 0.19). Patients went from having lower odds of receiving lipid-lowering pharmacotherapy to having higher odds of receiving lipid-lowering pharmacotherapy (OR2005 0.77 [95%CI 0.68-0.86] vs. OR2015 1.37 [95%CI 1.27-1.48]; P <0.01). However, patients with SMI who had comorbid cardiovascular disease had lower odds of redeeming prescriptions on lipid-lowering pharmacotherapy without statistically significant increase after 10 years compared with controls. This included patients with previous acute coronary syndrome (OR2005 0.29 [95%CI 0.17-0.50] vs. OR2015 0.44 [95%CI 0.27-0.71]; P = 0.26) and patients with ischaemic cerebrovascular disease (OR2005 0.43 [95%CI 0.30-0.61] vs. OR 2015 0.61 [95%CI 0.45-0.81]; P = 0.14).

Discussion: Across 10 years, we observed that the odds of having lipid profile measurements and redeeming lipid-lowering pharmacotherapy improved markedly amongst patients with SMI compared with controls without SMI in a primary care setting. Nevertheless, the odds of dyslipidaemia remained higher in patients with SMI, and the odds of treatment with lipid-lowering pharmacotherapy among patients with SMI and comorbid cardiovascular disease remained lower compared with controls. Our findings suggest an increased awareness of managing dyslipidaemia as primary prophylaxis for cardiovascular disease among patients with SMI but that secondary prevention among patients in high cardiovascular risk groups is warranted.

F153. RECOVERY OF AUDITORY EVOKED RESPONSE ATTENTIONAL GAIN MODULATION FOLLOWING THE FIRST PSYCHOTIC EPISODE INDEXES IMPROVEMENTS IN SYMPTOM SEVERITY

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Background: Deficits in attentional control of auditory N1/M100 is observed in individuals with first-episode psychosis (FEP) shortly following initial contact with clinical services. Persistent problems in the modulation of primary auditory cortex may impact multiple aspects of psychosis. As a follow-up to our prior work reporting deficits in attentional M100 gain modulation in auditory cortex, we examined changes in M100 gain modulation longitudinally, and further examine relationships between auditory M100 and symptoms of psychosis.

Methods: We compared changes in the amplitude of auditory M100 responses in auditory sensory cortex between timepoints separated by 220±100 days, between focused attention and diverted attention, and between 21 people with FEP and 29 healthy controls matched for age, parental SES, and WASI verbal IQ. Magnetoencephalography data were recorded while participants either

attended or ignored tones in an auditory oddball task. M100 was measured as the mean amplitude from 80-140 ms post-stimulus in source-localized evoked responses within bilateral auditory cortex. Symptoms were assessed using the Positive and Negative Syndrome Scales (PANSS) and Psychosis Rating Scales (PSYRATS).
Results: M100 amplitudes, attentional modulation of M100 amplitudes, and symptom severity all improved in FEP over time ($p<0.05$). Further, improvement in M100 modulation correlated with improvements in negative symptoms (PANSS) as well as physical, cognitive, and emotional components of hallucinations (PSYRATS) ($p<0.05$). Conversely, improvements in the overall size of the M100, rather than the difference between active and passive M100 amplitudes, was related to worsening of positive symptoms (PANSS) and physical components of hallucinations measured with the PSYRATS ($p's<0.05$).
Discussion: Results indicate a link between symptoms (particularly auditory hallucinations) and auditory cortex neurophysiology in FEP, where auditory attention and auditory sensation have opposed relationships to symptom change. These findings may inform current models of etiology of psychosis and could provide avenues for early intervention.

F154. LOW GRADE IN UTERO INFLAMMATION IS ASSOCIATED WITH IMPAIRED EXECUTIVE FUNCTIONING IN 10-YEAR-OLD CHILDREN

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Background: Maternal inflammation is associated with the risk of ADHD in offspring, and ADHD is characterized by compromised executive functioning. However, it is unknown if low-grade maternal inflammation during pregnancy is associated with less efficient executive functioning in the general population. We examined associations between inflammatory markers in utero and executive functioning at age 10.
Methods: The COPSYCH study is based on the unselected prospective COPSAC2010 birth cohort of 700 mother-child pairs. At age 10, the children's executive functioning was assessed in the COPSYCH study with neuropsychological tests and parental ratings using the Behavior Rating Inventory of Executive Function (BRIEF-2) questionnaire.

Inflammatory markers, specifically high sensitivity C-Reactive Protein (hs-CRP) and interleukin 6 (IL-6), were collected from the mother during pregnancy week 24 and the COPSAC2010 database allowed us to thoroughly control for multiple covariates.

Multiple regression analyses were applied to estimate associations between maternal inflammation and executive functioning in the offspring.

Results: 604 (86% of the cohort) completed the 10 year visit. Higher maternal IL-6 was associated with the severity of impairments of General Executive Function (BRIEF-2) (β=2.45 [0.67-4.22], p=0.007), Cognitive Regulating Index (BRIEF-2) (β= 1.44 [0.37-2.51], p=0.009), and Behavior Regulating Index (BRIEF-2) (β=0.48 [0.09-0.87], p=0.02). Maternal hs-CRP was not significantly associated with executive functioning (General Executive Function (BRIEF-2), p=0.2). All associations with neuropsychological tests were non-significant.

Discussion: Our prospective clinical data support that low-grade maternal inflammation, specifically higher IL6, but not CRP during pregnancy, is associated with impaired executive functioning in middle childhood in the general population.

F155. A FEASIBILITY STUDY OF FAMILY THERAPY FOR SCHIZOPHRENIA IN AN URBAN AFRICAN ENVIRONMENT

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Background: Family therapy is shown to decrease relapses and reduce cost of treatment for schizophrenia. Modification in content of such programmes in response to local challenges is considered important but has not been fully explored in Africa. The aim of this study was to assess the feasibility and acceptability of an interventional family study for people with schizophrenia and their families in a socially deprived urban community in South Africa and to explore the contextual factors that could influence implementation of the intervention.

Methods: A trained psychiatric nurse facilitated semi-structured interviews with 4 multifamily groups, each comprising adult outpatients with schizophrenia and their caregivers. Six sessions were held per group. Thematic analysis was applied.

Results: Three themes emerged: stigma and abuse, substance abuse co-morbidity, and caregiver burden of multiple stressors. Many of these stressors relate to the challenges of an impoverished urban environment.

Discussion: Multi-family groups with a psycho-educational and behaviour modification frame are acceptable. Negative symptoms are seen as protective in areas of community violence. Modification of traditional models of family therapy to include factors related to poverty, violence, caregiver burden, stigma, and limited health care access should be considered in this setting.

F156. COMPLEMENT SYSTEM EXPRESSION CHANGES DEMONSTRATE CNS REGIONAL SPECIFICITY IN SCHIZOPHRENIA AND MOOD DISORDERS

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[1]University of Melbourne, [2]Monash University

Background: Schizophrenia is known as a disorder of faulty programmed synaptic elimination during critical periods of development. It has also been hypothesized as a pro-inflammatory state, with immune activation at multiple levels which could perturb neurodevelopment. This altered immune signalling has been shown to involve multiple specific signalling pathways. Against this background dysregulation of the complement system, an innate immune system component also involved in synaptic pruning, is emerging as a key player in schizophrenia pathology. Here we aimed to determine if complement signalling is altered in two key brain regions, dorsolateral prefrontal (DLPFC; BA46) and orbitofrontal (OFC; BA11) cortices, in schizophrenia and mood disorder.
Methods: Expression of key complement genes, C1QA, C1QB, C1QC, C2, C3, C4A and C4B, were examined in post-mortem BA46 and BA11 from schizophrenia, mood disorder and healthy control subjects (n=68) using RT-qPCR. C3 and C4A protein levels were estimated by Western immunoassay.
Results: In BA46, C1QB, C1QC, C3 and C4A were significantly downregulated in schizophrenia compared to healthy controls with large effect sizes, the difference more discernible for C3. C3 and C4A were also downregulated in mood disorder against the controls but less markedly. C3 expression was significantly lower in schizophrenia than in mood disorder. C1QA and C2 were unchanged, while C4B was largely undetectable. C3 and C4A protein levels did not differ significantly between the diagnostic groups. There were no mRNA or protein changes in BA11.
Discussion: Complement system activity was decreased in schizophrenia and less distinctly in mood disorder. Moreover, C3 signalling dysregulation in the disease state aligns with the contention that reduced activity may promote infections which have consequential impacts on adult neurodevelopment.

F157. VERBAL MEMORY PERFORMANCE IN PSYCHOTIC DISORDERS AND MOOD DISORDERS: A SYSTEMATIC REVIEW OF COMPARATIVE STUDIES

Bryce Bogie*[1], Chelsea Noël[2], Étienne Lefebvre[3], Julia MacDonald[4], Jamie Mongeon[5], Ahmad Alftieh[5], Claire Mayaud[6], Patrick Dans[7], Synthia Guimond[8]

[1]University of Ottawa, [2]Lakehead University, [3]Carleton University, [4]Carleton University, [5]The Royal's Institute of Mental Health Research, [6]Université de Bordeaux, [7]The Centre for Addiction and Mental Health, [8]The Royal's Institute of Mental Health Research, University of Ottawa

Background: Psychotic and mood disorders are highly heterogeneous with marked differences in their clinical presentations. However, they share common features; notably, cognitive impairments. Both disorder categories are frequently associated with impairments in verbal memory, a sub-domain of cognition which defines memory for words and other stimuli involving language. Verbal memory has been identified as an important target for interventions in these populations given that it represents a strong predictor of outcomes. Despite this common feature in both diagnostic categories, there is a paucity of research directly comparing these two groups and a healthy control group using the same paradigm(s). These comparisons are needed to lend insight into the particular neurocognitive profiles of the specific diagnoses. Therefore, this systematic review sought to synthesize the current literature on verbal memory in studies directly comparing (a) psychotic disorder, mood disorder, and healthy control groups and (b) mood disorder with psychotic features, mood disorder, and healthy control groups.

Methods: This systematic review was prospectively registered in PROSPERO (CRD42020193722) and followed the PRISMA guidelines. The following inclusion criteria were used: participants aged ≥ 18; confirmation of diagnoses; a measure of verbal memory performance. Articles were excluded if they recruited participants with co-morbid alcohol and/or substance use disorder; used an intervention without including between-group baseline comparison(s); did not include a healthy control group. The search yielded 1,898 records, of which 172 survived title and abstract screening. Of these, 140 were excluded through full-text screening, resulting in 32 articles meeting the full eligibility criteria.
Results: On most outcomes, verbal memory performance did not significantly differ between psychotic and mood disorders for verbal working memory, immediate recall, delayed recall, and recognition memory. During the acute phase of the illness, the current evidence revealed lower performance in schizophrenia compared to bipolar disorder groups (with and without psychotic features) on immediate and delayed recall. Furthermore, during the acute phase, there was lower performance in major depressive disorder with psychotic features compared to major depressive disorder without psychotic features on delayed recall. There were no other observable differences between psychotic and mood disorder comparisons for any other memory system during the acute phase of the illness. Interestingly, most of the outcomes which evaluated verbal memory performance during the non-acute phase of the illness did not reveal a difference between psychotic and mood disorders.
Discussion: The preliminary evidence suggests that psychotic and mood disorders do not display widespread differences in verbal memory performance. The only differences that were observed between clinical groups occurred during memory recall, which is more cognitively demanding than working memory and recognition. Therefore, recall may represent a more sensitive marker of verbal memory impairment than working or recognition memory. These findings have important implications for providing shared therapeutic interventions, such as cognitive remediation therapy, to these clinical populations in a diagnosis-independent manner.

F158. FIRST-EPISODE PSYCHOSIS AND GAMING DISORDER: IMPROVING SCREENING AND PATIENT'S EVOLUTION

Maxime Huot-Lavoie[1], Olivier Corbeil[2], Laurent Béchard[3], Sébastien Brodeur[4], Charles Desmeules[5], Anne-Marie Essiambre[5], Émilien Fournier[2], Chantale Thériault[6], Isabelle Giroux[7], Yasser Khazaal[8], Marie-France Demers[3], Marc-André Roy[9], Élizabeth Anderson*[10]

[1]Universite Laval Faculty of Medicine, [2]Faculty of Pharmacy, Laval University, [3]Pharmacy Faculty, Laval University, [4]Faculty of Medicine, Laval University; IUSMQ, CIUSSS-CN, [5]École de Psychologie, Université Laval, [6]CERVO Brain Research Centre, [7]School of psychology, Laval University, [8]Lausanne University Hospital, [9]Faculté de médecine de l'Université Laval, Institut Universitaire en Santé Mentale de Québec, Centre de Recherche de lInstitut Universitaire en Santé Mentale de Québec, [10]University Laval

Background: There is a growing interest in understanding the impact of video games in the clinical field, especially with the recent addition of Gaming Disorder (GD) in the 11th international classification of disease. Although clinicians widely recognize the comorbidity of GD and psychotic disorders (PD), little is known about the consequences of this addiction in vulnerable populations.

Considering the importance of other addictions on PD patient recovery path, the study of comorbid psychotic disorder with GD is of high interest.

Our research program aims to: 1) summarize the available knowledge on the comorbidity between GD and PD; 2) determine the prevalence of GD in patients with PD; 3) determine the consequences of GD on the evolution of patients with PD.

Methods: First, we realized a scoping review to identify the depth and breadth of the literature regarding comorbid PD with GD. Secondly, a prospective cohort study of patients with PD is currently in progress to measure the impact of GD on patients' psychopathology using PANSS and SOFAS scales and to estimate the prevalence of this comorbidity.
Results: The scoping review highlights a significant lack of knowledge concerning comorbid PD with GD as only a few reported cases exposed the potential association between those conditions and shows that excessive video game play or abrupt gaming disruption could trigger psychosis. However, no empirical study yet supports these hypotheses. On the other hand, the preliminary results of our cohort study highlight the importance of this comorbidity in patients' recovery.
Discussion: This is the first study on the comorbidity between gaming and psychotic disorders. The preliminary results of our prospective cohort study highlight the importance of questioning gaming habits while treating patients with first-episode psychosis.

F159. BRAIN N-ACETIL-ASPARTATE IN CHILDREN AND ADOLESCENTS WITH A FIRST EPISODE OF PSYCHOSIS: A LONGITUDINAL PROTON MAGNETIC RESONANCE SPECTROSCOPY STUDY OVER 5 YEARS FOLLOW UP

Marta de la Torre-Cano[1], Chao Suo[2], Joost Janssen[3], Josefina Castro-Fornieles[4], Elena De la Serna[5], Mara Parellada[6], Dolores Moreno[7], Montse Graell[8], Inmaculada Baeza[9], Murat Yucel[7], Celso Arango[10], Marta Rapado-Castro*[11]

[1]Universidad Complutense de Madrid, [2]Turner Institute for Brain and Mental Health, Monash University, [3]Child and Adolescent Psychiatry Department, Hospital General Universitario Gregorio Marañón, IiSGM, CIBERSAM. Madrid, Spain., [4]Hospital Clinic Barcelona, [5]Centro De Investigación Biomédica En Red De Salud Mental, CIBERSAM, [6]CIBERSAM, Hospital General Universitario Gregorio Marañon, Universidad Complutense de Madrid, Spain, [7]Hospital General Universitario Gregorio Marañón, [8]Hospital Universitario Marqués de Valdecilla. Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM, [9]Hospital Clinic de Barcelona, [10]Hospital General Universitario Gregorio Marañon, [11]Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, School of Medicine, Universidad Complutense, IiSGM, CIBERSAM

Background: The Child and Adolescent First Episode of Psychosis Study (CAFEPS Study) is a multicenter longitudinal study in early onset psychosis. Early-onset Psychosis (EOP) is a severe disorder with its onset in childhood or early adolescence, and it is associated with several developmental and functional impairments. N-Acetyl-Asparte (NAA) concentrations, which are considered to be a good indicator of neuronal integrity, have shown to be reduced in psychosis-related disorders in comparison with their control counterparts.
Methods: Our aim was to study the NAA concentrations in the dorsolateral prefrontal cortex in children and adolescents diagnosed with EOP (n=67) and controls (n=65) at baseline, two years,

and five years after the onset of the first episode. Functional brain images were acquired using proton magnetic resonance spectroscopy (H-MRS). Absolute NAA concentrations were extracted using LCModel. The data was analyzed with lineal mixed models to examine the time x group interaction and secondary models were conducted to explore the potential influence of covariates such as age, gender, symptoms (measured through the PANSS), and anti-psychotic medication.
Results: Results did not show a significant time x group interaction in the non-adjusted main model (F=9.846; p=0.432), however, there were non-significant lower concentrations of NAA in children and adolescents with EOP than in the control group at 2 years follow-up (p=0.060) and significantly lower NAA concentrations at 5 years (p=0.030) follow-up.
Discussion: We found decreased NAA concentrations in children and adolescents with EOP in comparison to controls. Our findings suggest lower levels of neural integrity as measured by NAA may be related to the progression of the disease over the first five years after onset of the first psychotic episode.

F160. A FEASIBILITY STUDY OF FAMILY THERAPY FOR SCHIZOPHRENIA IN AN URBAN AFRICAN ENVIRONMENT

Laila Asmal*[1], Sumaya Mall[2], Robin Emsley[3], Bonginkosi Chiliza[1], Leslie Swartz[4]
[1]University of Stellenbosch, [2]University of the Witwatersrand, Johannesburg, [3]Faculty of Medicine and Health Sciences, Stellenbosch University, [4]Stellenbosch University

Background: Family therapy is shown to decrease relapses and reduce cost of treatment for schizophrenia. Modification in content of such programmes in response to local challenges is considered important, but has not been fully explored in Africa. The aim of this study was to assess the feasibility and acceptability of an interventional family study for people with schizophrenia and their families in a socially deprived urban community in South Africa and to explore the contextual factors that could influence implementation of the intervention.

Methods: A trained psychiatric nurse facilitated semi-structured interviews with 4 multifamily groups, each comprising adult outpatients with schizophrenia and their caregivers. Six sessions were held per group. Thematic analysis was applied.

Results: Three themes emerged: stigma and abuse, substance abuse co-morbidity, and caregiver burden of multiple stressors. Many of these stressors relate to the challenges of an impoverished urban environment.

Discussion: Multi-family groups with a psycho-educational and behaviour modification frame are acceptable. Negative symptoms are seen as protective in areas of community violence. Modification of traditional models of family therapy to include factors related to poverty, violence, caregiver burden, stigma, and limited health care access should be considered in this setting.

F161. COMPLEMENT SYSTEM EXPRESSION CHANGES DEMONSTRATE CNS REGIONAL SPECIFICITY IN SCHIZOPHRENIA AND MOOD DISORDERS

Tharini Ketharanathan*[1], Avril Pereira[1], Suresh Sundram[2]
[1]University of Melbourne, [2]Monash University

Background: Schizophrenia is known as a disorder of faulty programmed synaptic elimination during critical periods of development. It has also been hypothesized as a pro-inflammatory state, with immune activation at multiple levels which could perturb neurodevelopment. This altered immune signalling has been shown to involve multiple specific signalling pathways. Against this background, dysregulation of the complement system, an innate immune system component also involved in synaptic pruning, is emerging as a key player in schizophrenia pathology. Here we aimed to determine if complement signalling is altered in two key brain regions, dorsolateral prefrontal (DLPFC; BA46) and orbitofrontal (OFC; BA11) cortices, in schizophrenia and mood disorder.

Methods: Expression of key complement genes, C1QA, C1QB, C1QC, C2, C3, C4A and C4B, were examined in post-mortem BA46 and BA11 from schizophrenia, mood disorder and healthy control subjects (n=68) using RT-qPCR. C3 and C4A protein levels were estimated by Western immunoassay.

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Discussion: The preliminary evidence suggests that psychotic and mood disorders do not display widespread differences in verbal memory performance. The only differences that were observed between clinical groups occurred during memory recall, which is more cognitively-demanding than working memory and recognition. Therefore, recall may represent a more sensitive marker of verbal memory impairment than working or recognition memory. These findings have important implications for providing shared therapeutic interventions, such as cognitive remediation therapy, to these clinical populations in a diagnosis-independent manner.

F163. FIRST-EPISODE PSYCHOSIS AND GAMING DISORDER: IMPROVING SCREENING AND PATIENT'S EVOLUTION

Élizabeth Anderson*[1], Maxime Huot-Lavoie[2], Olivier Corbeil[3], Laurent Béchard[4], Sébastien Brodeur[5], Charles Desmeules[6], Anne-Marie Essiambre[6], Émilien Fournier[3], Chantale Thériault[7], Isabelle Giroux[8], Yasser Khazaal[9], Marie-France Demers[4], Marc-André Roy[10]
[1]University Laval, [2]Universite Laval Faculty of Medicine, [3]Faculty of Pharmacy, Laval University, [4]Pharmacy Faculty, Laval University, [5]Faculty of Medicine, Laval University; IUSMQ, CIUSSS-CN, [6]École de Psychologie, Université Laval, [7]CERVO Brain Research Centre, [8]School of psychology, Laval University, [9]Lausanne University Hospital, [10]Faculté de médecine de l'Université Laval, Institut Universitaire en Santé Mentale de Québec, Centre de Recherche de lInstitut Universitaire en Santé Mentale de Québec

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[1]Universidad Complutense de Madrid, [2]Turner Institute for Brain and Mental Health, Monash University, [3]Child and Adolescent Psychiatry Department, Hospital General Universitario Gregorio Marañón, IiSGM, CIBERSAM, [4]Hospital Clinic Barcelona, [5]Centro De Investigación Biomédica En Red De Salud Mental, CIBERSAM, [6]CIBERSAM, Hospital General Universitario Gregorio Marañon, Universidad Complutense de Madrid, [7]Hospital General Universitario Gregorio Marañón, [8]Hospital Universitario Marqués de Valdecilla. Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM, [9]Hospital Clinic de Barcelona, [10]Hospital General Universitario Gregorio Marañon, [11]Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, School of Medicine, Universidad Complutense, IiSGM, CIBERSAM

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Methods: Our aim was to study the NAA concentrations in the dorsolateral prefrontal cortex in children and adolescents diagnosed with EOP (n=67) and controls (n=65) at baseline, two years, and five years after the onset of the first episode. Functional brain images were acquired using proton magnetic resonance spectroscopy (H-MRS). Absolute NAA concentrations were extracted using LCModel. The data was analyzed with lineal mixed models to examine the time x group interaction and secondary models were conducted to explore the potential influence of covariates such as age, gender, symptoms (measured through the PANSS), and anti-psychotic medication.

Results: Results did not show a significant time x group interaction in the non-adjusted main model (F=9.846; p=0.432), however, there were non-significant lower concentrations of NAA in children and adolescents with EOP than in the control group at 2 years follow-up (p=0.060) and significantly lower NAA concentrations at 5 years (p=0.030) follow-up.

Discussion: We found decreased NAA concentrations in children and adolescents with EOP in comparison to controls. Our findings suggest lower levels of neural integrity as measured by NAA may be related to the progression of the disease over the first five years after onset of the first psychotic episode.

F165. MODELING THE RELATIONSHIP BETWEEN TRAUMA, BELIEFS ABOUT VOICES AND VOICE CONTROL

Hatice Eken[1], Catalina Mourgues[2], Alison Branitsky[3], Alyson Negreira[4], Brittany Quagan[2], Victoria Fisher[2], Albert Powers[2], Catalina Mourgues-Codern*[5]
[1]University of Pittsburgh Medical Center, Western Psychiatric Institute & Clinic, [2]Yale University School of Medicine, [3]Division of Psychology and Mental Health, Faculty of Biology, Medicine and Health, The University of Manchester, [4]Cincinnati Veterans Affairs Medical Center, [5]Yale University

Background: Trauma history has been strongly and consistently linked with the presence of auditory hallucinations and psychosis more broadly, as well as lower quality of life and a diminished sense of control over individuals' lives. However, some studies have shown that the relationship individuals build with voices might influence their sense of control over the voices despite their past traumatic experiences. We defined control as the ability to voluntarily "turn on and off" voices, which can be accomplished by using strategies geared towards direct engagement with voices, such as a dialogue, or non-engagement, such as distractions from voices. In this study, we model the relationship between the distress from past traumatic events and its relationship with perceived control over voice-hearing experiences in a diverse population of voice-hearers with and without psychiatric diagnoses. Specifically, we aimed to test the hypothesis that trauma-related distress would predict negative beliefs about voices, leading to higher levels of voice resistance and preferential employment of non-engagement methods of exerting control over voice-hearing.

Methods: We selected voice-hearers reporting trauma history from the Yale Control Over Perceptual Experiences (COPE) Project dataset (N = 413). We built a structural equation model to explore the relationship between trauma-related distress, voice content, beliefs and behaviors about voices, and control over voice-hearing experiences. The variables were derived from the Trauma History Questionnaire and Impact of Event Questionnaire, Beliefs about Voices Questionnaire (BAVQ-R), and the Yale COPE scale, respectively.

Results: We split the participants into high and low-distress groups based on reported levels of trauma-related distress. Individuals in the high-distress group were more likely to report having heard voices more recently, and had higher incidences of self-reported psychosis-spectrum disorders. The results of the path analysis overall supported a model by which higher levels of trauma-related distress predicted more negative (malevolent and omnipotent) and less positive (benevolent) beliefs about voices, which in turn predicted more resistance to voices, preferential employment of non-engagement-based methods of exerting control, and lower overall degree of control.

Then, using a multigroup approach, we found that significant pathways were largely similar between the high-distress and low-distress groups, although not completely invariant. For example, we found that beliefs about voice omnipotence decreased the likelihood of engaging directly with voices in the low-distress group, but not in the high-distress group. Furthermore, engagement with voices contributed to increased overall control over voices in the low-distress group, but not in the high-distress group.

Discussion: Our findings demonstrate that lasting distress from past traumatic experiences mediate individuals' perceptions and beliefs about their voice-hearing experiences, which in turn lead to differential development of control over those experiences. Our study is among the first to investigate the complex mediating relationship between trauma, beliefs about voices, and engagement with voices. Impaired control may be one of the paths by which trauma leads to maintenance of voice-hearing leading to distress and dysfunction. Future studies should aim to intervene on this pathway toward control development, encouraging engagement-based approaches and bolstering control over voice-hearing experiences in an effort to maximize functioning in individuals who hear voices.

F166. MATERNAL IMMUNE ACTIVATION AS AN ANIMAL MODEL OF PSYCHOSIS-LIKE BEHAVIOR: SEX-DEPENDENT EFFECTS

Antonio Armario[1], Roser Nadal[1], Silvia Fuentes[1], Joan Visa[1], Javier Labad*[2]
[1]Institut de Neurociències, Universitat Autònoma de Barcelona, Spain., [2]Consorci Sanitari del Maresme, Mataró

Background: Prenatal maternal immune activation is considered an animal model of schizophrenia. The viral mimic polyinosinic–polycytidylic acid (poly IC), mimics the well-known influence of infection of mothers during pregnancy on the incidence of schizophrenia. However, results are not always consistent, and the evidence of sex specific effects of the different maternal immune activation models is mixed. Two putative mediating mechanisms are the impact in maternal behavior and the changes in the hypothalamic-pituitary-adrenal (HPA) axis. Our aims were twofold: 1) to study of the effects of poly IC administration to pregnant rats in the adult male and female offspring in schizophrenia-related phenotypes; and 2) to characterize the changes in maternal behavior induced by poly IC and in the HPA axis, in resting conditions and in response to a stressor.

Methods: Long-Evans male and female rats from Janvier (France) were used. On days GD15 and GD17 pregnant rats were given vehicle (saline) or received 5 mg/kg (1 ml/kg) poly I:C in saline through the tail vein, while gentled restrained. For mating, two male pups and two females from each mother were selected at random. Maternal behavior was measured during PND 1-7 at 4 different times during the day, 25 measurements each time (arched-back nursing, licking-grooming and off-nest behavior). The influence of the prenatal treatment in pups was evaluated at adulthood in the following tests: saccharin (0.1% w/v) preference in a two-bottle preference test (anhedonia, 3 days, 24h free-access/day, as a measure of depressive-like behavior), social interaction (a single session, 15 min), T-maze (working memory, 5 days including habituation and pretraining), and pre-pulse inhibition of the startle response (PPI, a single day, as a measure of sensoriomotor gating). Blood samples were taken by tail nick and corticosterone levels were measured by RIA in resting conditions (morning).

Results: Maternal behavior was not affected by poly IC administration, precluding that the possible impact of poly IC could be in great part mediated by altered maternal behavior. Poly IC did not affect body weight of mothers, offspring size, or weight of pups. No effects were detected in social interaction. In contrast, maternal immune activation induced anhedonia-like behavior (as measured by a decrease in saccharin intake), in males but not in females. Impaired PPI in poly IC treated rats was observed also only in males. Poly IC did not exert a statistical significant effect in the T-maze working memory test, but tended to induce opposite effects in males (decreasing) vs females (increasing). In addition, control females showed a reduced PPI and lower number of correct responses in the T-maze, in comparison to control males. No differences in corticosterone levels in resting conditions were found.

Discussion: In our animal model, some changes reminiscent of some traits found in schizophrenic patients as well as in ultra-high-risk (UHR) individuals have been detected only in males, suggesting that females may be "protected" in some way or that other phenotypes should be evaluated when studying females. No changes in either maternal behavior nor resting corticosterone levels were detected, suggesting that those are not mediating mechanisms.

F167. APPLICABILITY OF PERSONAL RECOVERY MEASURES IN PERSONS WITH PSYCHOSIS ATTENDING FLEXIBLE ASSERTIVE COMMUNITY TREATMENT IN NORTH REGION DENMARK

Rikke Jørgensen*[1], Simon Johnsen[1], Ann-Eva Christensen[1]
[1]Unit for Psychiatric Research - Aalborg University Hospital

Background: A recent meta-analysis has shown peer support to have impact on self-reported recovery and empowerment. Peer support is a collaborative practice, where individuals are employed to make use of their personal experiences as mental health service users to support likeminded. Nevertheless, the results ought to be translated with caution to countries not included in the meta-analysis. Thus, there is a continuous need to explore and generate knowledge and insights into the practice of peer support and recovery. After employing peer support workers in Flexible Assertive Community Treatment (FACT) in the North Region Denmark, it was decided to apply the two questionnaires the Recovery Assessment Scale and the Netherlands Empowerment List as an outcome measure for peer support. To our knowledge the two measures have not been investigated in a Danish population of persons with psychosis.

Therefore, this study aims to investigate applicability in regard to administration by an electronic mailbox, floor ceiling effect and internal consistency of the Recovery Assessment Scale and the Netherlands Empowerment List in persons with psychosis attending care and treatment in Flexible Assertive Community Treatment teams in Region North in Denmark.

Methods: The design is a longitudinal study with baseline, six- and 12-months follow-up. The invitation to participate included a personal link to the study and was sent to all patients enrolled in FACT via a secure online digital mailbox (e-Boks) linked to a civil registration number. The

analysis will contain ease of administration, internal consistency by Cronbach's alpha and floor ceiling effects defined as >15% of the respondents attaining the lowest or the highest possible score.

Results: Enrolled patients in FACT counted for 1487, whereas 392 did not have an electronic mailbox, and five did not have an address. At baseline 200 (13.4%) consented to participate in the study, and at six months follow-up 108 out of the 200 responded. In April 2023, 12 months follow-up will be sent out. The poster will present the final results.

Discussion: The results will be discussed and compared with literature reporting from applicability of the Recovery Assessment Scale and the Netherlands Empowerment List from other countries with comparable populations.

Poster Session II

12:30 p.m. - 2:30 p.m.

S1. FEEDBACK UTILIZATION, INTROSPECTIVE ACCURACY, AND PERFORMANCE OVER TIME ON THE WISCONSIN CARD SORTING TEST IN BIPOLAR DISORDER AND SCHIZOPHRENIA

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Background: One of the critical features of schizophrenia (SCZ) and bipolar disorder (BD) is inaccurate self-assessment of abilities. Challenges in using external information, including directed feedback on performance, may underlie these challenges. A task such as the Wisconsin Card Sorting test (WCST), wherein success is dependent on responsiveness to feedback, is an excellent probe to identify poor utilization of external information.
Methods: A modified WCST was administered to participants with BD (n=67) and SCZ (n=99). Participants generated sorts, were asked to judge their accuracy and were given standard feedback on correctness. We treated the 64 sorts as a time series and examined task-related changes in two critical variables: correct sorts and accuracy judgments. We also examined more standard variables such as categories completed and trials to the first category.
Results: Participants with BD had more correct sorts, more categories, and fewer sorts to achieve their first category (all d>.53). A group x sort MMRM found that participants with BD improved more over 64 sorts in correct sorts (Group x time p=.02) and accuracy (Group x time p=.005). MCCB composite scores correlated equivalently (r=~.40) with correct sorts and a regression analysis suggested that composite scores shared no variance with accuracy in either group when correct sorts were considered.
Discussion: Participants with BD improved more in correct sorts and in accuracy judgments than SCZ, although self-assessment accuracy does not appear driven by cognitive performance. Other biases may influence incorrect self-assessments, with previous studies suggesting mood states or momentary psychosis may be the drivers.

S2. COGNITIVE BIASES AND SPEECH INCOHERENCE USING SPEECH GRAPHS IN SCHIZOPHRENIA SPECTRUM DISORDERS

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Background: Cognitive biases are systematic tendencies in the processing, selection and remembering of information. They are prevalent in schizophrenia-spectrum disorders (SSD) and are particularly associated with positive symptoms. The bias against disconfirmatory evidence (BADE) refers to a reluctance to integrate information that contradicts one's beliefs

and is associated with delusions. BADE has also been associated with formal thought disorder (FTD), though this relationship remains to be explored. Speech incoherence is a feature of FTD that can be objectively quantified via computerized processing of speech transcripts in both clinical and non-clinical samples.
Methods: We sought to examine the relationship between BADE and speech incoherence in SSD patients (n = 23) and non-clinical controls (n = 15). We hypothesized that greater severity of BADE would be associated with greater speech incoherence, as defined by speech connectedness attributes (Largest Connected Component, LCC; and Largest Strongly Connected component, LSC). Speech graphs assessing language connectedness were generated from manually transcribed speech samples acquired during semi-structured interviews.
Results: The results: supported previous findings of a greater BADE in patients relative to controls ($t(35) = 2.38$, $p < .05$). Furthermore, attributes of speech connectedness were linked to BADE in patients only ($r = -0.41$, $p < .05$; $r = -0.42$, $p < .05$ for LCC and LSC, respectively), indicating that patients with reduced coherence in speech had weaker evidence integration and higher bias against disconfirmatory evidence. The trend was reversed in control participants ($r = .30$, $p > .05$; $r = .34$, $p > .05$, for LCC and LSC respectively), where speech connectedness attributes demonstrated positive associations with BADE.
Discussion: Through these results we demonstrate for the first time that BADE is associated with speech incoherence in SSD, an effect that was reversed in non-clinical controls. These findings support the notion that cognitive biases are associated with formal thought disorder as indexed by speech and extend previous work using clinician-rating measures of FTD. This work also suggests that, though cognitive biases are dimensional constructs, they may demonstrate different patterns of associations to speech structure in clinical and non-clinical populations.

S3. CHILDHOOD TRAUMA AND REPRODUCTIVE HORMONAL PROFILES IN MIDLIFE WOMEN WITH AND WITHOUT SCHIZOPHRENIA

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Background: Childhood trauma is associated with lasting immunoendocrine changes, thought to be largely related to hypothalamic-pituitary-adrenal (HPA) axis activation and increased inflammatory response. These changes have been linked to numerous health outcomes and have received increasing attention for their suggested role in the pathophysiology of schizophrenia. There are high rates of trauma reported among people with schizophrenia, with a greater proportion of women reporting childhood trauma, and evidence suggests the physiological effects of early adversity may differ by sex. We investigated the relationship between early life trauma and reproductive hormones to characterize the endocrinological effects of early adversity in women and to examine whether these effects differ between those with schizophrenia and healthy controls.
Methods: Female participants with a diagnosis of schizophrenia and female healthy controls were assessed with the Childhood Trauma Questionnaire (CTQ). We measured serum levels of adiponectin, leptin, follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone and cortisol. We used Pearson correlations to identify associations between biomarkers and CTQ scores, including subscales for physical, emotional and sexual abuse. Standardized cutoffs were used to create dichotomous predictor variables to assess whether

abuse exposure predicted hormone levels in linear regression models. Relationships between abuse variables and hormones were examined both in the overall sample and in the schizophrenia and healthy groups separately.
Results: We enrolled a total of 40 participants (20 with schizophrenia and 20 healthy controls). Sixty percent reported some form of childhood abuse, with no relationship between study group and exposure to abuse X2(1, N=40)=1.67, p=0.197. In women with schizophrenia, exposure to sexual abuse was predictive of lower adiponectin (β=-0.555, p=0.037) and leptin levels (β=-0.554, p = 0.014). Exposure to any trauma (β=0.584, p=0.017), emotional abuse (β=0.584, p=0.017), emotional neglect (β=0.584, p=0.017) or physical abuse (β=0.509, p=0.044) was predictive of increased FSH level. No significant predictive relationships were found between trauma exposure and adiponectin, leptin or FSH in healthy controls. There were significant positive correlations between FSH and emotional abuse (r=0.541, p=0.031) and neglect scores (r=0.617, p=0.011) and significant negative correlations between leptin and total CTQ (r=–0.558, p=0.010), sexual abuse (r=–0.522, p=0.018), emotional neglect (r=–0.491, p=0.028), physical abuse (r=–0.463, p=0.040) and emotional abuse (r=-0.581, p=0.007) scores in participants with schizophrenia, suggesting a possible dose dependent effect of trauma exposure on hormone levels in this population.
Discussion: We found that exposure to childhood abuse and specific abuse and neglect subtypes was associated with midlife changes in adiponectin, leptin and FSH in women with schizophrenia, but not healthy controls. This may represent a unique neuroendocrine response to early life stress in schizophrenia and could help elucidate the pathophysiologic mechanisms by which early adversity contributes to the development of schizophrenia spectrum disorders.

S4. SELF-ESTEEM IN STABILIZED INDIVIDUALS WITH CHRONIC SCHIZOPHRENIA: ASSOCIATION WITH RESIDUAL SYMPTOMS AND COGNITIVE FUNCTIONING

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Background: Low self-esteem is regarded as a barrier to recovery from schizophrenia and the identification of factors affecting this psychological characteristic may help to implement effective therapeutic interventions. To this end, the present study aimed to assess whether residual symptoms of the disorder and cognitive functioning might differently impact self-esteem among 70 stabilized outpatients with chronic schizophrenia from public outpatient mental health services.
Methods: Next to performance on a comprehensive neuropsychological test battery the current study used the Index of Self-Esteem (ISE) and the Positive and Negative Syndrome Scale to assess self-esteem and psychopathology.
Results: Self-esteem inter-correlated with the severity of overall symptomatology, affective and negative symptoms, with premorbid intelligence, and with performance in the domains of verbal learning and memory, visual memory, working memory, and verbal fluency. Residual affective symptoms, premorbid intelligence, and female sex predicted poorer self-esteem in multiple linear regression analysis.
Discussion: The findings of this study implicate that next to psychological interventions therapeutic strategies that specifically target affective symptoms of schizophrenia may have a beneficial impact on patients' self-esteem.

S5. DO SOCIAL COGNITIVE DEFICITS IN SCHIZOPHRENIA DEPEND ON BASIC SENSORY INFORMATION PROCESSING?

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Background: SC (social cognition) deficits are one of the most relevant causes of impaired daily functioning in individuals with schizophrenia. SC depends on complementary processes which arise from activity of a number of neural networks. It has been evidenced that severe SC deficits in schizophrenia are related to non-social cognitive dysfunctions. Moreover, for efficient SC a good mechanism of filtering sensory information and reliable perception are both crucial.
Impairment of automatic analysis of basic auditory stimuli was confirmed in schizophrenia by extensive research with electroencephalographic.

Methods: ERPs (Event Related Potential). Deficits in both, SC and automatic analysis of auditory stimuli are linked with poor functioning in schizophrenia, but the relation between these dysfunctions has not been studied.

The aim of this study was to investigate if impaired SC in schizophrenia is determined by dysfunction in information selection. It was hypothesized that if the basic information selection is impaired it would be followed by dysfunctions in perception and encoding of social information and consequently in worse performance in tests evaluating emotion recognition and ability to infer others intentions.

The study is ongoing. Up to date, 45 participants with diagnosed schizophrenia (mean age 28.2 yo), all treated with antipsychotics, were recruited. MMN (mismatch negativity) was an auditory ERP chosen for evaluation of basic stimuli selection for this study. Diminished amplitude of MMN has been repetitively confirmed in schizophrenia. The typical oddball paradigm (with pure-sinusoidal tones and single deviant to duration increment) was the stimulation applied to elicit MMN. Subjective experiences related to the process of impaired information selection from the neuronal level were evaluated by Sensory Gating Inventory (SGI). SC processes were assessed with following tests: Hinting Test, Mini – PONS, Penn Emotion Recognition Task ER-40 and recognition of communicative and non-communicative gestures from point-light walkers. MATRICS Tests battery was applied for assessing non-social cognitive functions.
Correlations analysis between results of SC tests and MATRICS battery results and between SC tests and MMN amplitude and latency was used to measure relationship between variables.

Results: The preliminary results showed that SGI score correlated negatively with some SC test scores.
The participants with low scores in Hinting Test had high scores in overinclusion subscale of SGI ($r=-0.32$, $p=0,04$). The negative association between ability to infer communicative intentions from point-light walkers and total SGI score was also observed. ($\varrho=-0,33$, $p=0,034$).
The results did not show any significant correlations between amplitude and latency of MMN and performance in any of the tests evaluating SC.

Discussion: On the one hand, results of this study showed no correlation between electrophysiological measures and scores of SC tests. On the other hand, high SGI score correlated with the low recognition of communicative gestures and poor rating for Hinting Test

evaluating Theory of Mind. These findings suggest that individuals who tends to notice even weak background stimuli, might be easily distracted from social situations.
To sum up, the above ambiguous results indicate a need to extend the research on changes in perception in schizophrenia, to further investigate if it determines SC deficits in these individuals. We suggest applying electrophysiological and neuroimaging tools evaluating broader aspects of perception in future research in the field.

S6. COGNITIVE UNDERPINNINGS OF NON-AUDITORY AND MULTISENSORY HALLUCINATIONS IN PSYCHOSIS: A NARRATIVE REVIEW.

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Background: Multisensory hallucinations refer to unusual perceptual events in the absence of corresponding stimuli, experienced in two or more sensory modalities. Within the psychosis literature, a significant body of work has investigated the cognitive underpinnings for auditory hallucinations. In contrast, the cognitive underpinnings of multisensory hallucinations remain largely unknown. Likewise, scant research has examined non-auditory hallucinations in psychosis, with much of the relevant work in the visual domain conducted in neurological populations, and the other sensory modalities given limited attention. The current narrative review aimed to synthesise and critically analyse existing research regarding the cognitive underpinnings of hallucinations across non-auditory sensory modalities as well as multisensory hallucinations in psychosis.
Methods: Research that has explored cognition in psychosis and neurological populations was reviewed. Each non-auditory sensory modality, as well as multisensory hallucinations, was considered in turn, and evidence for cognitive mechanisms under investigation was reviewed and discussed.
Results: Using the available evidence collated in the review, as well as existing knowledge for cognition and auditory hallucinations, liable mechanisms which might plausibly be applied to non-auditory or multisensory hallucinations were proposed. For example, inhibition. An impairment in inhibition has been found to be associated with both auditory and visual hallucinations. Unlike a cognitive mechanism such as speech monitoring, inhibition does not appear to be constrained to a specific sensory modality and could therefore be applicable across modalities.
Discussion: There are a number of existing limitations in the literature, and areas of research that are of urgent priority in this field. For example, multisensory hallucinations have not been measured in existing investigations of unimodal experiences, and therefore the contribution of other modalities is unknown. There is also a lack of validated assessment tools to measure non-auditory and multisensory hallucinations. Additionally, the current nature of psychosis literature being constrained to auditory hallucinations, and neurological to visual hallucinations, has limited our ability to develop an understanding of the full range of hallucinatory experiences across these populations. Future investigations for the cognitive underpinnings for non-auditory and multisensory hallucinations in psychosis populations are warranted. For instance, specifically investigating inhibition and its potential relationship to multisensory hallucinations. Further exploration for mechanisms such as source monitoring across the different sensory domains would also be warranted, to identify the nature of mechanisms as being specific to one sensory modality, or not.

S7. INCLUSION OF COURT ORDERED PATIENTS/PRISONERS IN PSYCHIATRIC RESEARCH

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Background: Including prisoners into research studies has been a controversial topic. Past exploitation and abuse have contributed to strict regulations and reluctance to involve this vulnerable population as study participants. Hence, prisoners are routinely denied the opportunity to participate in research. However, many patients now in State psychiatric facilities meet the HHS definition of prisoners and it is often difficult to determine what constitutes prisoner status and what does not. This group also represents a population that may be denied the opportunity to participate in clinical research. Recent data suggests that prisoners and court ordered psychiatric inpatients have limited access to research participation which may be disadvantageous particularly if the research study is minimal risk and they are excluded from opportunities others may have. Data also suggest that the perceived burden of including prisoners is far more prominent in motivating researcher exclusion than due to regulations or ethical concerns. There is suggestion that it is time for research to be more accessible to prisoners in line with the principle of equivalence in healthcare. We have been successful in recruiting court ordered patients into clinical research and have worked to identify terminology to identify and rationale.

Methods: We have conducted clinical research with inpatients at a State Psychiatric facility over the past 25 years and the population has moved from that of voluntary status to more court ordered status over time. Regulations state that "prisoner" means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution*, and individuals detained pending arraignment, trial, or sentencing (45 CFR 46.303(c)). The penal institution clarification was added to the definition and 45 CFR in the 2018 regulatory changes. Since many patients in State psychiatric facilities locally and across the country are involved with the court system some patient designations would constitute a "prisoner" under the expanded regulations.

Results: We developed a process to better identify who is and who is not a prisoner in the State hospital. Broadly speaking individuals with psychiatric illnesses who have been committed involuntarily to an institution as an alternative to a criminal prosecution or incarceration are considered "prisoners". Individuals who have been voluntarily admitted to an institution for treatment of a psychiatric illness, or who have been civilly committed to nonpenal institutions for treatment because their illness makes them a danger to themselves or others, are not prisoners. We have summarized 11 terms regarding legal status that are typically found in the medical charts and 5 are considered prisoner status under the current regulations. Additionally, we have successfully had 9 protocols approved by the IRB and Office of Human Research Protections (OHRP) for inclusion of patients with "prisoner status". We have developed a process to summarize and work to address all 10 stipulations from the CFR to assist the IRB and OHRP decisions. We have included 479 patients to date with no complaints, issues, or problems.

Discussion: There is a lot of confusion regarding which court ordered inpatients are considered "prisoners". We have attempted to help to clarify terminology and assist with disseminating our successful process of IRB submission and have successfully enrolled hundreds of prisoners into clinical research. The sharing of this information is critical to bring more equity and opportunities to this much overlooked and misunderstood research population.

S8. MULTI-MODAL INTENSIVE LONGITUDINAL METHODS THE SOUTHERN UNITED STATES: PRELIMINARY EVIDENCE OF FEASIBILITY AND ACCEPTABILITY IN PARTICIPANTS WITH SCHIZOPHRENIA-SPECTRUM DISORDERS

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Background: People with schizophrenia-spectrum disorders (SSDs) experience deficits in social cognition and behavior, as well as high rates of sleep disturbance. Sleep disturbance is linked to reduced social cognition and behavior in other groups, but no study to date has investigated this link in people with SSDs. Importantly, both sleep disturbance and social behavior are dynamic experiences well-suited to assessment via intensive longitudinal methods. Indeed, both actigraphy and ecological momentary assessment (EMA) survey methods have been used separately to assess these phenomena. However, few studies have investigated simultaneous use of these methods in people with SSDs, and none have investigated dual use of these methods in the southern United States. The south is a unique geographical region of the US where many communities are rural and may be far from mental healthcare resources. Further, southern states are some of the poorest in the US; Mississippi tops this list with 18-20% of its population living below the poverty line. Given these key factors, it is important to investigate the feasibility and acceptability of more intensive data collection Methods: such as actigraphy and EMA in participants from the rural south. This study begins to inform that question.
Methods: This preliminary analysis uses data from 9 participants with SSDs and 5 healthy control (HC) participants recruited in southern Mississippi for larger, ongoing studies of sleep and social cognition and behavior. Participants were recruited from community sources and asked to wear an Actiwatch Spectrum PLUS wrist-worn device for 14 days while completing daily EMA surveys (7 per day). Participants were monetarily incentivized to complete as many surveys as possible. Feasibility and acceptability of the study protocol are investigated here through examination of survey completion rates, successful utilization of Actiwatches resulting in useable sleep data, and availability of smart devices among eligible participants. Additional barriers to study implementation are also examined.
Results: All participants completed at least some of the EMA surveys. Completion rates ranged from 14.3%-100% in the SSD group (M=65.3%) and 18.4%-95.9% in the HC group (M=54.3%). Five participants in the SSD group did not have a smart device available to them and were provided with iPods by the study team. Participants also did not have consistent Wi-Fi access which presented additional challenges to completing EMA surveys. All participants wore Actiwatches for the majority of the 14-day study period, with all but one in each group wearing Actiwatches continuously. Participants in the SSD group were recruited from a variety of sites, some far from the university. Participants and community members in the region are

broadly unfamiliar with the concept of research, requiring community education and outreach to establish potential recruitment sites, but willingness to engage with the research team remained low among potential participants.
Discussion: Results: suggest that use of multi-modal intensive longitudinal assessment is a feasible and acceptable method for people with SSDs in the southern United States, though participants may complete EMA surveys at slightly lower rates than in other published works and access to smart devices may be lower than seen in other, more urban samples. Ongoing data collection will continue to inform these questions. Lack of familiarity with research at possible recruitment sites among both clinical staff and potential participants is a significant barrier to recruitment in this region, and research teams may need to be flexible with their approach in order to reach and engage people with SSDs in the community.

S9. THE ROLE OF M1 AND M4 MUSCARINIC RECEPTORS IN COGNITIVE PERFORMANCE

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Background: Acetylcholine and cholinergic signaling are essential in normal cognitive functions, including learning and memory. The disruption of cholinergic neurons or postsynaptic muscarinic acetylcholine receptors (mAChRs) has been directly correlated with cognitive deficits in neuropsychiatric disorders, including schizophrenia. Antipsychotics, which are used to manage the positive symptoms of schizophrenia, have only modest effects on cognition and are not indicated to treat cognitive impairment. KarXT (xanomeline–trospium), an investigational dual M1/M4 preferring mAChR agonist with no direct dopamine receptor binding activity, may be a potential treatment for psychosis and cognitive impairment in patients with schizophrenia. In the randomized, double-blind, placebo-controlled, 5-week, inpatient phase 2 EMERGENT-1 trial (NCT03697252) in adults with schizophrenia, KarXT was associated with robust improvements in positive and negative symptoms of schizophrenia. KarXT was also associated with a trend toward greater cognitive improvement compared with placebo, and a statistically significant and robust effect was found in exploratory analyses among patients with at least modest cognitive impairment at baseline.
Methods: This report will "reverse engineer" xanomeline by tracing the preclinical evidence as to how xanomeline can regulate aberrant circuits associated with cognitive deficits.
Results: In the central nervous system, xanomeline has preferential functional activity for M1 and M4 receptor subtypes, providing insight on which muscarinic receptor subtypes are most likely to interact with cognitive circuits. M1 and M4 receptors are highly expressed in brain regions important for cognitive function. Further, stimulation of both M1 and M4 receptors has been shown to improve cognitive performance and enhance learning and acquisition in deficit and basal states in preclinical models, respectively.
M1 receptors in the cortex and hippocampus can modulate top-down neuronal function. In the hippocampus, M1 receptors can increase feed-forward excitability of CA1 pyramidal neurons. The procognitive effects of M1 receptors in the frontal cortex are most likely due to changes in plasticity via a mechanism that depends on retrograde neurotransmitters and second messengers. In preclinical models, M1 receptor activation can reverse cognitive deficits in genetic or pharmacological models, improve cognitive performance, and modulate sleep-wake architecture.

Within the hippocampus and the prefrontal cortex, the M4 receptor can modulate excitatory glutamatergic signaling within distinct subregions. M4 receptor selective activators reverse deficits in cognition that may involve actions at excitatory synapses, including corticostriatal terminals, to normalize the function of overactive excitatory projections from layer V pyramidal cells of the frontal cortex to the striatum; however, additional studies are needed to confirm the role of the M4 receptor in modulating cognitive function. Preclinical models have shown that M4 receptor activation can enhance cognition under both basal and deficit states as well as normalize amphetamine-induced changes in hippocampal activity, elevations of high-frequency gamma power, and state-dependent alterations in sleep architecture and arousal.

Discussion: There has been great progress in understanding the potential role of muscarinic receptor agonists or selective activators for cognition that supports future development of muscarinic agonists for the potential treatment of cognitive impairment in schizophrenia.

S10. WORKING MEMORY IMPAIRMENT IS INDEPENDENT OF INCREASING AGE IN SCHIZOPHRENIA

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Background: Cognitive impairment is considered a central symptom to schizophrenia, with deficits associated with a decrease in functionality and quality of life. A decline in cognitive functioning has been reported in persons with schizophrenia well before the onset of psychosis. Visuospatial working memory (WM) and attention are two cognitive operations that have been identified as especially important in investigating disturbed information processing in schizophrenia. WM deficits are present in clinical high-risk individuals and first-degree relatives, classifying them as an endophenotype of schizophrenia. However, it is not yet clear when WM and attention are affected during age-related decline in schizophrenia.

Methods: In order to investigate specific aspects of cognitive impairment in schizophrenia, we evaluated working memory (WM) capacity and attentional prioritization/control (AP/C) in 66 PSZ adults, and 74 matched healthy control subjects (HCS). WM capacity was evaluated with a canonical visuospatial color change detection task. AP/C was measured with a visuospatial change detection task with four Gabor patches- two of them being targets and two being distractors. Visual salience of the stimulus was manipulated (flickering / non-flickering) and an exogenous top-down (predictive / non-predictive) cue was displayed, creating four conditions: flickering / predictive cue (F/PC), non-flickering / predictive cue (NF/PC), flickering / non-predictive cue (F/NPC), non-flickering/ non-predictive cue (NF/NPC). We conducted Spearman's r bivariate correlations to investigate the relationship of increasing age on these cognitive measures, and compared the correlations between groups using the Fisher r to z transformation.

Results: Overall, there was a significant decrease in the amount of information encoded in all cognitive measures in PSZ compared to HCS. Although increasing age significantly correlated with decreased WM capacity in the matched healthy control group (HCS, $rs = -0.406$, $p < 0.001$), it did not in PSZ ($rs = -0.125$, $p = 0.316$; $z = 1.763$, $p = 0.039$). Overall the amount of

information encoded in the AP/C tasks significantly correlated with age in HCS (rs = -0.455, p < 0.001), yet this effect was not observed in PSZ (rs = -0.064, p = 0.612; z = 2.466, p = 0.007). Furthermore, a decrease in the amount of information encoded in each AP/C task significantly correlated with increasing age in HCS including the F/PC (rs = -0.428, p < 0.001), NF/PC (rs = -0.328, p = 0.004), F/NPC (rs = -0.420, p < 0.001), and NF/NPC (rs = -0.435, p < 0.001) conditions. However, there was no correlation between age and amount of information encoded in the following conditions in PSZ: F/PC (rs = -0.065, p = 0.605; z = 2.267, p = 0.012), F/NPC (rs = -0.102, p = 0.4115; z = 1.995, p = 0.023), and NF/NPC (rs = -0.010, p = 0.939; z = 2.635, p = 0.004) conditions. Interestingly, there was no significant correlation in PSZ in the NF/PC condition (rs = -0.113, p = 0.368), yet there was no significant difference to HCS (z = 1.312, p = 0.095).

Discussion: We observed that increasing age significantly correlated with a decrease in the amount of information encoded in all tasks in HCS, yet there were no correlations observed in PSZ. Our findings might be indicative of underlying neurodevelopmental disturbances, which alter the typical trajectory of cognitive ageing. These results underscore the importance of early intervention strategies to slow down the trajectory of cognitive impairment in schizophrenia. Importantly, the absence of a further deficit with increasing age in WMC and AP/C in PSZ comparison to HCS suggests differences in cognitive aging between groups.

S11. PSYCHOMOTOR SLOWING ALTERS GAIT VELOCITY, CADENCE, AND STRIDE LENGTH AND INDICATES NEGATIVE SYMPTOM SEVERITY IN PSYCHOSIS

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Background: Schizophrenia is a severe mental disorder, in which 50% of the patients present with motor abnormalities such as psychomotor slowing. Slow spontaneous gait has been reported in schizophrenia. However, comprehensive objective instrumental assessments of multiple gait conditions are missing. Finally, the specific gait patterns of subjects with psychomotor slowing are still unknown. Therefore, this study aimed to objectively assess multiple gait parameters at different walking conditions in schizophrenia patients with and without psychomotor slowing. Also, we hypothesised gait impairments to correlate with expert ratings of hypokinetic movement disorders and negative symptoms.

Methods: We collected gait data (GAITRite®) in 70 patients with psychomotor slowing (SRRS (Salpetriere retardation rating scale) ≥ 15), 22 non-psychomotor slowed patients (SRRS < 15), and 42 healthy controls. Participants performed four walking conditions (self-selected speed, maximum speed, head reclined, and eyes closed) and three main gait parameters were extracted (velocity, cadence, and stride length). Also, experts evaluated all schizophrenia patients on clinical scales for hypokinetic movement abnormalities, such as the UPDRS (Unified Parkinson Disease Rating Scale, Part III) and the BFCRS (Bush-Francis Catatonia

Rating Scale). Additionally, the BNSS (Brief Negative Symptom Scale) was applied to measure negative symptoms.
Results: Patients with psychomotor slowing presented slower velocity, lower cadence, and shorter stride length in all walking conditions compared to healthy controls, with the non-slowed patients in an intermediate position (all $F > 16.2$, all $p < .0001$). Secondly, slower velocity was associated with more severe hypokinetic movement disorders (self-selected: all $r < -.21$, all $p < .05$; maximum: all $r < -.35$, all $p < .001$) and negative symptoms (self-selected: $r = -.27$, $p = .01$; maximum: $r = -.32$, $p = .002$) in both self-selected and maximum speed walking conditions. Lower cadence was associated with stronger negative symptoms in both walking conditions (all $r < -.28$, all $p < .008$), but with more severe hypokinetic movement disorders only during maximum speed (all $r < -.33$, $p < .002$). On the other hand, a shorter stride length was associated with stronger negative symptoms ($r = -.24$, $p = .02$) and more severe hypokinetic movement disorders (all $r < -.25$, all $p < .02$) only during self-selected speed.
Discussion: In conclusion, gait impairments exist in a spectrum with healthy controls on one end and schizophrenia patients with psychomotor slowing on the other end. Gait performance varies depending on the walking condition used and are differentially associated with hypokinetic movement abnormalities and negative symptoms. Patients with psychomotor slowing are specifically impaired when an adaptation of gait patterns is required, contributing to the deleterious effects of sedentary behaviours.

S12. EXAMINING THE INFLUENCE OF THE SELF-REFERENTIAL BIAS ON ABERRANT SALIENCE AND JUMPING TO CONCLUSIONS BIAS IN INDIVIDUALS WITH SCHIZOPHRENIA-SPECTRUM DISORDERS

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Background: Neurobiological and cognitive processes such as aberrant salience (AS) and the jumping to conclusions (JTC) bias are implicated in the development of delusions. Self-referential thinking (SRT) has also been implicated in this process; however, no research has examined how SRT may interact with AS and JTC in individuals with schizophrenia-spectrum disorders (SSDs). The present study investigated the extent to which self-referential thinking interacts with AS and JTC in both individuals with SSDs and psychiatrically healthy controls. Specifically, we sought to examine whether self-referential stimuli increased AS and JTC bias in individuals with SSDs, compared to psychiatrically healthy controls We predicted that compared to healthy controls, individuals with SSDs would display a greater increase in AS and JTC bias when presented with self-referential stimuli, than when presented with neutral stimuli.
Methods: 20 Individuals with SSDs were recruited from community hospitals across the Greater Toronto Area, while 20 healthy community controls were recruited from online recruitment platforms. To assess AS and JTC bias, participants were asked to complete both self-referential and neutral versions of the Salience Attribution Test (SAT) and the Beads Task, as well as self-report measures of AS and JTC bias, with the Aberrant Salience Inventory (ASI) and the Davos Assessment of Cognitive Biases (DACOBS). To examine our aims, 2 (group; clinical, control) x 2 (task: self-referential, neutral) mixed-model ANCOVAs were used to compare groups on AS task performance controlling for motivation, insight and functioning.
Results: Mixed-model ANCOVAs revealed that there was no significant interaction, $F (1,38) = .52$, $p = .476$, $\eta p2 = .013$, nor main effects of self-referential thinking, $F (1,38) = .37$, $p = .546$, $\eta p2 = .010$, on ASI aberrant salience. However, there was a significant main effect of

group, F (1, 38) = 11.51, p = .002, ηp2 = .233, on ASI aberrant salience. There was also no significant interaction, or main effects of self-referential thinking or participant group when controlling for the covariates of functioning, insight, motivation, educational status, and years of education. There was no significant interaction, F (1,37) = .10, p = .752, ηp2 = .003, or main effect of self-referential thinking, F(1,37) = 1.26, p = .268, ηp2 = .033 , on DACOBS JTC Bias scores. However, there was a significant main effect of participant group, F (1,37) = 5.36, p = .026, ηp2 = .126, on DACOBS JTC Bias scores. There was also no significant interaction, or main effects of self-referential thinking or participant group when controlling for the covariates of functioning, insight, motivation, educational status, and years of education.

Discussion: Individuals with schizophrenia-spectrum disorders did not display increased aberrant salience or JTC bias when the stimuli being processed were self-referential. However, there was a trend-level finding indicating that psychiatrically healthy controls exhibited greater levels of JTC bias when exposed to self-referential stimuli. Manipulating self-referential thinking did not influence levels of aberrant salience or JTC bias and did not significantly interact with either aberrant salience of JTC bias to predict delusion severity. Thus, it is possible that while self-referential processing is related to delusion severity, it may not interact with other cognitive biases and/or processes implicated in the development and maintenance of delusions. Future studies should continue to explore the relationship between these variables, and specifically aim to examine if social-cognitive or emotional processing may also be implicated in this relationship.

S13. COMPARING TREATMENT DELAYS AND PATHWAYS TO EARLY INTERVENTION SERVICES FOR PSYCHOSIS IN URBAN SETTINGS IN INDIA AND CANADA

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Background: Research on pathways to care, defined as individuals' encounters with health services made in the process of help-seeking, emerged from the recognition that longer durations of untreated psychosis (DUPs) were linked to worse clinical outcomes, and to emphasize that efforts to simplify pathways and reduce DUP could improve such outcomes. Pathways to care have been studied extensively in early intervention services for psychosis, especially in high-income countries (HICs), and less so in low- and middle-income countries (LMICs). Few studies have compared cross-national data on DUP and pathways to care in early intervention for psychosis. This gap is unfortunate given that comparative analyses of service encounters and DUP across contexts can help elucidate how individual, clinical, or systemic factors influence pathways to care. With uniform definitions of samples, DUPs and pathways, cross-national studies can tease out the impacts of cultural, social, structural and policy determinants. As part of a multi-year investigation of first-episode psychosis in Chennai and Montreal, this study used identical recruitment, treatment, and data protocols assess pathways to early intervention for psychosis in an HIC (Montreal, Canada) and an LMIC (Chennai, India). We hypothesised that the duration of untreated psychosis (DUP) would be longer in Chennai than in Montreal.

Methods: This study was conducted from 2012 to 2018. At both sites, assessments were conducted by staff trained using similar rigorous protocols with well-established measures that have been deployed in prior research at both sites. Trained staff administered the semi-structured Circumstances of Onset and Relapse Schedule (CORS) interview, to create timelines

patients' pathways to services. The number of contacts preceding early intervention, referral sources, first contacts, and DUP and its referral and help-seeking components of first-episode psychosis patients at both sites were similarly measured and compared using chi-square analyses and t-tests/one-way ANOVAs.
Results: Overall and help-seeking DUPs of Chennai (N=168) and Montreal (N=165) participants were not significantly different. However, Chennai patients had shorter referral DUPs (mean =12 weeks) as the early intervention service was the first contact for 44% of them (vs. 5% in Montreal). Faith healers comprised 25% of first contacts in Chennai. Those seeing faith healers had significantly shorter help-seeking and longer referral DUPs. Those seeing psychologists/counsellors/social workers as their first contact had longer DUPs. Montreal patients entered the early intervention service through various medical services, with half the patients entering through hospital emergency services and only a small fraction (6%, n=5) coming directly from families or being self-referred. In Chennai, a majority of patients were brought by family or friends or were self-referred (64%, n=104).
Discussion: To our knowledge, this is the first HIC-LMIC comparison of DUP and pathways to care in patients receiving similar care in early intervention services for psychosis. Contrary to our hypothesis, overall DUP did not differ across the two sites. However, referral DUP was significantly shorter in Chennai, driven by the large number of Chennai patients (n=72) whose first contact was the early intervention service itself. Overall, differences in cultural views about mental illnesses and organizational structures shape pathways to care and their associations with treatment delays across contexts. Both formal and informal sources may need to be targeted to reduce delays. Early intervention services being the first portal where help is sought can reduce DUP especially if accessed early on in the illness course.

S14. NOVEL MEASURES OF SOCIAL COGNITION CAPTURES IMPROVEMENT FOLLOWING VIRTUAL REALITY SOCIAL SKILLS TRAINING IN SCHIZOPHRENIA.

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Background: Social impairments present a major barrier toward better outcome in individuals with schizophrenia (SZ). Social skills and competence protect against stress-related exacerbation of symptoms while supporting interpersonal interactions, social affiliation and improving the quality of life. Existing social interventions can be helpful but suffer from low adherence and weak transfer of skills outside of treatment settings. A viable alternative to conventional therapies is the use of virtual reality (VR) technology to develop interventions that target specific social cognitive mechanisms. Our past study showed the feasibility and acceptability of a VR-based social skills training 'game' for SZ (Adery et al, 2018) in which participants rehearsed everyday social skills in simulated social situations without having to explicitly learn rules of social skills. The present study aimed to test the effectiveness of the VR social intervention on key social cognitive mechanisms and extended the assessment to examine self-disturbance (emotion embodiment) and self-other boundary (interpersonal distance regulation) that may contribute to social impairments but are rarely investigated in the context of treatment.
Methods: 25 SZ participated in VR-based social skills training twice a week for 4 weeks (8 sessions). In each game, the participant was asked to approach an avatar and make appropriate

conversations to accomplish social 'missions'. Varying difficulty levels and social settings (bus stop, cafeteria and shop) provided scaffolding approach. Performance indices were the number of missions correctly completed, errors, mission completion time, and latency to engage with an avatar (SEL). At baseline, we assessed clinical symptoms, social functioning, loneliness, embodied emotion, interpersonal distance (IPD) and resting state functional connectivity (rsFMRI) for 25 SZ and 25 matched controls (CO); CO provided baseline comparison data but did not undergo training. Embodied emotion was visualized with a mapping task (emBODY; Nummenmaa et al., 2014). Preferred IPD was assessed with a visual scale to estimate the size of the social comfort space when interacting with another person. For rsFMRI, a hypothesized social brain network including TPJ and STS and a frontoparietal personal space network including diPS and PMv were the regions of interest. Post-treatment assessment was repeated within 2 weeks of completion of the VR training.

Results: Performance indices including SEL improved across the 8 sessions. Pre-Post assessments suggested improvements in clinical symptoms, social functioning, and embodied emotion. IPD measure also indicated that alteration of social comfort distance is alleviated after the training. rsFMRI data indicated that relatively weaker connectivity in brain areas related to social-cognitive function and frontoparietal action space network were observed in SZ at baseline.

Discussion: Our low-burden VR social skills training game appears to be effective in improving key social cognitive functions in SZ. In addition to improved symptoms and social functioning, we found 'normalization' of embodied emotion and interpersonal distance regulation. Our findings suggest the utility and efficacy of a VR intervention based on simulation and rehearsal of social interactions. Lastly, assessment of self-disturbance and self-other processing might be important to gauge effects of social interventions.

S15. IMPULSIVITY AND SCHIZOTYPAL PERSONALITY DISORDER TRAITS: AN INVESTIGATION OF SELF-REPORT AND BEHAVIOURAL MEASURES IN PSYCHIATRIC OUTPATIENTS

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Background: Impulsivity is a key feature in psychotic disorders that comprises a broad range of traits including disrupted impulse control and reward-directed behavioural disturbance. Previous research has supported the linkages between schizotypal personality disorder (SPD) and self-report measures of impulsivity; however, negligible findings were located in performance-based, neurocognitive tasks. The replication of these results in clinical samples with a broader range of psychiatric symptoms is needed, including the evaluation of impulsivity from both a subjective and performance-based standpoint.

Methods: This study investigates SPD traits and their associations with self-report and behavioural measures of impulsivity. A total of 201 outpatients (50% female) with clinically significant psychiatric symptoms aged 18 to 87 years old (M = 39.66, SD = 13.76) completed study measures. Six facets of the Personality Inventory for DSM-5 (PID-5) characterize SPD as operationalized in Section III of the DSM-5-TR: unusual beliefs/experiences, cognitive/perceptual dysregulation, eccentricity, restricted affectivity, withdrawal, and suspiciousness. Self-report measures of impulsivity (UPPS-P Impulsive Behavior Scale) and performance-based measures of risk taking propensity (Balloon Analogue Risk Task), response inhibition (Go-No-Go Task and Stop Signal Reaction Time Task), and valence weighting (Beanfest) were completed. Bayesian Pearson's r correlations between SPD traits and impulsivity outcome measures were conducted. To examine the combinative effects of SPD

traits using a person-centered approach, latent profile analyses were performed to distinguish whether profiles with high levels of SPD traits showed differentiation in self-report measures and performance-based, neurocognitive tasks.
Results: Negative urgency (r=.36-.41, BF10>100) and positive urgency (r=.38-.50, BF10>100) showed moderate associations with unusual beliefs, suspiciousness, eccentricity, and perceptual dysregulation. Lack of perseverance was linked with suspiciousness (r=.25, BF10>30) and withdrawal (r=.24, BF10>30) with smaller effect sizes. There were no meaningful associations between lack of premeditation and SPD traits (0<BF10<1). Valence weighting was negatively associated with eccentricity (r=-.28, BF10>100); there were no other associations between SPD traits and behavioural tasks (0<BF10<1).
In line with previous studies, latent profile analyses favored a three-profile solution (AIC= 3099; BIC=3185; Entropy = .85) of high, medium, and low SPD traits. Bayesian ANOVAs revealed no differences between groups across behavioural tasks (0<BFM<1). However, the high SPD group scored higher than moderate SPD and low SPD groups in self-report negative and positive urgency (BFM>100).

Discussion: Consistent with previous findings, this study revealed moderate associations between emotional urgency and SPD traits. Eccentricity was negatively associated with valence weighting and positively associated with negative urgency based on performance-based and self-report tasks, respectively. Results suggest SPD traits are linked with both negative attitude formation in neutral scenarios and strong impulses to act in emotionally charged situations. Future studies may examine whether these two tendencies have combinative effects in enhancing impulsive action under conditions involving negative emotions.

S16. BIOMARKERS OF BLOOD BRAIN BARRIER DYSFUNCTION IN THE PSYCHOSIS SPECTRUM: IMPLICATIONS FOR TREATMENT STRATEGIES

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Background: The primary function of the blood brain barrier (BBB) is to selectively allow passage of certain molecules into the brain while excluding most, in order to protect the brain's integrity and maintain homeostasis. This is largely accomplished through tight junctions found between epithelial cells located in brain vasculature and the choroid plexus of the ventricular system to a lesser extent. However, rather than being completely impermeable to external molecules, recent studies show that the BBB may be dysfunctional in several neuropsychiatric disorders including schizophrenia. Here, we review the published evidence for abnormal permeability of the BBB in schizophrenia as reflected by certain biomarkers. We also summarize some of the potential consequences of BBB porosity on neural inflammation and microglial activation, and the possible implications for developing novel treatment strategies.
Methods: A PubMed review was carried out using the keywords BBB, schizophrenia, psychosis, tight junctions, astrocytes, claudin, occludin, JAM, choroid plexus, CSF markers, immune markers, ROS, and microglia. There were no restrictions on date, but included controlled studies and systematic reviews published in English.
Results: There were 31 human imaging, animal, cell culture, and clinical studies that met our criteria. All studies featured either the blood-CSF barrier or the BBB, with most identifying a relationship to aspects of schizophrenia or psychosis. Studies showed that while there was no single biomarker for BBB pathology in schizophrenia, decline in claudin-5 (a major element of BBB tight junctions) appears to be associated with psychotic symptoms. Neuroinflammation

may also be mediated by inappropriate passage of peripheral white blood cells (WBC) through the BBB in schizophrenia as indicated by high CSF levels of adhesion molecules and cytokines. Moreover, this inflammation could subsequently suppress activity of T regulatory cells, which perpetuates neuro-inflammation in schizophrenia.
Discussion: Our literature review shows that there is evidence of increased BBB porosity that may contribute to the pathophysiology of schizophrenia and related psychoses, and that a decrease in proteins essential to tight junction integrity may ultimately lead to increased risk of neuroinflammation. This suggests that future treatments could include mending gaps in the BBB by correcting the the low level of claudin-5 and reducing inflammation. However, more research is needed to determine which anti-inflammatory treatments are most efficacious and how standard pharmacotherapy with antipsychotic agents impacts BBB integrity.

S17. HEAD CIRCUMFERENCE TRAJECTORIES IN AUTISM AND PSYCHOTIC EXPERIENCES

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Background: Early brain overgrowth is a replicated neurophenotype associated with autism while psychotic disorders are more commonly associated with attenuated volumes. Head circumference, which can be used as a proxy measure for brain development, may offer insights into distinct neurobiological trajectories in these two disorders which have previously shown overlap in genetics and negative symptomology.
Methods: Head circumference measurements were collected in the ALSPAC birth cohort at birth and ages 7 and 15 years in over 3000 participants, as well as smaller focus groups of ~ 700 participants at an additional 10 timepoints. Autism diagnosis was assessed using maternal questionnaires at age 9 years. Psychotic experiences were assessed using the Psychosis Like Experiences Semi-Structured Interview at age 18 years. Analyses of covariances assessed group differences in head circumference.
Results: Autism was associated with significantly larger head circumference compared to controls at birth ($F(1:5927) = 4.6$, $p = 0.03$) and a similar trend at age 7 years ($F(1:6275) = 3.45$, $p = 0.06$), with no difference at age 15 ($p = 0.26$). In contrast, psychotic experiences were associated with a trend towards reduced head circumference at birth ($p = 0.06$) and a significant reduction at age 7 compared to controls in a dose-dependent manner of severity ($F(3:4027) = 3.58$, $p = 0.01$). Post-hoc tests revealed significantly smaller head circumference in females with psychotic experiences compared to female controls ($p < 0.001$), with no significant group differences in males. Additional longitudinal analyses are currently underway (multi-level modelling for repeated measures).
Discussion: Differences in childhood head circumference in both autism and psychosis compared to healthy volunteers indicates the presence of atypical neurodevelopment. The finding of divergent trajectories across the two disorders suggest that head circumference may act as an early biomarker to distinguish autism from psychotic experiences.

S18. CELLULAR IMMUNOPHENOTYPE OF PSYCHOSIS AND THE ROLE OF INTERLEUKIN-6; A MULTI-COLOUR FLOW CYTOMETRY APPROACH WITH FUNCTIONAL ASSAYS

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Background: The burden associated with schizophrenia and other psychoses is one of the largest globally, with over 21 million people affected, resulting in 15-20 years of life lost per patient.
Current antipsychotic drugs are ineffective for around one-third of patients, and the same proportion display elevated blood cytokine levels. This low level of non-resolving inflammation may predict poor response to existing dopaminergic treatments. Several meta-analyses show that interleukin (IL)-6 is elevated in the blood and cerebrospinal fluid of patients, including patients in their first episode of psychosis and even before antipsychotic treatment initiation. Large prospective studies show that increased blood IL-6 during childhood precedes the onset of psychotic symptoms and experiences during adulthood. Mendelian Randomization suggests thatgenetically determined elevated IL-6 is causally related to schizophrenia aetiology and brain abnormalities, irrespective of confounding by lifestyle factors or reverse causation. It is becoming evident that not all but only a subset of patients have immune dysfunction. IL-6 induces cell activation via phosphorylation of STAT3 (pSTAT3), which can be inhibited by tocilizumab, a humanised anti-IL-6 receptor monoclonal antibody. Currently, however, there is a remarkable scarcity of investigations addressing immune mechanisms using peripheral blood mononuclear cells (PBMCs) in psychosis. We are investigating intracellular functional assessments of IL-6-related pathways (STAT3) in PBMCs to identify immune-relevant subgroups of psychosis. This study is part of the UK MRC PIMS, a multi-site experimental medicine study testing the effect of tocilizumab in psychosis pathogenesis and mechanisms.

Methods: We optimised a multi-colour flow cytometry assay that will be used to characterise the absolute number, frequency, and function of a variety of PBMC subsets isolated from the blood ofpatients in the early stages of psychosis and healthy controls. This deep-immunophenotyping protocol also includes an optimised phosflow assay to determine STAT3 phosphorylation in PBMCs after exogenous IL-6 exposure. Briefly, PBMCs were isolated from human leucocyte cones using SepMate density gradient centrifugation and quantified using a haemocytometer and resuspended in complete RPMI media. PBMCs (1 x 106 cells/well) were then stimulated with exogenous recombinant human IL-6 at different concentrations (0.1, 1, 10, 100 ng/mL) after incubation with tocilizumab (20 ug/mL) or vehicle. The geometric mean of fluoresce intensity (MFI) of total PBMCs was evaluated to select the optimal dose of exogenous IL-6. The proportion of pSTAT3 at different cell populations (CD14+ and/or CD16+monocytes, CD56+natural killer cells, CD3+ T cells,

CD3+CD56+ natural killer T cells, CD4+ T helper, CD8+ T cytotoxic, and CD25+CD127-CD39 Tregs) was measured by multi-colour flow cytometry (CytoFLEX, Beckman Coulter) after fixation, permeabilization, and staining procedures. All experiments were performed in triplicates.

Results: Exogenous IL-6 evoked increases in intracellular pSTAT3 in a dose-response fashion (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 wassubstantially inhibited by pre-incubating cells with tocilizumab (geometric mean±SD, minimum 358.3±1.0; maximum: 611±1.12). Using IL-6 at 10 ng/mL, we observed an augmented percentage of pSTAT3 in both innate and adaptive immune cells, with a significant decrease by pre-treatment with tocilizumab. pSTAT3 inhibition among innate cells included monocytes, such as intermediate CD14+CD16+ (72.6%) and classic CD14+ CD16- (47.6%). Inhibition in adaptive immune cells included CD3+CD56+ natural killer T cells (62.2%), CD4+ T helper (54.0%), Tregs CD25+CD127-CD39- (50.8%), T cells CD3+ (45.8%), Tregs CD39+ (22.7%), and CD8+ T cytotoxic (22.3%). Less responsive cells included CD56+ NK cells (7.7%) and non-classic CD14-CD16+monocytes (8.7%).

Discussion: Functional assessment of IL-6/STAT3 signalling in various subtypes of immune cell subsets could help in the identification of immune-dysregulated subgroups of psychosis and give better chances of effective and personalised treatments, and the development of novel targeted
treatments. This optimised protocol is now being applied to patients' samples.

S19. THE ASSOCIATION BETWEEN OBESITY AND CLINICAL OUTCOMES IN PATIENTS ON CLOZAPINE

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Background: Studies had found that antipsychotic-induced weight gain (AIWG) was associated with better clinical outcomes in adult schizophrenia spectrum disorder patients1,2. A systematic review with a total of 6063 patients with schizophrenia and related severe mental illness found that 22 of 31 independent studies reported a link between AIWG and therapeutic benefit3. Clozapine has specific indication for use in treatment resistant schizophrenia (TRS) and is associated with the greatest liability for weight gain among all antipsychotics. In this study, we seek to examine the association between obesity and metabolic morbidities with clinical outcomes in patients on clozapine.

Methods: We conducted a cross-sectional study at the Institute of Mental Health on patients aged 21 to 80 years, on a stable dose of clozapine for 2 weeks. Socio-demographic information, duration of illness, current medication regime, past antipsychotic exposure, smoking status, were collected through interviews and reviews of medical records. Weight, height, and waist circumference were also collected during the visits. All patients were assessed using the Structured Clinical Interview for DSM-IV-TR (SCID-I) to ascertain diagnoses. Each participant underwent a clinical assessment on the Positive and Negative Syndrome Scale (PANSS) with trained raters with established inter-rater reliability at >0.8. Linear regression model was performed to examine association between BMI and remission status in patients with schizophrenia. The final model included age, sex, duration of clozapine use and daily clozapine dosage. Remission in schizophrenia was determined using Andreasen criteria4.

Results: 159 individuals with schizophrenia or schizoaffective disorder were recruited. The mean age of patients was 40.01 years, majority were males (64.2%) and Chinese (85.5%). 69

(43.4%) patients were under or normal weight (i.e. BMI < 23), and 90 (56.6%) patients were overweight and obese (i.e. BMI ≥ 23) . Between the two groups. there were no significant differences in age, sex, duration of clozapine treatment or clozapine dose. BMI was significantly higher in the symptom remission group (26.6 kg/m2 vs 24.2 kg/m2, p = 0.007). In the regression model, BMI was significantly associated with remission status (p=0.047, adjusted R2=0.119), suggesting it to be a predictor for remission in patients with schizophrenia, who were on clozapine.

Discussion: Our study found a high proportion of overweight and obesity among patients on clozapine. Further, we found that BMI was significantly associated with patients on clozapine who were in symptomatic remission. This is in keeping with prior hypothesis of treatment-emergent weight gain as a prognostic indicator of therapeutic improvement5. Further research is needed to examine the mechanisms underpinning AIWG and clinical outcomes in schizophrenia.

S20. CHARACTERIZATION OF EARLY PSYCHOSIS PATIENTS CARRYING A GENETIC VULNERABILITY TO REDOX DYSREGULATION: A COMPUTATIONAL ANALYSIS OF MECHANISM-BASED GENE EXPRESSION PROFILE IN FIBROBLASTS.

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Background: In view of its heterogeneity, schizophrenia needs new diagnostic tools based on mechanistic biomarkers that would allow early detection. Complex interaction between genetic and environmental risk factors may lead to NMDAR hypofunction, inflammation and redox dysregulation, all converging on oxidative stress. Our aim was to identify (1) the role of a genetic background of vulnerability (GAG-gclc polymorphism) to redox dysregulation on different pathways in patients, (2) pathways that may be altered by other risk factors (genetic or environmental) in patients and (3) potential protective pathways that may be induced in controls bearing the same genetic vulnerability to redox dysregulation. Overall, this pathway analysis may lead to a specific biological profile of gene expression that would discriminate between patients and controls.

Methods: Using computational analysis, the expression of 76 genes linked to redox dysregulation, inflammation and NMDAR hypofunction, known to be abnormally regulated in schizophrenia, was studied in skin-fibroblasts from early psychosis patients (EPP) and age-matched controls (HC) (N = 30), under additional pro-oxidant challenge to mimic environmental stress. To evaluate the contribution of a genetic risk related to redox dysregulation, we investigated the GAG trinucleotide polymorphism in the key glutathione (GSH) synthesizing enzyme, glutamate-cysteine-ligase-catalytic-subunit (gclc) gene (GAG-gcl low risk-LR and high risk-HR), known to be associated with the disease. computational analysis consisted of a Principal Component Analysis (PCA), followed by a factorial analysis with a parsimax rotation, and a multivariate correlation matrix, with multiple correction. A discriminant analysis was done using the 2 or 4 groups, followed by the Support Vector Machine (SVM) algorithm.

Results: EPP and HC showed different gene-expression profiles that were modulated by GAG-gclc genotypes in combination with oxidative challenge. In GAG-gclc LR genotype EPP, a

global gene expression dysregulation was observed, especially in the antioxidant system, potentially induced by other risks. Both HC and EPP with GAG-gclc HR genotype showed similar gene expression profiles. However, under oxidative challenge, a boosting of other antioxidant defense, including the master regulator Nrf2 and thioredoxine systems was observed only in gclc-GAG HR HC, suggesting a protective compensation against the genetic GSH dysregulation. Moreover, RAGE (redox/inflammation interaction) and AGMAT (arginine pathway) were increased in the gclc-GAG HR EPP, suggesting some additional risk factors interacting with this genotype. Finally, the use of a machine-learning approach allowed discriminating EPP and HC with an accuracy up to 100%, paving the way towards early detection of schizophrenia.

Discussion: Our computational approach based on the expression of genes related to hypothesis-driven pathways highlighted some mechanisms involved in the early pathophysiology of SZ. We found specific signatures converging on oxidative stress even in patients not carrying the GAG-gclc genetic risk for redox dysregulation. In contrast, we identified compensatory antioxidant mechanisms that protect the controls bearing the same genetic risk. Thus, by combining machine learning with a well-chosen set of genes, we identified novel disease-related pathways and obtained a highly accurate approach to identify patients at the early stage of the disease. In turn, this approach may improve early detection and intervention for the disease.

S21. DO MOTOR SYMPTOMS INFLUENCE THE DIGITAL SPEECH ASSESSMENT OF NEGATIVE SYMPTOMS IN SCHIZOPHRENIA SPECTRUM DISORDERS?

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Background: Alterations in speech and language are prominent symptoms of schizophrenia, including negative symptoms (e.g., alogia, blunted affect). There is growing interest in using computational speech analysis to provide an objective and quantitative assessment of negative symptoms, which may help overcome limitations of symptom rating scales and enhance symptom monitoring and clinical prediction. However, it remains unclear whether digital speech variables are influenced by comorbid motor symptoms in schizophrenia (e.g., drug-induced extrapyramidal symptoms and movement disorders), which may represent a potential confounding variable in the use of objective speech as markers of negative symptom severity. In the present study, we examined whether motor symptoms were significantly associated with speech markers of negative symptoms in a sample of schizophrenia spectrum inpatient participants.

Methods: Baseline data were analyzed from 44 schizophrenia spectrum disorder inpatient participants completing a prospective longitudinal cohort study of acute psychosis. Negative symptoms were assessed using the Scale for the Assessment of Negative Symptoms (SANS) and motor symptoms were assessed with the Extrapyramidal Symptom Rating Scale (ESRS), which rates parkinsonism, akathisia, tardive dyskinesia, and dystonia. Speech was recorded while participants completed several tasks using the Winterlight Labs iOS app: paragraph reading, picture description, open-ended narratives, and phonemic and semantic verbal fluency. A set of eight acoustic and 10 timing variables capturing key speech production features were extracted for each participant from transcribed speech recordings. Associations between speech and negative symptoms, and speech and motor symptoms (ESRS global impression scores) were analyzed using partial Kendall rank correlations, adjusted for age and sex. The threshold for statistical significance was set at $p < .05$, corrected for the false-discovery rate (FDR) within

each task. Bayesian analyses were used to further evaluate evidence for the presence or absence of associations between speech and motor symptoms.
Results: One acoustic feature and eight timing features were significantly associated with negative symptom severity scores (Kendall's tau correlations = -0.37-0.31), and most feature associations were observed across multiple tasks. Correlations between speech and motor symptoms focused on parkinsonism (present in 57% of participants) and akathisia (present in 25% of participants), as tardive dyskinesia and dystonia were absent in >90% of participants. No association between speech features and parkinsonism or akathisia survived FDR correction; however, six features were associated with akathisia and one feature was associated with parkinsonism prior to FDR correction. Nonetheless, Bayes factors provided no more than anecdotal support for the alternative hypothesis for all but one feature (mean fundamental frequency; BF10 = .28; moderate support), and this feature was not associated with negative symptom severity. For speech features associated with negative symptom severity, Bayes factors indicated moderate support (BF01 > 3) for the absence of an association between speech and motor symptoms (i.e., the null hypothesis) for most features.
Discussion: Objective speech features are sensitive to negative symptom severity and do not appear to be confounded by motor symptoms in schizophrenia spectrum disorders. Additional research using samples with more severe comorbid motor symptoms and that examines other factors that may influence speech production (e.g., culture, cognition, medication) will help to further validate the digital speech-based assessment of negative symptoms.

S22. MENARCHE IS A NEURODEVELOPMENTAL CONTEXT IMPACTING ON THE HIPPOCAMPUS AND SEVERITY OF PSYCHOTIC-LIKE EXPERIENCES

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Background: Sex differences in psychosis onset and severity suggest that estrogen may be a protective factor. However, the precise protective mechanisms are still unclear. One explanation is that increased estrogens benefit neurogenesis in the hippocampal and increase plasticity and may reduce hippocampal dysconnectivity and volume redutions that are characteristically observed in psychosis. As a result, menarche- an indicator of available estrogen during critical adolescent development- may be related to the presence or severity psychosis-like experiences (PLE).
Methods: This study examined whether menarche would relate to PLE symptom severity and whether it would moderate the relationship between hippocampal volume and PLE symptom severity. PLE symptoms severity and hippocampal volume were examined in 4163 female participants (746 post-menarche and 3417 pre-menarche; age 8–13) using a cross-sectional approach using the Adolescent Brain Cognitive Development (ABCD) study.
Results: Menarche- the availability of circulating estrogen- (t=2.72) and hippocampal volume (t=2.43) have unique contributions to the severity of PLEs, there is also an interactive effect demonstrating that individuals who have smaller volumes despite the neuroprotective effects of estrogen on hippocampus have higher PLE severity (t=2.07).
Discussion: These findings may suggest vulnerability transcends protective effects of estrogens through development. These findings highlight the critical interplay between these developmental processes and highlight the importance of exploring the understudied impacts of pubertal development on neural mechanisms related to the emergence of psychosis-like symptoms.

S23. INFLAMMATORY PROTEIN ALTERATION CHANGES IN ACUTE AND CHRONIC STAGES OF SCHIZOPHRENIA SPECTRUM DISORDERS: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

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Background: Immune system involvement has been widely implicated in the aetiology and pathophysiology of schizophrenia. In people with schizophrenia spectrum disorders (SSD), changes in peripheral levels of inflammatory biomarkers, such as cytokines, has been cited as evidence for this immune hypothesis. However, there are inconsistencies throughout the literature concerning which specific inflammatory markers are altered in schizophrenia, and whether these alteration patterns differ between acute and chronic stages of illness. A systematic review and network meta-analysis was conducted to address this research question.
Methods: A systematic search was performed in PsycINFO, PubMed, CINAHL, EMBASE, and the Cochrane Central Register of Controlled Trials to identify studies published before the 31 March 2022 that had measured peripheral (plasma and serum) levels of inflammatory proteins in both cases of SSD and healthy controls without mental illness. Using both pairwise and network meta-analysis techniques, this study measured whether there were significant differences in mean levels of peripheral proteins between groups of acute SSD, chronic SSD, and healthy controls.
Results: The systematic search and screening process yielded 215 included articles with available data for meta-analysis. Network meta-analysis highlighted two distinct groups of peripheral markers. The first group consisted of peripheral markers that were significantly elevated ($p<0.05$) in both acute and chronic SSD consistently, when compared against healthy controls; these markers were interleukin (IL)-1β, IL-1 receptor antagonist (IL-1RA), soluble interleukin-2 receptor (sIL-2R), IL-6, IL-8, IL-10, tumor necrosis factor (TNF)-α, and high sensitivity C-reactive protein (hsCRP). The second group of markers were inconsistently altered between acute and chronic SSD cases, when compared against healthy controls: interferon (IFN)-γ and IL-2 were significantly elevated ($p<0·05$) in acute SSD only, whilst IFN-γ, IL-4, and IL-12 were instead decreased significantly ($p<0·05$) in chronic SSD. Aside from these groups, IL-17 was the only marker that was not significantly altered in both acute and chronic SSD.
Discussion: This study's findings suggest that there is a baseline degree of peripheral inflammatory protein alteration throughout both acute and chronic SSD stages, as per the group of consistently altered proteins which are hypothesised here as potential trait markers. Conversely, the group of markers that underwent inconsistent alteration patterns between stages of illness are hypothesised as possible state markers of SSD, which may represent dynamic superimposed immune activity that fluctuates throughout the course of illness. These findings are useful to the ongoing search for clinically relevant biomarkers of SSD that can be utilised for diagnosis and intervention, yet further research is required to examine whether peripheral inflammatory changes are mirrored in the central nervous system.

S24. APPLICATION OF BIOMARKERS OF TREATMENT RESPONSE TO THE STUDY OF RELAPSE IN SCHIZOPHRENIA

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Background: Following an acute psychotic episode, maintenance treatment for relapse-prevention is recommended. During this phase of treatment, clinicians and patients are currently limited in making predictions about relevant questions, such as how long the treatment should be, or whether they should anticipate a decrement in treatment responsiveness over time. Neuroimaging biomarkers could potentially inform these clinical decisions, but they need to demonstrate "state-like" properties, validity, and ultimately clinical utility. Here, we study the "state-like" properties of the striatal connectivity index (SCI), the functional striatal abnormalities (FSA), two validated resting state fMRI biomarkers of treatment response, and neuromelanin MRI, a biomarker of illness severity, with various aspects of maintenance treatment in schizophrenia.

Methods: In one cohort of maintenance treatment (n=34), we studied the association between mean symptom severity during 3 months of continuous treatment guaranteed by a long-acting injectable antipsychotic and SCI/FSA values, as well as the association between those same baseline SCI/FSA values and time to relapse during up to 2 years of LAI treatment. In a separate sample of relapsing individuals (n=50), we studied the association between treatment exposure upon relapse and SCI/FSA values. Both samples went through the same resting state fMRI acquisition protocol, which was used to generate individual SCI and FSA values. Neuromelanin sensitive MRI was acquired for a subset of the first cohort (n=25), preprocessed and analyzed to generate mean contrast to noise ratios (CNR) for region of interest analyses.

Results: Individual SCI/FSA values were not associated with the mean illness severity of the preceding 3 months of guaranteed antipsychotic treatment (r=0.06,p=0.72/r=1.21,p=0.52), and they were neither predictive of subsequent time to relapse while on LAI treatment (HR=0.93,p=0.81/HR=0.89,p=0.43). NM-MRI CNR was also not associated with treatment responsiveness (r=0.18, p=0.47) or subsequent time to relapse (HR=1.25, p=0.53). In the cohort of acutely ill individuals, lower SCI was associated with relapse despite guaranteed treatment delivery vs relapse after treatment discontinuation (d =0.58,p=0.032), though this was not the case for FSA (d=0.13,p=0.67).

Discussion: "State-like" properties of these biomarkers were not consistently shown in a way that would justify using them in their current form for validation studies in maintenance treatment. More research is needed to generate relapse specific biomarkers in schizophrenia that could be used in validation studies.

S25. COGNITION AND EDUCATIONAL ACHIEVEMENT IN THE TORONTO ADOLESCENT AND YOUTH (TAY) COHORT STUDY: RATIONALE, METHODS, FEASIBILITY, AND EARLY DATA

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Background: Impairments across multiple cognitive domains are related to psychopathology. The intelligence quotient as well as domains such as attention, working memory, learning and memory, processing speed, and executive function are impaired across psychiatric disorders, including in those with psychosis spectrum symptoms (PSS). Educational achievement is similarly negatively impacted across psychiatric disorders and linked to the development of psychotic disorders. The Toronto Adolescent and Youth Cohort study (TAY) follows 3000 youth aged 11-24, who are seeking treatment for mental health, over 5 years to characterize the trajectories of PSS, suicidality, and functioning. We outline methods and baseline cognitive and educational data collected for the first 10% of this sample, providing early data regarding the feasibility of this large-scale cohort investigation as well as quality control metrics and descriptives.

Methods: A sample of 300 youth and emerging adults aged 11 to 24 years were recruited between June 2021 - May 2022. Participants underwent an extensive baseline assessment including diagnostic and clinical characterization of psychopathology, substance use, cognition, and functioning. Follow-up assessments will occur biannually over 5 years. Participants completed a multi-informant comprehensive clinical assessment including validated diagnostic measures such as the Kiddie-SADS and self-report assessment of educational achievement; report cards were also requested. The package of cognitive measures aligns with the Adolescent Brain Cognitive Development and other large-scale youth-focused cohort studies including the NIH Toolbox, Rey Auditory Verbal Learning Test, Wechsler Matrix Reasoning Task, and Little Man Task.

Results: Participants met diagnostic criteria for an average of 3 to 4 mental disorders, most frequently anxiety disorders (80%) and depressive disorders (72%). Notably, 48% met criteria for PSS according to the PRIME revised criteria. 82% of the total sample completed cognitive testing. Cognitive tasks were well-tolerated and participants expressed interest in not only receiving their cognitive results but also sharing these results: with their providers. Cognitive task performance was generally normally distributed, and did not differ across demographic features, as anticipated. 87% of the total sample completed the educational attainment questionnaire. Report cards were collected for 45% of participants, occasioning modified procedures to optimize the timing of this data collection to increase available data. Participants meeting criteria for PSS demonstrated lower performance on key cognitive indices than those that did not, including the total, fluid, and crystalized cognitive composite scores of the NIH Toolbox, with small to medium effect sizes (all corrected $p < 0.05$).

Discussion: The current investigation provides initial evidence for the feasibility and distributional properties of educational and cognitive outcomes in youth seeking treatment for mental health. Educational outcomes such as report cards presented initial challenges; modifications to workflows have already resulted in improved data access. Cognitive tasks were consistently and robustly delivered and offered opportunities for integration between clinical and research activities. At baseline, youth with PSS had additional adverse impact in relation to cognitive functioning and educational outcomes. Longitudinal data may enable the identification of youth at greatest risk for psychosis based on cognitive and educational variables.

S26. THE MEDIATING ROLE OF INFLAMMATORY BIOMARKERS IN THE DEVELOPMENT OF EMOTIONAL PROBLEMS AND PSYCHOTIC EXPERIENCES IN ADOLESCENCE FOLLOWING EARLY LIFE ADVERSITY

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Background: Early life adversity (ELA) is associated with the development of psychopathology later in life. As both ELA and psychopathology have been shown to be associated with immune activation, inflammation has been proposed as a potential mechanism by which experiences of ELA could lead to the development of mental health problems. While most studies have focused on adults, here we investigated this potential mechanism in early adolescence.

Methods: A total of n=157 school adolescents, aged 11-14 (mean=12.8 years SD=0.9, 48% males) completed the Community Assessment of Psychic Experiences (CAPE), the Strengths and Difficulties Questionnaire (SDQ) and the Childhood Experience of Care and Abuse (CECA). We estimated levels of C-Reactive Protein (CRP) and cytokines (including IL-2, IL-6, IL-8, IL-12, IL-13, IL-4, IFN-gamma, TNFalpha, IL-1 and IL-10). A weighted CAPE score was calculated to estimate frequency and distress level of psychotic experiences. A weighted ELA score was calculated which considered frequency and severity of participants experiences across different adversity subtypes. We first conducted a series of univariable analyses to test the association between ELA, psychotic experiences and SDQ, and levels of inflammatory biomarkers. A mediation analysis was then performed to assess the effect of inflammation on the relationship between ELA and psychopathology.

Results: A total of 38% of participants reported some psychotic experiences (mean score=0.21 SD=0.4). The mean SDQ total score was 11.3 (SD=5.9) and the mean ELA score was 3.3 (SD=2.4). The emotional problems SDQ subscale was analysed separately due to the known relationship between ELA and affective symptoms. The mean emotional difficulties score in this sample was 3.1 (sd = 2.1).

A higher ELA score was positively correlated with higher CAPE score ($r= 0.33$, $p<0.001$) and higher SDQ total difficulties score ($r = 0.37$ $P <0.001$). Higher ELA scores were also positively correlated with higher CRP ($r= 0.21$, $p=0.007$) and IL-10 ($r=0.18$, $p=0.02$) levels. The CAPE score was not correlated with any inflammatory markers, while the SDQ total and emotional problem scores were correlated with higher CRP levels ($r=0.17$, $p=0.04$ and $r=1.78$, $p=0.02$ respectively). Higher emotional problems were also negatively correlated with lower IL-12 levels ($r=-0.19$, $p= 0.02$). In a linear regression model, ELA and CRP levels explained 16% of the variance in emotional problems score, with gender also significantly contributing to this model ($R2= 0.16$, $p<0.001$). Furthermore, the mediation analysis showed that CRP levels had a small but significant mediating effect on the relationship between ELA and SDQ emotional difficulties score (indirect effect = 0.03, $p<0.001$).

Discussion: The experience of ELA was significantly associated with psychotic experiences and psychopathology. However, inflammatory markers and specifically levels of CRP mediated only the relationship between ELA and emotional difficulties. This might reflect the finding of low scores for psychotic experiences in this school adolescent sample. Alternatively, it could also suggest that the mediating effect of immune activation is specific to the relationship between early adversity and the onset of emotional difficulties. Future research

will investigate the longitudinal trajectory of the relationship between ELA, inflammation, and mental health to identify the crucial time windows where interventions might be most beneficial in vulnerable individuals.

S27. DIETARY FLAVONOIDS INTAKE AND ITS RELATIONSHIP WITH PSYCHOPATHOLOGY IN ADOLESCENTS

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Background: Clinical trials have indicated that dietary flavonoids (polyphenolic compounds that are abundant in foods of plant origin) have a protective effect on cardiovascular and mental health, and cognition. Cumulative preclinical evidence has also suggested this may be related to their anti-inflammation effect. This is interesting considering that elevated levels of pro-inflammatory cytokines (such as TNF-α) and C-reactive protein (CRP) have been associated with psychopathology, mostly in adults. However, the relationship between flavonoid intake and psychopathology in children has not been explored, and no study has evaluated the role of inflammation in this relationship.

Methods: A total of n=122 school young adolescents (mean age 13.05 years ±1.00) were included in this study. Dietary flavonoids were estimated using the European Prospective Investigation into Cancer - Food Frequency Questionnaire (EPIC-FFQ) with the Phenol-Explorer 3.0 and the United States Department of Agriculture (USDA) databases. Psychopathology included the assessment of psychotic experience, depression, anxiety, internalising and externalising behaviours, and dysregulation. We evaluated blood levels of CRP and cytokines (TNF-α, IFN-γ, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-13). Dietary flavonoid intakes and inflammatory biomarkers values were log-transformed. We used Principal Component Analysis (PCA) to reduce the dimensions of dietary flavonoids, inflammation, and psychopathology, respectively, and the number of components was determined based on the Kaiser criterion. Mediation models were conducted by Hayes PROCESS macro for SPSS to test the role of inflammation in the relationship between dietary flavonoid intake and psychopathology.

Results: One component was extracted for psychopathology with cumulative loadings being 66%, and one component for dietary flavonoids with cumulative loadings being 52%, including anthocyanins, flavan-3-ols, proanthocyanins, flavanones, flavones, and flavonols. Two components were obtained for inflammation with cumulative loadings being 50%, which were component 1 (IL-2, IL-4, IL-8, IL-10, IL-12, IL-13) and component 2 (CRP, TNF-α, IL-6, IFN-γ). When adjusted for daily energy intake, flavonoid intake was negatively correlated with psychopathology (r=-0.207, p=0.023), but not with inflammation components. Inflammatory biomarkers were not found to be a mediator in the relationship between dietary flavonoids intake and psychopathology, with standardised indirect effects being -0.006 (95%CI: -0.041, 0.014) and -0.013 (95%CI: -0.054, 0.021), respectively for two inflammation components.

Discussion: Our findings show that already in adolescence a higher flavonoid intake is potentially associated with better mental health. While we did not find that inflammatory markers explained this relationship, future studies with a larger sample size and a longitudinal approach would be crucial to establish the role of the immune system on the potentially beneficial effects of flavonoids-rich diets.

S28. WHOLE PERSON MODELING OF ADOLESCENT PSYCHOSIS SYMPTOMS USING AN EXPLAINABLE GRADIENT BOOSTING BASED MACHINE LEARNING APPROACH

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Background: Adolescence is critical developmentally, with psychosis spectrum symptoms in early life increasing subsequent risk for serious illness, poor functioning, and long-term disability'. However, our understanding of the combined impact of behavioral, biological, cognitive and sociodemographic features on psychosis spectrum symptoms is limited. Most analyses seek to understand the influence of only one or a few data types, with minimal consideration for cross-domain, non-linear, or interactive effects. Our approach, whole-person modelling, uses machine learning to combine these features iteratively to understand the constellation of their effects.

Methods: We analyzed data from 11195 participants from the Adolescent Brain Cognitive Development (ABCD) study, an ongoing, population-based study of youth aged 9-10 being followed for 10 years. All participants receive comprehensive behavioral, biological, cognitive, and sociodemographic assessments. Our primary outcome was psychosis spectrum symptoms (PSS), measures by the prodromal questionnaire brief version. Summed responses were tested both as binarized and continuous variables. To build our whole-person model, we used a non-linear, tree-based machine learning algorithm - eXtreme Gradient Boosting (XGBoost) - iteratively combining layers of input features as reported by the participant or their parent. These layers included individual features (e.g. sociodemographic, blood hormone levels, physical health, and life events), family features (e.g. history of mental illness, parenting behaviors, and caregiver acceptance), immediate community features (school engagement, peer relationships, and residential neighborhood crime), and broader environment features (e.g. state level indicators of sexism, racism and sexual orientation bias). We built two sets of model, including and excluding of measures of psychopathology and neurocognition as predictors ("psych predictors"). Hyperparameters were tuned on a training data subset (80%, n=8956) and performance was evaluated on a held out validation set (20%, n=2239). SHapley Additive exPlanations (SHAP) analysis was used to measure feature importance.

Results: Our whole-person model of the presence or absence of PSS (binary) excluding psych predictors had a balanced accuracy of 69.6%, with the top five features being gender identity, family environment conflict, effect of negative life events, parental monitoring, and total number of life events. This model marginally outperformed models with only individual (66.6), individual and family (68.1%), and individual, family and immediate community features (69.0%). Inclusion of neurocognition and psychopathology features increased model accuracy (71.3%) with the top features representing problem behaviours and again included gender identity. Models of the continuous measure of psychosis symptoms explained 28.6% and 31.3% of variability, excluding and including psych predictors, respectively.

Discussion: Our data-driven whole person modeling approach created a biopsychosocial profile of adolescence psychosis illustrates the effect of psychosis risk and protective factors in consort and can potentially enable clinicians to take into account the full spectrum of possible

trajectories. We found that gender identity was among the top five features that had the most influence in both our models, underscoring its importance relative to other often-studied influences such as a family environment and adverse life events which ranked lower. Furthermore, family history of specific mental illnesses was not among the top five features.

S29. REVIEW OF THE TAAR1 AGONIST ULOTARONT: PART II - SUMMARY OF INITIAL CLINICAL EFFICACY/SAFETY RESULTS

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Background: Ulotaront is a trace amine-associated receptor 1 (TAAR1) agonist with serotonin 5-HT1A agonist activity whose efficacy in schizophrenia is distinguished from the antipsychotic class by its lack of D2 and 5-HT2A receptor blockade. Ulotaront has received FDA Breakthrough Therapy Designation for treatment of schizophrenia, and WHO, based on the INN naming convention, has specified "-taront" as the stem for this new drug class. Here we summarize ongoing clinical research characterising the efficacy and safety profile of ulotaront as a member of the novel TAAR1 agonist class.

Methods: Summarised are results from a double-blind, placebo-controlled study to evaluate the efficacy and safety of ulotaront (50 mg or 75 mg) in an acute exacerbation of schizophrenia, and a 6-month, open-label follow-up study. Also summarized are post-hoc analyses comparing the effect of ulotaront vs. lurasidone on negative symptoms (based on a Marder PANSS negative symptom factor [MPNS] enrichment strategy); and analyses comparing key safety and adverse event (AE) domains for ulotaront vs. atypical antipsychotics (APs), including an Empirical Bayes Geometric Mean (EBGM) analysis of the FDA Adverse Event Reporting System (FAERS) database.

Results: In the double-blind study, short-term treatment with ulotaront was associated with significant ($p<0.001$) endpoint improvement in the PANSS total score (effect size [ES]: 0.45), the CGI-Severity score (ES: 0.52) and the Brief Negative Symptom Scale (BNSS) total score (ES: 0.48) [1]. In a post-hoc enrichment analysis of clinical trials in schizophrenia, ulotaront demonstrated moderate-to-large treatment effects on negative symptoms with an endpoint MPNS factor score effect size of 0.84 (vs. 0.33 on the atypical antipsychotic lurasidone). The incidence of any AE was lower on ulotaront compared to placebo (45.8% vs. 50.4%), and the number needed to harm (NNH) for individual AEs on ulotaront were all >40. Results of additional NNH analyses, and EBGM analyses of the FAERS database, both found treatment with ulotaront to be associated with markedly lower risk of both antipsychotic class-related AEs (EPS, akathisia, somnolence, nausea/vomiting), and adverse safety events frequently associated with APs (weight gain, increase in metabolic labs, prolactinemia). The follow-up study [2] further confirmed the tolerability of ulotaront, with a 6-month completion rate of 67%, which compares favourably to benchmark 6-month completion rates in the CATIE study [3] (e.g., olanzapine, 55%; risperidone, 43%; quetiapine, 29%). Furthermore, 6 months of treatment was associated with a mean change from open-label baseline of -22.6 in PANSS total score and -1.0 in CGI-Severity score.

Discussion: The emerging profile of ulotaront, based on initial clinical trials, is characterized by statistically significant improvement in positive and negative symptoms of schizophrenia. The safety and tolerability profile of ulotaront is markedly different with respect to class-related AEs that are characteristic of both first- and second-generation antipsychotics. The benefit-risk profile of ulotaront, as a member of a novel TAAR1 agonist class, is distinguished from antipsychotics by lack of D2 and 5-HT2A receptor blockade.

S30. EVENAMIDE, A NEW CHEMICAL ENTITY, BENEFITS PATIENTS WITH TREATMENT-RESISTANT SCHIZOPHRENIA WHEN USED AS AN ADD-ON TO ANTIPSYCHOTICS: FINAL RESULTS FROM A PHASE II, INTERNATIONAL, RANDOMIZED STUDY

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Background: Resistance to treatment with antipsychotics (APs; at least 2) has been noted in ~30% of patients with schizophrenia. Treatment-resistant schizophrenia (TRS) may occur in up to 20% of first-episode patients, while another ~20% develop it within 5 years of starting AP treatment. TRS is associated with increased morbidity, suicidality, and mortality [1]. Clozapine, the only treatment approved for TRS, is used by <20% of these patients, due to its risks and side effects, and the fact that only ~30% of clozapine-treated patients show benefit. Findings from neurochemistry, neuro-metabolism, and functional imaging in TRS patients indicate abnormalities in glutamatergic neurotransmission [2], rather than excess dopamine synthesis [3,4], indicating the need to attenuate glutamate release. Evenamide, a selective inhibitor of voltage-gated sodium channels, devoid of activity at >130 CNS targets, normalizes glutamate release without affecting basal glutamate levels, and demonstrates benefits in animal models of psychosis as monotherapy and add on to APs, reversing deficits produced by amphetamine, scopolamine, phencyclidine, or ketamine. Combination of ineffective doses of evenamide and other APs, including clozapine, is associated with similar benefits, suggesting synergies in mechanisms that may benefit poor responders to current APs.

Methods: This is a 6-week, randomized, rater-blinded, multi-center, international study (India, Italy and Sri Lanka) to evaluate the safety, tolerability and preliminary evidence of efficacy of evenamide (7.5, 15 and 30 mg bid, po) in patients with TRS [5] not responding to a stable therapeutic dose of an AP. Efficacy was assessed on the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression – Severity/Change (CGI-S/C), while tolerability was assessed based on all safety measures. Patients were initially randomized to doses of 7.5 and 15 mg bid; after assessment of safety in the first 50 patients, randomization to 30 mg bid was approved by the ISMB. Patients completing Study 014 could continue in a 1-year extension study. Patients were moderately to severely ill (CGI-S of 4 to 6), with a PANSS total score of 70-90 and prominent positive symptoms (score ≥4 on at least 2 core symptoms; PANSS Positive total ≥ 20), along with functional deficits (GAF ≤50). Efficacy (ratings performed by a psychiatrist blinded to the evenamide dose) and safety assessments were conducted at 1 to 2-week intervals. Change from baseline within each dose group will be analyzed for the PANSS and CGI-S using a paired t-test. Descriptive statistics will be provided for the proportion of responders (score of 1, 2 or 3) on the CGI C at endpoint. Exploratory between-group comparisons will be performed for the PANSS total score to evaluate dose-response, using a mixed-model repeated measures (MMRM) approach, with a gate-keeping strategy to adjust for multiple comparisons.

Results: A total of 161 patients were randomly assigned to treatment in Study 014 (≥50/group); the last patient will complete the study in mid-January. Final results for all safety and efficacy (PANSS; CGI-S/C) assessments will be presented. Disposition data collected to date demonstrate a low rate of dropouts (5.0%), in particular for adverse events (0.6%), indicating good tolerability of evenamide (7.5, 15 or 30 mg bid); 94% of patients entered the extension.

Discussion: This is the first international trial of a drug acting on the glutamate system as an add-on to a single typical or atypical AP in patients with TRS. Positive results from this study

would lead to an international, Phase 3, double-blind, placebo-controlled study of evenamide as add-on to APs in patients with TRS.

S31. A PILOT FEASIBILITY, ACCEPTABILITY, AND EFFECT STUDY OF THE SOCIAL SKILLS AND EMOTION REGULATION TRAINING "SSERT" FOR TRAUMA IN PSYCHOSIS: STUDY PROTOCOL AND INTERIM RESULTS

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Background: Childhood adversity is a causal factor in the development of schizophrenia (SZ). A rich literature describes the disruption in emotion regulation and social functioning resulting from adversity in the general population. Such impairments are also evident in SZ. Research examining trauma-focused (TF) therapies for SZ present important limitations, notably high dropout rates and engagement and adherence difficulties to protocol-based intervention. This pilot study will evaluate the feasibility, acceptability, and effect of a flexible preparatory intervention to address known limitations. The Social Skills and Emotion Regulation Training "SSERT" for trauma in psychosis uses psychoeducation, emotion regulation and social skills-building to promote engagement and adherence prior to TF work. Here we describe the SSERT trial and assess preliminary feasibility, acceptability, and accessibility.

Methods: SSERT is a CBT-based intervention delivered weekly in 10, 60min individual sessions. Intervention goals are to 1) promote awareness of the relationship between childhood adversity, psychosis, emotion regulation, and social functioning difficulties, 2) build emotion awareness and regulation capacity to, 3) facilitate more effective social functioning. SSERT is currently being tested in a non-randomized pilot trial using a single arm baseline and post-intervention design (Trial registration NCT05100875). Adults (n = 20) with SZ and a history of adversity will be recruited. This mid-point interium analysis assesses 1) preliminary feasibility per study completion and adverse event rates, 2) acceptability per participant responses on the Satisfaction with Therapy Questionnaire (STQ) and the Client Satisfaction Questionnaire (CSQ), and 3) accessibility for hybrid (in-person and/or remote) sessions, to identify potential protocol adaptations and/or barriers to accessibility. Effects on emotion regulation, social functioning, and clinical measures will be reported at trial completion.

Results: Interim results included 10 participants, of which 8 completed SSERT (7 completed 10 sessions, 1 completed 8). One participant withdrew consent during the baseline evaluation. The other was clinically unstable at session 1 and discontinued the intervention at session 3. Of the 8 completers, 7 attended remotely and 1 attended a hybrid format. No intervention-related serious adverse events occurred and no barriers to accessibility were identified. Per the STQ, all participants were satisfied with SSERT (88% very satisfied, 12% satisfied). All participants 1) found homework exercises helpful (75% very helpful, 25% slightly helpful), 2) reported a better understanding their problems (50% strongly agree, 50% agree), 3) discovered new coping methods (62% strongly agree, 38% agree), and 4) had increased confidence to approach activities (50% strongly agree, 50% agree). Most reported increased ability to cope with moods and new ways to deal with social situations (25% strongly agree, 63% agree, 12% unsure). Per the CSQ, participants' experience attending SSERT was either excellent (75%) or good (25%). All would recommend SSERT, and all would continue the intervention if possible. Finally, one participant reported that "The behaviour and emotional regulation strategies, and

SMART goal setting were helpful and something new that I learned to help myself with the trauma."

Discussion: Interim results suggest that SSERT is feasible and acceptable, within an accessible hybrid modality. Participants were satisfied with the intervention, found SSERT helpful to explore the impact of trauma on psychosis, emotion regulation and social functioning, and developed new coping skills. As such, no protocol adaptations are currently deemed necessary.

S32. TRAJECTORIES AND RISK OF HOSPITALIZATION FOR PSYCHOSIS FOLLOWING PSYCHOSTIMULANT INITIATION IN INDIVIDUALS WITH PSYCHOTIC DISORDER: A REAL-WORLD STUDY

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Background: Attention-deficit/hyperactivity disorder (ADHD) is frequent in people with schizophrenia spectrum psychotic disorders (SZSPD) and significantly interferes with their functioning and recovery. Due to their well-documented effectiveness, psychostimulants (i.e., methylphenidate and amphetamines) are the first-line pharmacological treatment for ADHD in the general population. However, their use in people with SZSPD is limited by the sparse evidence and long-standing concerns about an increased risk of psychotic events. Thus, the aim of this study was to examine whether the initiation of a psychostimulant in these individuals was associated with an increased risk of hospitalization for psychosis in the following 12 months compared with the year prior to its initiation.

Methods: This is a retrospective cohort study using data extracted from the Régie de l'Assurance Maladie du Québec (RAMQ) registries. The study cohort included all patients who initiated psychostimulants or atomoxetine between January 1, 2010, and December 31, 2016, with continuous public drug plan coverage 1 year before and 1 year after psychostimulant initiation (index date), and with a prior diagnosis (from 2002 to the index date) of SZSPD. Patients claiming no antipsychotic treatment 30 days before and after psychostimulant initiation were excluded. The primary outcome was time to hospitalization for psychosis within 1 year of the index date. Secondary outcomes were time to hospitalization for any mental health disorder and for mental disorders other than psychosis. To assess whether individuals who initiated psychostimulants were comparable to the rest of the SZSPD population without psychostimulant use, a control cohort was composed using controls matched for sex, year of birth (± 3 years), and date of first psychosis (± 1 year).

Results: Among 2226 individuals who initiated a psychostimulant during the observation period, 1589 (71.6%) initiated methylphenidate, 339 (15.3%) amphetamines, and 291 (13.1%) atomoxetine. Compared with their matched controls, substance use disorders, personality disorders, and use of concomitant psychotropic drugs other than antipsychotics were more prevalent. After adjusting for confounders, there was a reduced risk of hospitalization for psychosis among individuals receiving an antipsychotic and a psychostimulant in the year after its initiation (adjusted hazard ratio 0.36, 95% confidence interval 0.25-0.54, $p < .0001$). Similar results were found when examining the risk of hospitalization for any mental disorder, and for mental disorders other than psychosis.

Discussion: These findings suggest that the use of psychostimulants in individuals with SZSPD may be safer than generally conveyed and justify that some patients may be allowed to benefit from adequate treatment of comorbid ADHD in order to support their recovery.

S33. SOMNOLENCE AND SEDATION WITH LUMATEPERONE TREATMENT: A COMPARISON OF MORNING AND EVENING ADMINISTRATION

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Background: Lumateperone is an FDA-approved antipsychotic to treat schizophrenia and depressive episodes associated with bipolar I or bipolar II disorder as monotherapy and as adjunctive therapy with lithium or valproate. Lumateperone has a unique mechanism of action that simultaneously modulates serotonin, dopamine, and glutamate neurotransmission. In placebo-controlled acute trials in patients with schizophrenia, lumateperone 42 mg administered in the morning was effective and well tolerated with a favorable safety profile. The only treatment emergent adverse events (TEAEs) that occurred at a rate >5% and twice placebo were dry mouth, somnolence, and sedation. An open-label long-term study of stable patients switched from standard of care (SOC) to lumateperone 42 mg administered in the evening further supported the safety and tolerability of lumateperone treatment.
Evaluation of these acute and long-term studies provides better understanding of the effects of morning vs evening administration of lumateperone on TEAEs of somnolence and sedation.

Methods: Data were pooled from 3 acute (4 or 6 week) placebo-controlled studies to evaluate lumateperone 42 mg administered in the morning in patients with an acute exacerbation of schizophrenia; 2 of the studies had risperidone 4 mg as an active control. Data from the open-label 1-year trial evaluated patients switched from SOC treatment to lumateperone 42 mg administered in the evening. Assessments included rates and severity of somnolence and sedation TEAEs and time to resolution.
Results: The short-term safety population comprised 1,073 patients (placebo, 412; lumateperone 42 mg, 406; risperidone 4 mg, 255). The long-term safety population comprised 602 patients (lumateperone 42 mg). Somnolence was reported less frequently with evening administration of lumateperone 42 mg (4.8%) than in patients administered lumateperone 42 mg in the morning (16.0%). Rates of sedation with lumateperone were also notably decreased with evening administration (1.0%) relative to morning administration (7.6%). In controlled, short-term trials, risperidone had similar rates of both somnolence (16.5%) and sedation (7.5%) as lumateperone. Rates of somnolence (5.3%) and sedation (4.6%) were lower with placebo.
In short-term studies, the majority of somnolence TEAEs were of mild intensity for lumateperone 42 mg (77%), risperidone 4 mg (81%), and placebo (77%); all sedation TEAEs were of mild intensity for lumateperone 42 mg and placebo, and 84% were mild in the risperidone group. In the 1-year open-label study, most TEAEs of somnolence (76%) and sedation (83%) were of mild intensity and none were of severe intensity.

Median time to resolution of somnolence with lumateperone treatment was similar in the long-term study (25.5 d) and short-term studies (26.0 d). Time to resolution of sedation was also similar in long-term (24.5 d) and short-term studies (29.0 d). In short-term trials, risperidone and placebo had similar times to resolution as lumateperone for somnolence (risperidone: 27.5 d; placebo: 27.5 d) and sedation (risperidone: 29.5 d; placebo: 21.5 d).

Discussion: Though limited by differences in study design, this post hoc analysis of acute and long-term studies suggests that sedation and somnolence events with lumateperone 42 mg are transient, usually mild, and are less frequent with evening administration.

S34. SAFETY AND EFFICACY OF KARXT (XANOMELINE–TROSPIUM) IN SCHIZOPHRENIA IN THE PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED EMERGENT-2 TRIAL

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Background: KarXT combines the M1/M4 preferring muscarinic receptor agonist xanomeline and the peripherally restricted anticholinergic trospium. In the phase 2 EMERGENT-1 study, KarXT met the primary endpoint of a significant reduction in Positive and Negative Syndrome Scale (PANSS) total score through week 5 vs placebo, improved other key secondary efficacy measures, and was generally well tolerated.
Methods: EMERGENT-2 was a phase 3, randomized, double-blind, placebo-controlled, 5-week trial of KarXT in acutely psychotic patients with schizophrenia in the inpatient setting. Eligible patients were randomized 1:1 to KarXT or matched placebo. Dosing of KarXT (mg xanomeline/mg trospium) started at 50 mg/20 mg BID and increased to a maximum of 125 mg/30 mg BID. The primary efficacy endpoint was change from baseline to week 5 in PANSS total score. Key secondary endpoints included change from baseline to week 5 in PANSS positive subscale, PANSS negative subscale, and PANSS negative Marder factor scores compared with placebo. Efficacy analyses were performed using the modified intent-to-treat population (patients with ≥1 dose of study medication, a baseline PANSS assessment, and ≥1 postbaseline PANSS assessment). All patients receiving ≥1 dose of study drug were included in safety analyses.
Results: 252 US patients were enrolled. KarXT demonstrated a statistically significant and clinically meaningful 9.6-point reduction from baseline to week 5 (effect size=0.61) in PANSS total score vs placebo ($p<0.0001$); a significant improvement in PANSS total score was demonstrated starting at week 2 (first postbaseline rating) and continued through the study end. KarXT also met key secondary endpoints. Results at week 5 included a 2.9-point reduction in PANSS positive subscale score with KarXT vs placebo ($p<0.0001$), a 1.8-point reduction in PANSS negative subscale score with KarXT vs placebo ($p=0.0055$), and a 2.2-point reduction in PANSS negative Marder factor score with KarXT vs placebo ($p=0.0022$). KarXT was generally well tolerated. Overall discontinuation rates were similar with KarXT (25%) and placebo (21%). The overall treatment-emergent adverse events (TEAEs) rate for KarXT and placebo was 75% and 58%, respectively. Discontinuation rates related to TEAEs were similar between KarXT (7%) and placebo (6%). Rates of serious TEAEs were similar with KarXT and placebo (2%, each group); no serious TEAEs were determined to be drug related. The most common TEAEs (>5%) with KarXT were all mild to moderate in severity and included constipation, dyspepsia, nausea, vomiting, headache, blood pressure increases, dizziness, gastroesophageal reflux disease, abdominal discomfort, and diarrhea. KarXT was not associated with weight gain, Parkinsonism, dystonia, akathisia, prolactin elevation, or sedation, which are common AEs of current antipsychotic medications.

Discussion: KarXT has the potential to be the first in a new class of treatments for patients with schizophrenia and a promising alternative to postsynaptic dopamine D2 receptor antagonists.

35. DOES TDCS CHANGE SYNAPTIC DENSITY IN THE BRAINS OF PATIENTS WITH SCHIZOPHRENIA?

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Background: Schizophrenia is a chronic disorder that affects approximately 1% of the world's population. The primary treatment for patients with schizophrenia is antipsychotic medications. However, approximately 25-30% of patients show partial or no response despite optimal treatment strategies. Moreover, antipsychotic medications have limited efficacy in treating negative or cognitive symptoms, suggesting the need for alternative treatment approaches. Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation method involving the application of a low-intensity electric current (≤2 mA) on the scalp via anodal and cathodal electrodes. Several studies demonstrated that tDCS improves positive, negative, and cognitive symptoms of schizophrenia. Despite the promising clinical outcomes with tDCS, the mechanism through which it achieves its effects remains largely unknown. The aims of this study are: (i) to examine if tDCS increases synaptic density in patients with schizophrenia, as measured with the novel positron emission tomography (PET) radiotracer [18F]SynVesT-1, which is currently the best method for measuring synaptic density in humans in vivo, and (ii) to assess if changes in synaptic density are associated with improvements in clinical symptoms.
Methods: This double-blind, sham controlled study will include up to 20 participants with schizophrenia recruited from the tDCS-Adherence parent study (NCT05435300). Participants will be randomized to receive either: (1) dual hemisphere active bi-parietal (anode right (P4), cathode left (P3)), or (2) dual hemisphere sham tDCS in the same regions. PET scans will occur pre and post treatment. Clinical assessments will occur pre and monthly for 3 months post treatment.
Results: It is expected that dual hemisphere active bi-parietal tDCS will be associated with increased synaptic density beneath the stimulated anode, as measured by [18F]SynVesT-1, and improvements in clinical symptoms in comparison with sham tDCS. Data will be ready for presentation by the conference date.
Discussion: The proposed study will assess whether tDCS induces changes in synaptic density in patients with schizophrenia. The results of this study can help elucidate the mechanism of tDCS in patients and provide support for larger treatment-controlled studies to determine if tDCS is a practical means of inducing lasting clinical benefits for schizophrenia. Further, this study will help elucidate the neuroplastic mechanisms that may contribute to the clinical benefits of tDCS.

S36. POPULATION PHARMACOKINETIC MODELING AND SIMULATION OF D2 RECEPTOR OCCUPANCY FOLLOWING DOSES OF TV 46000, AN EXTENDED RELEASE SUSPENSION OF RISPERIDONE FOR TREATMENT OF SCHIZOPHRENIA

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Background: TV 46000 is a long-acting subcutaneous antipsychotic (LASCA) injection with flexible dosing either once monthly (q1m) or once every two months (q2m) for the treatment of schizophrenia. Population pharmacokinetic (PopPK) modeling was used to characterize the pharmacokinetics (PK) of the parent drug, risperidone and the active metabolite, 9-OH risperidone, and to describe the time course of total active moiety (risperidone + 9-OH risperidone, TAM) exposure in comparison to oral risperidone dose regimens. Pharmacokinetic/pharmacodynamic modeling (PK/PD) was applied to predict dopamine D2 receptor occupancy (D2RO) levels from observed (oral risperidone) and predicted (TV 46000) TAM concentrations using a previously published model (Gomeni R et al. JCP 2013;53:1010–1019).

Methods: As the PopPK model included rich phase 1 PK data and sparse phase 3 PK data, two and three-fraction absorption models with first-order absorption with or without transit compartments were considered. A stepwise covariate analysis and model evaluations were performed. The PopPK model calculated TAM exposure at steady-state for use in PK/PD simulations to determine TV-46000 dose levels and intervals that will maintain estimated median D2RO levels within clinically acceptable range over the dosing interval (Vanover KE et al. Neuropsychopharmacology 2019;44:598–605).

Results: The PK of risperidone was best described by a 1-compartment model, with a double first-order absorption route (1 fast and 1 slow) and first-order elimination. The PK of 9-OH risperidone was best described by a 1-compartment model with first-order input from the risperidone compartment and first-order elimination. Simulations of TAM concentrations following TV-46000 administration identified that dose strengths for either q1m (50, 75, 100, or 125 mg) or q2m (100, 150, 200, or 250 mg) provide adequate exposure over 28 and 56 days with comparable exposure to daily doses of oral risperidone exposure 2-5mg/day. TAM concentrations reached therapeutic levels rapidly within 24 hours, with no lag time. The previously described relationship between TAM concentrations and D2RO were used to estimate the D2RO profile (a simple Emax model with Emax 100% and kd of 10.1 ng/mL).1 In general, for both the q1m and q2m dose regimens, the majority of the estimated median profile was within the preferable range of D2 receptor occupancy.

Discussion: The sequential parent metabolite model adequately described the PK of risperidone and 9-OH risperidone. Estimated TAM exposure following TV-46000 q1m and q2m dosing regimens was sustained over time and comparable to established oral risperidone regimens. Simulated D2 receptor occupancy identified TV-46000 dosing regimens that would provide therapeutic exposure levels of TAM to treat patients with schizophrenia.

S37. EXPOSURE–RESPONSE ANALYSIS TO COMPARE CHANGES IN THE CLINICAL ENDPOINTS FOR TARDIVE DYSKINESIA AND CHOREA IN HUNTINGTON DISEASE FOLLOWING ONCE-DAILY AND TWICE-DAILY TABLET FORMULATIONS OF DEUTETRABENAZINE

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Background: Deutetrabenazine (Austedo, Teva), as a twice daily (BID) formulation, is an approved treatment for tardive dyskinesia (TD) and chorea associated with Huntington disease (HD). Exposure (deuterated active metabolites, total (α+β)-HTBZ) – response (AIMS and UHDRS-TMC) models were developed from the phase 3 studies in patients with TD and HD following BID administration of deutetrabenazine. A newly developed once-daily (QD) extended release formulation has shown to deliver similar daily exposure to the BID formulation. The exposure-response (ER) models were leveraged to predict the changes in the clinical efficacy endpoints in patients with TD and patients with HD, following administration of the QD formulation, and to determine if there were differences in exposure and response due to the use of the different formulations.
Methods: The ER models were applied using simulated exposure levels of total (α+β)-HTBZ after administration of the BID and QD formulation to obtain predicted improvements in mean change from baseline in AIMS total motor score at week 12 for patients with TD and mean change from baseline in UHDRS-TMC score at week 12 for patients with HD-associated chorea. Different measures of metabolite exposure, average plasma concentration under steady state conditions (Cavg,ss) and maximum plasma concentrations under steady state conditions (Cmax,ss) were tested to assess impact on the clinical endpoints.
Results: The predicted placebo-corrected mean changes in AIMS scores in TD patients with Cavg,ss for total daily doses 12mg, 24mg, and 48mg were -1.75, -2.06, -2.68 and -1.72, -2.00, -2.57 for the BID and QD formulations, respectively. The predicted placebo-corrected mean changes in UHDRS-TMC scores in HD patients with Cavg,ss were -2.67, -2.95, and -3.50; and -2.65, -2.90, and -3.40 for total daily doses 12mg, 24mg, and 48mg for the BID and QD formulations. The predicted differences in absolute changes in AIMS and UHDRS-TMC scores between the BID and QD formulations were minimal with 90th percentiles overlapping, when assessing the impact of exposures (Cmax,ss versus Cavg,ss as predictor).
Discussion: Modeling predicted a ≥ 2-point decrease from baseline in the AIMS total motor score and an approximate 3 point decrease in the UHDRS-TMC score on average with the maintenance daily doses of 24mg and 48mg deutetrabenazine using both the BID and QD formulations.

S38. ASSESSMENT OF DOSE PROPORTIONALITY OF THREE DOSE STRENGTHS (6 MG, 12 MG AND 24 MG) OVER THE CLINICAL DOSE RANGE (6-48 MG) OF THE NEWLY DEVELOPED ONCE-DAILY EXTENDED-RELEASE TABLET FORMULATION OF DEUTETRABENAZINE

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Background: Deutetrabenazine (Austedo, Teva), a twice-daily (BID) formulation, is an approved treatment (daily doses 6-48mg) for tardive dyskinesia and chorea associated with Huntington disease. A newly developed once-daily (QD) extended-release formulation has been shown to deliver similar daily pharmacokinetic (PK) exposure to the BID formulation. A phase 1 study was conducted to assess the dose proportionality of three dosage strengths (6mg, 12mg and 24mg), and across recommended clinical dose range (6mg – 48mg), for the QD tablet formulation of deutetrabenazine.

Methods: In a randomized phase 1 study (Study TV50717-PK-10175), healthy adult males and females (n = 116) received single administrations of the QD formulation in a fed state (2×6mg, 1×12mg, 1×24mg, 2×24mg). Safety was assessed and blood samples for PK were collected pre-dose and up to 96 hours post-dose. The following PK parameters were computed: maximum plasma concentration [Cmax], area under the plasma concentration curve from time 0 to 36 hours [AUC0-36h], AUC from time 0 to last observed concentration [AUC0-t], and AUC extrapolated to infinity [AUC0-inf]) of deutetrabenazine, and active metabolites, deuterated α-HTBZ and β-HTBZ (individually and as a sum). A power model was fitted to describe the relationship between dose and PK parameters using a mixed model with sequence, period, and dose as fixed effects; and subject as random effect. To determine dose proportionality starting at 6mg, geometric mean ratios (GMRs) and 90% CIs were calculated for Cmax, AUC0-t, and AUC0-inf to assess relative bioavailability between 2x6mg and 1x12mg.
Results: GMRs and 90% CIs for Cmax and AUCs fell within the bioequivalence limits of 80.00%-125.00%, demonstrating similarity between 2x6mg and 1x12mg tablets. Dose proportionality was demonstrated for the PK parameters (Cmax, AUC0-36h, AUC0-inf), and all analytes for QD formulation dose strengths 6mg, 12mg, and 24mg; and over the clinical dose range (6-48mg), as the 90% CIs for the slopes were contained within 0.839 to 1.161 and 0.839 to 1.107, respectively.
Discussion: The QD formulation of deutetrabenazine exhibits dose proportional pharmacokinetics for dosage strengths (6mg, 12mg and 24mg), and across the full clinical dose range (6mg - 48mg).

S39. EFFECTS OF LONG-TERM DEUTETRABENAZINE TREATMENT IN PATIENTS WITH TARDIVE DYSKINESIA AND UNDERLYING PSYCHIATRIC DISORDERS

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Background: Deutetrabenazine is FDA approved for the treatment of tardive dyskinesia (TD) in adults. In two 12-week pivotal trials (ARM-TD/AIM-TD), deutetrabenazine significantly improved Abnormal Involuntary Movement Scale (AIMS) scores and was well tolerated. This post hoc analysis examined efficacy and safety of long-term deutetrabenazine treatment in patients with TD and comorbid psychiatric illness (schizophrenia/schizoaffective disorder [SCZ] or mood disorder [MD; bipolar/depression/other].
Methods: Patients who completed ARM-TD or AIM-TD were eligible to enroll in the 3-year, open-label extension (OLE) study (RIM-TD; NCT02198794). Deutetrabenazine was titrated based on dyskinesia control and tolerability. Change from baseline in total motor AIMS score, Patient Global Impression of Change (PGIC), and Clinical Global Impression of Change (CGIC) and adverse events (AEs) were analyzed by comorbid psychiatric illness.
Results: 337 patients in the OLE study were included in the analysis: 205 patients with SCZ (mean age, 55 years; 50% male; mean 6.4 years since diagnosis; 92% taking a dopamine

receptor antagonist [DRA]) and 131 patients with MD (mean age, 60 years; 35% male; mean 4.6 years since diagnosis; 50% taking a DRA). At week 145, mean (standard error [SE]) dose was 40.4 (1.1) mg/day in the SCZ subgroup (n=88) and 38.5 (1.2) mg/day for the MD subgroup (n=72). Mean (SE) changes from baseline to week 145 in AIMS scores in the SCZ and MD subgroups were –6.3 (0.49) and –7.1 (0.58), 56% and 72% achieved treatment success ("much improved" or "very much improved") per PGIC, and 66% and 82% achieved treatment success per CGIC. Overall, AE incidence (exposure-adjusted incidence rates [incidence/patient-year]) was low: any AE, 1.02 and 1.71; serious AEs, 0.10 and 0.12; and AEs leading to discontinuation, 0.07 and 0.05.
Discussion: Long-term deutetrabenazine treatment provided clinically meaningful improvements in TD-related movements, with a favorable benefit–risk profile, regardless of underlying comorbid psychiatric illness.

S40. MINDFULNESS BASED GROUP PSYCHOTHERAPY IN COMBINATION WITH OXYTOCIN FOR PATIENTS WITH SCHIZOPHRENIA SPECTRUM DISORDERS AND THE ROLE OF GENETIC VARIANTS OF OXYTOCIN RECEPTORS – A STUDY PROTOCOL AND RESULTS OF THE PILOT STUDY

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Background: The effectiveness of current treatment options for socio-cognitive deficits and negative symptoms (NS) in schizophrenia spectrum disorders (SSD) remains limited. The cause of NS is thought to be an interference between the mesocorticolimbic dopamine system for social reward expectancy and the network for socioemotional processes. Oxytocin (OXT) may enhance functional connectivity between these neuronal networks. Lower plasma OXT levels correlate negatively with NS severity and deficits in social cognition in SSD. It has been shown that intranasal OXT administration improves social cognition, including empathy, in healthy subjects but in SSD results are inconsistent. According to the social salience hypothesis, the effect of OXT varies depending on the social context and individual factors. Also, OXT-mediated effects on psychopathology, NS, and empathy may depend on genetic variants of OXT receptors (OXTR). In a pilot study, we demonstrated a reduction in NS by OXT administration in a positive social context in SSD. We also demonstrated that NS and other symptoms in SSD improved after mindfulness-based group psychotherapy (MBGT). The aim of this study in subjects with SSD is to examine the effect of combining OXT administration with MBGT on NS, empathy, affect, and stress. The main hypothesis to be tested is that the use of OXT compared to placebo prior to MBGT in patients with SSD will result in a greater reduction in NS.
Methods: The research design is based on an experimental, triple-blind, randomized, placebo-controlled trial. The manualized MBGT sessions are led by two psychotherapists over four weeks. Four sessions take place once a week in a group of six patients. The effects of OXT peak after 30-80 minutes for optimal reinforcement of social behavior. Therefore, patients receive 24 I.U. of OXT or placebo intranasally 30 minutes prior to each therapy session. Plasma OXT levels will be determined by radioimmunoassay. Recruitment will take place at the Department of Psychiatry and Neurosciences, Charité University Medicine, Berlin, Germany.

To exclude gender bias, both women and men will join mixed-sex groups controlled for hormones. The nasal sprays are indistinguishable according to the manufacturer's instructions. Change in NS as the primary endpoint will be measured with validated interviews (Positive and Negative Syndrome Scale, PANSS) and psychometric questionnaires (Self-Evaluation of Negative Symptoms, SNS) and analyzed by ANCOVA with the treatment condition and the respective assigned training group as covariates. Variables, including plasma OXT levels, will be measured at baseline and postintervention. Based on a conservative effect size of f = 0.25, a 1:1 randomization, a power of 80%, a two-sided significance level of 5%, and an expected drop-out rate of 10%, a total of N = 140 subjects will be recruited. The role of genetic variations of the OXTR genes for the NS will be looked at exploratively.
Results: The outlined study is dedicated to the question to what extent the positive effects of MBGT can be improved by augmentation with OXT. Based on the results of our pilot study, it is hypothesized that augmenting MBGT with OXT will significantly improve NS in patients with SSD.
Discussion: Current pharmacological and psychotherapeutic approaches are not efficient enough to adequately treat NS and socio-cognitive deficits of SSD. Therefore, new treatment strategies are urgently needed. Positive evidence for the benefits of augmented psychotherapy is mounting. The effect of combining MBGT with OXT has not yet been studied. The results of this study could hopefully pave the way for a more personalized and complementary psychiatric treatment of patients with SSD.

S41. PREOCCUPIED WITH THE PRESENT: EVIDENCE FROM QUANTIFYING THE BAYESIAN SURPRISE OF TIME ORIENTATION FROM SPEECH IN FIRST EPISODE PSYCHOSIS

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Background: Most psychotic disorders (e.g., depression, schizophrenia, bipolar illness) feature impaired time orientation (TO). TO implies temporal reasoning about events, people, and actions in the world where we live. Also, it implies a lexicon (i.e., meaningful vocabulary) grammatically constrained in language structure referred to as verb tenses (e.g., Past, Present, and Future tenses). We hypothesize that in schizophrenia, impaired TO is both reflected in the psychopathology of conceptual disorganization (a feature of formal thought disorder) and observed in the distinctive use of verb tenses.
Methods: First Episode Psychosis (FEP), Clinical High Risk (CHR), Healthy Control (HC), and Chronic Schizophrenia subjects (18 per group) produced three 1-minute speech samples describing pictures from the Thematic Appreciation Test. We investigated the conditional dependence of verb-tense use (focus past, focus present, and focus future) on group using a Bayes network. The probabilistic model comprised nodes for group, verb-tense and potential mediators age, sex, conceptual disorganization from PANSS scale (P2 score), and pictures. After identifying the conditional dependence, we searched for the patient group that showed the largest difference in verb-tense use, relative to the HC group. Between-groups differences were estimated via the Kullback-Leibler divergence (i.e., Bayesian surprise or relative entropy –expressed in nats as the units of information).
Results: The Bayes network showed that the use of present tense (Mean = 14.7, Sd =2.95) was conditional upon group and picture and independent of sex, conceptual disorganization

symptoms, and age –given group. Neither the use of past tense (Mean = 0.74, Sd =0.94) nor the use of future tense (Mean = 0. 9, Sd=1.04) depended on group or picture. Without conditioning verb-tense use on picture, the FEP group showed the largest Bayesian surprise relative to the HC group (15.9 nats). Finally, after conditioning verb-tense use on picture, the FEP group showed the largest Bayesian surprise in the use of present-tense verbs only when describing two of the pictures.

Discussion: The Bayes network showed that the use of present-verb tense is a strong feature of FEP regardless of age, sex, and PANSS-P2 score. Relative entropy indicates that in the presence of FEP and without prior information on the visual scene (the picture), the use of a high proportion of present-verb tense is highly expected. We conclude that in the presence of FEP, individuals largely rely on their internal models of the world regarding the 'present state' to describe most visual scenes. The peak expression of psychotic symptoms (Conrad's "climax of psychotic revelation") likely reflects present (rather than past or future) states and events of the world. The picture-specific variability in the use of present-verb tense requires further fine-grained analysis (lexical and grammatical aspects) associated with the TO. To conclude, tracking progressive changes in temporality could be a reliable marker of group membership, relapse, or treatment resistance, using automated natural language processing methods in a Bayesian framework to improve diagnostic confidence.

S42. COMPUTATIONAL MODELLING OF TRIAL-BY-TRIAL CHANGES IN THE MISMATCH NEGATIVITY RESPONSE IN TREATMENT-SEEKING YOUTH: A FEASIBILITY STUDY

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Background: Computational models have emerged as a powerful tool for understanding psychosis symptoms, including hallucinations and delusions. According to predictive coding theory, psychosis symptoms are hypothesized to originate from disturbances in hierarchical information processing, more specifically the misattribution of salience to irrelevant sensory stimuli driven by aberrant precision-weighting of prediction errors (PEs). Whether such models are also able to explain one of the most reliable biomarkers for psychosis, namely the auditory mismatch negativity (MMN), remains unclear. This study investigates the feasibility of applying a hierarchical Bayesian model of learning to a novel version of the auditory oddball paradigm in youth seeking mental health services.

Methods: Our preliminary analyses focused on 45 help-seeking youth, aged 11-24, recruited as part of the Toronto Adolescent and Youth Cohort (TAY) study between June 2021 - October 2022. TAY seeks to follow 3000 treatment-seeking youth over a 5-year period to assess

developmental trajectories of psychosis spectrum symptoms and functioning. The MMN was elicited using an auditory oddball paradigm with varying degrees of stability over time. We modelled single-trial EEG data using the Hierarchical Gaussian Filter and extracted belief trajectories of low-level sensory precision-weighted PEs ε2 and high-level volatility precision-weighted PEs ε3. We performed a model-based analyses to test whether trial-by-trial precision-weighted PEs correlated with EEG amplitude fluctuations over time. We report whole-volume family wise error corrected values at the peak level (ppFWE).

Results: We found significant correlations between low-level sensory precision-weighted PEs ε2 and EEG amplitudes peaking at 168 ms in central channels (peak, $F(1,37) = 35.82$; ppFWE = 0.005), at 172 ms in frontal channels (peak, $F(1,37) = 34.78$; ppFWE = 0.006) and 176 ms in temporo-parietal channels (peak, $F(1,37) = 31.89$; ppFWE = 0.012). In these clusters, higher low-level precision-weighted PE values, or more surprising events, correlated with more negative EEG amplitudes, coinciding with the timing of the auditory MMN. We also found significant correlations between high-level volatility precision-weighted PEs ε3 and EEG amplitudes peaking at 223 ms in temporo-parietal channels (peak, $F(1,37) = 55.14$; ppFWE < 0.001), at 301 ms in central channels (peak, $F(1,37) = 48.65$; ppFWE < 0.001) and 441 ms in central channels (peak, $F(1,37) = 28.31$; ppFWE = 0.022). The early ε3 cluster coincides with a later MMN component, while the second ε3 cluster coincides with the P3a component. The later ε3 cluster may be indicative of the reorienting negativity component, which typically peaks at latencies between 400 and 600 ms and signifies attentional reorientation.

Discussion: We find evidence for the role of hierarchical prediction error learning in MMN generation. Furthermore, in-line with previous studies, we find that earlier mismatch responses reflect low-level PEs about tones, while later mismatch responses reflect higher-level PEs about volatility of the auditory environment. Our findings highlight the value of computational models for understanding auditory perceptual inference and implicit, statistical learning in treatment-seeking youth. As a future direction, we will examine whether the representation of precision-weighted PEs predicts the emergence of psychosis spectrum symptoms at the individual level.

S43. LEXICAL PREDICTABILITY IN SCHIZOPHRENIA: A COMPUTATIONAL APPROACH TO QUANTIFYING AND UNDERSTANDING THOUGHT DISORDER

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Background: Language has long been considered a window into thought in schizophrenia. Computational language models allow us to extract objective, quantifiable data from natural speech that can potentially serve as a clinical biomarker. However, it is unclear how these measures relate to clinical symptoms (particularly positive thought disorder) and neurocognitive processes. In healthy adults, lexical predictability, the likelihood that a given word will be produced based on its prior context, is among the best predictors of behavioral processing and neural activity. There is also a large body of evidence that the predictability of language output plays an important role in communication. We therefore used a predictive language model, GPT-2, to quantify word-by-word predictability in natural speech from people with schizophrenia. We asked whether, relative to healthy adults, (a) lexical predictability is reduced in the language output of patients; (b) patients are relatively more impaired in using

global versus local context to produce upcoming words; and (c) whether these abnormalities are linked to clinical ratings of thought disorder.
Methods: We asked 74 first-episode psychosis patients (FEP), 16 chronic schizophrenia patients (CS), and 36 healthy controls to describe three pictures for one minute each. For each word in the transcribed speech, we used GPT-2 to extract measures of lexical predictability given different context lengths, ranging from all available context (very global) to only the previous word (very local). We then used mixed effects regression, controlling for demographic factors and item-level variables (e.g., transcript length), to test our hypotheses. Within the patient groups (FEP + CS combined), we also probed correlations with thought disorder, as measured using the Thought and Language Index (TLI).
Results: We found a main effect of Group on lexical predictability, such that the speech produced by FEPs was significantly less predictable than that produced by healthy controls (Est. = -0.09, p = 0.00); the difference between the CS group and controls was not significant (Est. = -0.06, p = 0.20), possibly due to the small sample size of the CS group. Moreover, there was a significant interaction between Group (FEP vs. controls) and Context Length (which ranged from 1 – 30 words), such that the effect of Context Length on predictability was smaller in the FEP group (Est. = -0.03, p = 0.00). Follow-up analyses confirmed that, as predicted, this interaction was driven by lower global predictability in the FEP group than in controls (Est. = -0.05, p = 0.03); in contrast, differences in local predictability were numerically smaller and non-significant (Est. = -0.01, p = 0.64). Among patients, the effect of Context Length on lexical predictability was smaller in patients with more severe thought disorder (a significant interaction between Context Length and TLI score; Est. = -0.01, p = 0.02). This effect was again driven by a reduced sensitivity to global context in patients with thought disorder.
Discussion: These findings suggest that the incoherent language output often seen in schizophrenia may relate to impairments in using global (vs. local) context. This is in line with previous neural evidence showing that patients with schizophrenia have difficulties using global (vs. local) context to predict upcoming words during language comprehension. At a mechanistic level, this work connects to a large body of research documenting abnormalities in predictive processing in schizophrenia across multiple domains. We suggest that lexical predictability may provide a useful metric that is easily quantified by computational models, has face validity with thought disorder, and may provide insights into neurocognitive mechanism.

S44. COMPUTATIONAL ANALYSIS OF AMOTIVATION IN SCHZIOPHRENIA BASED ON EXPLORATORY BEHAVIOR IN A VIRTUAL ENVIRONMENT

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Background: Negative symptoms of schizophrenia (SZ), such as amotivation, avolition, and anhedonia, are severely debilitating and result in diminished community functioning and quality of life. Intrinsically motivated exploration comprises one aspect of motivated behavior that may be impaired in SZ but has not been examined extensively. We, therefore, investigated how clinical amotivation in SZ relates to different types of exploratory behaviors assessed objectively in an experimental setting.
Methods: We analyzed data from 25 stable adult outpatients with SZ who were administered the Virtual Novelty Exploratory Task (VNET). The task allowed participants to freely explore

a virtual city without a given objective. Participants could encounter and interact with familiar objects (e.g., cars) and novel objects (e.g., spaceships) that were dispersed throughout the city. We characterized two types of exploratory behaviors based on participants' behavioral states during VNET: (1) interaction with familiar vs. novel objects ("novelty-driven behaviors"), and (2) exploration of the city in relation to time and distance ("time and distance behaviors"). To test whether these exploratory behavior types were related to amotivation, we used behavioral partial least square (PLS) regression with clinician-rated Apathy Evaluation Scale (AES) scores as the independent variable, while controlling for illness duration and medication dosage. We analyzed PLS-derived Bootstrap Weights (BWS) to determine which behavioral states contributed to any correlation between exploratory behavior types and AES scores – states with BWS > 2 were deemed robust. We subsequently performed post-hoc multiple regression analysis to assess relationships between behavioral states and AES scores.
Results: Our PLS analysis found a significant correlation between novelty exploration behaviors and AES scores ($r = 0.35$, $p = 0.015$). The behavioral state of "Familiar/Novel Objects Viewed" was the most robust (BWS = 4.69), indicating that the correlation was mainly driven by this behavior. Post-hoc multiple regression revealed "Familiar/Novel Objects Viewed" was strongly correlated with the AES ($R2 = 0.55$, $F = 8.31$, $p = 0.009$).
Discussion: Reduced novelty exploration behaviors (i.e., more familiar compared to novel object interaction) captured in a simulated naturalistic environment were correlated with greater amotivation captured by a standard clinical rating instrument. This relationship suggests that deficits in specific exploratory behaviors (particularly exploration invoked by novel stimuli) may share common underlying mechanisms with general amotivation in SZ. Further, these findings encourage the application of more complex behavioral models (e.g., Rescorla-Wagner model, Hierarchical Gaussian Filter model) to VNET performance, which may allow a more granular explanation of participants' exploratory behavior, and permit extensive validation based on Bayesian model comparison in conjunction with the prediction of clinical psychopathology. Such computational analyses potentially stand to provide a more refined mechanistic understanding of intrinsically motivated exploration and clinical amotivation, and ultimately advance treatment development for negative symptoms in SZ.

S45. THE PROMISE OF COMBINING AUTOMATIC SPEECH RECOGNITION (ASR) WITH SEMANTIC NATURAL LANGUAGE PROCESSING (NLP) IN SCHIZOPHRENIA

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Background: Natural language processing (NLP) tools have been increasingly used to quantify semantic anomalies for improving the diagnosis of schizophrenia-spectrum disorders (SSD). Despite the high accuracy of these methods participant interviews are still being transcribed manually for this purpose, which is an expensive and extremely time-consuming process. Automatic speech recognition (ASR) technology allows for the quick conversion of speech into text and could therefore highly speed up the NLP research process. In this study, we evaluated the performance of a state-of-the-art ASR tool and its impact on diagnostic classification accuracy in SSD.
Methods: Speech samples from 93 patients with SSD and 70 healthy controls were collected using a semi-structured interview on neutral topics. The audio files were transcribed manually, and automatically using the Kaldi NL Speech Recognition Toolkit. We assessed the performance of the ASR tool compared to human transcriptions quantitatively (using the Word Error Rate (WER)) and qualitatively by analyzing the most frequently mistaken words, their

grammatical parts of speech (POS), and their linguistic position. Additionally, we assessed possible correlations between the WER and symptom severity as measured by the Positive and Negative Syndrome Scale (PANSS). Mean, maximum, minimum, and variance semantic similarity per moving windows of 5-10 words were computed using Word2vec; for both the automatic and manual transcriptions separately. Subsequently, we trained two random forest classifiers with the similarity measures. McNemar's test was performed to verify whether the diagnostic accuracy of the two classifiers significantly differed based on the type of transcript used.

Results: The diagnostic classification accuracy of semantic similarity metrics reached 76.7% (sensitivity 70%; specificity 86%) using automated transcriptions and 79.8% (sensitivity 75%; specificity 86%) when employing manual transcriptions. McNemar's test revealed that the difference in performance between the two models was not significant (p=.791). Kaldi NL achieved a mean WER of 30.4%, with a higher rate in patients (32.3%) than in controls (27.8%) (p=.006). Men had a significantly higher WER than women (p=.009), however, the difference in mean WER between the sexes was larger in the patients' group, with male patients reaching a WER of 34.8% and female patients having a WER of 26.5% (p<.001). The WER was significantly correlated with PANSS negative (r=.295, p=.003), positive (r=.326, p=.016), general (r=.295, p=.005), and total (r=.429, p=.004) subscales. Grammatical analysis of ASR errors revealed that pronouns were the most mistaken part-of-speech class (25.3%) and 'Ik' ('I') was the most frequently mistaken word. Errors were most likely to occur at the end of a sentence and least likely to happen at the beginning of a sentence in transcripts from both patients and controls.

Discussion: These findings demonstrate that the use of ASR to support clinical semantic analysis is a promising method for the diagnosis of schizophrenia-spectrum disorders. We showed that, despite relatively high WERs, the diagnostic classification accuracy of the semantic model based on automated transcripts did not significantly decrease as compared to the model based on manual transcripts. This might be because most ASR errors were found in function words (e.g., pronouns), whereas semantic NLP models rely on content words (e.g., nouns) when assessing coherence features. As a result, combining ASR technology with semantic NLP models qualifies as a viable and robust method for diagnosis in SSD.

S46. COMPUTATIONAL MODELING OF RISK-TAKING TENDENCIES IN SCHIZOPHRENIA

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Background: The Balloon Analogue Risk Task (BART), assesses uncertain, sequential risky reward pursuit. Participants inflate a virtual balloon, increasing the amount of reward the balloon is worth and likelihood of the balloon exploding with each pump. If the balloon explodes, the participant receives no reward for that trial. Participants must learn to optimize risk-taking via trial and error, as the explosion probability is not explicitly provided. Thus, each inflation represents a choice between 1) keeping the current reward for the balloon or 2) pursuing greater reward at the risk of the balloon exploding. Risk-taking is typically quantified as average Adjusted Pumps (i.e., number of inflations on unexploded balloons), which does not integrate trials in which the balloon explodes and offers limited insight into dynamic task behavior. Previous work in schizophrenia has consistently found less risk-taking in the form of fewer adjusted pumps. Yet, other confounds such as lower cognitive ability could contribute to

group differences. The current analysis applies hierarchical Bayesian models of dynamic risk-taking in clinical and non-psychiatric samples matched on IQ.
Methods: The current analysis consists of 30 participants with schizophrenia/schizoaffective disorder (SZ) and 30 non-psychiatric controls (CT), matched on age, gender, race, and IQ. The reparameterized version of Wallsten's 4-parameter model, which has outperformed alternative BART models, was applied. This model includes four parameters: 'prior belief of the balloon not exploding', 'learning rate', 'risk propensity', and 'behavioral consistency'. The model was estimated for SZ and CT participants separately, to compare group level parameters via posterior group differences ([95% HDI], mean posterior difference). Intervals not containing zero are interpreted as a credible difference.
Results: Compared to CT, SZ participants exhibited higher 'prior belief of the balloon not exploding' [-0.038 -0.011; M = -0.024]. In other words, SZ participants had a lower initial belief that the balloon would explode. Furthermore, SZ participants exhibited lower 'risk propensity' [0.060 0.260; M = 0.164]. There were no group differences in 'learning rate' [-0.002 0.005; M = 0.001] or 'behavioral consistency' [-0.871 0.227; M = -0.303]. Using the full sample, correlations between model parameters and IQ were tested. 'Prior belief of the balloon not exploding' was negatively correlated with IQ ($r=-0.29$, $p=0.026$), such that those with lower IQ tended to have higher 'prior beliefs of the balloon not exploding'. 'Risk propensity' was positively correlated with IQ ($r=0.41$, $p<0.01$), such that those with lower IQ tended to take less risk.
Discussion: The current analysis parses the cognitive processes underlying BART behavior via hierarchical Bayesian modeling. Despite SZ participants having a higher 'prior belief of the balloon not exploding' and a similar 'learning rate', they still exhibited lower risk-taking and had fewer balloons explode. Further, the key parameters correlated with IQ, suggesting that higher cognitive functioning relates to strategically taking more risks for higher rewards. Surprisingly, there were no group differences in 'learning rate' or 'behavioral consistency', suggesting comparable updating of prior beliefs based on observations on each trial and stable strategy use. We will further discuss comparison to a second computational model (i.e., Exponential-Weight Mean-Variance model), and relationships between symptom measures and model parameters.

S47. SPEECH PATTERNS IN EARLY PSYCHOSIS: NLP FINDINGS FROM LARGE QUOTA SAMPLING

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Background: Spoken language is a key source of information in mental status evaluation. In the past few years, independent studies have investigated language in psychosis using automated natural language processing (NLP).
Methods: In this study, we present findings from a sample of 120 individuals—55 individuals with at risk mental state for psychosis (ARMS) and 65 healthy controls—screened from 4,500 participants selected through quota sampling in São Paulo, Brazil. We analyzed semantic

coherence, part-of-speech (POS) tagging, sentiment and speech graphs to generate features from transcribed texts related to specific tasks.
Results: Our results show that average and minimum speech coherence are correlated with psychotic traits. The use of adjectives was associated with positive symptoms, driven by unusual thought content. Sentiment and graph measures (centrality, density and size of largest component) were also associated with psychotic traits, and also highly correlated with verbosity.
Discussion: This proof-of-concept study spans sampling to clinical decisions supported by language analysis. Findings suggest that subtle patterns in speech might be valuable in screening for prodromal and subclinical manifestations of psychosis. in screening for prodromal and subclinical manifestations of psychosis.

S48. ABERRANT HIERARCHICAL PREDICTION ERRORS ARE ASSOCIATED WITH TRANSITION TO PSYCHOSIS: A COMPUTATIONAL SINGLE-TRIAL ANALYSIS OF THE MISMATCH NEGATIVITY

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Background: Mismatch negativity (MMN) reductions are among the most replicable biomarkers for schizophrenia and have been associated with risk for conversion to psychosis in individuals at clinical high risk for psychosis (CHR-P). However, a persistent challenge lies in developing interventions to delay or even prevent psychotic episodes, which has been attributed to a lack of mechanistic models of pathophysiological processes, especially in the clinical high risk population. Here, we adopt a computational approach to develop a mechanistic model of MMN reductions in CHR-P individuals and patients early in the course of schizophrenia (ESZ).
Methods: Electroencephalography (EEG) was recorded in 38 CHR-P individuals (15 converters), 19 ESZ patients (≤5 years), and 44 healthy controls (HC) during three different auditory oddball paradigms including 10% duration-, frequency-, or double-deviants, respectively. We modelled sensory learning with the Hierarchical Gaussian Filter and extracted belief trajectories of precision-weighted prediction errors about tone probabilities ε2 and environmental volatility ε3 and performed a model-based EEG analysis to assess how the expression of sensory prediction errors modulated EEG amplitudes over time. We assessed group differences using a factorial design with group as between- and MMN paradigm as within-subject factor, as well as sex and age as covariates.
Results: We observed a significant group effect on the expression of low-level prediction errors ε2 about the tone probability ε2 peaking at 105 ms over left, central channels ($F=26.05$, $p<0.001$) and at 113 ms over frontal channels ($F=16.08$, $p<0.001$). The first effect was driven by increased expression of prediction errors in ESZ compared to CHR-P (peak: 105 ms, $t=4.66$, $p=0.032$, and peak: 152 ms, $t=4.27$, $p=0.029$) and HC vs ESZ (peak: 105 ms, $t=6.91$, $p<0.001$). The second, frontal effect, was driven by increased expression of low-level prediction errors in HC vs ESZ (peak: 113 ms, $t=5.66$, $p<0.001$). Expression of high-level prediction errors about the volatility of the environment ε3 also showed a significant effect of group peaking at 125

ms over right, central channels (F=26.05, p=0.008). Pairwise comparisons revealed significantly increased expression of prediction errors in HC compared to ESZ (peak: 344 ms, t=3.77, p=0.015), as well as decreased expression in CHR-P vs ESZ (peak: 129 ms, t=4.96, p=0.012) and in HC vs ESZ (peak: 125 ms, t=5.74, p=0.007). Importantly, when comparing CHR-P converters to non-converters, we found a significant group effect on the expression of low-level precision-weighted PEs ε2 peaking at 137 ms over left, central channels (F=12.722, p=0.040; small-volume corrected for the group effect on ε2 between HC and ESZ). In CHR-P individuals that converted within 12 month, the difference between small and large low-level precision-weighted PEs was already reduced in baseline EEG measurements (peak: 137 ms, t=3.567, p=0.022; small-volume corrected for the group effect on ε2 between HC and ESZ).
Discussion: Our results point towards altered processing of hierarchical prediction errors as a key computational mechanism in early psychosis consistent with predictive coding accounts of psychosis. This computational model appears to capture pathophysiological mechanisms relevant to early psychosis and the risk for future psychosis in CHR-P individuals and may serve as a predictive biomarker and mechanistic target for novel treatment development.

S49. NEGATIVE SYMPTOMS AND NEUROCOGNITION AS PREDICTORS OF FUNCTION IN TREATMENT-RESISTANT SCHIZOPHRENIA

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Background: Treatment-resistant schizophrenia (TRS) makes up approximately 30% of all patients with schizophrenia and is associated with severe functional impairment. Multiple studies have looked into predictors of functioning in schizophrenia patients, but research in this area for TRS is lacking. In this study, we aim to bridge the gap in knowledge by investigating the relative contributions of five clinical symptom factors of schizophrenia and neurocognition, to predict functioning in a local TRS population. We also investigate relative contributions of the two negative symptom subdomains (Social Anhedonia and Diminished Expression) and individual aspects of neurocognition.
Methods: One-hundred and fifty-nine TRS patients were recruited from inpatient and outpatient settings from the Institute of Mental Health, Singapore. They were assessed on the Positive and Negative Syndrome Scale (PANSS) and factor scores were calculated for five symptom factors (Positive, Negative, Cognitive, Depressive and Hostility factors) in a model previously validated in a multi-ethnic population. Neurocognition was assessed using symbol coding and digit sequencing tasks from the Brief Assessment of Cognition in Schizophrenia (BACS), as we have previously shown these tasks to account for up to 76% of variance of global neurocognition in a large sample of the local population (unpublished data). Function was assessed using the Social and Occupational Functioning Assessment Scale (SOFAS), employment status and the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0). Multilinear and multi-logistic regression analyses were performed against SOFAS, WHODAS and employment status respectively. Hierarchical regression was further performed with the two subdomains of negative symptoms and two tasks in BACS.
Results: Our results corroborate what has been shown for the general schizophrenia population - negative symptoms, in particular the domain of social anhedonia (SA) (β=-0.378, t=-4.718, p<0.001), is the strongest predictor of functioning in our TRS population (as assessed through

SOFAS and employment status). Neurocognition, in particular BACS symbol coding (β=0.043, SE=0.021, p=0.041), was a significant positive predictor of employment status but not of SOFAS nor WHODAS. A higher severity of depressive symptoms (β=0.476, t=5.648, p<0.001) is the only significant predictor associated with increased disability and lower function, as measured through WHODAS.
Discussion: We show that negative symptoms contribute significant variance in predicting function in a TRS population, in line with what is known for the general schizophrenia population. The significance of neurocognition, specifically processing speed and attention as assessed by the symbol coding task, in predicting employment status also corroborates current literature. Our finding supports the important role of processing speed and attention in maintaining good vocational function. Despite varying results that could be attributed to psychometric properties of individual measurements of function, this study represents a first attempt at elucidating significant predictors of function in treatment-resistant schizophrenia and provides a framework for further research to build on. We also highlight the importance of furthering treatments to improve negative symptoms in view of its strong significance contributing to functional impairment in general schizophrenia and TRS patients.

S50. SYMPTOM LEVEL AND CHANGE BEFORE SUICIDE - A PROSPECTIVE COHORT STUDY OF 7000 PSYCHIATRIC ACUTE WARD PATIENTS

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Background: Research into symptom development over time before suicide for both depressive and psychotic symptoms is needed. Our aim is to investigate symptom development over time before suicide in a cohort prospective study of 7000 inpatients.
Methods: The study cohort consisted of 7000 unique patients, and over 18.000 admissions consecutively admitted to the Psychiatric Emergency Department at Haukeland University Hospital from May 2005 to June 2014. Assessments were conducted at each admission if several in the inclusion period and included ICD-10 diagnosis; clinical interview in the form of the Health of the Nation Outcome Scales and qualitative assessments of suicidal ideation and suicide attempts over the past week. Mean follow-up time was 5.5 years (minimum/maximum: 0/10.6 years). Multilevel models were used to explore level and change in symptoms over time and the relations with suicide risk.
Results: During the follow-up period, 152 patients died by suicide, 65% of these within the first year following admission. The symptom development of psychotic symptoms, depression severity and suicidal behavior before suicide completion will be described.
Discussion: We need more research regarding both clinical states and how suicidal ideation in e.g., psychotic states may increase in the risk of transition from suicidal ideation and attempts related to acute admissions to actual suicide completion at follow up.

S51. PSYCHOTIC SYMPTOMS AND SUICIDE RISK IN SUBSTANCE USE DISORDERS - RESULTS FROM A LARGE PROSPECTIVE STUDY OF CONSECUTIVELY ADMITTED PATIENTS.

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Background: Suicide risk is known to be elevated in patients with substance abuse. We investigated the role of psychotic symptoms in relation to risk of suicide death in patients with substance use disorders.
Methods: This is a prospective study of a representative and diagnostically mixed sample of 7000 consecutively, acutely hospitalized psychiatric patients between 2005 and 2014 in a well-defined Norwegian catchment area comprising 400 000 inhabitants. 1200 patients were diagnosed with substance abuse as their main diagnosis. Assessments were conducted at admission and included ICD-10 diagnosis; clinical interview in the form of the Health of the Nation Outcome Scales (scale 6 and 7) and assessments of suicidal ideation and suicide attempts over the past week. Suicide deaths were registered at one year post-admission. Survival and hazard functions were estimated, and Cox regression used in order to estimate the predictive relations of hallucinations and delusions (HoNOS item 6), and overvalued psychosis-like ideas of self-blame (HoNOS item 7) scores, controlled for suicidal behavior and gender.
Results: After one year, 101 (1.4%) patients had died by suicide, of whom almost 70% were men. The diagnostic group of substance abuse constituted 24.7 % of suicides, and a suicide rate after one year of 2%. This far exceeds suicide risk among mood-and psychotic disorders. The relation between psychotic symptoms and suicide risk will be described in detail, but it appears that symptoms such as overvalued ideas and thoughts of self-blame are over-represented in the group.
Discussion: Substance abuse represents a significant risk factor for suicide. Further, when assessing suicide risk in patients with substance use disorders, one should also assess the degree of psychotic phenomena, including overvalued psychosis-like ideas of self-blame. Patients with substance use disorders need more focus in clinical suicide prevention strategies.

S52. CHANGES IN PROLACTIN LEVELS AND SEXUAL FUNCTION AFTER SWITCHING FROM RISPERIDONE TO PALIPERIDONE PALMITATE IN SCHIZOPHRENIA

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Background: Hyperprolactinaemia is a significant side effect of antipsychotic medications and may cause sexual dysfunction. Risperidone and paliperidone are among the antipsychotic drugs that cause prolactin elevation. In a previous study by our group that included early psychosis patients we demonstrated a reduction in prolactin levels after switching from risperidone-long acting injectable (LAI) to paliperidone palmitate (PP) in patients with a psychotic disorder.
Our study aims to replicate these findings in a larger sample including patients with schizophrenia and extending the evaluation time to 6 months. The objective is to evaluate the effect of switching from risperidone to PP on sexual functionality and prolactin levels. We

include data from a larger prospective, observational, pragmatic study to assess functionality and cognition when switching from risperidone to PP.

Methods: Our sample included 27 patients (85.1% men) with schizophrenia attending to the Department of Mental Health from Parc Taulí Hospital (Sabadell, Spain). All patients were treated with risperidone (oral or R-LAI) in monotherapy at stable doses at least two months and had an indication to be switched to PP by their psychiatrists. Ethical approval was obtained from the local Ethics Committee and all participants provided written informed consent. Clinical diagnoses for schizophrenia were generated with the OPCRIT checklist v.4.0. Three assessments were completed: 1) baseline (pre-switch), 2) 3 months post-switch, 3) 6 months post-switch. Prolactin concentrations were determined in plasma. Sexual functioning was assessed with the Arizona Sexual Experiences Scale (ASEX). As a previous studies, we defined a dichotomic variable for clinically significant sexual dysfunction as an ASEX total score> 18, or a score ≥5 on any single item or any three items with individual scores ≥4. Longitudinal changes in prolactin levels and sexual function variables after switching from risperidone to PP were analyzed with linear mixed models using R and the package Ime4. Significance was set at $p<0.05$.

Results: Prolactin concentrations were reduced in women (119.9 ± 65.5 to 83.0 ± 40.7 ng/ml; $p <0.001$) with a significant time effect ($p = 0.035$). They also had higher prolactin levels throughout the follow-up than men. Antipsychotic doses influenced prolactin levels ($p=0.006$), such that higher antipsychotic doses were associated with higher prolactin concentrations. No significant differences were found in the ASEX total scores at 6 months after the switch. The prevalence of clinically sexual dysfunction was not statistically significant ($p=0.125$), although there was a reduction at 6 months (51.9% at baseline and 36.4% at 6 months).

Discussion: In women with schizophrenia was detected a reduction in prolactin concentrations with a significant time effect after switching risperidone to PP. A reduction in sexual dysfunction was detected at 6 months, although it was not statistically significant.

S53. DIAGNOSTIC VALUE OF THE MINNESOTA MULTIPHASIC PERSONALITY INVENTORY REVISITED: A MACHINE LEARNING METHOD

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Background: The Minnesota Multiphasic Personality Inventory (MMPI) is a widely used psychometric test. Although it was originally developed to identify specific mental disorders, a few previous studies based on classic statistical methods revealed that MMPI did not have a significant diagnostic value. As a result, in these days, the role of MMPI in clinical field is limited to partially assisting clinician's differential diagnosis. Thus, we tried to reevaluate the diagnostic value of the MMPI by applying the machine learning method.

Methods: We collected initial MMPI score results from total 524 patients who were diagnosed as bipolar disorder (BD), major depressive disorder (MDD), or schizophrenia (SPR) by clinician. Then we applied the Random Forest machine learning algorithm to predict the diagnosis from the scores from the initial MMPI-2.

Results: When the diagnosis estimated from MMPI by machine learning method were compared with final diagnosis made by clinician, the accuracy was 55.83%, with balanced accuracy of 61.74%, 73.81%, 58.28% for BD, MDD, SPR each.

Discussion: This study revealed the potential diagnostic value of the MMPI combined with the novel machine learning method, and further expanded the possibility of using the machine learning model in field of psychiatric diagnosis.

S54. AREA-LEVEL SOCIAL FRAGMENTATION DURING CHILDHOOD PREDICTS POORER SOCIAL FUNCTIONING AMONG YOUNG ADULTS AT CLINICAL HIGH RISK FOR PSYCHOSIS AND HEALTHY CONTROLS

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Background: Impairments in social functioning associated with schizophrenia are strong predictors of the day-to-day disability commonly observed in the disorder. This study seeks to investigate whether exposure to social fragmentation during childhood predicts social functioning at young adulthood, as well as the potential mediators (measures of premorbid maladjustment during childhood) and moderators (age, sex, and clinical high risk (CHR) status) of this association.

Methods: Data is collected at baseline from the North American Prodrome Longitudinal Study Phase 2 study, among young adults. Area-level social fragmentation was geo-coded from the city/town in which participants spent the most time during childhood to county-level factors via the US Decennial Census. It is defined as the average of the z scores of the following factors: residential instability (percent of residents who changed their address in the past five years), percent renter-occupied housing, percent single-parent households, and percent of residents who are divorced. Social functioning was measured with the Global Functioning: Social scale and rates peer relationships, peer conflict, age-appropriate intimate relationships, and family involvement. The Premorbid Adjustment Scale (PAS) was used to measure sociability and social withdrawal, peer relationships, scholastic performance, adaptation to school during childhood (through age 11). Generalized linear mixed models tested associations between social fragmentation during childhood and social functioning with unique counties as the random intercept. Six covariates included age, female sex, white non-Hispanic race/ethnicity, family history of mental illnesses, parental education index, and area-level deprivation. If there was a significant association between area-level social fragmentation in childhood and social functioning in young adulthood, then four items within the PAS-Childhood Scale were tested as potential mediators and 3 potential moderators were tested: age, sex, and CHR status.

Results: This study included 223 young adults with 122 males (54.7%), 110 (49.3%) white non-Hispanics, and 138 (61.9%) individuals with a family history of mental illnesses. The average age was 21.8 and there were 133 youth at CHR and 90 healthy controls. Greater area-level social fragmentation in childhood was associated with poorer social functioning in young adulthood (unadjusted β=-0.56; SE=0.15) even after adjusting for six covariates (adjusted β=-0.41; SE=0.15). For potential mediators measuring premorbid adjustment during childhood, only maladaptation to school had a significant indirect effect on the association between social fragmentation and social functioning (adjusted β=-0.10; SE=0.04). Other premorbid

adjustment measures including sociability and withdrawal (adjusted β=-0.02; SE=0.05), peer relationships (adjusted β<0.01; SE=0.06), and scholastic performance (adjusted β=-0.06; SE=0.04) were not significant indirect effects. For potential moderators, CHR status significantly interacted with social fragmentation in predicting poorer social functioning (adjusted β=-0.41; SE=0.20).
Discussion: This study finds that area-level social fragmentation during childhood predicts poorer social functioning during young adulthood. Moreover, this association was mediated by greater maladjustment to school during childhood. Perhaps, exposure to cumulative social stressors from area-level social fragmentation during childhood might impact peer relationships and social functioning through adverse social experiences at school. In addition, youth at high risk for psychosis might have been more vulnerable to the adverse effects of social fragmentation.

S55. MOMENTARY NEGATIVE SYMPTOMS IN EARLY PSYCHOSIS PATIENTS IN DAILY LIFE: AN EXPERIENCE SAMPLING STUDY

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Background: Negative symptoms refer to deficits in motivation, experience of pleasure and/or emotional expression. It is a key target in early intervention among psychosis patients but remains to be an unmet therapeutic need. Experience sampling methodology (ESM) provides an opportunity to investigate momentary symptoms over time and their associated contextual factors. Despite it has been demonstrated as a promising approach in assessing negative symptoms, it has not been commonly applied to patients in early psychosis, particularly in Asia. The present study aimed to examine patient's everyday experience of negative symptoms by comparing to that among healthy controls.
Methods: The ESM assessment lasted for 6 consecutive days, with 10 signals emitted each day. At each signal, participants were prompted to complete a brief questionnaire on momentary affective experiences, hedonic capacity during a recent event recalled, current activity and face-to-face social interaction, and their associated appraisals. Prior to the start of the ESM assessment procedure, a short training session was held to explain the study procedures and to complete a practice survey. A total of 75 participants were recruited and provided ESM data. All patients were clinically stabilized and within 3 years of treatment in early intervention services for first-episode psychosis. Seven patients were excluded due to a low response rate (i.e., fewer than 20 valid responses). The final sample consisted of 33 early psychosis patients and 35 demographically matched healthy controls.
Results: Adjusted multilevel linear-mixed models revealed patients experienced a greater intensity of negative affect compared to controls, but significant group differences in affect variability, instability and intensity in positive affect were not observed. Although significant group interactions were found between perceived pleasantness and intensity of positive affect in the context of currently engaged activity and face-to-face social interaction, patients demonstrated no significantly greater anhedonia in these contexts or in the event recalled, relative to controls. Patients also showed a stronger preference to have company when alone than controls. Significant group differences were not found in other measures of asociality: preference to be alone when in company, pleasantness being alone, or proportion of time spent alone.

Discussion: Our results indicated clinically stabled early psychosis patients experienced more intense negative affect in daily life. Otherwise, they showed no evidence of affective blunting, anhedonia in both non-social and social contexts, and asociality. The findings suggest that negative symptoms might not be pronounced in early psychosis patients. Future research can consider combining ESM and other digital phenotyping measures to facilitate a more refined negative symptom assessment in everyday life of early psychosis patients.

S56. INTERACTION EFFECTS OF GENDER AND COGNITIVE FUNCTION ON TOM IMPAIRMENTS IN INDIVIDUALS WITH FIRST-EPISODE SCHIZOPHRENIA SPECTRUM DISORDERS

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Background: Impairment in theory of mind (ToM) has been regarded as one of the main features in schizophrenia, negatively influencing patients' psychosocial functioning. Although neurocognitive function has been proposed as a major moderator on ToM, specific pathways of neurocognition on ToM in psychosis remained largely unknown. Besides, while previous meta-analyses did not suggest gender effect on ToM, gender differences on hypermentalization impairements have not been investigated and warrant our attention to facilitate the understanding of the underlying mechanism of ToM impairments in psychosis. The current study aims to investigate the interaction effects of cognitive impairment and gender on ToM impairments in patients with firs-episode psychosis (FEP), compared with healthy controls.

Methods: Eighty-six patients with diagnosed with first-episode schizophrenia spectrum disorders (FES) according to DSM-IV by psychiatrists and recruited from the Early Intervention Service for Psychosis in Hong Kong. 60 healthy controls matched with age and gender without previous psychiatric history were recruited through community. Hinting task and the attributional to intention comic strip were implemented to measure verbal and non-verbal cognitive ToM respectively. The gaze perception task was also used to assess self-referential hypermentalization. The Positive and Negative Syndrome Scale (PANSS) was used to examine psychotic symptoms in FEP patients. Cognitive function was measured by digit span tests, digit symbol substitution test, information test and arithmetic test in Wechsler Adult Intelligence Scale-Revised (WAIS-R). K-means clustering analysis was then used to separate patients' cognitive function into mild cognitive impairment (MI) and severe cognitive impairment groups (SI).

Results: The k-means clustering analysis distinguished 49 FES patients with mild cognitive impairment (mean age 30.84 ± 12.40 years old; Male: 61.2%) and 37 FEP patients with severe cognitive impairment (mean age 35.65 ± 13.36 years old; Male: 43.2%). Healthy controls (mean age 33.72 ± 14.12 years old; Male: 55%) were also attempted to implement clustering analysis but homogeneous grouping was suggested as the most preferable option. There was a significant interaction effect of gender and conditions on non-verbal ToM ($F(2, 140) = 5.835$, $p = .004$) and self-referential hypermentalization ($F(2, 140) = 3.500$, $p = .033$). In post hoc pairwise comparison tests, non-verbal and verbal cognitive ToM showed similar patterns of impairments in gender. Only the FEP-SI group was significantly poorer than FEP-MI group and healthy controls in male, whereas both FEP groups performed significantly worse than healthy controls in female. In addition, female FEP-SI group was significantly better in non-verbal cognitive than male FEP-SI group ($p < 0.001$). For self-referential hypermentalization, while male did not show any significance in hypermentalization error, only female patients in SI groups displayed more self-referential error than female MI group ($p < 0.001$) and female

healthy controls ($p < 0.001$), as well as male FEP-SI group ($p = 0.007$). After controlling age, years of education, and psychotic symptom (using total PANSS score), the differences in ToM impairments between FEP-MI and FEP-SI groups remained significant.
Discussion: The current findings indicated that neurocognition was an essential factor for accurately understanding and predicting others' thoughts and behaviors in male. Yet, the ability to mentalize others' mental states in female was more dependent on their psychiatric condition than cognitive functions. On the other hand, the tendency to perceive ambiguous stimuli as self-referential was only significantly impaired in female patients with severe cognitive impairments. Our results suggested that cognitive functions and gender played important roles and would produce interaction effects in ToM impairments and hypermentalization error. Future study could explore specific cognitive domains and subcategories of psychosis to comprehensively understand mechanisms of ToM impairments and hypermentalization in psychosis.

S57. BEHAVIORAL, COMPUTATIONAL, AND NEURAL INDICES OF STATE LEARNING IN EARLY PSYCHOTIC PSYCHOPATHOLOGY

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Background: The psychosis spectrum involves aberrant perception and cognition. State representation and reinforcement learning (RL) are critical for navigating a dynamic environment and incorporating feedback to adapt and function. RL deficits in tracking reward outcomes are observed in people with schizophrenia (SZ), early psychosis (EP) and psychosis risk. These deficits are linked to striatal-cortical dysfunction, symptom severity and functional impairment. Changes in RL could reflect underlying differences in tendency to explore alternate options vs exploit rewarding options. Previous work shows more win switch behavior (switching away from a previously rewarding stimulus) in SZ than controls, suggesting over exploration. We examined novel computationally informed behavioral and neural indices of state learning in EP.
Methods: Data collection is ongoing. Thus far 18 EP participants and 50 controls (Ctrl) completed a novel, translational variant of restless bandit (Translational Bandit Task; TBT) measuring state learning associated with identifying the switching of most rewarding stimuli over time. Task reward is probabilistic and changes independently across the choice options. A 200 trial 3 arm TBT was administered during 3 T fMRI and approximately 2 weeks later a 300 trial version during simultaneous 3 T fMRI and EEG (MRI protocol was similar to ABCD: FOV=216mm, flip angle=52, TE=37ms, TR=800ms, 60 slices, MB=6). Participants completed symptom and functioning assessment and received compensation and bonus payments for task performance. We fit a Hidden Markov Model to infer latent states (explore/exploit) from participant choice sequences. We fit a Reinforcement Learning model with 4 parameters that capture both value based and value independent decisions. fMRI data were processed using FSL; recommended voxel and clusterwise thresholds were used.
Results: Based on RL and HMM modeling, Ctrl and EP performed as expected, engaging in value based decision making, learning from rewards and exhibiting exploit and explore behavior proportional to what was expected given the volatility of the task environment. RL modeling characterized both Ctrl and EP choice behaviors, with no significant differences in model parameters across groups (and small effect sizes). Overall, task performance was consistent over time with little evidence of a practice effect (moderate reliability of explore state; Ctrl ICC of p(explore)=.595; Ctrl+EP ICC = 0.664). As predicted, EP engaged in more

exploration than Ctrl (t(59)=-2.05, p=.023, Cohen's d=-.596). Controls showed significant neural activation of salience (SN), central executive (CEN), and default mode networks (DMN) along with nucleus accumbens during reward. Task relevant neural activation of SN was evident in both Ctrl and EP during the latent state of exploration in contrast to exploitation.
Discussion: Initial results indicate TBT is a valid and reliable measure of state learning. Computationally informed behavioral indices of state learning suggest over exploration in EP, consistent with prior work in SZ. In the absence of group differences on RL parameters, results suggest different cognitive processing strategies but similar reward learning across groups. Task relevant neural activation of SN, CEN, and DMN is consistent with the triple network theory and literature on striatal-cortical dysfunction in psychosis. Next steps include direct group comparisons on neural activation and EEG informed fMRI analysis.

S58. RATES OF CIGARETTE SMOKING AND VAPING AMONG PERSONS WITH FIRST EPISODE PSYCHOSIS

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Background: The prevalence of cigarette smoking among youth with first episode psychosis (FEP) is significantly elevated compared with persons of the same age in the general population. A review of research prior to 2012 found that 60% of those with FEP report smoking at the start of treatment; more recent studies have found lower rates (13%-50%). These rates are in stark comparison to the general population smoking rate of 7.5% in adults ages 18-24. Many youth/young adults consume nicotine through vaping. The 2019 Monitoring the Future Survey found 25% of 12th graders reported last month nicotine vaping; 7% of young adults' report some days or daily e-cigarette use. Smoking and nicotine vaping have deleterious effects on health and on brain development. Research finds that young people are at increased risk for initiating cigarette smoking and smoking regularly if they've already used vaping products. To better understand tobacco smoking and nicotine vaping in a recent sample of youth with FEP, we examined data collected by Connection Learning Health System (CLHS). This is a NIMH-funded regional hub that is part of the Early Psychosis Intervention Network (EPINET) and includes Coordinated Specialty Care (CSC) programs in Maryland and Pennsylvania.
Methods: Data were collected as part of standard program evaluation procedures at all 23 CSC sites in the EPINET hub. Questions about tobacco smoking and nicotine vaping were part of a standard assessment completed by CSC staff. The admission sample (N=377) showed Mage=20.6 (SD=4.2), 62.3% male, 34.5% female, 43% Black/African American, 39.5% white, 17.4% other race/prefer not to say. Smoking and nicotine vaping data were available for 295 youth.
Results: At admission, 32.5% (N=96/295) of participants identified themselves as lifetime tobacco smokers and 20% (N=59/295) reported smoking in the past month. Most past-month smokers (N=53/59, 90%) were age 18 or older and reported smoking daily (N=39/57, 68%). In a subsample of respondents with tobacco use data at both admission and 6-month follow-up (N=130), 18.5% (N=24/130) were identified as current smokers at admission and almost all (17.3%, N=22/127) remained current smokers at 6 months. At admission, 27.7% (N=78/282) reported having tried nicotine vaping in their lifetime and 13.5% (N=38/282) reported vaping nicotine in the last month. Overall, 29% (N=11/38) of those who were currently vaping nicotine

were under age 18, 71% (N=27/38) were 18 or older, and 67.6% (N=24/34) were vaping daily. In a subsample of respondents who provided vaping data at admission and 6-month follow-up (N=125), 11.2% (N=14/125) reported current nicotine vaping at admission and 10.7% (N=13/122) continued to report current nicotine vaping at 6 months. While most participants reported either tobacco use or nicotine vaping at admission, a small group reported both in the past month.

Discussion: Rates of tobacco use in this sample were lower than in previously published studies of youth with FEP. For nicotine vaping, rates in this sample are similar to persons of the same age range in the general population. In our sample, smoking and nicotine vaping were fairly stable over 6 months. Data collection began in January 2021 when most youth and young adults were accessing school online and experienced curtailed social interaction due to the COVID 19 pandemic which may have impacted access to smoking and vaping. These rates may be an underestimation, as patients may be hesitant to disclose smoking and vaping to CSC staff. Nevertheless, smoking and vaping warrant the development of specialized interventions to reduce nicotine use in persons with recent onset psychosis.

S59. GETTING THROUGH THE DOOR: A RETROSPECTIVE COHORT STUDY OF CARE PATHWAYS TO EARLY PSYCHOSIS INTERVENTION SERVICES

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Background: Despite the clear mandate for early psychosis intervention (EPI) programs to promote their services and minimize barriers to care, most youth with psychosis either never access these services or access them far later than indicated. Acute services act as the main entry point into EPI services, with more than half of all new psychotic disorders diagnosed in the emergency department (ED) or inpatient units. Although advancements have been made to improve access to EPI services more broadly, some studies have found that Black patients are at a higher risk of coercive referral, involuntary admissions, and emergency service use, relative to other racial/ethnic groups; however, the use of self-identified health equity data is limited across studies. The objective of this study was to understand factors associated with acute referral to EPI services, with a focus on pathways to care and health equity factors using self-identified equity data from patients referred to EPI services.

Methods: We examined the electronic medical record (EMR) data for all patients aged 16-29 who were referred to a large urban EPI program over a 2-year period from January 2018 to December 2019. Our primary outcome was rate of EPI referral from acute pathways (including the emergency department and its bridging clinic [ED] and inpatient units) compared with other referral sources. Demographic and equity-related variables, including age, gender, self-reported racial/ethnic group, country of birth, and sexual orientation, were extracted from a routine patient-reported standardized health equity form. Pathways to care variables were gathered from clinical documentation and days to consult was calculated as the number of days from referral to consultation appointment. We used descriptive statistics to calculate the characteristics of patients referred to EPI services based on referral source. Multinomial logistic regression was used to model the risk of acute referral, controlling for demographic and equity-related factors.

Results: After excluding referral data that did not meet study eligibility, a total of 999 unique patient referrals were received by the EPI program from 2018-2019. In adjusted multinomial

models, participants more likely to be referred to EPI services from inpatient units included those who were older (RRR, 1.10; 95% CI, 1.05-1.15) and those who identified as Black (RRR, 2.11; 95% CI, 1.38-3.22) or belonging to other visible minority/don't know/prefer not to answer (RRR, 1.79; 95% CI, 1.14-2.79) compared with White participants. Older patients (RRR, 1.16; 95% CI, 1.11-1.22) and those who identified as Black (RRR, 1.67; 95% CI, 1.04-2.70) or belonging to other visible minority/don't know/prefer not to answer (RRR, 2.11; 95% CI, 1.33-3.36) compared with White participants were also more likely to be referred from the ED. Participants who identified as female (RRR, .506; 95% CI, 0.35-.743) were more likely to be referred from other referral sources compared with those who identified as male.
Discussion: We found that demographic and equity-related factors, including age and race/ethnicity, were associated with acute referral to EPI, with female patients more likely to be referred from outpatient or other external referral sources compared with males. These findings indicate health disparities in the early stages of accessing care and can be used to develop a targeted and stepped care approach to outreach. Systematically evaluating and monitoring outcomes through an equity lens can also help identify gaps and local challenges within EPI programs, leading to program improvements that make treatment more accessible for vulnerable groups.

S60. GUT PERMEABILITY AND RELATIONSHIP TO INFLAMMATION, ANTIGLIADIN ANTIBODIES AND KYNURENINE PATHWAY METABOLITES IN PEOPLE WITH SCHIZOPHRENIA

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Background: Zonulin, an endothelial growth factor receptor stimulator, has previously been shown to regulate tight junction permeability of the gut and the blood brain barrier, but its role in the pathogenesis of schizophrenia (SZ) has only recently been investigated. Elevated zonulin has previously been implicated in a loss of barrier function of the gastrointestinal tract, allowing the passage of macromolecules, including endotoxins, into the body and possibly resulting in an immune response. This process may lead to the establishment of chronic inflammation as suggested by many other chronic inflammatory diseases, including Celiac disease. Our group has previously found that a model of higher zonulin and higher IL-1β and TNF-α was associated with higher BPRS, anxiety/depression scores, and ratings of hostility, hinting that the combination of gut permeability and chronic inflammation may have some relationship to brain function. Here we examine the relationship of zonulin to peripheral inflammation, antigliadin antibodies (AGA IgG) and kynurenine pathway metabolites, which are modulated by inflammation, in individuals with SZ and healthy controls (HC).
Methods: We had a cohort of 215 participants with zonulin levels assayed (N=187 SZ and N=28 HC). We also tested for inflammatory markers, kynurenic acid (KYNA) and kynurenine (KYN). Zonulin was measured by a quantitative sandwich enzyme immunoassay technique and inflammatory markers were analyzed by the Cihakova Laboratory at Johns Hopkins University using a multiplex kit (Sigma Millipore). KYN and KYNA were analyzed using

HPLC by the Notarangelo Laboratory at the Maryland Psychiatric Research Center. All cytokine values were log transformed. We used the Wilcoxon rank-sum test to assess intergroup differences, and multivariable linear regression modeling to investigate the association between zonulin and demographic/biomarker variables.
Results: Mean serum zonulin was elevated in the SZ group ($\mu = 0.56$ ng/mL; SD = 0.47) in relation to the HC group ($\mu = 0.36$ ng/mL; SD = 0.24) ($p = 0.0020$). Mean serum zonulin level was lower in the AGA IgG positive group ($\mu = 0.51$ ng/mL; SD = 0.53) compared to the AGA IgG negative group ($\mu = 0.55$ ng/mL; SD = 0.39) ($p = 0.0365$). This was true among both SZ ($\mu = 0.54$ ng/mL among AGA IgG positive vs. $\mu = 0.58$ ng/mL among AGA IgG negative; $p = 0.0412$) and HC ($\mu = 0.32$ ng/mL among AGA IgG positive vs. $\mu = 0.38$ ng/mL among AGA IgG negative; $p = 0.5157$) stratifications. In those with SZ, elevated zonulin was associated with lower IL-17A ($rs = -0.16$, $p=0.03$), IL-1β ($rs = -0.25$, $p=0.0008$), IL-6 ($rs = -0.25$, $p=0.0007$), GM-CSF ($rs = -0.22$, $p=0.0028$), IFN-γ ($rs = -0.21$, $p=0.004$) and a trend for IL-23 ($rs = -0.13$, $p=0.08$). In the HC group elevated zonulin was associated with lower IL-23 ($rs = -0.54$, $p=0.03$) only. No relationship was noted between KYNA or KYN and zonulin levels in either SZ or HC. In a multivariable model controlling for age, race, diagnosis, and sex, we found that TNF-α is independently associated with higher serum zonulin ($\beta = 0.24$, $p = 0.0499$) and IL-6 with lower serum zonulin ($\beta = -0.16$, $p = 0.0002$).
Discussion: We replicate our earlier finding that serum zonulin levels are higher in SZ compared to HC. Interestingly, we find that zonulin levels were lower in SZ patients and HC with AGA IgG positivity compared to those without gluten sensitivity. We find in SZ that high zonulin levels are correlated to lower levels of many inflammatory markers. This finding shows that in patients with high inflammation and a high immune response to AGA IgG, zonulin levels are lowest, suggesting a dysregulation of zonulin or a negative feedback mechanism of gut permeability. This negative correlation is of interest in understanding the unique role of zonulin in SZ.

S61. PERCEIVED SOCIAL SUPPORT AND PSYCHOTIC-LIKE EXPERIENCES: TESTING THE STRESS-BUFFERING HYPOTHESIS

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Background: Social relationships are associated with better psychological health outcomes. For individuals on the psychosis spectrum, strong social networks are associated with improved quality of life (QOL; Bengtsson-Top and Hansson, 2001), better social functioning (Vazquez Morejon et al., 2018), reduced symptoms, and fewer hospitalizations (Norman et al., 2005). Despite extensive evidence of the benefits of social relationships, clarity regarding the driving mechanisms is still unclear, and research to test specific theories is needed.
One such theory is the stress-buffering hypothesis, which states that social relationships lessen the negative effects of stress. From this perspective, individuals with higher stress are expected to receive greater benefits from social relationships. We aimed to test the possibility that perceived social support (PSS) buffers the stress caused by psychotic-like experiences (PLEs). By confirming or refuting whether the stress-buffering conceptualization can be applied in this way, we aimed to learn whether PSS is particularly important in psychosis, above and beyond the importance that it holds for the general population.

We hypothesized that PLE distress scores would correlate negatively with QOL, and that the stress-buffering effects of PSS would be observed through a moderating effect wherein the

negative correlation is weakened when PSS is higher. Our conceptualization of PLEs as a stressor is guided by prior findings that even subthreshold levels of psychosis cause stress (Stein et al., 1995) and are associated with lower QOL (Brosey and Woodward, 2015).

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Methods: Data included scores from self-report measures by English-speaking participants ages 18+ recruited online and from previously completed studies in the laboratory (N=117, 71% female, M age = 31.68). The following measures were included: Prodromal Questionnaire-Brief (Loewy et al., 2011); Multidimensional Scale of Perceived Social Support (Zimet et al., 1988); and World Health Organization Quality of Life–Brief (Skevington et al., 2004). All analyses were completed using JASP Version 0.16.3 (JASP Team, 2022).
Results: Results showed a significant, strong correlation ($r = .70$, $p < .001$) between PSS and QOL. Additionally, PLE-related distress had a significant, strong, negative relationship with QOL ($r = -.53$, $p < .001$). Moderation analysis then tested whether PSS moderates the correlation between PLE-related distress and QOL. Results indicated that the interaction term was not significant ($b = -.05$, $p > .05$), meaning the expected moderation was not present. From these resultsit can be concluded that although PLE-related distress is related to lower QOL, PSS does not seem to change the strength or direction of that relationship.
Discussion: The present study's findings allowed us to investigate whether the stress-buffering hypothesis applies to the subjective symptom-related distress often associated with PLEs. Results of the moderation analysis did not support our hypothesis. Instead, we found that PSS has the same effect on QOL regardless of a person's level of PLE-related distress. The finding that the stress-buffering hypothesis does not play out in relation to PLE-related distress tells us that for individuals with psychosis, PSS is equally as important as, but not more than, it is for any other individuals with low QOL. Improving wellbeing for any population with a lower subjective quality of life is important, and given the observed findings of the present study, it can be inferred that individuals with psychosis are no exception. Clinical recommendations should include methods to improve quality of life, and one of these recommendations may be to bolster perceived social support.

S62. FEASIBILITY AND ACCEPTABILITY OF A PEER-LEAD PHYSICAL ACTIVITY INTERVENTION USING TELEREHABILITATION IN MULTIPLE EARLY INTERVENTION FOR PSYCHOSIS SERVICES

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Background: Although physical activity (PA) is beneficial to young people with early psychosis (YEP) to improve physical health and psychiatric symptoms, few YEP initiate and maintain PA. Telehealth has shown promising results in different fields of health services including mental health, PA and peer support can foster engagement in services, PA and recovery.

Methods: Descriptive retrospective study aiming to determine the feasibility and acceptability of a multicenter telekinesiology intervention (TechnokinPEP) for YEP lead by a peer-support worker, and to describe its implementation. The PA sessions were offered by a kinesiologist, peer support worker(s), and health sciences students. Feasibility was measured by the number of programs 12023 Congress of the Schizophrenia International Research Society approached which referred participants and the proportion of referred YEP who participated to at least one PA session. Acceptability was measured by the proportion of participants who attended more than one PA session, the number of sessions attended per participant and by surveys on patient satisfaction.
Results: Of the 35 early intervention services approached, 150 YEP (of 214 referred) from 13 clinics participated to at least one of the 204 telekinesiology sessions (offered 2-3 times/week from 20202022) YEP participated to 5.5 sessions (mean). 106 YEP engaged in more than one session (mean 7.3 sessions per persistent patient). The mean number of participants per session was 4 (1–12). 99% of the survey respondents were very satisfied/or satisfied with the sessions.
Discussion: Telekinesiology appears acceptable and feasible to be implemented simultaneously in multiple early intervention services. Leadership of persons with lived experience is an asset.

S63. PRIMARY CARE FOLLOWING A FIRST DIAGNOSIS OF PSYCHOSIS IN ONTARIO, CANADA: AN ANALYSIS OF ELECTRONIC MEDICAL RECORD DATA

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Background: Psychotic disorders are associated with higher prevalence of chronic physical health conditions and greater probability of multimorbidity. In Ontario, primary care physicians are well positioned to address the physical health of young people during the initial stages of psychosis, as the prevention, treatment, and management of physical illness is central to their role in the public health care system. Recent research has shown that the majority of people make help-seeking contacts in primary care prior to a first diagnosis of psychotic disorder, and a substantial proportion receive ongoing mental health care from primary care physicians after diagnosis. There is minimal information, however, regarding the nature of care that primary care physicians provide to their patients with first-episode psychosis, particularly in terms of physical health. Therefore, the objective of this study was to examine the provision of primary care for young people following a first diagnosis of psychotic disorder in Ontario.
Methods: Our sample included Ontario residents between the ages of 14 and 35 years with an incident diagnosis of non-affective psychotic disorder between April 2005 and March 2015 who also had a record in the Electronic Medical Record Primary Care (EMRPC) database. Cases were identified using linked population-based health administrative databases at ICES based on: (i) a discharge diagnosis of non-affective psychotic disorder from a hospitalization; or (ii) at least two visits to an outpatient clinic or emergency department for non-affective psychotic disorder in a one-year period. Cases were linked to the EMRPC database, which contains the electronic medical records of 450 primary care physicians that provide care for approximately 600,000 patients in Ontario. Cases were identified within the medical records using unique encrypted identifiers from the administrative data (n=719). Information on the provision of primary care was extracted for the one-year period following the first diagnosis of psychotic disorder and included: (i) clinical assessments; (ii) laboratory tests; (iii) monitoring of cardiometabolic disease; (iv) monitoring of psychotropic medication side effects; (v) smoking cessation strategies; and (vi) involvement of specialist care. We used latent class

analysis to define clusters of co-occurring care patterns, and multivariable regression analyses to identify patient and physician characteristics associated with the defined clusters of care.
Results: We are currently conducting analyses, which will be ready in time for the conference.
Discussion: The proposed study will provide important information on the provision of primary care following a first diagnosis of psychotic disorder. These findings will allow for the identification of patient-, physician-, and system-level factors that must be addressed in order to support primary care physicians to better meet the needs of young people with psychotic disorders.

S64. EFFECTS OF BENZODIAZEPINE PRESCRIPTION ON REAL-WORLD CLINICAL OUTCOMES IN INDIVIDUALS AT CLINICAL HIGH-RISK FOR PSYCHOSIS

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Background: Recent preclinical research suggests that GABA-enhancing drugs may present a promising strategy for preventing psychosis onset, as peripubertal benzodiazepine administration prevents the emergence of adult psychosis-like behavioural and neurophysiological phenotypes in a well-validated neurodevelopmental rodent model of psychosis. Benzodiazepines are occasionally prescribed to people at Clinical High-Risk for Psychosis (CHR-P) as part of clinical care. This provides a unique opportunity to investigate whether benzodiazepine exposure is associated with a reduced risk of subsequently developing an adverse clinical outcome, including transition to psychosis, in a large sample of CHR-P individuals.
Methods: We present results from a naturalistic, retrospective, observational cohort study using electronic health records from 820 CHR-P individuals accessing a secondary mental health care CHR-P service within the South London and Maudsley NHS Foundation Trust (London, UK) between 2001-2022. Cox proportional-hazards regression models assessed whether benzodiazepine exposure +/- 3-months of accessing the service reduced the risk of adverse clinical outcomes, defined as developing an ICD-10 psychotic disorder or event indicative of clinical crisis (home visit, presentation at Accident and Emergency (A and E), or hospital admission) compared to individuals who remained benzodiazepine-naïve in this period. Observation periods included time to outcome event from 3-months after first contact with the CHR-P service, and when an event did not occur last observation carried forward was used. Individual models were run on each outcome variable using i.) the whole, unadjusted sample, and ii.) a subset of benzodiazepine-naïve individuals identified using Propensity Score Matching (PSM), to account for confounding-by-indication. PSM included age, black ethnicity, severity of attenuated psychotic symptoms, duration of untreated attenuated

psychotic symptoms, CHR-P subgroup, and timepoint of accessing services as covariates, due to their known associations with benzodiazepine prescription and/or outcome variables in previous research. In PSM, each individual with early benzodiazepine exposure becomes matched to a benzodiazepine-naïve individual with a near identical propensity score, generating equally numbered groups.
Results: After removal of individuals with missing data or follow up period < 3 months, 567 individuals were included in the analysis, with either benzodiazepine exposure (n=105) or who were benzodiazepine naïve (n=462). In the whole sample analysis, CHR-P individuals with benzodiazepine exposure had an increased risk of developing psychosis (HR=1.61; 95% CI: 1.03-2.52; p=0.037), receiving a home visit (HR=1.64 95% CI: 1.18-2.28; p=0.004), attending A and E (HR=1.88; 95% CI: 1.31-2.72; p<0.001), and being admitted to hospital (HR=1.95; 95% CI: 1.14-3.34; p=0.015). In the PSM sample analysis (n=105 in both groups), benzodiazepine exposure did not significantly modulate the risk of developing psychosis (HR=0.86; 95% CI: 0.49-1.48; p=0.579), receiving a home visit (HR=1.58; 95% CI: 0.99-2.51; p=0.055), attending A and E (HR=1.52; 95% CI: 0.91-2.55; p=0.112), or being admitted to hospital (HR:1.07; 95% CI: 0.53-2.15; p=0.844).
Discussion: These findings suggest that contrary to our hypothesis, benzodiazepine exposure in CHR-P individuals is not associated with a reduced risk of developing psychosis or other adverse clinical outcomes. However, the PSM analysis results suggest that the increased risk of adverse clinical outcomes found in the unadjusted whole sample analysis could be due to confounding-by-indication, such that benzodiazepines may be prescribed to CHR-P individuals who are clinically more unwell.

S65. A QUALITATIVE STUDY EXPLORING THE ACCEPTABILITY OF PERCEPTION (A PSYCHOEDUCATION AND PEER SUPPORT INTERVENTION) FOR RELATIVES OF PEOPLE EXPERIENCING A FIRST EPISODE PSYCHOSIS

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Background: Family members of people experiencing a first episode psychosis (FEP) can experience high levels of carer burden, stigma, emotional challenges, and uncertainty. This indicates the need for support and psychoeducation. Due to the necessity to ensure services continued despite COVID-19, we developed a multidisciplinary, blended, telehealth intervention, incorporating psychoeducation and peer support, for family members of FEP service users: PERCEPTION (PsychoEducation for Relatives of people Currently Experiencing Psychosis using Telehealth, an In-person meeting, and ONline peer support). The aim of this study was to appraise the acceptability of PERCEPTION for family members of people who have experienced a FEP.
Methods: Ten semi-structured interviews (lasting approximately 45 minutes) were conducted online via Zoom and audio recorded. Maximum variation sampling was used to recruit a sample balanced across age, gender, relatives' prior mental health service use experience and participants' relationship with the family member who is experiencing psychosis. Data was analysed by hand using Thematic Analysis.
Results: Four shared themes were produced: reduced misinformation led to confidence in participants' understanding of, and dealing with, psychosis; support added meaning to

intervention; the realities of caregiver burden; and telehealth was experienced as an accessible platform for service delivery.
Discussion: Findings indicate that PERCEPTION is a largely acceptable intervention and illustrate the importance of a well-informed and supported family member. The timing of the intervention is critical as family members may find the experience of participating emotionally draining. Early Intervention in Psychosis services could consider offering a self-care component to family members to reduce carer burden. PERCEPTION has the potential to address unmet needs of family members. Future research evaluating its feasibility and efficacy is warranted.

S66. SOCIAL ANXIETY TREATMENT IN SCHIZOPHRENIA USING MINDFULNESS AND VR

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Background: Recent reports suggest that social anxiety, when diagnosed, is found in about 23% of individuals with schizophrenia living in the community. New treatments for social anxiety have emerged over the past decade but have not yet been thoroughly studied in people with comorbid social anxiety and schizophrenia. We propose to offer a third wave cognitive behavioral treatment (called CAM: Compassion, Acceptance, and Mindfulness) combined with a virtual reality (VR) exposure to a classroom environment. The VR exposure is tailored to the participant and can be modified during the therapy (making the classroom more or less stressful by increasing stares, laughter or indifference).
Methods: The pilot study wished to determine the potential impact of the CAM intervention offered with VR exposure for young people with schizophrenia and comorbid social anxiety (N=11) compared to a group with social anxiety only (N=36). CAM with VR exposure was offered weekly for 8 weeks. Inclusion criteria: aged 14 to 30, a diagnosis of social anxiety (SCID), not receiving another treatment for social anxiety and consent to the study.
Results: Results were similar for both groups. Participants missed few sessions, qualitative data suggests appreciation and behavioral change. A statistically significant improvement in social anxiety (large effect) was found for all three measures (LSAS, SPIN and SAQ), as well as for overall anxiety (GAD-7), tolerance toward uncertainty (IUS) and quality of life (WHOQoL).
Discussion: The results are preliminary and promising. A larger study is needed to establish the effectiveness of this novel intervention.

S67. AN IDENTIFICATION SYSTEM FOR AT-RISK MENTAL STATE FOR PSYCHOSIS AMONG COMMUNITY WOMEN IN HONG KONG

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Background: Identification of individuals in at-risk mental states (ARMS) for the development of psychosis is a key goal of current preventive efforts in mental health research.

The use of the traditional two-level system consisting of a screener and a semi-structured interview, however, indicated relatively low specificity and efficiency.
Methods: We presented and evaluated a three-level screening system for ARMS as part of a community mental health program for women in Hong Kong. Women were invited to complete the pen-and-paper version or web-based screener during public awareness events assisted by social workers, or through social media promotions.
Results: The 21-item version of the prodromal questionnaire brief (PQ-B-21) was completed by 14420 women to assess their psychotic-like symptoms. 39 percent (n = 5621) of respondents met the a priori cut-off criterion of PQ-B-21 and were eligible for telephone contact to clarify their understanding of the items in the screener. We successfully contacted 1971 women, and 465 completed semi-structured interviews (response rate: 89.3 percent) using the Comprehensive Assessment for At-Risk Mental State (CAARMS). A total of 248 ARMS and 34 first-episode psychosis were found in the final sample. Based on PQ-B-21 scores, ROC curve analysis revealed excellent and good sensitivity and specificity for predicting ARMS status. The AUC decreased significantly after telephone screening and then to CAARMS interviews, indicating that telephone screening plays a significant role in eliminating false positive cases and thus saving unnecessary resources for CAARMS interviews.
Discussion: When compared to the two-level system, the findings of the current study showed that the three-level screening system can improve the efficiency of detecting ARMS/psychosis from a population-wide screening programme.

S68. MULTIVARIATE BRAIN STRUCTURE-COGNITION SIGNATURES OF EARLY PSYCHOSIS

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Background: Cognitive impairment is frequently observed in recent-onset psychosis (ROP), does not improve with medications, and predicts functional outcomes. ROP patients present widespread grey matter (GM) reductions and more widespread and subtle white matter (WM) abnormalities, but their relationship to cognitive impairment is unclear. This is the first study investigating multivariate structure-cognition correlations in ROP using a novel, multiblock partial least squares correlation analysis (MB-PLS-C). Our previous MB-PLS-C studies on treatment-resistant schizophrenia (TRS) patients and this population both showed differential patterns between GM and cognitive abilities. Thus, we hypothesised that MB-PLS-C would show differential GM-WM patterns between controls and ROP patients in the current study, and the differential pattern would be correlated with the cognitive abilities of patients.
Methods: We used the Human Connectome Project for Early psychosis and the Human Connectome Project Development datasets, including cognitive assessments of the NIH Toolbox, T1 and diffusion-weighted MRI data from 71 nonaffective ROP patients (age 22.1±3.1) and 71 matched healthy controls (age 22.0±3.2). We performed MB-PLS-C analyses using GM thickness and surface area (Desikan-Killiany atlas) and fractional anisotropy from WM tracts (JHU atlas) to identify multivariate GM-WM patterns. We analysed correlations

between the GM-WM patterns and cognitive abilities including cognitive flexibility, attention, working memory, episodic memory, processing speed, reading and vocabulary.
Results: MB-PLS-C between GM thickness and WM revealed two significant latent variables (LVs) explaining 64.19% of the sum-of-squares variance: LV1 (51.18%) described a widespread and shared GM-WM pattern: LV2 (13.01%) comprised a differential GM-WM pattern with widespread GM regions and WM tracts including fornix, cerebellum peduncles and medial lemniscus. MB-PLS-C between GM surface area and WM revealed three significant LVs explaining 80.57% of the sum-of-squares variance: LV1 (56.09%) described a widespread and shared GM-WM pattern: LV2 (13.70%) and LV3 (10.78%) showed differential GM-WM patterns implicating GM in frontal and cingulate regions and WM tracts including medial lemniscus and cerebellum peduncles in LV2, and GM in frontal and temporal regions and WM tracts including corpus callosum and superior cerebellar peduncle in LV3. The differential GM-WM pattern with surface area was significantly correlated with reading, vocabulary and working memory in patients. The differential GM-WM pattern with thickness was significantly correlated with all cognitive abilities in patients.
Discussion: MB-PLS-C demonstrated the differential GM-WM patterns largely involving relationships between widespread GM regions and WM tracts in the cerebellum and pons. The differential patterns with GM surface area were mainly correlated with crystallised intelligence, whereas GM thickness was correlated with crystallised and fluid intelligence in patients, indicating the different developmental processes of surface area and thickness. The differential GM-WM pattern indicates a potential signature of brain alterations contributing to multidomain cognitive dysfunction in the early stages of schizophrenia.

S69. EMERGENCY DEPARTMENT PRESENTATIONS FOR PSYCHOSIS AMONG YOUNG ADULTS DURING THE COVID-19 PANDEMIC: IMPACT ON VOLUME, ACUITY, AND LENGTH OF STAY

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Background: Young adults globally faced heightened levels of stress and social isolation during the COVID-19 pandemic, as well as interruptions in school and work. Young adults with psychotic illness were particularly vulnerable to adverse mental health outcomes during the pandemic due to socioeconomic adversity, interruptions in outpatient care, technological barriers to telehealth, and the need for in-person visits for long-acting injectables and other specialized psychosis treatments. The impact of the COVID-19 pandemic on the acuity and volume of emergency department (ED) visits for acute psychosis among young adults is not well understood.
Methods: We retrospectively analyzed 711 ED visits for psychosis (defined by the international classification of disease billing code) by adults ages 18-30 between 03/01/2019-02/28/2021. Poisson regression analysis was employed to explore ED visit volume between the first year of the pandemic compared to the year prior. Chi-square tests were used to compare differences in markers of acuity (physical restraint, parenteral [e.g. intramuscular or intravenous] medication treatment, and inpatient psychiatric [IP] hospitalization). Independent t-tests were employed to explore differences in ED length of stay (LOS) across the pre-pandemic and pandemic periods. We utilized multivariate logistic regression to further explore the relationships between the pandemic and restraint use, parenteral medication administration,

and IP hospitalization. Additional analyses will explore potential neighborhood-level sociodemographic factors associated with ED volume and outcomes for young adults with psychosis prior to and during the pandemic.
Results: There were no significant differences in volume of ED visits for psychosis, IP hospitalization, physical restraint use during the first year of the pandemic compared to the year prior. The odds of a visit resulting in parenteral antipsychotic (OR 1.81 95% CI 1.24-2.68 CI, p=0.002) and parenteral benzodiazepine (OR 1.53 95% CI 1.04-2.25, p=0.032) treatment was significantly higher during the pandemic versus the prior year, even after controlling for socio-demographic covariates. ED LOS was significantly longer during the pandemic compared to pre-pandemic (M = 28.76, SD = 1.69 vs M = 20.27, SD = 1.22, t = -4.02, df = 718, p < .001).
Discussion: In this population of young adults presenting to the ED for psychosis, we found significantly higher rates of parenteral medication administration and longer ED LOS during the pandemic compared with the prior year. These results may reflect complex factors, including increased acuity of psychosis among young adults and decreased IP bed availability in our geographic region. These findings highlight the strain of the COVID-19 pandemic on the mental healthcare system.

S70. DEVELOPMENT OF A COMPONENTS OF CARE ASSESSMENT FOR CLINICAL HIGH RISK FOR PSYCHOSIS UTILIZING A DELPHI APPROACH. THE CLINICAL HIGH RISK FOR PSYCHOSIS SERVICE - FIDELITY SCALE (CHRPS-FS)

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Background: Coordinated Specialty care is a team based, multi-element intervention validated to treat individuals with early psychosis (EP). However, many such programs also treat people at clinical high risk for psychosis (CHRP). To systematically record what components of care an EP program delivers, tools such as the First Episode Psychosis services Fidelity Scale have been developed and validated. However, no measures have been validated to assess the specific components of care that are delivered to individuals with CHRP. Such a tool could be useful to assess what components of care are delivered both within and across CHRP programs, facilitate benchmarking, and support future research in the field of CHRP care. Therefore, we conducted a Delphi study with international experts in the field of CHRP to validate a components of care assessment tool for team-based care for individuals experiencing CHRP.
Methods: A recently published systematic review identified randomized controlled trials of treatments CHRP. We identified the clinical investigators from all those studies and invited them to participate. Participants were sent a survey including all items of the Clinical High Risk for Psychosis Services – Fidelity Scale (CHRPS-FS). Participants were asked to rate the importance and the validity of the measure of each item on a scale of 0-4 and were provided space to provide more detailed feedback. Items focused on areas such as service structure, delivery of psychotherapy, assessment and care planning, pharmacotherapy, coordination with external services, peer involvement, and supported education and employment service delivery. Item-level consensus was considered to be achieved at a semi-interquartile range of ≤.5. Items were amended based on participants feedback and sent out for further review until a consensus of 80% across all items was achieved.
Results: Our search identified 50 academic experts. Of those, nine agreed to participate. Two participants were based in the US, two in Canada, and one each from the UK, Germany, Denmark, Australia, and the Netherlands. After two rounds, consensus regarding the

importance of each component was achieved on 28 of 31 items (90.3%), and consensus regarding the validity of the assessment method for each item was achieved on 22 of 31 items (71%), resulting in an overall consensus of 80.6%. In total, 27 of 31 (87.1%) components of care presented to participants were considered to be at least 'very important' to CHRP care.
Discussion: A high degree of consensus was achieved regarding what components of care should be considered important in CHRP care amongst academic experts. In the next stage of the project, a Delphi study with clinical experts in CHRP care will be conducted. These data will be used to develop a tool that will be piloted in multiple CSC clinics across California.

S71. EFFECTS OF ANTICHOLINERGIC BURDEN ON VERBAL MEMORY PERFORMANCE IN FIRST-EPISODE PSYCHOSIS

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Background: Antipsychotics are widely used for the treatment of a first episode of psychosis but some of those may have an anticholinergic burden, a cumulative effect of medications that block the cholinergic system. Studies suggest that high anticholinergic burden has negative effects on memory in early psychosis where cognitive deficits, particularly those in verbal memory, represent a core feature of the disease. The present study sought to replicate in a large cohort of well-characterized first episode psychosis patients this association. We expected that patients in the highest anticholinergic burden group would exhibit the poorest verbal memory compared with those with low anticholinergic burden and controls at month 3. We further hypothesized that over time, at month 12, patients' verbal memory performance will improve, but will remain poorer than controls.
Methods: Patients (n=311; low anticholinergic burden [n=241] and high anticholinergic burden [n=70]) followed at the PEPP-Montreal clinic (program between 2003 and 2022) and controls (n=128) completed a clinical and neurocognitive battery including parts of the Wechsler Memory Scale at month 3 and 12.
Results: Cross-sectionally using an ANOVA, patients in the highest anticholinergic burden group had the poorest performance in verbal memory when compared to the other groups at month 3 ($F(2,430)=52.33$, $P<0.001$). Longitudinally using a Generalized Estimating Equation model, verbal memory performance of all groups improved over time, however patients' performance (from high and low anticholinergic burden groups) remained poorer than controls.
Discussion: These findings highlight the importance of considering anticholinergic burden when prescribing medications in the early stages of the disease.

S72. LONGITUDINAL MODELLING OF NEGATIVE SYMPTOMS IN THE NAPLS-3 CLINICAL HIGH-RISK FOR PSYCHOSIS COHORT: TRAJECTORIES DISTINGUISHED BY TRANSITION STATUS, MOOD, FUNCTIONING, AND COGNITION

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Background: Psychotic illness is associated with significant psychosocial functional burden; hence, research has sought to understand symptom mechanisms to inform early monitoring efforts of individuals who may be at clinical high risk (CHR) for psychosis. Traditionally, psychosis conversion risk identification has primarily relied on monitoring for emerging or worsening attenuated positive symptoms. Negative symptoms can also be prominent during the prodromal period of psychotic illness and have been found to play a role in conversion and poor life functioning. The potential of negative symptoms as a reliable marker for psychosis risk is limited by our understanding of how these symptoms initially present and change over time in CHR samples. Preliminary findings suggest that dynamic negative symptom courses could be implicated in the psychopathology of CHR individuals. Thus, objectives of the current CHR study were to (1) characterize longitudinal trajectories of negative symptoms, (2) examine whether symptom trajectories distinguished clinical subgroups, and (3) identify patient characteristics that moderated worsening symptom trajectories.

Methods: CHR participants (n = 699) from the North American Prodrome Longitudinal Study (NAPLS-3) were monitored over a 24-month period on negative symptoms (SOPS), depressive symptoms (CDSS), social and role functioning (GF-S; GF-R), and intellectual functioning (WASI-II). Three clinical subgroups were defined by transition to psychosis, putative deficit syndrome (elevated negative symptoms without elevated mood symptoms), and early persistent negative symptom statuses. Growth-curve models of negative symptoms, clinical subgroups, and patient characteristics were systematically fit to address study questions.

Results: All clinical subgroups, including the “early persistent negative symptom group”, showed a curvilinear trend of negative symptoms, where baseline symptoms were more elevated compared to the rest of the sample, initially improved, and then gradually continued to improve. The transition group exhibited a delayed negative symptom improvement while the putative deficit group showed an earlier rapid improvement. Greater role and intellectual functioning were associated with slower rates of negative symptom resolution but stronger stability of improvements.

Discussion: With a larger window of frequent symptom monitoring, this study is the first to confirm that CHR individuals consistently showed elevated negative symptom presentations at study outset and eventual improvement in a curvilinear pattern. This finding contrasted with prior reports of "persistent elevated" and "negative linear" symptom trajectories in psychosis spectrum groups during shorter observation periods. Characteristics of the negative symptom trajectory were also uniquely distinguished by clinical subgroups and patient characteristics. The transition and putative deficit syndrome groups both exhibited more elevated baseline negative symptoms and delayed improvements over time compared to the rest of the sample. CHR individuals with greater role functioning and IQ manifested a "slow but steady" negative symptom course where symptoms were resolved at a slower rate but the rate of improvement was sustained longer. Findings highlight the need to improve long-term monitoring standards for negative symptom courses that may distinguish worse clinical profiles in CHR individuals.

S73. RICH-CLUB AND STRUCTURAL NETWORK CONNECTIVITY DEFICITS IN YOUTH AT CLINICAL HIGH-RISK FOR PSYCHOSIS AND INDIVIDUALS WITH EARLY ILLNESS SCHIZOPHRENIA

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Background: Brain dysconnectivity has been posited as a biological marker of schizophrenia, with decreased structural brain connectivity present throughout the course of schizophrenia, including in individuals at clinical high-risk for psychosis (CHR-P) and early in the course of schizophrenia (ESZ). Brain connectomic methods combine magnetic resonance imaging (MRI) anatomical data with diffusion tensor imaging (DTI) connectivity data; thus allowing for interrogation of specific white matter pathways and networks. Recent connectome research in schizophrenia has focused on the rich-club, a set of highly-connected brain hubs considered to be the "backbone" of global brain communication but disproportionately vulnerable to dysconnectivity. Although rich-club deficits have been found in chronic schizophrenia, it is unclear whether rich-club abnormalities are present in the CHR-P syndrome or how they compare to abnormalities in ESZ.

Methods: Combining structural MRI with DTI to reconstruct the structural pathways between anatomical regions, we created cortical connectome maps and concurrently examined rich-club connectivity and structural network connectivity in CHR-P (n = 41) and ESZ (n = 70) relative to healthy controls (HC; n = 74) after accounting for the effects of normal aging. To assess whether connectome measures predict psychosis conversion, CHR-P individuals who subsequently converted to a full-blown psychotic disorder (n = 9) were compared with CHR-P indviduals who were followed for a full 24-months without converting to psychosis (n = 19).

Results: Rich-club regions were identified as the top 13% most highly-connected cortical brain regions in HC: left/right superior frontal, left/right superior parietal, left/right insula, right precuneus, left superior temporal, and left rostral middle frontal. Intact rich-club organization was found in all three groups. However, ESZ had fewer connections among rich-club regions relative to HC ($p = .024$) and CHR-P ($p = .022$), but no significant difference for connections with non-rich-club regions (ps>.289). This reduction was specific to the rich-club after accounting for non-rich-club connections in ESZ relative to HC (ps < .048). Although abnormalities were not present in CHR-P overall, CHR-P converters to psychosis had fewer connections among rich-club regions compared to CHR-P non-converters ($p = .037$).

Using a complementary network-based statistic analytic approach to identify affected subnetworks that show decreased connectivity in ESZ and CHR groups, a subnetwork comprised of 22 cortical regions and 21 connections showed significant differences between groups ($p = .016$), with overall less connectivity across these connections for ESZ relative to HC ($p < .001$) and CHR-P ($p = .003$). We next examined each of the 21 connections. Notably, for the two connections spanning rich-club regions, ESZ had significantly fewer connections between right precuneus-right superior parietal ($p = .005$) and right precuneus-left superior parietal relative to HC ($p = .041$). For the connections spanning non-rich-club regions, some connections showed less connectivity for CHR-P and ESZ relative to HC, and others showed greater connectivity.

Discussion: Overall, results are consistent with the view that schizophrenia is a progressive brain disorder, with connectivity abnormalities predating schizophrenia illness onset. These results suggest that decreased structural dysconnectivity, in particular rich-club dysconnectivity, may be an early feature of schizophrenia. Further, findings from the current study provide novel insights into the neurobiological mechanisms underlying schizophrenia and highlight the critical roles of rich-club connectivity early in schizophrenia.

S74. AN INTERSECTIONAL EXAMINATION OF THE RELATIONSHIP BETWEEN RACIAL/ETHNIC DISCRIMINATION AND PSYCHOTIC-LIKE EXPERIENCES: THE ROLE OF OTHER PSYCHIATRIC SYMPTOMS

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Background: Racial/ethnic experiences of discrimination (EODs) are associated with numerous psychiatric symptoms, including outcomes along the psychosis spectrum; however, less is known about mechanisms by which EODs confer risk for psychotic-like experiences (PLEs; subthreshold psychotic symptoms). Furthermore, the intersection of race and gender impacts the nature of EODs experienced. Gender may also inform the mechanisms by which EODs impact symptomatology given known differences in stress pathology.
Methods: Undergraduates at a diverse, semi-public university (N=1,759) completed self-report questionnaires to investigate whether psychological sequelae of EODs (symptoms of post-traumatic stress, anxiety, depression, and dissociation) mediate the EOD—PLE relationship. To examine the role of intersectionality in these relationships, we stratified our sample by race [Non-Hispanic White (NHW), Black, Asian] and examined three multiple mediation models moderated by gender. All models controlled for age.
Results: In the full sample, all four psychological symptoms significantly and partially mediated the relationship between EODs and PLEs. There were significant indirect effects of anxiety (b = 0.091, 95% CI = 0,029, 0.152), dissociative (b = 0.023, 0.009, 0.037), and post-traumatic stress (b = 0.039, 0.013, 0.064) symptoms in female NHW, but not male NHW. For male Asian participants, there were significant indirect effects of symptoms of dissociation (b = 0.012, 95% CI = 0.001, 0.024) and PTSD (b = 0.056, 95% CI = 0.004, 0.108), while the EOD-PLE relationship was mediated with dissociation (b = 0.01, 95% CI = 0.002, 0.019), PTSD (b = 0.011, 95% CI = 0.011, 0.082), and anxiety (b = 0.092, 95% CI = 0.007, 0.176) symptoms in Asian females. All four mediators assessed were non-significant in Black males and females.
Discussion: These findings provide evidence for differential pathways from EODs to PLEs dependent on participants' race and sex. This underscores the importance of accounting for intersectionality in examinations of psychological symptoms and may assist in identifying targets of intervention after exposure to EODs.

S75. DOES THE SOCIAL INFLUENCE ON LINGUISTICS EXTEND TO CLINICALLY ASSESSED FORMAL THOUGHT DISORDER IN PSYCHOSIS? A PRELIMINARY STUDY

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Background: Psychosis is associated with abnormal speech patterns, thought to be the result of an underlying formal thought disorder, that includes disorganised and impoverished thinking. As speech patterns are influenced by social and sociolinguistic variations, it is reasonable to assume that formal thought disorder can also be influenced by a person's socioeconomic status (SES). SES itself relates to one's own and parental educational background, which can affect our communication styles. In addition, a discrepancy in the language spoken at home and the language of clinical interaction may also lead to a false inference of the presence of thought disorder. Of note, some authors have reported that immigrants with first episode psychosis to have notably higher clinical scores of disorganized thinking. In this preliminary study, we ascertained if the diagnostic differences in observer-rated impoverishment of thinking (IoT) and disorganization of thinking (DoT), is more pronounced than the effect of socioeconomic status and language spoken at home in the presence of established schizophrenia.
Methods: We collected data from 20 subjects (8 with chronic psychosis and 12 healthy controls). We applied the Thought and Language Index (TLI) scale which required the participants to view three different pictures one at a time, and describe each for up to two minutes while being audio recorded. These speech samples were then scored across eight categories, which were then collapsed into two main categories. The first three categories included poverty of speech, weakening of goal, and perseveration, contributing to the impoverishment of thinking (IoT) category. The remaining categories included looseness, peculiar word usage, peculiar sentence construction, peculiar logic, and distractibility, which represent the disorganization of thinking (DoT) category. The average scores of IoT and DoT across the three pictures were considered for further analysis. A higher score on the TLI indicated more severe FTD.
Results: Our findings showed that patients had significantly higher IoT when compared to healthy controls. This difference persisted even when using (SES) ($F = 6.76$, $p = 0.02$) and language spoken at home ($F = 4.11$, $p = 0.05$) as covariates. DoT was not significantly different between groups, however the results indicated a possible trend towards significance, especially after accounting for language at home ($F = 3.92$, $p = 0.06$) and SES ($F = 3.72$, $p = 0.07$).
Discussion: Our results indicate that in patients with psychosis IoT and DoT are not dependent on SES or language spoken at home, though we cannot rule out type-2 error in this sample. It is possible that while speech readouts (language markers) per se are affected more strongly by social variables, the observer rated formal thought disorder may be impervious to this effect; this remains to be tested in a larger sample.

S76. ALTERATIONS OF BRAIN TOPOLOGY IN ANTIPSYCHOTIC-NAIVE PATIENTS WITH SCHIZOPHRENIA

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Background: Abnormalities in brain gray matter (GM) topology comprising cortical surface areas and cortical thickness have been consistently observed in first-episode psychosis (FEP). The GM topology is inherently complex and nonlinear dynamic analysis of these spatial data can support the research on structural biomarkers in psychosis. Converting images into

sequences with time-series analysis tools has been used to solve various image data mining problems. The present study aimed to employ the chaos analysis approach for the identification of specific brain topology changes related to the onset of psychosis beyond classical approaches based on structural MRI. We hypothesized that the structural complexity expressed by the chaos analysis a) differs in antipsychotic-naïve FEP compared to HC and b) it is independent of the brain volume changes in FEP patients.
Methods: T1-weighted magnetic resonance imaging (MRI) of 150 first-episode antipsychotic-naïve schizophrenia (FEP) patients (82 females; mean age of entire sample: 23.5±7.1 years, range: 16-44 years; duration of untreated psychosis: 9.1±15.1 months) and 164 healthy participants (HC) (82 females; mean age: 24.7±7 years, range: 16-45 years) matched by age and sex were included in this study. Voxel-based morphometry was applied to identify between-group differences using gray matter images. The identified regions were then tested for changes in brain structural complexity by applying the chaos analysis approach in two steps: First, the center of mass in gray matter images was identified and the distances between voxels were calculated. Next, these distances multiplied by the voxel intensity were defined as spatial-series, which were then analyzed by extracting the Largest-Lyapunov-Exponent (lambda). Then, we mapped the lambda in the frequency domain using the correlation of the Morlet wavelet with the lambda spatial series resulting in a measure that reflects cortex folding complexity. Note, high lambda values represent high folding complexity.
Results: Decreased gray matter volumes for FEP patients compared to HC were identified in bilateral lingual gyrus, left parahippocampal gyrus, left temporal fusiform cortex and cerebellum. Findings from chaos analyses indicate that gray matter complexity in FEP patients was increased in bilateral lingual gyrus and left temporal fusiform cortex while reduced gray matter complexity was observed in the parahippocampal gyrus left. Furthermore, we found that structural complexity in the right parahippocampal gyrus was increased in FEP patients while no statistically significant volume differences compared to HC were identified in this region. In addition, statistically significant differences in the frequency domain between both groups reflect differences of cortical folding.
Discussion: Our findings support the notion that defining gray matter complexity by lambda offers a novel approach for identifying structural differences in brain regions related to psychosis. They are in line with previous studies reporting reduced morphological measures extracted from lingual gyrus and fusiform in patients with schizophrenia. Furthermore, indicators of cortical folding across multiple brain regions revealed differences between FEP patients compared to healthy controls, consistent with previous studies. In conclusion, we can show that the proposed method provides interesting insights into specific brain alterations in FEP; beyond those provided by standard volumetric comparisons. Further analysis of the brain topology of regions without volume changes will shed light to the identification of structural biomarkers in psychosis.

S77. RELAPSE IN SCHIZOPHRENIA: THE ROLE OF FACTORS OTHER THAN NON-ADHERENCE TO TREATMENT

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Background: Treatment non-adherence is the most common risk factor for relapse in patients with schizophrenia. Here, we examined the predictors of relapse over 24 months in patients

with first-episode schizophrenia (n = 107) for whom treatment adherence could be assured via treatment with a long-acting injectable antipsychotic.
Methods: Clinical and socio-demographic data were collected using valid instruments. Relapse was defined using modified Csernansky criteria. Substance use was assessed based on collateral family interviews and urine toxicology. Biochemical testing for fasting lipids and blood glucose levels were also performed. First, we used Cox regression analysis to examine time to relapse.
Results: Poor-quality social relationships (Hazard ratio [HR] = 0.85; 95% CI: 0.76–0.95; p = 0.003) and more pronounced neurological soft signs (HR = 1.05, 95% CI: 1.01–1.10, p = 0.03) predicted a shorter time to relapse, adjusting for age, sex, highest level of education, and duration of untreated psychosis.
Discussion: The association between poor social relationships with a shorter time to relapse suggests that quality of life may be an important determinant of prognosis in first-episode schizophrenia. Future prospective studies in larger samples are needed to better understand the risk factors for relapse in schizophrenia other than treatment non-adherence.

S78. DOES THE LOSS OF A GOOD NIGHT'S SLEEP OCCUR WEEKS BEFORE A RELAPSE? A SCOPING REVIEW OF SLEEP AND EXACERBATIONS OF PSYCHOSIS

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Background: Sleep disturbances, notably insomnia, are associated with more severe psychotic symptoms in patients with schizophrenia and may predict both onset and relapse of psychosis. Monitoring sleep activity may provide an important remotely sensed measurement for relapse prediction in those who are being treated for schizophrenia. A key requirement for such relapse prediction markers to be successful is their ability to provide a timely warning that allows clinicians to intervene soon before a relapse occurs. Such proactive therapeutic strategies may particularly help patients who wish to discontinue their antipsychotics due to intolerance. We conducted a review of the published literature on the period between a reported sleep disturbance and relapse in schizophrenia.
Methods: We followed the recommendations from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, searched MEDLINE/PubMed, EMBASE, and Google Scholar databases from inception through September 2022. The following search string was used: ((sleep OR insomnia OR dream OR nightmare OR circadian rhythm OR Periodic Leg Movements OR Pittsburgh) AND (paranoia OR Hallucination OR Psychosis OR Schizophrenia OR Delusion) AND (Relapse OR hospitalization OR rehospitalization)). All published human studies, written in English and French pertaining to either schizophrenia or psychosis which reported time between onset of sleep disturbance and symptom relapse were considered for inclusion.
Results: A total of 13720 articles were identified through Google Scholar (n = 3108), Embase (n = 754), PubMed (n = 10400) and through reviewing the bibliographies of included studies (n = 8). Of these 13720 articles found, 13608 were excluded, leaving 112 articles to be evaluated based on the full article, and finally, 11 studies were included in our review. We detail the main results of each study and highlight that a delay between 2 and 4 weeks seems

to be the average delay between the onset of sleep disorders and relapse of psychosis. We also assimilated information on the nature of different sleep disturbances.
Discussion: To our knowledge, this is the first review to provide an answer to the question of temporality between the incidence of sleep disorders and relapse. Although the studies that specified a delay between the onset of sleep disorders and relapse were heterogeneous, precluding a meta-analytical synthesis, most relapsing patients had sleep disorders between 2 and 4 weeks before the documented relapse/exacerbation. This has also been observed in some studies that did not focus specifically on relapse but a mere increase in psychotic symptoms. In general, overnight sleep disturbances could induce an increase in psychotic symptomatology the next day, with the total duration of sleep predicting the severity of paranoid symptoms and auditory hallucinations the next day. These observations will be of value to the ongoing efforts to generate digital markers for clinical use in the care of psychosis.

S79. PREDICTORS OF EARLY AND LATER REMISSION IN CLINICAL HIGH RISK OF PSYCHOSIS. A LATENT CLASS ANALYSIS

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Background: Clinical high risk for psychosis (CHR-P) research has mainly focused on transition to psychosis. Most individuals however do not transition, and many remit. In this study we explore latent classes for remission, and their associated baseline predictors and functional outcomes.
Methods: The study is a prospective seven-year follow-up study of CHR-P as assessed by the Structural Interview for Prodromal Syndromes (SIPS). Participants were recruited through systematic early detection strategies in a Norwegian catchment area (N=141). We conducted SIPS (scores 0=absent to 6=severe and psychotic) 13 times over the first two years, each time classifying individuals scoring 0 through 2 on all positive items as “remitted” and those with scores >3 as non-remitted. The resulting 13 dichotomous variables were used to perform a latent class analysis (LCA). Class affiliation was applied both as an outcome for baseline predictors and as a predictor for global functioning (GAF-F) after 24 months. T-tests and chi-square were used to estimate the association between class affiliations, predictors and outcomes.
Results: The latent class analysis showed moderate fit. The smallest class, “poor chance of remission”, (16.7 %) had a stable very small chance of remission. The second largest class, “later remission” (34.3 %), included participants with the highest chance for remission starting after five months. The largest class, “early remission” (49.0 %), consisted of participants with a high chance of early remission, one-three months after baseline. Baseline age, SIPS symptoms, drug use, years in school or gender were not significantly associated with early vs later remission. The early remission class had significantly better premorbid as well as two-year global functioning compared to the later remission class.
Discussion: The main study finding is the conceptual and statistical supported division of CHR-P remission into early and later remission. The monthly follow-up during the first six study months allowed for this division being spotted. Premorbid school adaptation and baseline global functioning predicts class affiliation. Early poorer functioning is associated with later poorer functioning despite symptomatic remission. These findings confirm functioning should

be a central focus of CHR-P field and strengthens the argument that different subgroups with different treatment needs exist in the CHR-P population.

S80. SPEECH PATTERNS IN PEOPLE WHO EXPERIENCE A PSYCHOTIC RELAPSE IN THE FIRST YEAR OF INTERVENTION

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Background: The unpredictable occurrence of relapses is one of the most debilitating aspects of psychosis, which leads to a high degree of uncertainty among patients and caregivers. In practice, speech is used as a primary source of information to routinely assess risk of relapse in patients. We previously reported a particular speech pattern characterised by a lower analytic thinking as the linguistic style indicative of the syndrome of disorganization during a descriptive discourse (picture description). In this work, we use a longitudinal design to relate lower analytic thinking with the occurrence of relapse over a period of 1-year in first episode psychosis.

Methods: In a sample of 68 patients referred to a first episode programme for psychosis, we undertook a baseline speech assessment using a picture description task (3 pictures from Thought and Language Index, 1-minute each). We later followed up the clinical trajectory over the next 1 year to assess relapse rates. Relapse was defined as an inpatient psychiatric admission within 1-year follow-up from study engagement, based on hospital electronic records. The speech samples were transcribed and preprocessed removing meaningless fillers, and altering stuttering and abbreviations. Three linguistic tools were sued for parsing the components of interest from speech. First, using Pennebaker's LIWC, we obtained Analytic Thinking Index (ATI) based on the proportional use of eight function words (articles, prepositions, pronouns, conjunctions, nonreferential adverbs, negations, and auxiliary verbs). This index reflects a bipolar narrative-categorical linguistic style continuum whose numerical values (in a 0–100 scale). Second, we also estimate components of syntactic complexity counting instances of nominal clauses (previously reported in Silva et al., 2022) and Mean Length of Clauses (MLC) using the tool TAASC. The last tool estimated the weakness in cohesion based on the percentage of temporal connectives (a score previously reported in Mackinley et al., 2021). All scores were standardised across 3 pictures by correcting for number of words spoken and compared between the relapse and non-relapse groups.

Results: 12 relapses occurred over 1 year; Patients that later relapsed had significantly lower mean ATI per word (relapse = 0.33(0.22); non-relapse =0.52(0.32), Cohen's d = 0.7, p=0.028, df=67) but not on MLC or the frequency of temporal connectives. Nevertheless, lower ATI was related to higher temporal (non-causal) connective use and lower complexity of clauses. The time to relapse did not relate to the ATI scores (r=0.07, df=11).

Discussion: Our results suggest that an inexpensive approach of recording speech over 3-minutes may provide important clues about later relapse. Computerised speech analysis may support our efforts to assess the probability of favorable prognosis and functional recovery in schizophrenia. We call for large-scale assessment of relapse prediction with speech sampling obtained during routine clinical assessments of first episode psychosis.

S81. COGNITIVE PERFORMANCES ACROSS INDIVIDUALS AT HIGH GENETIC RISK FOR SCHIZOPHRENIA, HIGH GENETIC RISK FOR BIPOLAR DISORDER,

AND LOW GENETIC RISKS: A COMBINED POLYGENIC RISK SCORE APPROACH

Poster

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Background: Individuals with schizophrenia (SCZ) and bipolar disorder (BD) display cognitive impairments, but the impairments in those with SCZ are more prominent, supported by genetic overlap between SCZ and cognitive impairments. However, it remains unclear whether cognitive performances differ between individuals at high and low genetic risks for SCZ or BD.

Methods: Using the latest Psychiatric Genomics Consortium (PGC) data, we calculated PGC3 SCZ-, PGC3 BD-, and SCZ vs. BD polygenic risk scores (PRSs) in 173 SCZ patients, 70 unaffected first-degree relatives (FRs) and 196 healthy controls (HCs). Based on combinations of three PRS deciles, individuals in the genetic SCZ, genetic BD and low genetic risk groups were extracted. Cognitive performance was assessed by the Brief Assessment of Cognition in Schizophrenia.

Results: SCZ-, BD-, SCZ vs. BD-PRSs were associated with case–control status (R^2=0.020-0.061), and SCZ-PRS was associated with relative–control status (R^2=0.023). Furthermore, individuals in the highest decile for SCZ PRSs had elevated BD-PRSs (OR=6.33) and SCZ vs. BD-PRSs (OR=1.86) compared with those in the lowest decile. Of the three genetic risk groups, the low genetic risk group contained more HCs, whereas the genetic BD and SCZ groups contained more SCZ patients ($p<0.05$). SCZ patients had widespread cognitive impairments, and FRs had cognitive impairments that were between those of SCZ patients and HCs ($p<0.05$). Cognitive differences between HCs in the low genetic risk group and SCZ patients in the genetic BD or genetic SCZ groups were more prominent (Cohen's $d>-0.20$) than those between HCs and SCZ patients in the no genetic risk group. Furthermore, SCZ patients in the genetic SCZ group displayed lower scores in verbal fluency and attention than those in the genetic BD group ($d>-0.20$).

Discussion: Our findings suggest that cognitive impairments in SCZ are partially mediated through genetic loadings for SCZ but not BD.

S82. ADJUSTING FOR POPULATION STRATIFICATION IN POLYGENIC RISK SCORE ANALYSES: A GUIDE FOR MODEL SPECIFICATIONS IN THE UK BIOBANK

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Background: The UKB is a large general population sample that is often used to test PRS associations of various outcomes. However, different sets of PCs are available for the UKB such as 40 PCs for all genotyped samples under Data Field 22009 and 10 PCs from the ProPCA for "White British" individuals. Furthermore, no generally accepted strategy exists specifying how many PCs should be included in PRS analyses. In a previous guideline, the inclusion of 10 PCs was recommended to control for population stratification. However, the authors state that this number is arbitrary.

The current study aims to provide a general guide for model specifications such as the adjustment for covariates (i.e. age, sex, recruitment centers, and genetic batch, principal components [PCs]) and the number of PCs that need to be included in PRS analyses. Therefore, this study compared the model performance of PRS analyses under different model specifications for different physical, mental, and behavioral phenotypes in the UKB.

Methods: To test whether model specifications (i.e. addition of covariates) impacted the associations between each PRS and each respective outcome, unadjusted and adjusted analyses were performed under different model specifications. Linear regression analyses were applied for continuous outcomes. Logistic regression analyses were applied for binary outcomes. Covariates included sex, age, genetic batch, recruitment center, and up to 40 PCs. For each PRS, one unadjusted model as well as 655 adjusted models were built by using different combinations of covariates. PCs were added in sets such that when adding the 40th PC, the other 39 PCs were also included in the adjusted model (See the supplementary material for details).

For each model, we retrieved the coefficients, R-squares, and p-values for the association between the PRSs and the respective phenotypes. To test whether the addition of age, sex, recruitment center, and genetic batch improved the PRS prediction, we applied ANOVA tests comparing the adjusted models to the unadjusted reference model without any covariates. To test whether the addition of PCs improved the PRS prediction, the models with PCs were compared to the models with the same set of covariates and one additional PC (e.g. the model including age and one PC was compared to the model including age and two PCs). We compared the Bayesian information criterion (BIC), Akaike information criterion (AIC), and p-value from the ANOVA tests of the model pairs.

Results: We applied 3,280 (656 per phenotype) unadjusted and adjusted analyses for the five outcomes. We first investigated the PRSs prediction with the addition of age, sex, recruitment center, and genetic batch. Among those models, the most parsimonious PRS models are reported in Table 1. The ANOVA tests showed that for most outcomes, models with one to three of these covariates significantly improved the PRSs prediction ($P<2.8x10\text{-}200$). The addition of any of the covariates (i.e. age, sex, recruitment center, and genetic batch) did not improve the model for PRS-MDD.

Subsequently, we investigated the PRSs prediction with the addition of PCs. Among these models, the most parsimonious models are reported in Table 2. The ANOVA tests showed that for most outcomes, a low number of PCs significantly improved the model performance. The model performance of MDD did not improve by adding any PCs. The ANOVA tests comparing the reference models (the model with the same set of covariates but one less PC) with the most parsimonious models showed that the addition of age, sex, recruitment center, and genetic

batch had generally more influence on the model performance (Table 1) than the addition of PCs. Overall, the ANOVA tests for the parsimonious models including PCs had larger p-values (0.033 to 3.1x10-7) than the ANOVA tests for the parsimonious models without PCs (2.8x10-200). Furthermore, for all phenotypes, the variance explained by PCs were less than the variance explained by other covariates. For example, age explained 0.22% of the variance of BMI, whereas 3 PCs explained 0.02% of the variance of BMI

Discussion: This study aimed to provide an insight into the impact of model specifications of PRS analyses by comparing the predictive performance of PRSs for a select physical, mental, and behavioral phenotypes under different model specifications in the UKB. Findings suggest that the predictive performance of the PRS models can be improved by the addition of covariates including age, sex, genetic batch, and recruitment center. For most PRSs, the inclusion of up to three PCs appears to be sufficient for controlling population stratification.
Our findings provide insight into the impact of model specifications in PRS studies. Although PCs aid detecting and correcting for population stratification, only a lower number of PCs appear to improve the model performance for most outcomes, whereas the inclusion of other covariates (particularly age and sex) appears to be more essential for model performance. Therefore, these covariates should also be carefully considered in genetic studies to avoid confounding and improve model performance.

S83. UNDERSTANDING SEX- AND GENDER-BASED DRIVERS OF RISK, OUTCOMES, AND HEALTH SERVICE UTILIZATION IN MIGRANT GROUPS WITH PSYCHOTIC DISORDERS: A SYSTEMATIC SCOPING REVIEW

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Background: Research suggests that the risk of psychosis is more than two-times higher in some first-generation migrant groups. However, the causes underlying the migration-psychosis association remain unclear. Previous meta-analyses have not found significant differences in the risk of psychosis among migrants compared to non-migrants by sex. But there may be sex- and gender-based differences in the factors that modify psychosis risk. For example, a recent study shows that women migrating alone may be at higher risk compared to women migrating with or to join family, whereas men joining family are at higher risk than men migrating alone. This scoping review aims to summarize what is known about the relationship between sex/gender, migration, and psychosis. Specifically, this review examines sex- and gender-based differences in the factors that differentiate psychosis risk, outcomes, and health service utilization among migrant groups.
Methods: We identified 7,617 articles for title and abstract review from the MEDLINE, Embase, PsycINFO, and Web of Science databases. This first level of screening is in progress. After identifying relevant articles through full-text review, data will be extracted and organized by theme.
Results: Results will be presented at the conference.
Discussion: It is necessary to understand sex- and gender-based differences in psychosis risk, outcomes, and health service utilization to identify subgroups that may face greater risk or additional barriers to care. This will help inform targeted public mental health interventions, and thereby address psychosis-related inequities among migrants.

S84. DIGITAL TRAINING FOR COMMUNITY HEALTH WORKERS IN THE DETECTION AND REFERRAL OF SCHIZOPHRENIA IN PRIMARY CARE IN RURAL INDIA: FINDINGS FROM PILOT STUDY

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Background: People living with Schizophrenia in low-income and middle-income countries face shortage of mental health specialists. Task sharing is an approach that can help to address unmet mental health needs in rural and other low-resource areas by building capacity of frontline health workers such as Accredited Social Health Activist called ASHAs. This pilot trial evaluated the feasibility and acceptability of a digital program for training non-specialist health workers in the detection and referral of patients with schizophrenia in in rural India.

Methods: An iterative design process was employed to adapt an evidence-based psychosocial intervention for delivery by ASHAs in rural Madhya Pradesh, India. Development of the training program involved human centred design for content review by subject matter experts, caregivers, service users, and ASHAs. 20 ASHAs were recruited from primary care facilities from a rural district in Madhya Pradesh. The primary outcome was the feasibility and acceptability of digital training program. Preliminary effectiveness was explored as changes in knowledge outcomes, assessed using a self-reported measure covering the specific knowledge and skills required to identify and refer patients with Schizophrenia. Outcomes were collected at pre-training and post-training and focus group discussions were conducted at the end of the training.

Results: All the 20 ASHAs completed the training. The overall knowledge outcome mean score improved across all participants with no significant pre-post differences (Pre-Mean=44.3; SD=8.09 and post-Mean=48.7; SD-10.03). Four key themes emerged from the focus group discussions including: 1) recognizing schizophrenia in the community and the importance of treatment; 2) understanding the symptoms and impact of schizophrenia on individuals and their families; 3) the need for rehabilitation and the importance of referral and follow-up; and 4) acceptability of digital training for building skills and knowledge about schizophrenia among ASHAs. Importantly, ASHAs described their experiences seeing people in the community with similar symptoms but mentioning that prior to the training that they were unaware of this illness and the possibility of treatment for such an illness. The training helped the ASHAs better understand the need for adequate treatment and to look for side-effects. The ASHAs also found that the training helped them better understand misconceptions about and discrimination towards people with schizophrenia, and how to address these challenges by supporting others and spreading awareness about schizophrenia in their communities. They were also keen on asking other ASHAs to do the training.

Discussion: ASHAs in this study reported that training can help them identify symptoms of schizophrenia and connect patients with specialists by doing adequate referrals. This suggests that ASHAs recognise the importance of training about schizophrenia which could support efforts to address the demand for such interventions in community settings in rural India. This work holds merit as ASHAs would also be better positioned to cater to the health needs of persons with Schizophrenia through identification and referrals to the government health system in community settings. This may have a cascading effect on the clinical stability of the person with Schizophrenia, resulting in better functioning.

S85. GENDER DIFFERENCES IN THE SOCIAL ETIOLOGY OF PSYCHOTIC EXPERIENCES IN THE UNITED STATES

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Background: Psychotic experiences are sub-clinical hallucinations and delusions that serve as a useful proxy for psychosis vulnerability in studying the etiology of psychosis. However, the body of literature on the social epidemiology of psychotic experiences has rarely focused on gender differences in the relative contributions of known risk factors. In this study, we test whether associations between psychotic experiences and a range of established risk factors vary by gender in a U.S. national probability sample of young adults.

Methods: Data on demographics, psychotic experiences, and socioenvironmental risk factors were collected through the National Survey of Poly-victimization and Mental Health, a probability sample of young adults aged 18-29 years (N=1048), residing in the U.S. at the time of data collection (2021). All analyses were weighted to adjust for non-response and unequal probability of selection. Psychotic experiences were measured using the World Health Organization psychosis screen, coded as a binary variable indicating the self-reported presence/absence of any psychotic experience. Sociodemographic and risk factors included income, education, region, urban/rural living, and exposure to various forms of violence, trauma, discrimination, and other adverse events. Separate logistic regression analyses were used to identify significant correlates of psychotic experiences among male and female respondents, with associations reported as odds ratios (OR).

Results: Psychotic experiences were reported by 27.9% of female respondents and 51.9% of male respondents. Although there were unadjusted racial/ethnic inequities in the reporting of psychotic experiences, this difference was only significant among females, specifically comparing Black to White women, OR(95% CI)=2.03(1.24-3.31). Women were also more likely to report psychotic experiences if they had experienced intimate partner violence, OR(95% CI)=1.89(1.22-2.93). This factor was not significant for males; instead, males were more likely to report psychotic experiences if they had experienced childhood trauma, OR(95% CI)=1.68(1.07-2.64), which conversely, was not significant for females. In addition, males (but not females) were at greater risk of reporting psychotic experiences if they had less education, OR(95% CI)=0.71(0.55-0.92) and if they lived in rural (compared to urban) areas, OR(95% CI)=1.79(1.02-3.15). The one commonality between men and women was that indicators of structural racism (i.e., police violence exposure) and day-to-day discrimination (everyday discrimination scores) was similarly associated with psychotic experiences for both groups, although the magnitude of associations with police violence were stronger for males, OR(95% CI)=3.19(1.71-5.92) compared to females, OR(95% CI)=2.16(1.14-4.12).

Discussion: While both male and female respondents were more likely to endorse psychotic experiences if they had experienced discrimination or police violence, the commonalities ended there. Risk for psychotic experiences was notably associated with childhood trauma for males but adolescent/adulthood trauma for females. In addition, sociodemographic correlates of psychotic experiences varied by gender, with racial inequities only persisting for females in the fully adjusted models. Further research with longitudinal data should continue to explore distinct pathways in the social etiology of psychosis, and potential gender differences in the likelihood of following one pathway versus another.

S86. MATERNAL SCHIZOPHRENIA AND CHILDHOOD ASTHMA RISK AND SEVERITY: A POPULATION-BASED COHORT STUDY

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Background: Maternal schizophrenia is associated with certain perinatal complications, yet there has been minimal focus on longer-term childhood health. Pregnant individuals with schizophrenia have higher rates of exposure to poverty, poor health status, smoking, substance use, and domestic violence; these risk factors could increase vulnerability to and severity of chronic illness among their children, and may also contribute to difficulties managing their children's health. Asthma is the most common chronic disease in children, and is considered an ambulatory care sensitive condition (i.e. acute care visits for asthma exacerbations are potentially avoidable if children receive appropriate primary care). In the current study, we used population-based health administrative data to identify children exposed and unexposed to maternal schizophrenia and compared 1) the risk of developing a new diagnosis of asthma and, 2) among children with pre-existing asthma, the rate of asthma-related hospitalizations.
Methods: Using health administrative data from Ontario, Canada on 2,989,657 children born from April 1, 1995 to March 31, 2018 and followed until March 31, 2022 (a maximum age of 18 years for the child), asthma risk was compared between 5,066 children with maternal schizophrenia (defined as being born to individuals who were diagnosed with schizophrenia prior to delivery) and 25,325 propensity-matched children without maternal schizophrenia. Then, among children with asthma diagnosed by March 31, 2021 (n=560,477), asthma-related acute care utilization was compared between 1,498 children with maternal schizophrenia (defined as being born to individuals who were diagnosed with schizophrenia prior to the child's asthma diagnosis) and 558,979 children without maternal schizophrenia. Asthma-related hospitalizations were compared using Poisson regression to estimate unadjusted relative rates (RR), and relative rates adjusting for maternal income quintile, medical and mental health comorbidities, and child sex, year and age at asthma diagnosis, and other chronic conditions (aRR).
Results: The incidence of asthma was 23.1/1000 person-years (py) in children with maternal schizophrenia vs. 22.4/1000 py in propensity-matched children without maternal schizophrenia (Hazard Ratio 1.03, 95%CI 0.96-1.10). Among children with asthma, the asthma-related hospitalization rate was increased with maternal schizophrenia (9.6 vs. 7.7/1000py; RR 1.26, 95%CI 0.99-1.59; aRR 1.34, 95%CI 1.07-1.69).
Discussion: While not at higher risk for developing asthma, children with maternal schizophrenia who have asthma had slightly elevated rates of asthma-related hospitalization, suggesting poorer asthma control. Further work is needed to understand confounding factors and relationships with maternal illness severity, which together might contribute to the development of interventions that benefit mothers and their children.

S87. WOMEN WITH SCHIZOPHRENIA AND THE RISK FOR BREAST CANCER ASSOCIATED WITH LONG-TERM EXPOSURE TO ANTI-PSYCHOTIC MEDICATIONS: A POPULATION-BASED NATIONWIDE STUDY

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Background: Most antipsychotics cause an increase in prolactin secretion, a hormone hypothesized to increase the risk for breast cancer. Several epidemiological studies showed an association between exposure to antipsychotic medications and the risk of breast cancer. The objective of the current study was: to assess the relationship between differential levels of exposure to prolactin associated antipsychotics and the risk for breast cancer in a long-term follow up

Methods: We utilized population-based data from the Clalit Health Services (CHS) database, the largest provider of health insurance in Israel (N=5.5 million persons), followed up between 2005 and 2020. In 19,196 female patients with schizophrenia who were exposed to more than one year of antipsychotic medications. We measured the cumulative sum of the defined daily dose (DDD) and duration of exposure for prolactin-sparing anti-psychotics, prolactin non-sparing antipsychotics, and all antipsychotics. The outcome was incident breast cancer, following differential exposure periods of 1, 5, or 10 years, using a survival model adjusted to other factors.

Results: during follow-up, there were 589 women (3.1%) with an incident diagnosis of breast cancer. For a one-year measurement of exposure, prolonged use of prolactin-elevating antipsychotic compounds was associated with HR of 1.61 [1.2-2.16] and 1.86 [1.39-2.47] for at least 96 days of exposure, and 4th quartile (almost a year), respectively, of the duration of exposure, compared to less than 96 days (1st quartile). Moreover, a higher commutative dose of prolactin-elevating antipsychotic compounds was also associated with an increased risk for breast cancer (HR 1.42 [1.1-1.84]) compared to a low commutative dose. The same trend was observed in more prolonged exposure periods such as 5 or 10-year follow-up of medication purchase.

Discussion: Our main finding was that while long-term exposure to any antipsychotic medications was associated with an increased risk of breast cancer, it was mainly attributed to the use of prolactin-elevating drugs whereas prolactin-sparing drugs (i.e clozapine, aripiprazole, and quetiapine) were not associated with increased risk. This was found, regardless of the duration of exposure to prolactin-elevating drugs, beginning with one year of exposure to medication, 5 and 10 years.

The consistent report of increased risk for breast cancer associated with prolonged exposure (time and dose) of prolactin elevating antipsychotic compound calls for action by the psychiatric community. As ours and previous studies suggest, using antipsychotic compound for years in women with a diagnosis of schizophrenia, require continuous assessment of benefit and harm, especially with other risk factors for breast cancer, such as obesity, smoking or genetic predisposition.

S88. AUDITORY HALLUCINATIONS IN GENERAL HOSPITAL PATIENTS.

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Background: Auditory hallucinations (AHs) are associated with common mental disorders. However, their occurrence among general medical conditions is less well described. Knowing what general medical conditions are present with psychotic experiences will help identify patients at risk of psychosis and guide preventative interventions. We therefore aimed to describe which general medical conditions co-occur with AHs in a non-psychiatric help-seeking sample.

Methods: We conducted a survey in Qatar among patients who attended Hamad Medical Corporation (HMC), a centralized system of hospitals covering all clinical departments for inpatient, outpatient and emergency care. We identified, from a sample of 402,575 English or Arabic speaking patients who used HMC services between 2013 and 2022, 11,291 who had completed the Questionnaire of Psychotic Experiences (QPE) online and who had agreed to their medical records being examined for main medical complaints. We selected 22 participants who on the QPE had reported only AHs in the past week, occurring daily or more often, and who did not experience hallucinations in any other modality. From this sample, symptoms were divided into 13 common medical complaints within 20 health system categories as reported below.

Results: Among those 22 hospital patients who were surveyed and who reported AHs in the past week, a total of 947 service encounters were recorded. Among those encounters, the most common reported complaints (n=591) were:

Inflammation/infection (n=282; 47.7%), pain (n=163; 27.6%), trauma (n=43; 7.3%); swelling/blockage (n=36; 6.1%), cough/breathlessness (n= 18; 3.1%), seizures (n=16; 2.7%), hypo/hypertension (n=1, 0.9%). Mental Health-related symptoms included fatigue, addiction, anxiety, depression, sleep problems, isolation, and psychosis (n=27; 4.6%)

The most common systems affected in this sample of 947 encounters were:

Gastro-intestinal (n= 150; 15.8%), musculo-skeletal (n=99; 10.5%), respiratory (n=72; 7.6%); pregnancy (n=71; 7.5%), skin (n=71; 7.5%), mouth/teeth (n=53; 5.6%), endocrine (n=53; 5.6%), genito-urinary US (n=50; 5.3%), generalized problem (n=48; 5.1%), and the eyes (n=38; 4.0%). The mental health category accounted for only 2.1% (n=20).

Discussion: AHs occur in general hospital patients who present with a range of medical and surgical conditions affecting a spectrum of bodily systems. These hallucinations are not necessarily related to established psychiatric diagnoses, so should be enquired about in general hospital patients by all admitting physicians in case those patients require further investigation and treatment.

S89. A CROSS-CULTURAL EXAMINATION OF THE SELF-RATED HEALTH AND SELF-RATED MENTAL HEALTH MEASURES IN EARLY INTERVENTION SERVICES FOR PSYCHOSIS

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Background: Patient-reported outcome measures (PROMs) provide valuable insight into patient symptoms and promote shared-decision making. Self-Rated Health (SRH) and Self-Rated Mental Health (SRMH), two single-item PROMs in which individuals rate their health and mental health on a 5-point scale, are widely used but not in early psychosis. Little has been explored about their psychometric properties in early psychosis. Whether responses vary depending on gender, age, cultural context and over time for early psychosis patients has also yet to be examined. This two-step research project sought to ask: 1.) What is the reliability and validity of the SRH and SRMH among persons with first-episode psychosis in Montreal, Canada and Chennai, India? 2.) Are there any differences between patients in Chennai and Montreal on these PROMs? Specifically, do patients in Chennai have better patient-reported

outcomes, akin to their previously established better clinician-reported symptom outcomes (Malla et al., 2020)?
Methods: Data was collected from a prospective cohort of patients with first-episode psychosis in Chennai (N=168) and Montreal (N=165) that received similar two-year regimens of early intervention. For the psychometric evaluation, a separate standardization sample (N=30 at each site) that filled out the SRH and SRMH two weeks apart was also used to allow for the estimation of test-retest reliability. Participants also completed a detailed assessment protocol with sociodemographic and clinical assessments, at entry to the service, Months 12 and 24. Assessments were carried out in French/English in Montreal and Tamil/English in Chennai depending on patients' preferences. Intra-class correlation coefficients were calculated to estimate test-retest reliability. To examine validity, the SRH and SRMH data was compared with clinician-reported outcomes of positive and negative symptoms, depression, anxiety, and overall functioning. Chi-square analyses and effect size calculations were carried out between each the SRH and SRMH, and each of the other measures. To address the secondary aim, linear mixed model analyses will be carried out to examine the effects of time (Baseline to Month 24), site (Chennai vs. Montreal) and the time x site interaction on SRH and SRMH scores. Relevant covariates (e.g., age and gender) will be integrated into the models.
Results: SRH and SRMH had good to excellent test-retest reliability (ICC >0.63) at both sites and for both the English and Tamil versions. Test-retest reliability could not be established for the French version in our sample, possibly due to the relatively small sample size. In both Montreal and Chennai, SRH and clinician-rated functioning were associated, indicative of criterion validity. In Montreal, SRH was also associated with clinician-rated positive symptoms and patient-rated quality of life, further establishing validity. However, in Chennai, these constructs were associated with the SRMH. Results: for the longitudinal analyses component are currently in progress.
Discussion: Our findings show the promise of single-item PROMs that may be more feasibly integrated into early intervention settings. Nonetheless, PROMs may psychometrically behave differently in differing contexts, and thus, should be examined in various languages and cultures. The extent to which patient and clinician perceptions vary may also be shaped by cultural differences around the language of mental health and the extent to which and ways in which contexts support patients in evaluating and describing their mental states. Our findings highlight the need to use both patient-reported and clinician-reported measures in early intervention and cross-cultural research.

S90. COGNITIVE ARCHITECTURE IN SCHIZOTYPY: FINDINGS FROM A HOT AND COOL COMPONENT APPROACH

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Background: Schizotypy is a latent personality organization that putatively harbours the liability for schizophrenia. Evidence suggests the people with high levels of schizotypy exhibit subclinical symptoms resembling schizophrenia patients, and are associated with cognitive dysfunctions. Previous research investigating the cognitive functions of schizotypy seldom included both hot (emotion-dependent) and cool (emotion-independent) domains. Moreover, very few studies in this area have utilized rigorous epidemiological samples with schizotypy.

Methods: The Hong Kong Youth Epidemiological Study for Mental Health (HK-YES) is a territory-wide, household-based epidemiological study conducted in 2019-2021. Based on the ratings of the brief version of the Schizotypal Personality Questionnaire (SPQ-B) in 2000 young people in the HK-YES sample, we identified 102 high schizotypy individuals who scored the top 10th percentile on SPQ-B, and 105 low schizotypy individuals who scored the bottom 10th percentile on SPQ-B. We used the Sustained Attention Response Task (SART) and the Hayling Sentence Completion Task (HCST) to capture cool cognitive domain, and the Anticipatory Consummatory Pleasure (ACP) Task and the Faux Pas (FP) Task to capture the hot cognitive domain. The SART measures attention and motor inhibition, and the HCST Task B measures semantic inhibition. The ACP Task utilizes emotion-inducing pictures of different valence and asked participants to alter the current and future exposure of the slides by pressing buttons on the computer. The ACP Task can estimate liking, motivated behaviour and emotion-behaviour decoupling. The FP measures social knowledge and theory of mind.
Results: High and low schizotypy participants showed comparable age, gender ratio, and paternal education (ps > 0.05). High schizotypy participants showed lower SART hit rate ($t = -2.582$, $p = 0.011$) and more HCST Task B error ($p = 0.014$) than low schizotypy participants. Whilst high schizotypy participants had better FP inference of emotion of other people ($p = 0.037$), they showed poorer FP inference of intention of other people ($p = 0.037$) than their low schizotypy counterparts. The ACP Results: showed that, relative to the low schizotypy group, the high schizotypy group reported lower pleasantness ratings to positive and negative slides in ACP Task, and reported lower arousal ratings to negative slides in ACP Task. Moreover, high schizotypy participants exhibited emotion-behaviour decoupling compared with low schizotypy participant ($p < 0.001$).
Discussion: Using a large and epidemiologically representative youth sample, and a psychometric definition of schizotypy, we demonstrated the hot and cool cognitive architecture of schizotypy. Our findings suggested that high schizotypy individuals exhibited poorer semantic inhibition and attention than low schizotypy individuals. Moreover, high schizotypy individuals showed emotion deficits with lower pleasantness and arousal ratings than their low schizotypy counterpants. They also showed emotion-behaviour decoupling. However, high schizotypy individuals showed better inference of emotion of other people, but poorer inference of intention of other people, relative to low schizotypy counterparts. Longitudinal research is needed to clarify whether high and low schizotypy groups would differ in their trajectories of hot and cool cognitions.

S91. PREVALENCE AND CORRELATES OF SUBCLINICAL PSYCHOTIC SYMPTOMS AMONG CHINESE YOUTHS IN HONG KONG

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Background: Subclinical psychotic symptoms (PS) are associated with functional disability and lower quality of life. Previous research suggested that PS might be associated with an increased risk of developing psychotic disorder. Literature reveals a large variation of prevalence rates for PS in different countries. Relatively few data have been reported in the Chinese populations. This study aimed to evaluate the prevalence of PS and its correlates among the Chinese youths in Hong Kong.

Methods: Hong Kong Youth Epidemiology Study of Mental Health (HKYES) was a territory-wide, population-based study examining mental health condition of Chinese youths aged 15-24 years in Hong Kong, who were recruited using stratified random sampling method by sending invitation to household randomly starting between May 2019 and June 2022. HKYES adopted 2-phase design from previous epidemiological studies, such as HKMMS. In phase 1, participants were screened for PS by the Psychosis Module of WHO Composite International Diagnostic Interview (CIDI). It assessed the frequency and types of PS, including two hallucinatory experiences (HE): visual hallucination, auditory hallucination; and four delusional experiences (DE): mind control, thought insertion or withdrawal, persecutory beliefs and ideas of reference. For PS symptoms occurred in past 12 months, they would be divided into two natures of samples: prevalent (regardless of past history) and incident samples (without prior history). Data on socio-demographics and risk factors for mental illnesses using questionnaires was also collected. Participants who screened positive for CIDI for PS were invited for phase II interviewed-based diagnostic ascertainment based on DSM-5 criteria to verify diagnosis of psychotic disorder by psychiatrists. Participants who have ever been diagnosed with psychotic disorder or bipolar disorder, or have ever taken antipsychotics were excluded from subsequent PS prevalence analysis.
Results: A total of 3352 participants were assessed. The lifetime prevalence, 12-month prevalence and the 12-month incidence were 14.6%, 6.9% and 2.2%, respectively. Among participants with PS, 62.1% experienced less than 6 PS episodes during their lifetime. Concerning the types of PS symptoms, 24.9% displayed at least 2 types. For those with PS, 84.6% endorsed hallucinatory experience while 27.6% had delusional experience. The presence of PS was associated with younger age (OR=0.938 [95% CI: 0.909-0.969]), fewer years of education (OR=0.894 [95% CI: 0.858-0.930]), fewer years of parental education (OR=0.970 [95% CI: 0.944-0.998]) and parents not being married (OR=1.474 [95% CI: 1.187-1.829]), extensive use of alcohol (OR=3.352 [95% CI: 1.671-6.724]), smoking (OR=1.876 [95% CI: 1.386-2.540]), substance use (OR=1.810 [95% CI: 1.327-2.468]), traumatic experience or stressful life event (OR=1.939 [95% CI: 1.581-2.378]), past history of physical (OR=1.601 [95% CI: 1.265-2.026]) or psychiatric disorder (excluding psychotic or bipolar disorder) (OR=1.782 [95% CI: 1.417-2.240]), and family history of psychiatric disorder (OR=1.790 [95% CI: 1.383-2.317]). The aforementioned study characteristics were also associated with increased number of types and frequency of PS.
Discussion: The lifetime prevalence of PS in Chinese youths in Hong Kong was comparatively higher than those reported in meta-analyses. Our results were consistent with prior studies that HE was more common than DE, and the majority of the participants experienced brief episodes of PS. We observed significant association of the presence, types and frequency of PS with most of our identified study characteristics. Further investigation is warranted to track the persistence and changes of PS status over time.

S92. REAL-WORLD TREATMENT PATTERNS, HEALTHCARE RESOURCE UTILIZATION, AND PREDICTORS OF RELAPSE AMONG U.S. MEDICAID INSURED PATIENTS WITH SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER

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Background: Relapse (i.e., acute exacerbations of symptoms) among patients with schizophrenia and schizoaffective disorder can lead to employment, economic, and social instability. This study aimed to identify patient characteristics related to relapse frequency and predictors of relapse.
Methods: Medicaid-enrolled patients ≥12 years across five states with newly diagnosed schizophrenia or schizoaffective disorder (index date) between 01/01/2014 and 08/31/2020 were retrospectively identified from the HealthCore Integrated Research Database. Eligible patients were continuously enrolled in the health plan for one year before and after the index date. Three cohorts were created based on the frequency of relapses within one-year post-index: 0 relapses, 1 relapse, and ≥2 relapses (defined as inpatient encounters for schizophrenia/schizoaffective disorder or emergency room encounters for psychiatric disorders). Post-index treatment patterns and healthcare resource utilization (HCRU) were described by relapse cohort and compared using ANOVA and chi-squared tests. Time-varying multivariable logistic regression models were used to identify predictors of relapse. Time-invariant predictors were measured at baseline while time-varying predictors were measured in each quarter and used to predict the probability of relapse in the subsequent quarter.
Results: Among the 4,858 patients included, 63%, 19%, and 18% experienced 0 relapses (mean age 35 years; 49% male), 1 relapse (mean age 35 years; 45% male), and ≥2 relapses (mean age 35 years; 49% male), respectively. Prevalence of baseline behavioral health comorbidities were high, including anxiety (0 relapses: 33%; 1 relapse: 41%; ≥2 relapses: 52%), bipolar disorder (29%; 41%; 48%), and substance use disorder (SUD; 20%; 34%; 48%). Prevalence of post-index use of atypical antipsychotics (63%; 74%; 82%; p<0.01), typical antipsychotics (11%; 21%; 35%; p<0.01), and second generation long-acting antipsychotics (LAIs) (5%; 9%; 11%; p<0.01) increased by the frequency of relapse. On the other hand, mean adherence (proportion days covered) decreased by relapse cohort for atypical (0.54; 0.50; 0.47; p<0.01), typical (0.30; 0.22; 0.13; p<0.01), and second generation LAIs (0.60; 0.57; 0.49; p=0.03). Prevalence of all-cause post-index HCRU was highest in the ≥2 relapse cohort for use of inpatient hospitalizations (48%; 70%; 82%; p<0.01), ER visits (46%; 83%; 95%, p<0.01), outpatient visits (95%; 97%; 98%; p<0.01), and psychotherapy use (44%; 45%; 51%; p<0.01). In adjusted models, those with behavioral health comorbidities including anxiety (odds ratio [OR]: 1.19; p<0.01), bipolar disorder (OR: 1.18; p<0.01), and SUD (OR: 1.32; p<0.01) had a higher risk of relapse than those without. For each one unit increase in the number of prior relapses, the odds of relapse in the subsequent quarter increased (OR: 1.34; p<0.01). Those who had office visits with a psychiatrist in each quarter had lower odds of relapse in the subsequent quarter than those without office visits (OR: 0.88; p=0.01).
Discussion: Overall, patients with schizophrenia or schizoaffective disorder had high levels of co-morbidities and HCRU. Many patients experienced relapse with the ≥2 relapse cohort having the highest HCRU and antipsychotic usage but low adherence. Behavioral health comorbidities and prior relapse increased the odds of relapse while office visits with a psychiatrist decreased the odds. These findings illustrate a high burden and unmet need for managing this disease and opportunities to improve care for these underserved patients, which may include the development of interventions aimed at increasing access to psychotherapy and care by psychiatrists and improving adherence to medications.

S93. PSYCHIATRIC PATIENTS' ATTITUDES TOWARDS BEING HOSPITALIZED: A NATIONAL MULTICENTRE STUDY IN NORWAY

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Background: Patients' lack of insight in their mental illness is a challenge and may interfere with patients' willingness for admission (1). Patients often deny being ill despite obvious symptoms such as psychosis, mania or severe depression (2-4).
The aim of the study was to explore patients' attitudes towards voluntary and involuntary hospitalization in Norway, and predictors of wanting admission in involuntary patients.

Methods: A multi-centre study of consecutively admitted patients to emergency psychiatric wards over a 3 months period in 2005-06. Data included demographics, admission status (voluntary / involuntary), symptom levels, and whether the patients expressed a wish to be admitted regardless of judicial status. To analyse predictors of wanting admission (binary variable), generalized linear mixed modelling was conducted, using random intercepts for the site, and fixed effects for all variables, with logit link-function.
Results: The sample comprised of 3.051 patients of whom 1.232 (40.4%) were involuntarily hospitalised. As expected, 96.5% of the voluntarily admitted patients wanted admission, however, unexpectedly as many as 29.7% of the involuntary patients did the same. The involuntary patients who stated they wanted hospitalisation were less likely to have been transported by police, displayed less aggression, had lower levels of hallucinations and delusions, were more depressed, used less drugs, and had lower levels of suicidality before admission. They also had better social functioning and were less often referred by general practitioners compared to those who did not want admission. In a multivariate analysis, predictors for involuntary hospitalization while wanting admission were not being transported by police, less aggression and less use of drugs.
Discussion: In the last decade, there has been increased focus on the use of involuntary hospitalization (IH). The United Nations Convention on the Rights of Persons with Disabilities (CRPD) identifies the rights of persons with disabilities as well as the obligations for States parties to promote, protect and ensure those rights (5).
In our study, IH patients who said that they wanted admission had a better mental health state with better global functioning, fewer used drugs and evaluated with less suicidal danger before admission. However, they had a higher score on depression. In the multivariate analysis the factor regarding depression was not significant as a predictor. These Results: are all descriptions of IH patients with less severe psychiatric symptoms, and - we could presume - with a better insight.

The police are the only agency with the right to use force against individuals outside the psychiatric hospital (6). The police are only needed when patients are aggressive and have to be secured and prevented from harming self or others. This corresponds with our Results: that predictors of IH patients who wanted admission were; less transported by police, less aggressive and agitated behaviour and less likely to use drugs. Overall, IH patients who wanted admission may not have been in need of police assistance due to their less challenging behaviour and not being affected by illegal drugs.

Almost a third of involuntary admitted patients stated that they wanted admission. This raises serious questions about the practice around admission of involuntary referred patients, representing a possible threat to the patients' autonomy. A basis for a future dialogue about alternative ways of dealing with the patient's serious mental condition could be by using more time, more in-depth ask what options the patient could imagine for developing a positive admission by preserving the patient's autonomy and co-determination.

S94. BRAIN METABOLIC SUBSTRATES OF SUBCLINICAL PSYCHOTIC EXPERIENCES IN EARLY ADOLESCENCE

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Background: rain structural metabolic status have an important role in the pathophysiology of psychosis. Previous large-scale magnetic resonance spectroscopy (MRS) studies reported altered glutamate levels in the anterior cingulate cortex (ACC) in schizophrenia. It remains unclear, however, whether the alteration may represent vulnerability to psychosis onset or whether it is epiphenomenon triggered by the exposure to medication or illness chronicity. Subclinical psychotic experiences (SPEs) can be present in some adolescents in the general population and increase the odds of psychosis development in young adulthood. It would clarify the issue to explore the association between SPEs and ACC glutamate levels in the general adolescent population. However, ACC glutamatergic alterations in subjects at high risk for psychosis, the causal associations of ACC glutamatergic function with psychotic experiences, and the effects of common emotional/social stress on glutamatergic function in adolescents remain unclear.
Methods: We explored longitudinal associations of combined glutamate-glutamine (Glx) levels in the ACC with SPEs and the effects of being bullied on ACC Glx levels. Specifically, we collected longitudinal MRS data from the ACC in the population-neuroscience study of the TTC (pn-TTC) and explored over-time associations of ACC Glx levels with SPEs and the associations of bullying victimization (BV) and help-seeking intentions (HSIs) with ACC Glx levels.
Results: Negative associations were revealed between ACC Glx levels and SPEs at both Times 1 (n = 220, mean 11.5 years) and 2 (n = 210, mean 13.6 years), as well as for changes over time (n = 157). Moreover, the causal effects of ACC Glx levels on SPEs were found. Furthermore, longitudinal associations for SPEs were at least partially explained by longitudinal associations for ACC Glx levels. Finally, BV decreased ACC Glx levels, whereas HSIs increased ACC Glx levels only in adolescents with BV.
Discussion: This is the first study to report a longitudinal association between ACC glutamatergic function and SPEs in general adolescent populations and to elucidate the effect of common emotional/social stress on glutamatergic function. We expect these findings to be helpful for the early detection of high-risk adolescents and the prevention of schizophrenia onset.

S95. IMPROVING SYNAPTIC FUNCTION AND COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA BY MODULATING ARC

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Background: There is convergent evidence that implicates synaptic dysfunction in the disease biology underlying schizophrenia, especially in the context of cognitive deficits. Well-replicated postmortem studies show abnormalities in dendritic spines and synapses in the cortex of schizophrenia patients. Genomic studies investigating mutations in synaptic networks in schizophrenia have found an overrepresentation of de novo mutations in ARC, which codes

for the Activity-regulated cytoskeleton-associated protein; Arg3.1. Levels of Arc protein have been shown to be reduced in postmortem brains of patients with schizophrenia, specifically in cortical layer III - the same cortical layer where decreased dendritic spine density is observed. ARC is an immediate early gene with a central role in synaptic plasticity and cognition. In animal studies, loss of Arc causes deficits in memory consolidation, whereas Arc overexpression increases dendritic spine density and enhances cortical plasticity. These studies suggest that enhancing Arc may be a promising approach for regulating synaptic plasticity in schizophrenia. Here, we investigate the role of Arc in human cortical neurons generated from schizophrenia patients and examine whether specific antipsychotics that increase Arc levels can rescue synaptic deficits in schizophrenia neurons.
Methods: We quantified Arc levels, dendritic spines, synapses and neuronal activity in cortical neurons derived from induced pluripotent stem cells (iPSCs) from individuals with schizophrenia and matched healthy control subjects. We tested a set of antipsychotics in current clinical use to assess their ability to increase Arc in human cortical neurons. We further investigated the effects of our top hit, lurasidone, on the density of dendritic spines and synapses, and on neuronal activity using multi-electrode arrays. Lastly, we investigated whether lurasidone can rescue dendritic spine deficits in schizophrenia neurons.
Results: Cortical neurons generated from iPSCs of schizophrenia patients showed significant reduction in levels of Arc and dendritic spine density compared to cortical neurons from iPSCs of healthy subjects. In screening the effects of antipsychotic compounds on Arc levels, we identified lurasidone as the strongest potentiator of Arc protein expression in human cortical neurons. We found that the increase in Arc expression was accompanied by an increase in dendritic spine density, rescuing synaptic deficits in schizophrenia cortical neurons.
Discussion: Our studies suggest that regulating Arc may provide a tractable way to regulate synaptic biology in schizophrenia neurons and ameliorate the effects that arise from synaptic dysfunction in schizophrenia. We show that lurasidone can increase both Arc levels and dendritic spines in human cortical neurons. These results suggest small molecules that increase Arc provide novel therapeutic approaches to target synaptic dysfunction and cognitive deficits in schizophrenia.

S96. VULNERABILITY AND RESILIENCE TO PRENATAL STRESS EXPOSURE: BEHAVIORAL AND MOLECULAR CHARACTERIZATION OF ADOLESCENT RATS.

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Background: Exposure to adverse conditions early in life may shape mental health and represents an important risk factor for the development of psychiatric disorders. Adverse perinatal events are indeed associated with profound epigenomic and transcriptomic changes in the progeny, which often become manifest during the transition between adolescence and adulthood. With this regard, animal models are particularly useful to investigate the molecular and functional mechanisms that are persistently affected after exposure to early life stress (ELS) and that may represent important targets for pharmacological interventions. In the present study, we employed the prenatal stress model (PNS) in rats to investigate the behavioral and molecular alterations that develop as a consequence of this adverse experience in adolescent rats, also considering sex- differences in such effects.

Methods: Pregnant rats were exposed to the prenatal stress (PNS) paradigm, consisting of 3 daily sessions of immobilization for 45 minutes from gestational day 14 to birth, while control dams were left undisturbed. During adolescence male and female offspring were exposed to a battery of behavioral tests to investigate sociability, anhedonia, and anxiety-like phenotypes. Following sacrifice, transcriptomics as well as candidate gene analyses were performed in different brain regions to identify mechanisms that may be relevant for the behavioral phenotypes observed in animals exposed to PNS.
Results: We found that PNS exposure produces emotional dysregulation in male and female adolescent offspring, including anhedonia, anxiety as well as reduced sociability. Based on a two-step cluster analysis of the behavioral data, we identified 30% of PNS animals as resilient (PNS-res), whereas the remaining 70% were classified as vulnerable to PNS exposure (PNS-vul). At the molecular level, we found that such behavioral patterns were associated with selective changes in the expression of activity-dependent genes as well as of immune-related mechanisms in different brain regions including the amygdala, dorsal and ventral hippocampus·that play a key role in emotional regulation.
Discussion: Overall, we showed that stress exposure during gestation produces emotional dysregulation only in a sub-group of adolescent male and female offspring. The characterization of the neurobiological mechanisms contributing to resilience or vulnerability to stress will be instrumental to identify mechanisms that may be targeted by therapeutic approaches to counteract specific pathologic domains of mental disorders, including schizophrenia.

S97. A BRAIN NETWORK INTERACTION MODEL OF PERSECUTORY IDEATION USING THE MINNESOTA TRUST GAME

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Background: The Minnesota Trust Game (MTG), a targeted economic social decision-making task, recently helped distinguish three brain networks sensitive to distinct mistrust decisions during fMRI: A salience network, an executive network, and an affective valuation network. From these networks, we observed individuals with higher persecutory ideation showed lower connectivity between the executive control network and affective valuation network during social decision-making, implicating deficits in affective control. While the salience network was implicated in suspicious mistrust at the group level, its role in individual differences in persecutory ideation remained unclear. Here we extend the work by examining multivariate models of between-network connectivity to assess whether the salience network may indirectly contribute to persecutory ideation through its interactions with the aforementioned two networks. The current goal is to develop a systems-level mechanistic model of persecutory ideation.
Methods: fMRI data was collected while the MTG was completed by people with schizophrenia or schizoaffective disorders (n=30, mean age 32.7, 69% male, 81% White). After preprocessing and motion removal, brain networks were derived using a meta-level independent components analysis (MELODIC) followed by dual regression in FSL. We evaluated full interaction models of between-network connectivity for the three networks, while controlling for age, sex, and in-scanner movement using linear regression. Persecutory ideation was measured using the Brief Psychiatric Rating Scale.
Results: The most parsimonious model was a two-way interaction of connectivity metrics that explained 45% of the variance in persecutory ideation. Here, the level of connectivity between

the salience and affective valuation networks moderated ($p<0.05$) the previously observed relationship. Specifically, in participants with high connectivity between the salience and affective valuation networks, the previous relationship involving executive control and affective valuation networks with persecutory ideation was diminished; whereas in those with low salience and affective valuation network connectivity, the previous relationship involving executive control and affective valuation networks with persecutory ideation was stronger.
Discussion: Findings support multivariate prediction of persecutory ideation in the schizophrenia spectrum. The present Results: also highlight a possibly important but indirect role of the salience network in persecutory ideation during social decision-making that align with the aberrant salience hypothesis of psychosis and implicate arousal processes. Ongoing causal modeling, and goals to replicate the findings in a larger sample, will also be discussed.

S98. MEGA-ANALYSIS OF DIFFERENTIATION OF SCHIZOPHRENIA USING STRUCTURAL MRI WITH CONSIDERATION OF SCANNER DIFFERENCES.

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Background: Many MRI studies have indicated that gray matter volume of patients with schizophrenia (SZ) reduced compared to healthy controls (HC). However, the difference in

volume between patients with SZ and HC is small, and there is still no discriminant method that can be applied uniformly across different MRI scanners and protocols. Nemoto and colleagues showed that the difference between the predicted and measured ROI volumes could discriminate between patients with SZ and HC across MRI scanners and protocols. In the present study, we will adapt the method of Nemoto et al. to a larger sample and examine its ability to discriminate between schizophrenic patients and healthy controls.
Methods: A total of 1414 patients with SZ and 3278 HC undergoing MRI at 11 centers and 18 protocols were included. The ROI was the same as in the previous study. The sample size was calculated based on the previous study and the regression equation was created with 20 subjects. For each protocol, 20 HC were randomly selected, and an equation to predict ROI linearly from age, gender, and intracranial volume was created, and the difference from the actual measured value was calculated. Using the value of this difference, the remaining HC group (30-609) and the SZ group (10-235) were discriminated by receiver-operator curve (ROC) analysis for each protocol. This procedure was repeated 1000 times to calculate the mean and 95% confidence interval of the area under the curve (AUC) value and the accuracy (percentage of correct answers) for each site. For the HC for whom the equation was created, outliers (values outside the mean ± 2 SD range) of the ROI were excluded. For the SZ group, outliers outside the age range of the HC creating the equation were excluded. The study was approved by the ethics committees of each participating institution.
Results: The mean AUC values for 18 protocols ranged from 0.54 to 0.84; 17 (94.4%) protocols had AUCs greater than 0.65 and 12 (66.7%) had AUCs greater than 0.7. The mean accuracy ranged from 54 % to 77 %. There were 14 (77.8%) protocols with more than 65 % correct and 8 (44.4%) protocols with more than 70 % correct.
Discussion: Our method generally discriminated schizophrenic patients from healthy subjects with good performance in MRI imaging data from different scanners and different imaging protocols at multiple centers. The present results indicate that MRI brain imaging data can be used to discriminate between SZ and HC, regardless of the scanner type or protocol, if data from at least 20 HC can be obtained.

S99. LONGITUDINALLY INVESTIGATED STRUCTURAL BRAIN CHANGES IN PATIENTS WITH TREATMENT-RESISTANT SCHIZOPHRENIA AFTER SWITCHING TO CLOZAPINE: ASSOCIATIONS WITH PHARMACOLOGICAL VARIABLES AND FUNCTIONAL OUTCOMES

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Background: Cortical and subcortical gray matter volume decreases have been reported in patients with schizophrenia, highly associated with the progression of disease and the effect of antipsychotics. In patients with treatment-resistant schizophrenia taking clozapine, volume reduction has been observed, especially in the caudate and putamen. However, the effects of clozapine on the brain alterations and its associations with other clinical and functional variables are poorly investigated. We examined longitudinal effects of clozapine treatment on structural brain changes, and potential moderating factors associated with the brain changes.
Methods: Patients with schizophrenia who planned to start clozapine were recruited and prospectively investigated. T1-weighted brain magnetic resonance images were obtained before and 18 weeks after the initiation of clozapine treatment. Longitudinal changes in gray matter volume, white matter volume and cortical thickness were evaluated. Serum clozapine and nor-clozapine level and concomitant antipsychotic dose were measured, and clinical

symptoms and cognitive performances were also assessed using Positive and Negative Syndrome Scale and MATRICS Consensus Cognitive Battery.
Results: A total of 38 patients (diagnosis of schizophrenia 33, schizoaffective disorder 2, schizophreniform disorder 2, unspecified psychotic disorder 1) were enrolled. After initiation of clozapine treatment, patients with treatment-resistant schizophrenia presented longitudinal gray matter volume reductions in bilateral fronto-temporal gyrus, and limbic areas (insula, putamen, caudate, and cingulate gyrus) while we observed no regions with gray matter volumetric excess (voxel-level FWE corrected $p < 0.05$). There were also significant white matter volume changes in corpus callosum and cingulum gyrus. The reduction was sustained after correction for concomitant antipsychotics. Cortical thinning was matched with the abovementioned gray matter volume deficits regions. These brain alterations were associated with changes in clinical, clozapine-related pharmacological factors and cognitive variables.
Discussion: Switching to clozapine is associated with cortical and subcortical volume deficits and cortical thinning in the regions which mainly involve the mesolimbic dopamine pathway and its downstream areas, as proposed by the dopamine hypothesis of schizophrenia. Clozapine/nor-clozapine ratio was found to be an important factor influencing brain structural changes, and these changes may partially affect cognitive changes. Further investigation is needed to better understand whether brain changes can explain the link between clozapine treatment and functional outcomes.

S100. ASSOCIATION BETWEEN URBAN UPBRINGING AND CORTICAL GYRIFICATION IN PERSONS WITH SCHIZOPHRENIA

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Background: Several studies have implicated Urban upbringing to be a risk factor for the development of schizophrenia. However, the neurobiological changes associated with an urban upbringing in schizophrenia are still not known completely. Hence, we investigated the association between urban upbringing and cortical gyrification, a sensitive measure of brain structural development.
Methods: We recruited 70 healthy volunteers and 87 patients with schizophrenia or schizoaffective disorder in the age range of 18 to 50 years. A trained mental health professional interviewed the participants and caregivers to collect the details regarding the place of birth and upbringing. We later categorized the study participants' place of upbringing into three groups, namely 1) rural area 2) town 3) city using census India data from 1971 to 2011 and calculated the urbanicity index using a previously validated method. Brain MRI images were acquired using a 3 Tesla scanner. We used FreeSurfer to process the images and performed a regression analysis with the gyrification index as the dependent variable and urbanicity index age and gender as explanatory variables in the QDEC interface.
Results: Overall, we found a significant positive association between the urbanicity index and the gyrification index in the left rostral middle frontal gyrus (BA10; $pcorr<0.001$), left supramarginal gyrus (BA40; $pcorr=0.001$), left and right lateral occipital gyri (BA18; $pcorr=0.001$). There was a significant diagnosis*urbanicity interaction in the left superior

parietal cortex (BA7; p=0.0001), right inferior temporal cortex (BA19; p=0.0001) and right rostral middle frontal cortex (BA46; p=0.0001).
On group-wise sub-analysis, schizophrenia patients had a significant positive association between urbanicity index and gyrification in the right lateral orbitofrontal cortex (BA11; pcorr<0.001) and right rostral middle frontal cortex (BA46; pcorr=0.019). HV had a significant positive association with left rostral middle frontal gyrus (BA10; pcorr<0.001) and left lateral occipital gyrus (BA19; pcorr<0.001), and right lateral occipital gyri (BA18; pcorr<0.001). These results suggested that the greater the urbanicity index, the greater the gyrification.

Discussion: We found decreased gyrification mainly in frontal and occipital cortices in patients compared to healthy individuals. These findings align with previous studies that reported reduced gyrification in the frontal lobe and other brain regions in schizophrenia patients. However, some studies have also reported increased gyrification in frontal and other brain regions in patients with schizophrenia. While interpreting this finding, one needs to consider the confounding effect of the duration of illness as we observed a significant negative correlation between the duration of illness and the gyrification index. Like our study, a few earlier studies have reported decreased gyrification in chronic patients but increased gyrification in first-episode schizophrenia. A previous longitudinal study reported decreased gyrification in schizophrenia patients over two years of follow-up

In summary, the findings suggest the effect of both places of birth and upbringing on neurodevelopment. While the current study does not propose specific risk factors, future longitudinal studies should examine the contribution of individual risk factors. As developing countries are witnessing migration to cities, it is essential to understand the effects of urbanicity on neurodevelopment. Identification of the risk factors and potential mechanisms could have implications in devising preventive strategies and creating urban environments that promote well-being.

S101. IMPACT OF CANNABIS USAGE ON GYRIFICATION IN SCHIZOPHRENIA: A BIPOLAR-SCHIZOPHRENIA NETWORK OF INTERMEDIATE PHENOTYPES STUDY

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Background: Studies on the impact of cannabis on brain morphology in schizophrenia (SZ) and controls (HC) suggest that cannabis can affect brain neurodevelopmental processes in adolescence and trajectory into adulthood. Cannabis has been found to act on the brain's endocannabinoid system, which plays a key role in prefrontal cortex maturation. Furthermore, cannabis has been implicated in upregulation of microglia, and microglia have been implicated in separate studies to contribute to altered synaptic pruning in SZ compared to HC. A theory on the mechanism behind gyrification proposes that differential tensions during neuronal

migration interact globally across the cortical surface to form gyri and sulci. This theory has been extended to suggest that pruning-induced alterations during adolescence can affect gyrification. However, few studies have investigated the implications of cannabis usage during adolescence or early adulthood (between the ages of 15 to 18) on gyrification. Hence, we sought to investigate the impact of early adulthood cannabis usage on gyrification in HC and SZ by comparing the local gyrification index (LGI) in probands who have used cannabis to probands who have not. We hypothesized that bilateral frontal lobe hypogyria will be found in SZ and HC probands who used cannabis during early adulthood (SZY and HCY) compared to HC and SZ probands who have not used cannabis (HCN and SZN).

Methods: Participants were recruited within the Bipolar-Schizophrenia Network of Intermediate Phenotypes Consortium and received MRI and clinical assessment. Gyrification was measured using LGI, measured using Freesurfer 7.1.0. Outliers greater than 3 standard deviations from the group mean of LGI subregions were removed through winsorization. Pairwise contrasts using general linear models were conducted in R with age, sex, race, site of acquisition, and estimated total intracranial volume as covariates. SZ proband analysis also included age of onset as a covariate. P values below 0.05 after false discovery rate correction were considered significant.

Results: Significant positive correlations between age and severity of subregions' hypogyria were found in both HC (r = - 0.12 to -0.57) and SZ (r = -0.16 to -0.50) probands. Significant bilateral hypogyria in 13 subregions located in the frontal lobe was found in SZY compared to SZN. Significant bilateral hypogyria in SZY - SZN comparisons was identified in the superior parietal (L: d= -0.55; R: d= -0.44) and inferior parietal (L: d= -0.48; R: d= -0.46). Hypogyria in the right banks of the superior temporal sulcus (d= -0.51), right superior temporal (d= -0.47), right middle temporal (d= -0.51), and right temporal pole (d= -0.48) for SZY compared to SZN was also identified. No statistically significant differences in gyrification were found between HCY and HCN.

Discussion: Our findings suggest early adulthood cannabis alters SZ probands' gyrification, supporting the hypothesis that cannabis usage intersects with neurodevelopmental processes in SZ probands and contributes to hypogyria in the frontal, parietal, and temporal lobes for SZY.

S102. PROGRESSIVE DEFICITS IN RIGHT-HEMISPHERE AUDITORY PROCESSING IN FIRST-EPISODE PSYCHOSIS AS REVEALED BY LONGITUDINAL ASSESSMENT OF MAGNETOENCEPHALOGRAPHIC (MEG) DURATION MMN

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Background: Mismatch Negativity (MMN) is considered a biomarker of cortical dysfunction in schizophrenia (SZ) because it is severely reduced to pitch (pMMN) and to duration (dMMN) deviant stimuli. However, it is less clear if MMN is reduced in first episode psychosis, and if MMN shows progressive impairment within the early disease course.

Methods: We investigated the neural generators of pMMN and dMMN with Magnetoencephalography (MEG) in first episode psychosis individuals (FE) and healthy controls (HC) at baseline and at a 3-to-12 months follow-up (23 FE and 25 HC). We projected MEG inverse solutions to participant's individual MRI-based cortical surfaces, parcellated using the Human Connectome Project Glasser quasi-functional parcellation, and localized

MMN activity in left and right primary auditory cortices (A1), Lateral Belts (LBelt) and ParaBelts (PBelt).
Results: Two-way rmANOVAs with Time (Baseline vs Follow-up), Hemisphere, and Group factors at each parcel revealed an overall trend-level reduction of dMMN in FE relative to HC at A1 ($p = 0.6$), LBelt ($p = 0.6$) and PBelt ($p = 0.6$), while no differences were observed for pMMN. In dMMN, trend-level significant Time x Hemisphere x Group interactions were found at A1 ($p = 0.5$) and LBelt ($p = 0.6$). Further exploring these interactions revealed a right-hemisphere selective dMMN deficit in FE relative to HC, present only at the follow-up and specific to A1 ($p = .013$) and LBelt ($p = .006$).
Discussion: Our results, albeit preliminary, suggest a right-hemisphere selective pathophysiology in the auditory cortex during early psychosis that worsens with psychosis duration and affects the processing of stimulus duration. We continue to test participants longitudinally for this project to increase the sample sizes and power to reveal the course functional auditory processing deficits in early psychosis.

S103. CEREBRO-CEREBELLAR GRAY MATTER ABNORMALITIES UNDERLYING EXECUTIVE DYSFUNCTION IN PATIENTS WITH SCHIZOPHRENIA

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Background: Schizophrenia is a brain disorder involving the cerebral and cerebellar structures. The cerebellum is reciprocally connected with the cerebrum and constitutes cerebro-cerebellar networks responsible for the cognitive and affective function, as well as the traditional sensorimotor network. We aimed to investigate the volumetric alterations in cerebro-cerebellar gray matter (GM) in patients with recent-onset and chronic schizophrenia compared to healthy controls (HCs) and explore their relationships with executive function.
Methods: Seventy-two patients with recent-onset schizophrenia (50 women), 43 patients with chronic schizophrenia (26 women), and 127 HCs (66 women) underwent T1-weighted magnetic resonance imaging (MRI) scan. The regional volume difference in the cerebellum among the three groups was examined using voxel-based morphometry (VBM) and its associations with cerebral cortical volumes were assessed using FreeSurfer. Executive function was measured using the Wisconsin Card Sorting Test.
Results: Compared to HCs, both groups of participants with schizophrenia had significantly smaller GM volumes in the left lobule V, left lobule X, left Crus I, left lobule VIIIa, right lobule VIIb, and right lobule I-IV; no significant differences were observed between participants with recent-onset schizophrenia and those with chronic schizophrenia. The GM volumes in these cerebellar regions significantly correlated with the GM volumes in the fronto-temporal cortices associated with the higher-order cognitive and affective function. The smaller GM volume in the left Crus I was significantly correlated with poorer executive performance in participants with schizophrenia (total error: $r = -0.298$, $p = 0.006$); non-perseverative error: $r = -0.308$, $p = 0.004$; conceptual level response: $r = 0.315$, $p = 0.006$).
Discussion: Our findings suggest that patients with schizophrenia show cerebellar GM abnormalities from the early stages of the illness. The volumetric changes in the cerebellum were associated with the GM volume in the functionally corresponding cerebral regions. Furthermore, in line with the theory of cognitive dysmetria, cerebellar GM abnormalities were correlated with executive performance, including attention and working memory which requires a fine adjustment of mental processing. We expect that these findings may expand our

understanding of the neurobiology of schizophrenia based on the cerebro-cerebellar interconnectivity of the brain.

S104. PRECISION OF METABOLITE-SELECTIVE MRS MEASUREMENTS OF GLUTAMATE, GABA AND GLUTATHIONE: A REVIEW OF HUMAN BRAIN STUDIES

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Background: Single-voxel proton magnetic resonance spectroscopy (SV 1H-MRS) is an in vivo non-invasive imaging technique used to detect neurotransmitters and metabolites. It enables repeated measurements in living participants to build explanatory neurochemical models of pyschiatric symptoms and testing of therapeutic approaches. Given the tight link among glutamate, gamma-amino butryic (GABA), glutathione and glutamine within the cellular machinery, MRS investigations of neurocognitive and pyschiatric disorders must quantify a network of metabolites simultaneously to capture the pathophysiological states of interest. Unfortunately, there has been no sequence to date that reports on multiple isolated metabolites simultaneously in a single-shot.
We report on the quality of simultaneously-acquired MRS metabolite data of the human brain to date and determine factors that influence data quality, such as internal in vivo references, brain regions of interests, field strength of scanner, and/or optimized acquisition parameters. The secondary aim of this review was to highlight the strengths and weaknesses of various single-voxel spectroscopy techniques that were able to quantify glutamate, GABA, and GSH in vivo simultaneously.

Methods: For the inclusion of this review, we identified 12 articles that fit the criteria. Studies that were excluded were found to be reviews, duplicate studies, unclear CRLBs or CV reporting, or did not explicitly mention targeting metabolites of interest (GABA, glutamate along with Glx and glutamine, and glutathione) simultaneously.
Results: A total of 9 studies at 3 T and 3 studies at 7 T were included in this review. Study details were reported such as participant demographic, pulse sequence used, brain region of interest, voxel size, and reported metrics to assess quality of acquisition data (CV, CRLB, linewidth). In total, the studies contained 158 healthy controls where 52 were female identified as women and 18 were healthy neonates; there were 87 patients where 52 were identified as women with psychiatric or neurological disorders. The common pulse sequences used were PRESS and HERMES and the most reported brain ROI was anterior cingulate cortex. Out of 12 studies, 12 reported GABA, 6 reported glutathione, and 6 reported glutamate as one of the simultaneously acquired metabolites in the pairs or triplets.
Discussion: We note several factors that influence the data quality for single-shot acquisition of multiple metabolites of interest using metabolite-selective MRS: (1) internal in vivo references, (2) brain regions of interests, (3) field strength of scanner, and/or (4) optimized acquisition parameters. We also highlight the strengths and weaknesses of various single-voxel spectroscopy techniques that were able to quantify in vivo glutamate, GABA, and glutathione simultaneously. The insights from this review will assist in the development of new MRS pulse sequences for simultaneous, selective measurements of these metabolites and simplified spectral modeling.

S105. STRUCTURAL NEUROIMAGING SIMILARITIES BETWEEN INDIVIDUALS WITH NON-CLINICAL AND CLINICAL PSYCHOTIC SYMPTOMS

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Background: Schizophrenia (SZ) and related psychotic disorders are a clinical manifestation of quantifiable traits that co-occur in the general population along a continuum. While psychotic disorders are consistently associated with patterns of brain deficits including reduced cortical thickness and subcortical grey matter volumes, the evidence for morphometric abnormalities associated with psychosis proneness has been scarce and inconclusive. We aimed to evaluate neuroimaging similarities in individuals with non-clinical voice hearers (NCVH) versus patients with schizophrenia (PSZ), and healthy controls (HCs).

Methods: We investigated structural neuroimaging similarity in a sample of 71 PSZ (Age range 19-63 years, 34% Female), 49 HCS (Age range 23-64 years, 63% Female), and 37 NCVH (Age range 20-65 years, 73% Female). ENIGMA analysis pipelines for T1/T2 structural scans was used to measure regional cortical thickness (GMT) for 33 cortical areas and subcortical volumes for eight primary subcortical structures (GMV). We utilized a regional vulnerability index (RVI) as a measure of agreement between an individual's pattern of regional neuroimaging traits and the expected pattern of schizophrenia derived from ENIGMA meta-analyses that were the largest studies of PSZ-HC difference to date and included thousands of cases.

Results: ANCOVA with between factor 'group' for each brain region, with age and gender being entered as covariates was used to evaluate GMT and GMV across groups. We found that overall, PSZ had significantly lower average GMT than HCs, with intermediate values in NCVH (ANCOVA p's<0.05 in 24/33 regions). Similarly, there were significant reductions in subcortical GMT in PSZ relative to HCs across 8 regions with NCVH showing volume reductions in five regions (ANCOVA p's<0.05). While the post-hoc NCVH-HCs structural differences were not significant, maximal thinning was observed in Superior frontal, Banks of STS and Parahippocampal regions and maximal volume reduction in Amygdala and Accumbens regions. (Cohen's d range: 0.3-0.7). As such, the profile of group differences between NCVH and HCs resembled that seen in the contrast of PSZ and HCs: The PSZ-HCs group regional effect sizes were correlated with the corresponding NCVH-HCs effect sizes for GMT (r=0.37,p=0.03) and GMV (r=0.62,p=0.09) respectively.

PSZ showed significantly elevated RVI versus HCs: Subcortical RVI (Cohen's d=0.91,p<0.001); Cortical RVI (Cohen's d =0.47,p=0.047)]. The subcortical RVI was lower for NCVH as compared to PSZ, (Cohen's d =0.72,p=0.004), but similar between NCVH and HCs, (Cohen's d =0.20,p=0.60). The cortical RVI was similar between NCVH and PSZ (Cohen's d =0.31,p=0.29) as well as between NCVH and HCs(Cohen's d =0.15,p=0.80).

Discussion: We show that NCVH subjects have a similar but less pronounced cortical and subcortical deficit patterns compared to PSZ. This pattern of similarity between PSZ and NCVH yields new insights into a dimensional neurobiological continuity across clinical and nonclinical individuals with psychotic experiences. Additionally, RVI may provide a useful phenotype of individual similarity to the expected patterns of structural abnormalities rather than absolute difference between patients and controls.

S106. POSTER WITHDRAWN

S107. TRENDS OF ANTIPSYCHOTIC POLYPHARMACY AFTER LAI FROM A NATIONWIDE INSURANCE DATA

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Background: Many studies showed superior treatment outcome such as admission rate or all-cause discontinuation of long acting injectable antipsychotics (LAI). However, the effects of LAI on antipsychotic polypharmacy is not well known. Although antipsychotic polypharmacy is not recommended and potential demerits, the rate of polypharmacy is increasing trend in many countries. In this study, we will investigate the trend of polypharmacy after initiating LAI in schizophrenia.
Methods: We obtained the claim data between 1 September 2009 and 31 August 2021, in the HIRA database. For identifying the prevalent patients with schizophrenia, the following criteria were applied: (1) the ICD-10 diagnostic code of F20 (schizophrenia), (2) exclude the patients who had the exclusion diagnoses before the diagnosis of schizophrenia and (3) more than 30 days of antipsychotic prescriptions during the total observation period. The final study population consisted of 288,547 prevalent patients with schizophrenia. Among them, 17,413 patients were prescribed at least one or more LAI. We compared the number and equivalent dose of antipsychotics before and one year after LAI initiation.
Results: Mean of cumulative one month olanzapine equivalent dose of antipsychotics during one year before LAI initiation was 273-367 mg. After LAI initiation, mean of equivalent dose were steadily decreased from 547 to 233 mg (one year later). Also, similar decreasing trend of number of concomitant antipsychotics were found.
Discussion: We showed a decrease of antipsychotics polypharmacy after LAI initiation. This study presented the effectiveness of LAI in real-world population.

S108. CONTROL OF GLUCOSE METABOLISM BY CENTRAL LACTATE IS BLUNTED BY OLANZAPINE

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Background: Antipsychotics like olanzapine are associated with increased risk of developing impaired glucose metabolism, including type 2 diabetes mellitus. It has been previously reported that glucose in the central nervous system (i.e., central glucose) decreases peripheral circulating glucose concentrations by diminishing the production of glucose by the liver, known as endogenous glucose production (EGP). The ability of central glucose to suppress EGP requires glucose to be metabolized to lactate in the central nervous system. Moreover, increased central tricarboxylic acid cycle activity, which is downstream of lactate, suppresses EGP. We have already found that olanzapine impairs the ability of central glucose to suppress EGP. In the current study, our objective was to determine if olanzapine's detrimental effects on central glucose-induced peripheral glucose metabolism are downstream of central lactate.
Methods: Male Sprague Dawley rats underwent surgery for intracerebroventricular (ICV, 3rd ventricle) cannula implantation. Following recovery, rats underwent a second surgery where

cannulas were inserted into the jugular vein and carotid artery. Four to five days later, a pancreatic euglycemic clamp with tracer methodology was performed. The pancreatic euglycemic clamp is the gold standard technique for the assessment of glucose metabolism in vivo under basal insulin concentrations. On the day of the clamp experiment, sodium L-lactate (5mM) or vehicle was administered ICV, while olanzapine (3mg/kg) or vehicle was administered subcutaneously. Hence, there were 4 study groups (ICV-subcutaneous), namely vehicle-vehicle, lactate-vehicle, lactate-olanzapine, and vehicle-olanzapine; n=5-6 per group. Glucose kinetics results during the clamp experiment were compared to those of the vehicle-vehicle group.
Results: ICV lactate increased glucose infusion rate during the clamp, which is a measure of insulin sensitivity ($0<0.05$, lactate-vehicle vs. vehicle-vehicle). Olanzapine blocked the stimulation in glucose infusion rate by ICV lactate. Glucose utilization is the rate at which glucose is taken up by tissues and, compared to the vehicle-vehicle group, the lactate-vehicle group had greater glucose utilization ($p<0.05$), while the lactate-olanzapine group had reduced glucose utilization ($p<0.05$). Only the lactate-vehicle group had suppressed EGP during the clamp ($p<0.05$ vs. vehicle-vehicle group).
Discussion: ICV lactate stimulated whole-body insulin sensitivity as well as glucose utilization and suppressed EGP. However, these effects were diminished in the presence of olanzapine. Taken together with our previous findings that olanzapine blocks the effects of central glucose on peripheral glucose metabolism, our current results suggest that an underlying mechanism could be olanzapine-induced disruptions in the tricarboxylic acid cycle.

S109. HIGHER CLOZAPINE DOSES ARE ASSOCIATED WITH DEFICIENT IMMUNOGLOBULIN RESPONSE TO COVID-19 VACCINATION AND COVID-19 INFECTION IN PEOPLE WITH SERIOUS MENTAL ILLNESSES

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Background: Adverse reactions to clozapine can include increased susceptibility to infections and pneumonia, even in the absence of neutropenia, which might be explained by a reduced immunoglobulin response to infections. However, no previous studies have explored whether clozapine treatment is associated with lower immunoglobulin response to COVID-19 infection or to COVID-19 vaccination. Therefore, the main aim of our study was to explore this issue by analysing the concentrations of SARS-CoV-2 antibodies against to protein S (spike) and to protein N (nucleocapside) in COVID-19 vaccinated people with serious mental illnesses.
Methods: We included 119 stable (receiving antipsychotic treatment without changes in the previous month), COVID-19 vaccinated outpatients with serious mental illnesses. The sample included a 2:1 sampling ratio of clozapine:non-clozapine users of similar age and sex (79 clozapine users; 40 non-clozapine). Clinical data was obtained by semistructured interview by a clinician with an additional revision of the electronic medical records, and included socio-demographic data, smoking habits, antipsychotic treatment, medical comorbidities (hypertension, diabetes mellitus, dyslipidaemia), vaccination (type, number of doses and dates of vaccination), COVID-19 infection. All cases of previous COVID-19 infection were verified by electronic chart review and had a positive SARS-CoV-2 testing (positive CRP test). A

fasting blood testing was obtained for determining SARS-CoV-2 antibodies (proteins S and N) and clozapine plasma concentrations. Statistical analyses were performed with SPSS v. 25.0. Skewed variables were log transformed for reducing skewness. T-test and Chi-square were used for comparing continuous and categorical data. Multiple linear regression analyses were conducted for exploring the relationship between clozapine treatment and Sars-CoV-antibodies while adjusting for covariates (age, sex, smoking, BMI, previous COVID-19 infection, number of COVID-19 vaccine doses, time between last COVID-19 vaccination). The first regression analyses considered clozapine dose. We conducted sensitivity analyses using clozapine levels instead of clozapine dose.

Results: Twenty out of 119 patients (16.8%) had a previous COVID-19 infection. There were no significant differences in COVID-19 infection or vaccination variables (number of doses, time since the last vaccine) between clozapine users.

In the multiple linear regression analyses, clozapine dose was associated with lower concentrations of SARS-CoV-2 antibodies (both protein S [Beta= -0.179, p=0.008] and protein N [Beta= -0.097, p=0.029]). Previous COVID-19 infection and vaccination against COVID-19 were associated with increased concentrations of SARS-Cov-2 protein S antibodies (infection: Beta= 0.386, p<0.001; vaccination: Beta= 0.597, p<0.001), whereas COVID-19 infection was also associated with greater Sars-CoV-2 antibodies against protein N (Beta= 0.882, p<0.001). The sensitivity analyses including clozapine plasma concentrations instead of clozapine doses did not bring significant associations with clozapine levels.

Discussion: Our Results: are in accordance with previous studies that have also reported reduced immunoglobulin concentrations in patients with serious illnesses receiving clozapine and support for a deficient antibody response in patients being treated with clozapine. Our findings also suggest that patients receiving higher doses are at greater risk of a diminished immunoglobuline response. Limitations include the cross-sectional design and lack of determination of norclozapine concentrations.

S110. OLANZAPINE IMPAIRS CENTRAL LIPID-MEDIATED REGULATION OF GLUCOSE HOMEOSTASIS

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Background: Antipsychotics are the cornerstone treatment for schizophrenia and are widely prescribed for other conditions. However, antipsychotics are associated with adverse metabolic side effects, increasing the risk for type 2 diabetes in a population suffering from early cardiovascular mortality. Antipsychotics can directly perturb whole-body glucose metabolism independently from changes in body weight, and this occurs in part through actions on the central nervous system (CNS). We have previously shown that the antipsychotic olanzapine impairs CNS insulin and glucose sensing, resulting in whole-body insulin resistance. In addition to key metabolic regulatory functions of insulin and glucose in the brain, postprandial increases in circulating free fatty acids act as a signal of nutrient abundance and can strongly regulate food intake and whole-body glucose homeostasis. In the current study, we set out to examine the effects of olanzapine on central sensing of the fatty acid oleic acid and subsequent regulation of peripheral glucose metabolism.

Methods: Gold standard pancreatic euglycemic clamps were used to assess changes in glucose kinetics in response to a primed, continuous intracerebroventricular (ICV) infusion of oleic acid or vehicle solution (1.71 mM, 5 μL/hour, into the third ventricle). Male rats were co-

treated with an acute injection of olanzapine (3 mg/kg, SC) or vehicle (Veh). Antipsychotic dosing is based on clinical D2 receptor occupancies. Groups included (ICV–peripheral) Veh–Veh (n = 4), oleic acid (Ole)–Veh (n = 5), Ole–olanzapine (Ola) (n = 5), and Veh–Ola (n = 5). The peripheral glucose infusion rate needed to maintain euglycemia during the clamp procedure was used as a measure of whole-body glucose metabolism. A radioactive tracer (3-3H-glucose) infusion throughout the clamp procedure was used to assess glucose kinetics, including hepatic glucose production and peripheral glucose uptake.

Results: As expected, ICV oleic acid infusion caused a significant increase in the peripheral glucose infusion rate (mg/kg/min) compared to ICV vehicle (Ole-Veh 7.88±0.76 vs Veh-Veh 2.09±0.81, $p<0.001$). This effect was inhibited by co-treatment with olanzapine (Ole-Ola 1.90±0.46 vs Veh-Veh 2.09±0.81, $p>0.05$). ICV oleic acid also significantly suppressed hepatic glucose production compared to ICV vehicle (clamp relative to basal: Ole-Veh 93.65%±18.75 vs Veh-Veh 8.01%±8.43, $p<0.001$) and this effect was prevented by co-treatment with olanzapine (Ole-Ola 28.86%±6.64 vs Veh-Veh 8.01%±8.43, $p>0.05$). ICV oleic acid did not alter glucose utilization (clamp relative to basal: Ole-Veh 19.14%±16.66 vs Veh-Veh 19.59%±9.48, $p>0.05$), however, glucose utilization was suppressed after olanzapine treatment (clamp relative to basal: Ole-Ola -3.51%±9.72 vs Veh-Veh 19.59%±9.48, $p<0.05$). In summary, olanzapine disrupts central oleic acid sensing through actions on glucose production and glucose utilization, resulting in impaired whole-body glucose metabolism.

Discussion: Lipid sensing in the hypothalamus has an important role in the regulation of peripheral glucose homeostasis. In this study, we show that olanzapine disrupts the ability of central oleic acid to regulate peripheral glucose kinetics. Impairments in brain nutrient sensing are expected to have detrimental metabolic effects and have been observed in diabetes. The results of this study suggest that impairments in central lipid sensing represent another mechanism by which antipsychotics mediate their metabolic adverse effects.

S111. ARE SLOW CLOZAPINE TITRATIONS SAFER THAN FAST ONES? A LITERATURE REVIEW

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Background: Clozapine is vastly underutilized in many countries across the globe, and within countries, there is often considerable geographic variation in clozapine prescribing practices. For countries, regions, or individual practices seeking to increase patient access to clozapine, the only way to decrease the clozapine utilization gap is to initiate new patients on clozapine. To accomplish this, one of the first steps is for the prescriber to determine the appropriate titration speed.

The initial titration period is critical for several reasons: 1) many of the most serious adverse effects of clozapine can occur within the first eight weeks, 2) the patient's first impression of the medication matters, and early tolerability issues can lead to self-discontinuation and contribute to patient reluctance to agree to subsequent trials if indicated, 3) clear guidance is needed for prescribers for how to initiate clozapine, and 4) experiences with adverse effects early in a titration may make prescribers less likely to recommend and ultimately prescribe clozapine for the next patient that needs it. Although the stakes around the initial titration speed are high and the concept is of significant clinical importance, there is a paucity of literature on the matter.

Methods: Herein, we will review what is known about clozapine titration speed and its relationship to adverse events. The US package insert recommends a target dose of 300-450 mg per day of clozapine after two weeks, but in some circumstances, this may be too rapid. Multiple elements of clozapine initial titration speed will be presented including a review of the safety on ultra-rapid titration, a discussion on the relationship between myocarditis and inflammation and titration speed, the potential value of serial C-Reactive Protein monitoring and therapeutic drug monitoring, and an analysis of the emerging data around differences in ancestral origin and recommended clozapine titration speeds.
Results: Like the lesson offered by the fable of the tortoise and the hare, there may be advantages to the slow and steady approach. We also argue that there is not, nor should there be, a one-size fits all approach for assigning the clozapine titration speed, and this should be determined by the clinical context and urgency. Clozapine initiations require significant clinical vigilance and prescribers need to be flexible and responsive as the titration unfolds. A feedback system must be in place for the patient to reach the prescriber urgently if needed in the outpatient setting. Finally, we will discuss what research questions and study designs could help provide additional insight into this dilemma.
Discussion: Clozapine titration speed should be personalized for each individual depending on a variety of clinical considerations. Further research is needed in this area to guide clinicians, as clear guidance can help to remove barriers to clozapine utilization.

S112. EXTENDED CLOZAPINE HEMATOLOGICAL MONITORING INTERVAL DURING THE COVID 19 PANDEMIC: A CHART REVIEW STUDY.

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Background: Debate continues about the safety, underuse, and delayed use of clozapine in patients with schizophrenia. Hematological monitoring is required to mitigate safety concerns associated with clozapine use, and these monitoring intervals vary across countries. The federal department responsible for health policy in Canada, Health Canada, issued a directive in March 2020 allowing patients who were on clozapine for more than 12 months to reduce frequency of hematological testing. The impact of reduced blood monitoring frequency on hematological events in patients prescribed clozapine for more than 12 months remains unclear. Thus, the current retrospective chart review study investigated the impact of Health Canada's directive on the rate of leukopenia, agranulocytosis, and other relevant clinical outcomes for patients followed at a major psychiatric hospital.
Methods: A chart review was conducted on all patients enrolled at the Royal Ottawa Mental Health Centre between March 2019 to March 2021 who were on clozapine and were registered with the Clozaril Support and Assistance Network (CSAN). Clinical and hematological data was extracted from the electronic health record (EHR) and CSAN database. Rates of adverse hematological events (e.g., leukopenia, agranulocytosis) were compared between patients on standard and reduced frequency (i.e., extended) blood monitoring protocols. Hospitalization days and rate of discontinuation of clozapine were also compared 12 months before and after March 2020. Data are presented as means +/- standard deviation.
Results: Of the 621 patients, 419 (67.5%) were males and 202 (32.5%) were females. Ninety percent were single, 19.8% were living independently and 22.7% were cigarette smokers. Two-hundred twenty-eight (36.7%) patients were on the extended blood monitoring protocol and 393 (63.3%) were on the standard blood monitoring protocol. The mean clozapine dose was 364.6+/-192.9 mg (standard: 369+/-206; extended: 357+/-168, p=0.44; Cohen's d=-0.06). Mean duration of clozapine treatment up to March 2021 was 12.6+/-8.3 years (standard:

13.9+/-8.4; extended: 10.4+/-7.5, p<0.01; Cohen's d=-0.43). The extended blood monitoring group had a significantly lower number of patients with comorbidities (standard: 78; extended: 257, p<0.05). Mean number of days spent as an in-patient from March 2020 to March 2021 was 21.9 days (standard: 18.6+/-70.3; extended: 27.8+/-89, p=0.18, Cohen's d=0.12). Preliminary analyses demonstrated similar rates of hematological abnormalities between patients with standard (percentage of all blood results normalized to participant; 2.8%) and extended blood monitoring intervals (2.6%) (p>0.05, eta-squared<0.01). More comprehensive analysis is forthcoming.

Discussion: These preliminary results provide evidence that rates of hematological abnormalities do not increase when patients who were prescribed clozapine for greater than a year reduce their frequency of blood monitoring. Patients in our sample were able to safely continue taking clozapine despite reduced frequency of blood monitoring during COVID-19.

S113. PDE2 AND PDE9 INHIBITION IMPROVES COGNITIVE FLEXIBILITY IN A RAT MODEL RELATED TO SCHIZOPHRENIA

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Background: Evidence from numerous clinical and preclinical studies has led to the hypothesis that impaired glutamatergic transmission and NMDA receptor hypofunction play an important role in cognitive impairment associated with schizophrenia (CIAS). Second messenger pathways depending on cAMP and/or cGMP are key regulators of glutamatergic transmission and NMDA receptor related pathways. Specific cyclic nucleotide phosphodiesterases (PDEs) such as PDE2 and PDE9, expressed in cognition relevant brain regions, cortex and hippocampus are therefore putative targets for cognition enhancement [1, 2]. In fact, it has been shown previously that the PDE2 or PDE9 inhibition led to an improvement of memory performance in animal cognition tasks related to working and episodic memory. However, effects of these targets on executive function/cognitive flexibility, a particularly debilitating aspect of CIAS, have not been fully investigated. The aim of the present study was to assess functional target engagement with a PDE2 inhibitor, BI 474121 and the PDE9 inhibitor, Bay 73-6691 on cGMP increase in the brain. Subsequently, these compounds were evaluated for their efficacy to restore an executive function deficit in the attentional set shifting task, in a rat model of NMDA receptor hypofunction.

Methods: Adult male mice were orally administered with BI 474121, Bay 73-6691 or vehicle, and after sampling of brain regions prefrontal cortex, hippocampus and striatum, all tissues were homogenized and the supernatants were analyzed for cGMP levels via ELISA technique. For cognitive testing, an attentional set shifting task was performed as described [3]. Briefly, female Lister Hooded rats were treated with the NMDA receptor antagonist phencyclidine (PCP) at 2 mg/kg i.p. twice daily for 7 days followed by 7 days washout (sub-chronic PCP). Afterwards, following acute oral treatment with drug or vehicle, rats were tested in the 7 stage attentional set shifting task.

Results: BI 474121 and Bay 73-6691 significantly and dose-dependently increased cGMP in mouse brain regions (p<0.05 for BI 474121; p<0.005 for Bay 73-6691), demonstrating central target engagement. Both inhibitors demonstrated efficacy in the rat attentional set-shifting task, significantly reversing the selective extra-dimensional shift deficit induced by sub-chronic PCP (p<0.001 for both compounds).

Discussion: PDE2 and PDE9 inhibition led to an improvement of cognitive flexibility as evaluated in the attentional set shifting task using a rat model related to schizophrenia, i.e. NMDA receptor hypofunction induced by sub-chronic treatment with PCP. These Results: support previous findings showing that PDE2 inhibition restores cognitive flexibility in rats, whereas for the first time we demonstrate these effects for PDE9 inhibition. Overall, BI 474121 showed memory enhancing effects in animal cognition tasks further demonstrating that PDE2 inhibition may be a potential approach to pharmacologically improve cognition in psychiatric disorders such as schizophrenia.

References:

[1] Duinen et al. (2015), Curr. Pharm. Des. 21, 3813-3828.

[2] Dorner-Ciossek et al. (2017), Adv. Neurobiol. 17, 231-254.

[3] McLean et al. (2012), J. Psychopharmacol. 26,1265-1270.

S114. THE EFFECTS OF PREVENTATIVE CANNABIDIOL IN A MALE NEUREGULIN 1 MOUSE MODEL OF SCHIZOPHRENIA

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Background: Cannabidiol (CBD) is a non-intoxicating cannabinoid with antipsychotic-like properties, however its potential to prevent schizophrenia development has not been thoroughly investigated. Brain maturation during adolescence creates a window where CBD could potentially limit the development of schizophrenia. The Nrg1 transmembrane domain heterozygous (Nrg1 TM HET) mutant mouse shows face, predictive, and construct validity for schizophrenia. Here we sought to determine if CBD given in adolescence could prevent the development of the schizophrenia-relevant phenotype, as well as susceptibility to the psychoactive cannabinoid Δ^9-tetrahydrocannabinol (THC) in Nrg1 TM HET mice.

Methods: Adolescent male Nrg1 mutants and wild type-like (WT) animals were administered 30 mg/kg CBD i.p. daily for seven weeks, and were tested for locomotion, social behaviour, sensorimotor gating and cognition, and sensitivity to acute THC-induced behaviours. GAD67, GluA1, and NMDAR1 protein levels were measured in the hippocampus, striatum, and prefrontal cortex.

Results: Chronic adolescent CBD increased locomotion in animals regardless of genotype, was anxiolytic, and increased social behaviour when animals were tested in the THC battery. CBD did not alleviate the schizophrenia-relevant hyperlocomotive phenotype of Nrg1 mutants, nor deficits in social behaviours. Nrg1 mutant mice treated with CBD and THC showed no habituation to a startle pulse, suggesting CBD increased vulnerability to the startle habituation-reducing effects of THC in mutant mice. CBD increased levels of GluA1, but reduced levels of GAD67 in the hippocampus of Nrg1 mutants.

Discussion: These Results: suggest adolescent CBD is not effective as a preventative of schizophrenia-relevant behavioural deficits in mutants and may actually contribute to pathological changes in the brain that increase sensitivity to THC in particular behavioural domain.

S115. OCEAN EMPIRE: DEVELOPMENT OF A MOBILE APP TO UNDERSTAND PHYSICAL ACTIVITY MOTIVATION AND AFFECT IN PSYCHOTIC DISORDERS

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Background: Despite the benefits of physical activity (PA) on physical and mental health, people with psychotic disorders are less physically active than the general population and can spend up to 80% of their time in sedentary activities. Previous studies underlined that intentions and affect are associated with PA. One method to facilitate PA increase and incorporate motivational features is by using exergames (contraction between Exercise and Game). Exergames have the particularity to require PA from the player (e.g., a participant can be asked to walk to move an avatar). In people with psychosis, the use of exergames have been found to be feasible and acceptable interventions, to improve mood, and to facilitate higher adherence to PA.

Methods: Using a 3-step process, we developed the Ocean empire app: a mobile app to increase PA and to understand the role of motivation and affect in PA initiation among early psychosis.

Results: In a first study including 15 young adults, we showed that the Ocean Empire exergame was considered by the participants as a viable option for increasing PA. In a second study, using a mixed design study, 5 young adults with early psychosis tested an updated version of the exergame, and indicated that the mobile app was pleasant and encouraged them to do more PA. However, they reported that they would want more autonomy in the game, more PA challenges, a better notification system regarding the PA planning, and a better system to examine the progress towards their goal. After updates to the last exergame version, a third study was developed and incorporated new motivational features to facilitate PA such as a daily reward system and upgrades available in the game only when doing PA. Afterwards, the third step of our process will be to examine whether the mobile app could modify their PA motivation and or affect.

Discussion: Preliminary results indicated that our mobile app could increase PA but also facilitate motivation towards PA in young adults with psychosis

S116. CONNECTING TOBACCO SMOKERS WITH SCHIZOPHRENIA AND OTHER SERIOUS MENTAL ILLNESS TO A DIGITAL CESSATION INTERVENTION DURING AN INPATIENT PSYCHIATRIC HOSPITAL STAY

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Background: Tobacco smoking prevalence in persons with schizophrenia and other serious mental illnesses (SMI) in the US is approximately 3x that of the general population. Persons with SMI die 10-15 years earlier than those in the general population; tobacco smoking is the strongest preventable risk factor for this elevated mortality. Psychiatric hospital admissions for SMI are common. The hospital is an optimal setting to provide smoking cessation services: patients experience abstinence, are available for counseling, and have access to cessation medications. However, most return to smoking after discharge. A digital intervention introduced in the hospital can bridge the post-hospitalization treatment gap. Developed by Truth Initiative, the EX Program (EX) is a digital tobacco cessation program with real-time 1:1

coaching by tobacco treatment specialists via live chat, a large online social network for peer support, nicotine replacement therapy decision support and delivery, and a fully integrated text message program. We adapted EX for hospitalized SMI smokers and examined feasibility and acceptability in a demonstration project.
Methods: Adaptations to EX occurred via iterative input from stakeholders, usability testing, and clinical demonstration in the hospital setting. Stakeholders included SMI researchers, individuals with SMI with lived experience of quitting smoking, and inpatient leaders and clinicians. Usability testing was conducted with 10 hospitalized SMI smokers (mean age 40 years, 60% female, 50% African American). For the demonstration we recruited hospitalized SMI smokers who were interested in trying to not smoke after discharge, had a smartphone, and used the internet three+ times per week.
Results: Adaptations to EX included added video content for easier consumption; custom text message and email library with more prescriptive, clear suggestions for next steps; made scheduling a coaching session easier to find; made mental health content easier to find. We developed a well-specified protocol for identifying smokers via the electronic health record, approaching them in the hospital to talk about smoking and quitting, registering them with EX, sampling EX features such as the digital coaching and EX community, and completing a post-discharge call to troubleshoot any problems using EX. The most frequent reason for declining participation in the demonstration was lack of interest in not smoking after discharge. In the final demonstration sample of 22 hospitalized SMI smokers (mean age 34 years, 50% female, 50% African American), 50% had a schizophrenia spectrum disorder/psychosis diagnosis. Participants had started smoking regularly at a mean age of 19 (sd=7.1), on average had 2 lifetime quit attempts (sd=2.5) and reported a mean of 9.2 (range 1-30) cigarettes/day prior to hospitalization. Participants reported a mean of 2.28 (sd=1.45) on the Heaviness of Smoking Index, indicating low to moderate nicotine dependence. Eighteen participants registered for EX with instruction, 17 fully sampled EX in the hospital, and 14 completed the post-discharge phone call. Of the 10 participants who completed 2- or 4- week post discharge follow-ups, 5 reported no smoking, 4 reported decreased smoking, and 1 reported no change. Qualitative interviews revealed that participants liked discussing quitting in the hospital, found learning to use EX easy, appreciated the calls after discharge, and enjoyed the coaching sessions.
Discussion: Connecting hospitalized SMI smokers who are interested in trying to remain smoke-free with a digital intervention is feasible and acceptable. A larger and randomized trial is currently underway.

S117. INSIGHTS FROM A QUALITY IMPROVEMENT PROJECT FOCUSING ON THE IMPLEMENTATION OF DIGITAL TECHNOLOGIES INTO COORDINATED SPECIALTY CARE PROGRAMS FOR FIRST EPISODE PSYCHOSIS (FEP) AND CLINICAL HIGH RISK FOR PSYCHOSIS CARE (CHR-P)

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Background: Coordinated Specialty Care (CSC) has demonstrated efficacy in improving outcomes in Clinical High risk for psychosis (CHR-p) and First Episode Psychosis (FEP) populations. To help support CSC service delivery, the augmentation of services using digital mental health interventions (DMHI's) may be explored. This study sought to explore effective methodologies of implementing and supporting technology into routine CSC care.
Methods: Clients and clinicians from a CHR-p clinic (CEDAR) and a FEP clinic (ASPIRE) participated in a quality improvement project exploring the feasibility of following the AACCS implementation framework to implement mindLAMP, a flexible and evidenced-based DMHI.

Digital navigators were used at each site to assist clinicians and clients to implement mindLAMP. To explore differences in implementation effectiveness associated with application format, a menu-style format was delivered at CEDAR, and a module approach was utilized at ASPIRE. Qualitative baseline and follow-up data were collected to assess specific implementation outcomes.
Results: Participants (n =5) included 3 white (60%), 2 (40%) males, 2 (40%) females, and 1 (20%) transgender with a mean age of 19.6 years old. Implementation outcome data demonstrated that clinicians and clients had high levels of access, connection, and sustainability of technology. Clients and clinicians reported variability in the types of clinical care they wished the technologies could support, ranging from case-management, exposure and response prevention, and measurement-based care. Differences in implementation styles revealed that clients are more responsive and engaged in the intervention when delivered in a module approach including a schedule for data collection and interventions.
Discussion: Utilizing specific case studies, these findings provide insights to guide best practices of implementation of technologies supporting CSC care. This study demonstrates the importance of technology to provide autonomy for clients in and clinicians in their use, the utility of a digital navigator in training and implementation, and that technologies are best implemented when they are versatile, rather than complex.

S118. A DIGITAL TOOL FOR THE ASSESSMENT OF AUDITORY VERBAL HALLUCINATIONS IN SCHIZOPHRENIA: PROOF OF CONCEPT

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Background: A mobile application (app) called MIMO was devised in order to monitor the auditory verbal hallucinations (AVH) assessed by the patients themselves. The originality of this device is based on a self-evaluation possibly used at any time compatible to an ecological momentary assessment (EMA) and allowing a monitoring by the patients and practitioners. The present study aimed to validate this device in demonstrating first the feasibility and acceptability of such digital tool and second the good psychometric properties of the scale included, the Self-Assessment of Verbal Hallucinations (SAVH). The present research is a proof-of-concept observational study, conducted in routine care in 41 patients with schizophrenia or schizoaffective disorders (DSM-5).
Methods: After loading the app, the patients self-assess their hallucinations with 13 questions. For 9 questions that constitute the SAVH, the patients choose the best answer among five what generates a score from 0 to 5. A total score is also generated ranging from 0 (no hallucinations) to 45 (severe hallucinations). The patients were also evaluated with the Brief Psychiatric Rating Scale (BPRS), the Auditory Hallucination Rating Scale (AHRS), the Birchwood Insight Scale (BIS). Moreover, a global satisfaction of the device scoring from 0 (“Not at all satisfied”) to 10 (“Very satisfied”) and 22 questions (concerning the habits in using apps, the acceptability and content of the app, the impact of the device on mental health) were asked to the patients. The Internal consistency of the SAVH was tested by α Cronbach coefficient. Construct validity was evaluated with a principal component analysis (PCA) with varimax rotation on the 9-question scores. Convergent and discriminant validities were tested with Pearson’s correlations between the SAVH total scores and on one hand the AHRS total scores and the BPRS hallucinatory behavior subscores and on the other hand the BPRS negative subscores and insight scores.

Results: The patients' satisfaction was in mean (SD) at 8.073 (3.8) indicating very good overall satisfaction of the app. The patients' habits in using a mobile app were quite heterogeneous (39 % not at all or little familiar; 53% somewhat or very familiar). Nighty two percent of patients found this app somewhat or very easy to use with 70.7% wanting to continue using it. Fifty six percent were not reluctant in loading the app on their mobile but 34% were somewhat reluctant. The majority found the questions appropriate (90.3%) and found the length of the questionnaire as much adequate (68.3%). The majority of patients (85.4%) reported that this app could be fruitful in the awareness of their AVH.
Regarding the 9-question scores of the SAVH, α Cronbach's coefficient was 0.67. The correlations between the SAVH total scores and AHRS (r= 0.858) or BPRS hallucinatory behavior subscores (r=0.569) were significant ($p<0.001$). There were no significant correlations between the total scores and: i) the levels of insight (r=0.09, p=0.574); ii) and the BPRS negative subscores (r=-0.118; p=0.463). Factor analysis on the 9 scores of the SAVH extracted 3 factors (descriptive, functional and time dimension) that accounted for 59.3% of the variance.

Discussion: Taken together, the results showed that the patients' acceptance and feasibility for the mobile app MIMO were very satisfactory. The SAVH presents good convergent and discriminant validities, good internal consistency and construct validity. Such a device can be quite useful to assess the efficacy of the treatment of AVH, to monitor the AVH and to increase the patient's empowerment.

S119. ACCESS TO COGNITIVE REMEDIATION IN AUSTRALIA FOR PEOPLE WITH SCHIZOPHRENIA

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Background: Cognitive remediation (CR) is effective in improving neurocognition and functioning in schizophrenia, yet throughout most countries it is not part of routine mental health services. The current study investigated knowledge of, access to, and interest in accessing CR in individuals with schizophrenia in Australia. We hypothesised that participants with higher neurocognitive insight would be more interested in accessing CR, taking into account self-esteem, motivation orientations, and affect.
Methods: Sixty-one participants with schizophrenia (self-declared) living in Australia completed an online survey with questions about cognitive challenges, use of coping strategies, and access to CR and other cognitive-oriented interventions. Subjective cognitive functioning (Subjective Scale to Investigate Cognition in Schizophrenia Brief version; Cella et al., 2020), self-esteem (Rosenberg Self-Esteem Scale; Rosenberg, 1965), motivation orientations (General Causality Orientation Scale for Clinical Population; Cooper et al., 2014), and affect (International Positive and Negative Affect Schedule Short Form; Thompson, 2007) were also assessed on self-rating scales.
Results: Around 70% of participants reported experiencing cognitive challenges and 80% of them wanted to receive help for it. More than half of the participants had never heard of CR, and around half of those who had heard of CR had never been offered CR. Yet, most said they

would be interested in participating in CR if they were given the opportunity (76.3%). Demand for accessing CR was high but not related to neurocognitive insight, even when controlling for self-esteem, motivation and affect. However, negative affect was a significant predictor of consumers' interest in CR (OR = 1.614 [1.062 – 2.453], p = 0.025).
Discussion: Our results suggest that CR access in Australia as well as knowledge about CR and other cognitive-enhancing therapies is scarce, yet people with schizophrenia displayed help-seeking intentions regardless of their subjective cognitive complaints and most were interested in accessing CR. It is suggested that CR should be offered more broadly to clients regardless of the cognitive complaints they manifest. Affective dispositions should also be considered when investigating help-seeking behaviours in relation to cognition in schizophrenia. The current study offers preliminary evidence of relatively poor CR knowledge and access in Australia, and calls for larger scale studies involving consumers across different health services (i.e., public and private). Future research should also further investigate barriers and facilitators of CR access.

S120. NETWORK ANALYSIS OF CO-OCCURRING AUTISTIC AND PSYCHOSIS FEATURES IN SUBCLINICAL AND CLINICAL SAMPLES

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Background: The relationship between autism and psychosis spectrum disorders (ASD and PSD, respectively) and their extended phenotypic continua in the general population has been the subject of considerable debate. While several models have been used to explain the nature of their relationship, two models have dominated the debate: The overlapping and the diametric models. According to the overlapping models, ASD and PSD features are expected to be positively correlated, while according to the diametric model, these features are expected to be anti-correlated. The putative overlapping and diametrical relationships between ASD and PSD features within the same individual is yet to be examined in clinical populations.
Methods: To shed light on this important question, we perform network analyses of autism and schizophrenia symptoms/features that were assessed in tandem in five existing datasets (N = 5,427): 3 non-clinical (N= 4004) and 2 clinical (N= 1423), to tests these two competing models. Specifically, we fitted Gaussian Graphical Models to estimate the network models in each of the five samples, separately. These models yielded regularized estimation of a partial correlation networks determined by Graphical Least Absolute Shrinkage and Selection Operator (GLASSO) using Extended Bayesian Information Criterion (EBIC) model selection, with a tuning hyperparameter γ, set to 0.5. The networks were then constructed using the Fruchterman-Reingold algorithm, where nodes with stronger connections are positioned closer to each other and more centrally within the network. Finally, robustness analyses were performed to ascertain the stability of the networks, which was conceptualized in terms of how stable the centrality indices were when estimating the network based on subsets of the data.

Results: Across all non-clinical and clinical samples, we obtained stable networks in which dimensions of autistic and psychotic features were positively associated, while others were anticorrelated. Specifically, the analysis revealed that (1) autistic and negative symptom were strongly correlated, forming a separate community, and (2) positive psychotic features were anticorrelated with autistic features.
Discussion: This approach offers a comprehensive intraindividual characterization of the nature of the association of defining features within the autism and psychosis spectra. The results support both the overlapping and the diametrical models. The identification of a community consisting of autistic and negative psychotic features suggests that these features might be associated with shared mechanism. The presence of anticorrelated autistic and positive psychotic features suggest that phenotypic expressions in people with ASD or PSD might be modulated by anti-correlated processes. If confirmed, this may usher a new research area of reciprocal therapies in both ASD and PSD. These results also emphasize the importance of assessing autistic and psychosis features in tandem within the same individual.

S121. ASSOCIATIONS BETWEEN GPS-DERIVED MOBILITY INDICES, MOTIVATION AND HEDONIC CAPACITY, FUNCTIONING, AND AFFECT AMONG UNDERGRADUATES WITH AND WITHOUT ELEVATED SCHIZOTYPAL CHARACTERISTICS

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Background: Emerging evidence supports GPS derived mobility indices as possible digital phenotypes of negative symptoms of schizophrenia. Certain features of negative symptoms, including motivation and pleasure deficits, are also seen among individuals with schizotypy. For this project, we compared mobility and activity space patterns using three commonly reported GPS-derived indices between individuals with and without elevated schizotypal characteristics. In addition, associations with relevant clinical and functional outcomes, including motivation and hedonic capacity, well-being, academic functioning, and affect, were tested.
Methods: Interim data collected from 41 undergraduates with high (n = 21) and low (n = 20) levels of schizotypal features at the University of Iowa were analyzed; data collection is ongoing. Schizotypal characteristics were assessed with the Schizotypal Personality Questionnaire-Brief, Revised, Updated (SPQ-BRU). Participants completed in-lab measures of motivation and hedonic capacity (Motivation and Pleasure Scale – Self Report), well-being (Satisfaction with Life Scale and Psychological Wellbeing Scale), academic functioning (GPA), and affect (Positive and Negative Affect Schedule). Participants subsequently carried a GPS tracking device (recording at 0.05 Hz) during a 14-day at home period. Three mobility indices (i.e., average proportion of time spent at home, average distances traveled, and average maximum distance traveled from home) were calculated. Group differences in GPS indices were tested, as were correlations between the mobility indices and clinical and functional outcome measures.
Results: Adherence to the GPS device via self-report (M = 81.5%, SD = 15.8) and calculated number of days containing GPS data (M = 13, SD = 1.7) were high. Contrary to our expectations, the high and low schizotypy groups did not statistically differ on the three mobility indices (p's > .449). However, consistent with our expectations, within the high schizotypy group mobility was significantly associated with academic functioning (proportion of time at home $\rho = -.53$, $p = .016$) and with motivation and hedonic capacity at a trend-level

(max. distances traveled ρ = .37, p = .100). Among the entire sample, mobility was associated with greater satisfaction with life (max. distances traveled ρ = .35, p = .027), academic functioning (proportion of time at home ρ = -.43, p = .006), and positive (avg. distances traveled ρ = .33, p = .036) and negative affect (avg. distances traveled ρ = -.37, p = .019).
Discussion: These interim findings indicate that traveling more, traveling further distances from home, as well as spending less time in one's home is related to improved well-being, academic functioning, and affect among undergraduate students. There was a trend-level association with negative symptoms in the high schizotypy group, which will be investigated further in the complete sample. The high levels of adherence indicate that assessing mobility and activity in daily life among undergraduates with GPS tracking devices is feasible for researchers and acceptable to participants. Implications of this study include the potential for early detection of negative symptoms and the possibility of mobility as a modifiable treatment target to improve functional outcomes among a group who may be at increased risk to develop a psychotic disorder. Additional analyses will be presented with the complete sample, including an examination of entropy, an additional mobility index to capture variability in movement, among GPS-derived overall and social specific activity spaces.

S122. USING NETWORK ANALYSIS TO UNDERSTAND THE EFFECTS OF PHYSICAL ACTIVITY IN PSYCHOSIS AND STUDY REPLICATION

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Background: In people with psychosis, physical activity (PA) is known to positively impact psychotic symptoms, however, the mechanisms underlying these effects are unclear. In the network approach, mental disorders are defined as complex systems of interconnected symptoms mutually influencing each-other. In this context, PA could influence the connection between the symptoms. Objectives: Using data from two independent PA trials, the aim was to investigate the impact of PA on network density, then compare the network structure pre and post intervention.
Methods: The first trial used data from a randomized controlled trial including 64 participants with psychosis and obesity involved in a 6-month training program. The second trial used data from a 3-month open trial including 66 participants with psychosis and obesity. The Positive and Negative Syndrome Scale (PANSS) assesses symptom severity using semi-structured interviews. Networks before and after PA were modelized using partial correlations with a Holm adjustment, and stability re-estimated by Bootstrap.
Results: In study 1, the PANSS network at baseline was a highly connected structure and this structure slightly changed with PA. The most influential symptoms in the network were essentially from negative and psychopathological domains. Network structure was different between the control and intervention groups (M=0.48, p = 0.04) as well as connectivity (S = 5.29, p = 0.02). In study 2, as in study 1, the PANSS network at baseline was highly connected and this structure was modified following the PA intervention to represent a disconnected network structure with less connectivity between the different symptoms.
Discussion: This study is the first to show that PA seems to ameliorate symptom connectivity compared to control group, as to show that PA could modify the PANSS structure, providing a first mechanism of action which would require more investigation.

S123. SELF-ASSESSMENT OF PHYSICAL FITNESS IN PATIENTS WITH SCHIZOPHRENIA

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Background: Recent reports suggest that physical exercise may be beneficial for people with schizophrenia as it may potentially improve cognitive abilities, clinical symptoms, and quality of life. That said, there is increasing interest in research regarding the motivation of individuals with severe mental illnesses such as schizophrenia to engage in physical activity and exercise. Studies of the general population show a positive correlation between self-assessments of physical fitness and the motivation for physical activity. It is unclear whether this also applies to individuals with schizophrenia.

Methods: In our ongoing, randomized controlled study we focus on the relationship between subjective and quantitative measures of physical fitness. To do this, participants are assessed via Borg's Rating of Perceived Exertion (RPE) and a visual analogue scale (VAS) of subjective physical fitness prior to and following exercise or a non-exercise control session on a bicycle ergometer.

Prior to exercise, individual physiological fitness scores are defined using heart rate, lactate and power output derived from an incremental exercise test and are used to prescribe exercise work rates to individual fitness levels. During subsequent test sessions, physiological data (i.e., heart rate, blood pressure, weight, and ECG) are recorded along with estimates of daily physical activity via the German Movement and Sport Activity Questionnaire (BSA) and the Godin Leisure-Time Physical Activity Questionnaire (GLTPAQ). Clinical data (i.e., Positive and Negative Syndrome Scale (PANSS), medication, age, duration of disease) are also collected. We hypothesize that, compared to healthy controls (N=25), patients with schizophrenia (N=25), will have impaired estimations of physical fitness compared to their objective physiological measures.

Results: Preliminary results suggest that patients generally indicate lower self-ratings of physical fitness than healthy controls ($p<0.001$). Indeed, patients yield lower objective physical fitness scores than healthy controls ($p=0.043$). However, while there is a positive correlation between self-assessments on the VAS and physiological fitness scores in controls ($\rho=0.731$, $p=0.040$), this correlation is absent in patients ($\rho=0.190$, $p=0.651$). This would suggest that patients are impaired in rating their objective physical fitness. Notably, regardless of whether exercise occurs, patients' self-ratings on the VAS increase by 9.69% from pre- to post-session assessments ($p=0.020$). Also, patients' self-assessed fitness on the VAS correlates positively with self-reported sport activity (BSA, $\rho=0.658$, $p=0.004$), but not with symptom severity rated on the PANSS or its subscales ($ps>0.050$).

Discussion: Patients with schizophrenia demonstrate impairments in estimating their physical fitness, a finding which may be explained by generally lower self-esteem reported previously from this patient group. Despite this, patients seem to adjust their sport activities in daily life to their subjective fitness estimations. The finding that patients' subjective fitness ratings increase from pre- to post-sessions irrespective of whether exercise occurs suggests that patients benefit from settings where others (e.g., the study personnel) pay attention to their needs and offer support. Interestingly, psychosis related symptom severity does not seem to impact self-ratings in patients. Together, our findings offer important insights for optimizing

therapeutic approaches aimed at enhancing physical fitness in patients with schizophrenia, such as in cases of severe weight gain induced by antipsychotic treatment.

S124. DEMOGRAPHICS AND CAUSES OF DEATH IN A TERTIARY SCHIZOPHRENIA PROGRAM: A RETROSPECTIVE CHART REVIEW

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Background: Schizophrenia is a life-shortening illness: people with schizophrenia have a mortality rate 2-3 times higher and a life expectancy 10-25 years shorter than the general population. Despite this urgent health risk, mortality rate and causes of death among patients with schizophrenia spectrum disorders (SSDs) have not been studied in the context of a Canadian tertiary mental healthcare centre.
Methods: We conducted a retrospective chart review of patients (≥18 years) diagnosed with an SSD who died during their admission to the Royal Ottawa Mental Health Centre's (ROMHC) inpatient or outpatient schizophrenia program from June 1, 2014, to July 20, 2022.
Results: 74 deceased patients (mean age = 54.6, 75.7% males) with an SSD (schizophrenia: n = 59, 79.7%, schizoaffective disorder: n = 14, 18.9%, psychosis not otherwise specified, n = 1, 1.4%; mean age of first episode psychosis = 24.4) were identified. The most common cause of death was medical illness (n = 45, 60.8%), followed by undetermined causes (n = 21, 28.4%), suicide (n = 5, 6.8%), and accidents (n = 3, 4.1%). 19.0% of deaths of undetermined cause (n = 4) were deemed to be unnatural (i.e., drowning), while the rest are unknown due to insufficient data in the electronic medical record and/or incident report.
Discussion: As the second most common cause of death was undetermined, adverse event identification and reporting at the ROMHC requires improvement. In future, we aim to calculate the overall mortality rate in the ROMHC schizophrenia program, characterize clinical factors associated with deaths among SSD patients using a case-control design and make recommendations to improve the recognition of factors associated with premature mortality in the clinical setting.

S125. PATIENTS UNDER CLOZAPINE TREATMENT HAVE HIGHER RISK OF COVID-19 INFECTION AND MORE SYMPTOMATIC ILLNESS

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Background: Clozapine, an antipsychotic with an indication for treatment-resistant schizophrenia, is associated with an increased risk for infection, including pneumonia. Emerging evidence points out that treatment with clozapine could affect both innate and adaptive immune systems. We aimed to investigate if psychotic patients under clozapine treatment have an increased risk of acquiring SARS-COV-2 infection when compared to psychotic patients under other antipsychotic treatments. We also aimed to explore if the clozapine group showed more symptomatic COVID-19 compared to the non-clozapine group.

Methods: We recruited 1001 patients with a psychotic spectrum disorder that were attending the mental health outpatient unit from Corporació Sanitària Parc Taulí (Sabadell, Spain), of whom 286 (28.6%) were under treatment with clozapine and the remaining 715 (71.4%) under treatment with antipsychotics other than clozapine. We collected data from clinical records, including SARS-COV-2 infection, the number of symptoms presented and the severity of infection measured by the need for hospitalization, ICU admission, and death. We tested associations between clozapine treatment and COVID-19 infection, the degree of symptoms, and the severity of the infection adjusting for potential confounders such as body mass index, smoking status, comorbidities, vaccination status, and prescribed antipsychotic doses. We performed a multinomial logistic regression exploring the association between clozapine treatment and SARS-COV-2 infection and COVID-19.
Results: The prevalence of COVID-19 was higher in the clozapine group compared to the group treated with other antipsychotics. Of the total 122 (12.2%) patients contracting SARS-COV-2, 52 (18.2%) were under treatment with clozapine, while the remaining 70 (9.8%) were treated with other antipsychotics (p 0,000). Being under treatment with clozapine meant a risk factor for contracting both mild-moderate and severe COVID-19 (OR 2.71 and 10.08, respectively). Among the COVID positive patients, receiving clozapine treatment was associated with a higher risk of contracting SARS-COV-2 ($p < 0.0001$). After adjusting for the considered covariates, clozapine treatment was a risk factor for developing both mild-moderate (p 0.005 OR 2.71 CI [1.35 – 5.43]), and severe COVID-19 (p 0.002 OR 10.08 CI [2.32 – 43.81]).
Discussion: Our study suggests that patients with a psychotic disorder receiving clozapine treatment show an increased risk of SARS-COV-2 infection as well as more symptomatic COVID-19 than patients with a psychotic disorder taking antipsychotics other than clozapine. The effect of clozapine on the immune system could be the mechanism that explains these associations. These patients under treatment with clozapine could be considered a population at risk for infections. Larger samples are needed to explore whether patients with clozapine have greater severity of SARS-COV-2 infection.

S126. IDENTIFYING PREDICTORS OF CLOZAPINE-INDUCED WEIGHT GAIN THROUGH A NATURALISTIC RETROSPECTIVE CHART REVIEW

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Background: Antipsychotic (AP)-induced weight gain is a distressing and concerning side-effect for patients treated with these medications. Clozapine (CLZ), which is presently the only AP with an approved indication for treatment refractory schizophrenia, carries the greatest risk for weight gain of all APs. However, it is unclear whether patients who have already gained a substantial amount of weight during the course of their illness and treatment with other APs will continue to experience significant weight gain after starting CLZ. As such, the goal of this study was to stratify patients according to their pre-CLZ BMI and track their weight trajectories after CLZ initiation. Furthermore, this study also mapped the weight trajectory of patients from their pre-diagnosis weight to post-CLZ weight to explore if pre-CLZ weight gain predicts the amount of post-CLZ weight gain that is experienced.

Methods: This is a secondary analysis of a retrospective chart review of patients newly initiated on CLZ at the Centre for Addiction and Mental Health in Canada. To address the first question, patients were stratified according to their baseline (pre-CLZ) BMI: a) normal weight (BMI 18-24.9 kg/m^2), b) overweight (BMI 25-29.9 kg/m^2), and c) obese (BMI 30+ kg/m^2). A mixed model analysis with subjects as random effects was used to assess how weight changes differently over time between BMI classifications. Time (baseline, 6-, 12-months post-CLZ), group (normal, overweight, obese), and the interaction between group and time were included as predictor variables, while controlling for age and sex. To answer the second question, an ANCOVA model was performed in which weight at 6- and 12-months post-CLZ was the dependent variable, and pre-CLZ weight gain was the predictor of interest, while controlling for baseline (pre-CLZ) weight.
Results: This chart review included 396 patients (males: 71.5%, mean age: 42.8 +/- 15.2 years) initiated on CLZ (mean dose: 286.4 mg/day +/- 92.6). The following number of patients were in each BMI category: a) normal: n = 118, b) overweight: n = 123, c) obese: n = 120. In the full sample, there was a significant interaction effect between baseline BMI categories and time, indicating that change in weight depends on baseline BMI. At both timepoints, the greatest increase in body weight was observed in the overweight group (6 months: 4.50 (0.99) kg, $p<0.001$; 12 months: 8.00 (1.19) kg, $p<0.001$) compared to the normal weight (6 months: 3.44 (1.06) kg, $p<0.001$; 12 months: 2.34 (1.39) kg, $p=0.093$) and obese groups (6 months: -0.81 (1.02) kg, $p=0.43$; 12 months: -0.61 (1.22) kg, $p=0.62$). Pre-diagnosis weight was available for 25 patients and was used to calculate pre-CLZ weight gain (pre-CLZ weight – pre-diagnosis weight). Among this subgroup of patients, pre-CLZ weight gain was a significant predictor of body weight 6- ($R^2=0.37$, $B=-0.52$, $p=0.02$) and 12-months ($R^2=0.61$, $B=-0.87$, $p=0.012$) post-CLZ initiation.
Discussion: This analysis revealed that patients with an increased metabolic risk and propensity to gain weight are more likely to experience significant weight gain after CLZ initiation than those who are normal weight or already obese. Furthermore, those who gained the most weight during their illness and treatment before CLZ experienced a lesser degree of weight gain post-CLZ initiation compared to those who did not gain as much weight during their previous AP trials. Understanding predictors of weight gain could allow for early identification of the minimum metabolic threshold and clinical profile that would warrant and benefit from adjunctive metabolic interventions to prevent significant weight gain with CLZ.

S127. ENHANCING PHYSICAL AND MENTAL HEALTH IN FIRST EPISODE PSYCHOSIS THROUGH COST-FREE GYM MEMBERSHIPS: EMPOWERING CHANGE THROUGH INDIVIDUAL CHOICE

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Background: Morbidity and mortality of individuals diagnosed with schizophrenia is higher than that of the general public. Individuals diagnosed with schizophrenia can experience a reduction in life expectancy of between 15 and 20 years, in large part due to cardiovascular disease. Changes in diet and activity level could, in part, counteract the reduction in life expectancy. Increased physical activity can have a positive impact on physical health, reductions in depression, improvements in anxiety, and enhanced executive functioning. It is also known that early collaborative mental health treatment in first episode psychosis (FEP), including therapy, medication management, and supportive social interventions, can improve long-term outcomes.

Methods: One way to address development of cardiovascular disease is to increase physical activity, which, in turn is improved with enhanced access to gyms. Our FEP team has obtained grant funding to cover the cost of client gym memberships, at a gym of the client's choice. We will discuss the potential benefits to increasing access to gyms through decreased cost of gym membership, which could otherwise be prohibitive. We will consider how improved access to gyms could also improve long-term health outcomes. We will also discuss how this scenario enhances collaborative care between clients in a FEP program. We will also discuss ongoing barriers to clients increasing regular physical activity, despite having zero-cost gym access.
Results: All clients enrolled in our FEP program were offered a free gym membership at the gym of their choice. Not all clients chose to utilize this resource, regardless of zero cost to them. 3 current clients have chosen to accept the coverage of a gym membership and all 3 regularly go to the gym. Many clients note ongoing barriers as reasons why they do not want to accept funds to cover gym memberships.
Discussion: Despite being offered no-cost gym memberships at the gym of their choice, many FEP clients choose not to participate in physical exercise at a gym or local recreation center. Many barriers exist in enhancing comfort for individuals with psychosis to participate in regular physical exercise. Many of our clients continue to express discomfort in being around strangers due to paranoia or anxiety. In addition, many gyms require members to have checking account information as part of the membership application process, which some of our clients do not currently have. Regardless of removal of the cost barrier and despite ongoing education related to the importance of maintaining physical health, individuals offered no-cost memberships to gyms of their choice continue to experience challenges in engaging in regular physical activity. In our experience, those who chose to accept gym memberships were appreciative and enjoyed going to the gym. They found benefit to both their physical and mental health through regular physical activity.

S128. THE ROLE OF METFORMIN IN PREVENTING ANTIPSYCHOTIC INDUCED WEIGHT GAIN

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Background: Antipsychotic medications are associated with weight gain at time of initiation. We aimed to review the evidence for adjunctive metformin versus control at time of antipsychotic commencement to attenuate weight gain.
Methods: We systematically reviewed the literature on the role of metformin at time of antipsychotic initiation to ameliorate antipsychotic induced weight gain. The primary outcome was difference in change in weight between metformin and control groups between time of antipsychotic commencement and endpoint. We explored the impact of factors including type of antipsychotic and study design.
Results: Five studies were identified including three randomized controlled trials and two naturalistic cohort studies. Two of the RCTs were of olanzapine while the other three studies were of clozapine. Study duration ranged from 12 to 24 weeks for the RCTs, and one year

follow up in both of the cohort studies. Four of the studies found statistically significant reductions in weight gain among the metformin arms compared to the placebo or treatment-as-usual arms, while one of the olanzapine RCTs found no weight difference between the metformin and placebo groups. Difference in change in weight at endpoint ranged from 1.3kg to 5.4kg, favouring metformin.
Discussion: Included studies suggest that there is a small but clinically meaningful amelioration of weight gain associated with the use of metformin at time of antipsychotic initiation. These findings suggest that metformin may ameliorate weight gain at time of antipsychotic initiation. Given the favourable safety profile of metformin, it may be worth discussing metformin as an option for people with schizophrenia to consider at time of antipsychotic medication initiation.

S129. CONCEPTUALIZING RELAPSE FROM THE PERSPECTIVES OF YOUNG ADULTS RECEIVING SERVICES FOR FIRST-EPISODE PSYCHOSIS: A QUALITATIVE, FOCUS GROUP STUDY

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Background: Relapse following a first-episode psychosis (FEP) is a major clinical challenge for specialized early intervention services. Understanding patient perspectives on the meaning of relapse, its processes, and the factors related to it, can help to inform the development of strategies and interventions to prevent relapse. However, limited research has examined the perspectives of young adults recovering from FEP on the phenomenon of relapse. In this presentation, we will describe how young adults receiving services for FEP conceptualize relapse.
Methods: This study was part of a larger qualitative research project on the subject of relapse conducted with family members and patients with FEP. We used focus groups as the main method of data collection. We recruited 25 young adult patients (Mean Age ±SD years: 24.4±5.0) from four early intervention services in Canada that were within 2 to 5 years of initial treatment for FEP. The audio recordings from the four focus groups were transcribed verbatim and analyzed using a descriptive content analysis approach.
Results: A dominant theme across the focus groups was uncertainty about the meaning of relapse. The uncertainty was often related to which symptoms and behaviors constituted relapse, how severe symptoms needed to be, and how long they needed to last. In general, however, most participants defined relapse broadly in relation to a change in: a range of symptoms (i.e., psychosis symptoms, change in mood, and increase in anxiety); thoughts and behavior (e.g., "behaving really weird"); functioning ("not functioning normally anymore"); or physical state ("extra energy that's causing you not to sleep"). They also conceptualized relapse in relation to hospitalization ("going back to the hospital") and the reuse of substances (e.g., marijuana). Participants also had difficulty distinguishing early warning signs from an episode of relapse.
Discussion: The conceptualization of relapse by the participants in this study was broader than how it is typically defined or measured in the relapse literature (i.e., recurrence of positive symptoms or hospitalization). Participants' uncertainty highlights a need for focused education and clarity on what relapse is, how to recognize it, and how to identify its early warning signs.

The extent to which conceptualization of relapse may differ for patients with and without a history of relapse is unclear. This difference would be a relevant area to examine in future research as such knowledge could help inform relapse prevention strategies and interventions.

S130. QUANTIFYING THE TOLERABILITY OF ANTIPSYCHOTIC TREATMENT-RELATED SIDE EFFECTS IN SCHIZOPHRENIA: A SURVEY STUDY OF PATIENTS AND CAREGIVERS

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Background: Antipsychotic medications are considered a mainstay of treatment for schizophrenia. However, these medications often confer a high side effect burden – including cognitive, metabolic, and neurological effects – that can lead to reduced adherence, decreased satisfaction with treatment, impaired quality of life, and negative health outcomes. Understanding how patients perceive the tolerability of various antipsychotic-associated side effects ensures that therapeutic choices address patient needs and provides information on patients' preferences that may inform shared decision-making discussions about treatment options. This study sought to quantify, from the perspective of people with schizophrenia and their caregivers, the tolerability of antipsychotic side effects and how specific side effects may impact their propensity to initiate or discontinue treatment.

Methods: This is an observational, cross-sectional survey study of n=200 individuals with schizophrenia and n=100 unpaid, informal caregivers serving as proxy respondents for individuals with severe illness. The survey included a Maximum Difference Scaling (MaxDiff) module to assess reported tolerability of 11 side effects associated with antipsychotic medications: feeling tired or drowsy, significant weight gain, reduced interest in or enjoyment of sex, problems with memory, concentration or thinking, insomnia or having problems falling or staying asleep, feeling slowed down like a "zombie", high blood sugar that may lead to diabetes, dry mouth, akathisia, pseudoparkinsonism and tardive dyskinesia. Included side effects were identified via a targeted literature review and in discussion with patient advocacy group partners. Survey topics were organized by domain and also included questions related to side effect-related treatment initiation, switching, or non-adherence, current treatment satisfaction and expectations, treatment-related side effect burden, quality of life, and sociodemographic information. Pilot testing (n=8) was performed to ensure instructional and question clarity. We are currently collecting data from the full sample of patients and caregivers. Results will be analyzed according to a prespecified framework and findings will be available by April 2023.

Results: Results from the pilot survey interviews indicate that both patients and caregiver proxies found the survey instructions and questions to be clear and germane to the research topic. The survey length was deemed appropriate and overall respondent experience was described positively. Minor edits to formatting were implemented prior to the survey launch. Full results from the survey will be available by April 2023.

Discussion: Side effects associated with antipsychotic medication have been shown to confer substantial burden to patients with schizophrenia, often resulting in reduced medication adherence and persistence, social and self-stigma, and diminished quality of life. Capturing how patients perceive the tolerability of various side effects, make decisions about disease management, and describe unmet needs is thus highly important and may inform aspects of treatment decision-making. This work is especially relevant considering the growing emphasis

placed on patient-focused drug development by the US Food and Drug Development, as well as other global health technology assessment bodies.

S131. PSYCHOPATHOLOGICAL AND METABOLIC PREDICTORS FOR QUALITY OF LIFE IN ANTIPSYCHOTIC-NAïVE PATIENTS WITH FIRST-EPISODE PSYCHOSIS

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Background: The complex construct of quality of life (QoL) in the background population is dependent on both psychological and somatic factors. For patients with severe mental illness, both these domains are accentuated, but their impact on QoL is challenging to disentangle, since the risk of especially metabolic complications is running in parallel with illness chronicity. The current study aims to evaluate the predictive value of psychopathological and metabolic parameters on QoL in a cohort of antipsychotic-naïve patients with first-episode psychosis (FEP), and to investigate the temporal stability of these parameters after initiation of antipsychotic treatment.

Methods: At baseline 128 (46.1% female) patients underwent psychopathological assessment with Positive and Negative Syndrome Scale (PANSS), assessment of Metabolic Syndrome (MetS) according to the International Diabetes Federation (IDF), and subjective QoL assessed by Satisfaction with Life Scale (SWLS). After six weeks of initial antipsychotic monotherapy with either amisulpride (50-800 mg) or aripiprazole (5-30 mg), 90 (46.7 % female) patients were re-investigated. Linear correlation analyses were performed to examine associations between clinical assessments and SWLS subdomains at both time-points.

Results: At baseline, mean PANSS total score was 78.2 (± 15.7), general symptoms (PANSS-G) score was 39.2 (± 8.4), positive symptoms (PANSS-P) score was 19.2 (± 4.1), and negative symptoms (PANSS-N) score was 19.8 (± 6.4). After six weeks, there was a significant reduction in PANSS total score of -14.6 (95% CI -17.3 to -11.8, $p < .001$), PANSS-G score of -7.8 (95% CI -9.3 to -6.2, $p < .001$), PANSS-P score of -5 (95% CI -5.9 to -4.2, $p < .001$), and PANSS-N score of -1.8 (95% CI -3 to -0.6, $p = .003$). During six weeks, there was a significant increase in Body Mass Index (BMI) of 0.41 kg/m2 (95% CI 0.23 to 0.60, $p < .001$), weight of 1.28 kg (95% CI 0.72 to 1.84, $p < .001$) and waist circumference of 1.38 cm (95% CI 0.13 to 2.63, $p = .031$). The prevalence of MetS at baseline was 19.8% (n = 23), of which only 48.8% (n = 11) were re-investigated after six weeks. Further, 3.5% (n = 4) developed MetS during the

six weeks, leaving a total prevalence of MetS of 18.8% (n = 15) at follow-up (p = .851). At baseline, SWLS subdomain mean scores were 7.9 (± 3.5) for Living Situation (LS), 10.1 (± 5.5) for Social Relationships (SR), 6.8 (± 4.4) for Self and Present Life (SPL), and 2.7 (± 2.4) for Work (W). During six weeks, there was a significant increase in SR of 2.3 (95% CI 1.5 to 3.1, p < .001) and SPL of 3.8 (95% CI 2.9 to 4.7, p < .001). PANSS-P correlated negatively with SR at both baseline (r = -.190, p = .032) and follow-up (r = -.239, p = .023), and with SPL only at follow-up (r = -.252, p = .016). PANSS-N correlated negatively with SR and SPL at both baseline (r = -.408, p < .001; r = -.219, p = .014, respectively) and follow-up (r = -.325, p = .002; r = -.272, p = .009, respectively). Further, at follow-up BMI, weight, and waist circumference correlated negatively with SR (r = -.257, p = .015; r = -.296, p = .005; r = -.304, p = .005, respectively).

Discussion: Our analyses reveal significant interrelationships between core psychopathological features, metabolic parameters and QoL in FEP, in the absence of confounding factors of previous antipsychotic exposure and chronicity. Although six weeks of antipsychotic treatment reduced PANSS scores, psychopathology still impacted on QoL at follow-up. Moreover, the metabolic aberrations induced after six weeks of antipsychotic treatment impacted negatively on QoL. These data underline the importance of developing strategies to prevent metabolic side-effects already from initial antipsychotic exposure.

S132. PREDICTING QUALITY OF LIFE IN INDIVIDUALS WITH PSYCHOTIC DISORDERS

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Background: Previous research has shown that negative symptoms inversely predict about a third of the variance in quality of life in schizophrenia-spectrum disorders. The literature shows significant relationships between social functioning, negative symptoms, and quality of life. The current study aimed to examine the combined utility of social functioning, social skills, and negative symptoms in predicting quality of life in individuals with psychotic disorders.

Methods: Thirty-five individuals with psychotic disorders and thirty non-psychiatric controls completed measures of social functioning (Global Functioning: Social Scale), social skills (Social Skills Performance Assessment), negative symptoms (Positive and Negative Syndrome Scale- Negative Scale), and quality of life (Quality of Life Scale). Stepwise multiple regression analyses were used to examine whether quality of life can be predicted by social functioning, social skills, and negative symptoms.

Results: As expected, the control and psychosis groups differed significantly on measures of social functioning, social skills, negative symptoms, and quality of life (all p<.001). In the psychosis group, social functioning, social skills, and negative symptoms together accounted for 81% of the variation in quality of life [F(3, 31) = 43.03, p<.001]. In the control group, social functioning and negative symptoms together accounted for 67% of the variance in quality of life [F(2, 19) = 19.14, p<.001]. In both groups, social functioning was the strongest predictor, accounting for 58% of the variance in the psychosis group and 56% in the control group.

Discussion: Our findings suggest that social functioning, social skills, and negative symptoms account for about four-fifths of the variance in quality of life in psychotic disorders. Social functioning accounted for over half of the variance in both groups. Assuming the goal of treatment is to improve individuals' quality of life, future interventions should target the amelioration of social functioning deficits in psychotic disorders.

S133. PREFERENCES FOR CHARACTERISTICS OF ORAL ANTIPSYCHOTIC TREATMENTS: SURVEY RESULTS OF PATIENTS LIVING WITH SCHIZOPHRENIA

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Background: Oral antipsychotic treatments are often prescribed to manage schizophrenia (SZ). While effective in treating SZ symptoms, oral antipsychotics are associated with various side effects, including weight gain and sexual dysfunction. The goal of this study was to assess patients' preferences for characteristics of oral antipsychotics. Further, this study explored tradeoffs that patients may make between treatment efficacy and tolerability.

Methods: A cross-sectional online survey was designed to collect patient preference data using a discrete choice experiment (DCE). The DCE consisted of a series of choice questions between pairs of hypothetical oral antipsychotics characterized across five attributes: efficacy (i.e., improvement in symptom severity), weight gain over six months, sexual dysfunction, risk of sedation, and akathisia. The survey was pretested among fifteen people with SZ to ensure comprehension and understanding of the DCE and other survey questions. The final survey was administered to US adults with a self-reported physician diagnosis of SZ. A random parameters logit model was used to estimate preference weights and to explore patients' acceptability of treatment tradeoffs.

Results: A total of 144 respondents with SZ completed the survey (mean age of 41 years, 50% female, 69% White). Approximately 44% of respondents were diagnosed with SZ within five years of survey participation. When asked about SZ symptoms at their worst in the past week, 27% reported their symptoms to be severe, 45% reported moderate symptoms, and 28% reported mild to no symptoms. Most respondents experienced side effects assessed in the DCE with a previous treatment, including weight gain (85%), sexual dysfunction (75%), sedation (82%), and akathisia (71%).

Symptom improvement was the most important attribute across those included in the DCE (relative importance=31%). Sexual dysfunction (23%) and weight gain (21%) were the two most important side effects respondents wanted to avoid, followed by sedation (16%). Akathisia was considered the least important attribute to avoid (8%) among those included in the DCE. Respondents preferred treatments associated with 0, 4, or 7 pounds of weight gain significantly more than treatments associated with 11 pounds of weight gain over six months of treatment.

Respondents were willing to accept an increase in weight of 9 to 10 pounds over six months for the smallest improvement in symptom control as assessed in this study (one incremental step of improvement of disease severity). For the largest improvement in symptom control (two incremental steps of improvement in disease severity), respondents were willing to accept an increase in weight of more than 11 pounds over 6 months (the maximum weight gain included in the DCE). In addition, respondents were willing to accept higher than a 25% risk of sedation for any incremental improvement in symptoms assessed in the DCE.

Discussion: In this survey, treatment efficacy was the most important attribute of oral antipsychotics endorsed by respondents with SZ; sexual dysfunction and weight gain were endorsed as the two side effects patients most wanted to avoid. Respondents were willing to accept some weight gain as a side effect for better efficacy (greater improvement in symptoms).

As oral antipsychotics have different efficacy and tolerability profiles, it is important to understand what patients value in a treatment and how they balance the benefits and risks of different treatments. Patient preference research may be a valuable tool to incorporate patient voice and inform treatment decision making.

S134. THE EFFECTS OF ANTIPSYCHOTIC DISCONTINUATION OR CONTINUATION ON THE PROCESS OF PERSONAL RECOVERY IN REMITTED FIRST-EPISODE PSYCHOSIS PATIENTS – SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Background: Reviews on antipsychotic discontinuation following symptomatic remission of patients with first-episode psychosis have been focused on medical outcomes such as psychotic relapse. However, the impact of such practice on the process of achieving personal recovery, the most important outcome for patients, is unknown. Personal recovery can be defined as an individual process towards achieving a satisfying life despite limitations imposed by mental illness. Although psychotic remission and recovery are related concepts to some degree, they are far from synonymous. Patients may have persistent psychotic symptoms and still achieve personal recovery. Current clinical guidelines recommend using a shared decision-making process to decide on antipsychotic discontinuation or not, but knowledge on the outcome of personal recovery is crucial for stakeholders to ensure the quality of such process. This meta-analysis aims to determine the effects of antipsychotic discontinuation in comparison to antipsychotic continuation on personal and functional recovery in remitted first-episode psychosis patients. The effect of antipsychotic discontinuation on different side effects and quality of life were also sought.

Methods: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (Ovid), Embase, and PsycINFO were searched on October 27, 2022, with no date or language restrictions. The search strategy was elaborated using synonyms for "first-episode psychosis," "discontinuation" and "antipsychotic" in both free-text terms and controlled vocabulary with the support of an information specialist. All randomized controlled trials evaluating the effect of antipsychotic discontinuation in patients with remitted first-episode psychosis were selected. Risk of bias was evaluated with the Cochrane risk-of-bias tool 2 and the certainty of evidence was assessed with GRADE. A random-effect model with an inverse-variance approach was used to conduct the meta-analysis.

Results: 2185 studies were screened for eligibility and 8 studies were included (n = 560). No studies measured the effect of antipsychotic discontinuation on personal recovery and two studies measured functional recovery, defined as a composite outcome of both symptom remission and good functioning. Patients in the discontinuation group were more likely to attain functional recovery (RR 2.36; 95% CIs: 1.24, 4.51; I2=0%; n=128; k=2). However, no statistically significant difference was observed for the functioning, the positive symptoms, employment, and quality of life outcome. Fewer trial dropouts due to adverse drug reactions were observed in the antipsychotic discontinuation group than in the treatment as usual group (RR 0.39; 95% CIs: 0.18, 0.84; I2=0%; n=250; k=3).

Discussion: Although personal recovery is the most important outcome for patients, no published or ongoing antipsychotic discontinuation trial in remitted first-episode psychosis included personal recovery as an outcome. The observed positive effect of antipsychotic discontinuation on functional recovery come from only two studies with high methodological bias and with possible publication bias. Thus, it was graded with very low certainty evidence. Also, the lack of observed difference for the functioning, positive symptoms and employment outcomes consolidates the idea that the true effect of antipsychotic discontinuation on recovery is probably different. More patient-reported outcome measures, such as personal recovery, quality of life and information on drug side effects, need to be reported in antipsychotic discontinuation trials to help stakeholders in the decision to discontinue or not antipsychotics.

S135. GLOBAL IMPROVEMENTS AND PSYCHIATRIC STABILITY IN ADULTS WITH TARDIVE DYSKINESIA AND SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER: POST HOC ANALYSES OF TWO LONG-TERM VALBENAZINE STUDIES

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Background: Tardive dyskinesia (TD) is a persistent and potentially disabling movement disorder associated with prolonged exposure to dopamine receptor blocking agents (e.g., antipsychotics). Effective and comprehensive TD treatment requires reducing patients' abnormal involuntary movements while maintaining their psychiatric stability. This can be especially challenging when patients have complex psychiatric conditions that require multiple medications, such as schizophrenia or schizoaffective disorder. The clinical trials of valbenazine, which is approved for the treatment of TD, were conducted in participants who had a primary psychiatric disorder (i.e., schizophrenia, schizoaffective disorder, or mood disorder). To assess long-term TD improvements and psychiatric stability in participants with TD and schizophrenia/schizoaffective disorder, post hoc analyses were conducted using data pooled from two studies (KINECT 3 and KINECT 4) in which participants received valbenazine (40 or 80 mg) once daily for up to 48 weeks.

Methods: Data were pooled and analyzed from KINECT 3 and KINECT 4 participants with TD and schizophrenia/schizoaffective disorder who completed 48 weeks of study treatment. Concomitant, stable-dose medications were allowed for maintenance of psychiatric and medical conditions. Global improvement was based on the percentage of participants who achieved response thresholds of "minimally improved" or better (score ≤3) or "much improved" or better (score ≤2) at Week 48, as assessed using the Clinical Global Impression of Change-Tardive Dyskinesia (CGI-TD) and Patient Global Impression of Change (PGIC). Psychiatric stability was monitored using the Positive and Negative Syndrome Scale (PANSS) and the Calgary Depression Scale for Schizophrenia (CDSS). Suicidal ideation/behavior was monitored using the Columbia-Suicide Severity Rating Scale.

Results: Two hundred and nine participants with TD and schizophrenia/schizoaffective disorder completed 48 weeks of study treatment in KINECT 3 or KINECT 4 and were included for analysis. Long-term global improvements with valbenazine (40 and 80 mg) were observed, with >90% of valbenazine-treated participants having a clinician-reported (CGI-TD=94.3%) or patient-reported (PGIC=91.9%) rating of "minimally improved" or better at Week 48. Moreover, >75% of valbenazine-treated participants had robust global improvements, as

indicated by CGI-TD (79.7%) or PGIC (78.0%) ratings of "much improved" or better. Mean changes from baseline to Week 48 for PANSS scores (positive symptoms [-0.7], negative symptoms [0.6], general psychopathology [-1.9], total [-3.2]) and CDSS total score (-0.5) indicated psychiatric stability was maintained throughout valbenazine treatment.
Discussion: Pooled analyses from two 48-week studies indicate that participants with TD and a primary diagnosis of schizophrenia/schizoaffective disorder who received long-term treatment with once-daily valbenazine met rigorous thresholds for clinician- and self-reported global improvement while maintaining their psychiatric stability.

S136. IMPLEMENTING COGNITIVE AND REHABILITATION PSYCHOSOCIAL CENTERS IN FRANCE: THE FRENCH SECRET SAUCE IN A REGIONAL NETWORK

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Background: The pioneer French speaking adult clinical psychiatrist associated with the AFRC describe the "secret French sauce" allowing the implementation of Cognitive Remediation (CR) care in the regions. It is a common language among all health professionals, users, families, a timing and a leadership.
In 2019, the French Ministry of Mental Health has structured the offer of PsychoSocial Rehabilitation (PSR) care in the national territory based on the pioneering French Centers for CR and PSR (Lyon, Paris, Clermont de l'Oise, Lille, Dijon, Limoges, Fleury-Les-Aubrais) and according to international data (ANAP, mars 2019).

The Ministry of Health recommends PSR care combines specific tools: cognitive remediation, therapeutic education programs, care for caregivers and a recovery-oriented posture. PSR care must be accessible and close to users, multi-professional, integrative, personalized after an assessment needs-resources-skills. At the same time a national resource center (CRR LYON) was funded by the Ministry of Health to promote a national network including training and research. The France's Regional Health Agency (RHA) must decline this care organization in each french region.

Methods: The aim of the presentation is to show how we support the implementation of PSR in the HAUTS de FRANCE region (population of 6 million, area of 31813 Km2) noticed by its heterogeneity of diversity, density, access to care.
A "regional secret sauce" inspired by the national recipe of "the secret French sauce" and accompanied by "Le Chef" From CRR LYON has been cooked. Professionals from the pioneer centers CRISALID-HDF (CHI) of Clermont de l'Oise, ESM MGEN of Lille and the department of psychiatry Universitary Hospital of Lille carried out pluri-professional exchanges of practices, training, sharing of transnosographic therapeutic education and assesment tools. In 2020, we have been then labeled as support centers by the HAUTS de FRANCE's RHA to implement homogeneous PSR clinical practice centers close to users in all the region (personalized training and tutoring). These support centers were linked with the CRR Lyon for training and research (national PSR cohort study).

Results: In 2022, 30 PSR centers have been created and distributed in all the region (urban, sub-urban, rural territories). All these centers offer a personalized and integrative recovery-oriented program to people suffering from schizophrenia spectrum disorder (according to DSM 5 criteria) and their caregivers, at any stage. It combines several modules of psychoeducational (therapeutic education), CR and cognitive behavourial therapy, after a global individual assessment (clinical, cognitive, functional). A personal care plan of PSR is then created with all the care partners around the patient. We created also a free regional website for users and professionals and professional sessions exchanges of practices (between neuropsychologists; nurses and social workers; peer helpers) as well academic training for clinicians.
Discussion: PSR cares is part of non-drug care essential for people suffering from schizophrenia. It is challenging to implement these specifics cares for users, in a personalized and integrative recovery-oriented way. We propose an implementation method « a regional french HAUTS de FRANCE method » based first on a national mental health policy law, a national PSR network but above all on a regional network associating health professionals, users, families, academics and researchers. This method implies personalized training and tutoring taking account all the local specificities. Further studies must be conducted in order to assess this implementation method in improvement and development of PSR cares for users and health professionals.

S137. IMPACT OF PROFAMILLE, A MULTIFAMILY PSYCHOEDUCATIONAL PROGRAM, ON HEALTH CARE FAMILY CAREGIVERS AND PEOPLE SUFFERING FROM SCHIZOPHRENIA

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Background: Psychoeducation programs for caregivers are essential to support psychosocial rehabilitation in patients with severe psychiatric disorders. But these programs must be assessed not only in order to improve health care in family caregivers but also to improve the disease of people suffering from schizophrenia. Data from the literature report high rate risk of attempted suicide or suicide among people suffering from schizophrenia in comparison with general population. Likewise, relapses and hospitalization duration represent poor prognosis factors with an increased risk of mental disability. The aim of the presentation is first to describe the program then to show the impact of this specific psychoeducational program on health care family givers, attempted rate suicide and number of days of hospitalization of the patients
Methods: The Profamille multifamily psychoeducational program for family caregivers with a loved one suffering from schizophrenia in its V3 version is the program used in many French speaking countries including Algeria, Belgium, France, Morocco and Switzerland. It is delivered by more than 80 teams in these countries with more than 6000 caregivers registered in this program between 2009 and 2022. This program was created in Quebec in 1987 and has been the object of regular improvement thanks to a systematic evaluation of the Results: obtained and a sharing of the teams that run it. The improvements are co-constructed with professionals and family caregivers involved in its delivery. All the caregivers are assessed with several socio-demographic, clinical and psychological tools during all the program,

including assessments regarding their relative ill mental health.The V3 version of the program consists of 2 consecutive modules, one of 14 sessions over 6 months, the second of 5 sessions over 2 years, with sessions composed of 12 caregivers for two specifically trained professionals or caregivers. The data presented are from the V3.2 version with recruitment between 2012 and 2018.
Results: Out of 1200 participants (72% female, mean age 59 years, standard deviation 8.8) with matched data for the different time points, 6.4% described that their ill relative had attempted suicide in the 12 months preceding participation in the first module and this rate fell to 2.6% in the 12 months following participation in this module ($p<0.00001$).The number of days of hospitalization of their relatives decreased from an average of 48 days to 28 days 1 year later (40% reduction, $p<0.0001$). Caregivers' mood measured with a CESD self-questionnaire showed a rate of 51% above 16 at the beginning of Module 1, 29% at the end of Module 1 and 28% one year later ($p<0.00001$).The number of caregivers hospitalized in the year before the program was 27% and it dropped to 22% in the year following the 1st module ($p<0.006$).
Discussion: In conclusion, this is the first family psychoeducational program which improves the mood and the health of the family caregivers, reduces suicide attempts and the number of days of hospitalization of the patient. What's more this program is very easy to implement following a structured training. It is currently being translated into Arabic and Spanish languages. Then further studies must be conducted including group controls to confirm these first results.

S138. MULTIPLE COGNITIVE-BASED MECHANISMS UNIQUELY MEDIATE THE RELATIONSHIP BETWEEN EXPERIENCES OF RACIAL DISCRIMINATION AND SUBCLINICAL PARANOIA AMONG DIFFERENT RACIAL GROUPS

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Background: Experiences of racial discrimination (RD) are considered chronic stressors that increase risk for positive psychosis-spectrum symptoms, particularly subclinical paranoia, in individuals of marginalized racial identities. However, the mechanisms underlying the relationship between RD and subclinical paranoia have been under examined, and further, have not been studied simultaneously in a multiple mediation model. Several cognitive-based mechanisms previously found to mediate the relationship between trauma exposure and positive psychotic-like experiences (PLEs) could also contribute to the RD-subclinical paranoia relationship, including increased perceived stress, negative self/other schemas, increased dissociative experiences, and external locus of control. We hypothesized these mechanisms would similarly mediate the RD-subclinical paranoia and RD-PLE relationships, particularly in individuals of marginalized racial identities.
Methods: Undergraduate students (N=1,614) at a racially diverse urban university in the United States completed several self-report assessments, including RD with the Experiences of Discrimination instrument, subclinical paranoia and positive PLEs using the Prodromal Questionnaire, perceived stress with the Perceived Stress Scale, negative self/other schema using the Brief Core Schema Scale, dissociative experiences with the Dissociative Experiences Scale, and locus of control using the Rotter Internal-External Scale. After assumptions were met, multigroup multiple mediation analyses were conducted in PROCESS Macro in SPSS stratified by race, with RD as the independent variable, dependent variables subclinical paranoia and positive PLEs, and all potential mediator variables in the model. The indirect

effect was tested using bootstrapping with 5,000 samples. Significant resultsare indicated by the 95% CI of the effect not including 0.
Results: Among Asian participants, increased perceived stress significantly mediated the RD-subclinical paranoia (95% CI=0.0051, 0.0334) and RD-PLE (95% CI=0.0278, 0.1398) relationships, and increased negative-self schemas also mediated RD-PLE (95% CI=0.0012, 0.1103). Among Black participants, no mediators were significant among the RD-subclinical paranoia nor RD-PLEs relationships. Among White participants, RD-subclinical paranoia was significantly mediated by increased perceived stress (95% CI=0.0041, 0.0216), negative-other schemas (95% CI=0.0006, 0.0138), and dissociative experiences (95% CI=0.0237, 0.0642). RD-PLE in White participants was also mediated by increased perceived stress (95% CI=0.0218, 0.0922), negative-other schemas (95% CI=0.0009, 0.0361), and dissociative experiences (95% CI=0.1409, 0.3570).
Discussion: To our knowledge, this is the first study to simultaneously examine multiple cognitive-based mechanisms mediating the RD-subclinical paranoia and RD-PLE relationships in Asian, Black, and White participants. Our results suggest that mediators of the relationship between experiences of racial discrimination and PLEs may differ by race, with potentially important clinical implications for treatment of individuals experiencing subthreshold psychotic symptoms following these experiences. Our findings also suggest some overlap with previous findings linking a history of trauma to PLEs, further bolstering the idea that experiences of racial discrimination may result in similar sequelae as traumatic experiences. Further post-hoc analyses will explore ethnicity, religion, and immigration status in White participants as potential confounding variables.

S139. REMOTE COGNITIVE ADAPTATION TRAINING: FEASIBILITY AND PRELIMINARY RESULTS

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Background: Cognitive Adaptation Training (CAT) is an evidence-based treatment that uses environmental supports such as signs, text messages, checklists, smart pill containers and the organization of belongings to bypass cognitive and motivational impairments and to cue and sequence adaptive behavior in the home or work environment. CAT has been shown to improve community tenure, motivation, targeted behaviors such as adherence and IDLs and global functional outcomes. Because CAT is only available near centers with trained practitioners, we worked to develop and test a remote version of CAT. Given that CAT is not a talk therapy and is dependent on interventions established in the home, it was not clear whether remote treatment (RCAT) using this model was feasible. In an earlier study of 204 Medicaid recipients with serious mental illness, in person and RCAT were equally preferred after participants were provided with a description of the treatments. 78% and 87% of individuals said they would accept CAT or R-CAT respectively if offered the day of the survey.
Methods: We describe data from a follow up study in which 56 Medicaid members received either CAT or R-CAT based upon preference or assignment to treatment condition for 6-months. Assessments were conducted monthly (pill counts conducted in the home or through video conferencing) or every other month (rating scales) to examine changes in adherence, habit formation and automaticity (as potential mechanisms of action) and functional outcomes (social and occupational functioning scale) over time.
Results: While in the earlier survey indicated high levels of acceptance, recruitment from Medicaid members for actual participation in a research study examining these treatments provided at no cost found that only 23% of all eligible members who were contacted agreed to

participate. As the COVID-19 pandemic wound down, individuals stated they were too busy and overwhelmed to participate. For those who did enroll, results demonstrated improved adherence across the 6 months of follow up for both groups. There was also an improvement in the Self-Reported Habit Index indicating the formation of habit or automatic behaviors. Social and Occupational Functioning improved within the sample as a whole over time and also within the in-person CAT group.
Discussion: Remote CAT is feasible, can produce similar results to in-person CAT in some domains and would allow CAT to be offered to those who have difficulty accessing traditional services due to transportation or childcare issues or rural dwelling. If people participate in these programs, improvements are observed. It would be important to understand the observed low recruitment rates in this trial given that historically this has not been the case. Increasing motivation to participate would be important for a definitive efficacy trial of R-CAT to have practical value.

S140. THE IMPACT OF ANTIPSYCHOTIC-INDUCED WEIGHT GAIN ON NONADHERENCE IN PSYCHIATRIC DISORDERS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Nonadherence to antipsychotic (AP) medications is a growing problem in severe mental illnesses, including schizophrenia spectrum disorders and bipolar disorder. Decreased adherence to AP medications can lead to exacerbation of mental health symptoms, hospitalizations, and poor outcomes. While antipsychotic-induced weight gain (AIWG) is a reported contributor to nonadherence in psychiatric disorders, a systematic review of the association between AIWG and medication nonadherence has not been previously described. Therefore, the primary objective was to systematically explore the role of weight gain in nonadherence among individuals receiving treatment with APs for an approved mental health indication. The secondary objective was to explore whether APs that cause more weight gain than others, are more likely to lead to nonadherence.
Methods: A systematic search was conducted in MEDLINE, EMBASE, PsychINFO, CINAHL and CENTRAL databases. We reviewed studies which explored nonadherence or discontinuations associated with metabolic adverse events during AP treatment for regulatory body approved conditions (i.e. on-label). The eligibility of studies, along with their respective data extractions and appraisals were independently conducted by two reviewers. A random effects model was utilized for the meta-analysis.
Results: We identified three studies for our primary research question which had data available to conduct a meta-analysis (N=812), all consisting of individuals with schizophrenia-spectrum disorders. When compared to normal weight individuals, those who were overweight or obese had an increased odds of nonadherence to APs (OR 2.59; 95% CI 1.61 - 4.17; $p<0.0001$). Six other studies were included in the narrative summary as they referenced nonadherence due to AIWG but did not have extractable data. The narrative summary supported our meta-analysis by emphasizing that AIWG is a commonly reported reason for nonadherence, particularly with second generation antipsychotics prescribed for schizophrenia spectrum disorders. Additionally, we identified eight studies (N=1960) that addressed the secondary research

question. APs that cause more weight gain led to greater nonadherence when compared to others with less weight gain (OR 2.91; 95% CI 1.77 - 4.77; p<0.0001). A subgroup analysis revealed that there is a significant effect of olanzapine on nonadherence due to weight gain compared to others. However, due to insufficient data, the effect of these APs on other metabolic parameters could not be assessed in depth.
Discussion: This systematic review and meta-analysis suggests that AIWG plays a significant role in medication nonadherence, and that specific APs like olanzapine are more likely to contribute to nonadherence due to weight gain. The finding carries clinical implications, including the possibility that early interventions to mitigate AIWG could help patients adhere to treatment. Additional studies examining AIWG along with other AP-related metabolic adverse effects in relation to medication adherence will be important to confirm these findings.

S141. DATA-MINING ANALYSIS OF MEDIA FRAME EFFECTS ON SOCIAL PERCEPTION OF THE NEW NAME FOR SCHIZOPHRENIA (ATTUNEMENT DISORDER) IN KOREA

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Background: In 2011, Korean neuropsychiatric association renamed schizophrenia from 'mind split disorder' ('Jungshinbunyeolbyung' in Korean) to 'attunement disorder' ('Johyeonbyung' in Korean), in a way to reduce social stigma of schizophrenia. However, there remains elusive consensus that how the renaming effort contributes to changes in the social perception of schizophrenia in Korea. With this regard, we explored whether media frames change the social perception, in ways of respecting or disrespecting patients with schizophrenia before and after the renaming. Specifically, this study targeted news articles related to schizophrenia (i.e. mind split disorder as 'Jungshinbunyeolbyung' in Korean before the renaming and attunement disorder as 'Johyeonbyung' in Korean after the renaming) to identify how the perception of members of society, which may hinder early diagnosis and continuous treatment of schizophrenia, changed from renaming. By investigating the difference in social perception of "mind split disorder" and "attunement disorder" after the revision of the disease name and also elucidating the media effect on the medical use patterns of patients with schizophrenia, it aims to help establish a desirable direction for media reporting stance and also contribute to creating a fair therapeutic environment for patients with schizophrenia.
Methods: This study investigated media keywords related to schizophrenia across the time and medical use patterns of patients with schizophrenia using big data analytics. Firstly, qualitative language analyses were used to elucidate the schizophrenia renaming effect on media keywords deciphering the disease: Latent Dirichlet Allocation (LDA) topic modeling and Term Frequency-Inverse Document Frequency (TF-IDF) are advanced language analytic approaches to reveal media keywords that have significant relevance to a specific word of interest (i.e. schizophrenia). Secondly, quantitative epidemiologic analysis was further performed to elucidate the medical use patterns by patients with schizophrenia according to the frequencies of negative media keywords: Linear regression model was applied to assess the association between the counts of media keywords referring to negative aspects of patients with schizophrenia and the nationwide frequencies of hospital admissions for patients with schizophrenia. Finally, the analysis of social perception of schizophrenia (mind split disorder as 'Jungshinbunyeolbyung' before the renaming and attunement disorder as 'Johyeonbyung'

after the renaming) was performed using both macroscopic and microscopic linguistic analyses.
Results: LDA topic modeling shows the significant increase in the media topics of the conflict frames implicating schizophrenia in crimes regardless of the schizophrenia names. TF-IDF weight analysis indicates that media frames' focus shifted from the medical aspects to the conflict aspects on schizophrenia regardless of renaming. There was an association between media frames containing negative aspects of schizophrenia and medical use patterns of nationwide patients with schizophrenia. The media used significantly more negative keywords describing schizophrenia after the Gangnam homicide case committed by a patient with schizophrenia compared to before the case.
Discussion: This study shows the consistent findings that social perception of schizophrenia has maintained the negative stereotypes of those patients who are described as being implicated in violent crimes. This negative media frame on schizophrenia has been especially emphasized and fortified through cases of crimes of a few patients with schizophrenia, and in turn associated with the adverse impact on the general medical use patterns of nationwide patients with schizophrenia. Of note, the effort of the revision of the schizophrenia name from mind split disorder to attunement disorder was found diluted by those negative media frames keeping the stereotypes of schizophrenia. Thus, the cooperative approaches of establishing the corrective media frames and revising the disease name are required to improve the stigmatization of schizophrenia.

S142. A LONGITUDINAL EXAMINATION OF PSYCHIATRIC AND FUNCTIONAL OUTCOMES IN BLACK AND WHITE U.S. VETERANS WITH AND WITHOUT PSYCHOSIS DURING THE COVID-19 PANDEMIC

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Background: The coronavirus disease (COVID-19) pandemic continues to disproportionately impact marginalized communities which has resulted in higher infection and mortality rates among Black Americans. These disparities occur against the backdrop of longstanding systemic inequities in healthcare, housing, employment, and education. According to the double jeopardy hypothesis, the disproportionate impact on Black Americans could lead to worse psychiatric and functional outcomes for vulnerable populations such as Black military Veterans with psychotic disorders. The present study examined whether there were racial differences in psychiatric symptoms and functional outcomes between Black and White Veterans with and without psychosis over the course of a 15-month period during the COVID-19 pandemic.
Methods: Participants were recruited through the U.S. Department of Veterans Affairs (VA) administrative databases and by contacting Veterans who have participated in previous lab studies. Participants were administered self-report questionnaires and interviews over the phone by trained research staff at five assessment periods between May 2020 through July 2021. The sample consisted of 46 Black Veterans and 26 White Veterans with a psychotic disorder diagnosis as well as 30 Black Veterans and 37 White Veterans without psychosis. Research staff rated participants' social integration, work/role productivity, and independent living. Participants completed self-report measures of depression, anxiety, loneliness, and

obsessive-compulsive symptoms. Measures were completed at all study time points. Analyses consisted of time varying coefficient models implemented using generalized additive models structure conducted in R.
Results: Family integration was higher for Black Veterans with ($p = .03$) and without ($p = .04$) psychosis compared to their White Veteran counterparts across all time points. There were no significant racial differences in either the control or psychosis groups in social integration, role functioning, or independent living. There were also no significant racial differences in depression, loneliness, anxiety, or obsessive-compulsive symptoms in Veterans with or without psychosis.
Discussion: Black Veterans with and without psychosis had better family integration compared to White Veterans during the first half of the pandemic. There were no significant racial differences in any psychiatric symptom domains. These findings are inconsistent with the double jeopardy hypothesis, in which we would expect Black Veterans with psychosis to have significantly worse outcomes. Expected differences by race could have been mitigated by wrap-around mental health and social services offered by the Veterans Administration. Further investigations into U.S. non-Veteran samples would allow us to better understand the protective effects that these services may have had on mental health and functional outcomes for vulnerable Veterans.

S143. MODELING THE MOMENT-TO-MOMENT DYNAMICS BETWEEN PARANOIA AND LONELINESS: AN EXPERIENCE SAMPLING STUDY

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Background: Paranoia exists as a phenomenological continuum in the general population, encompassing a range of expressions from milder forms as ideas of social reference to clinically significant psychotic symptoms as persecutory delusions. While there is robust evidence supporting the association between paranoia and loneliness, their temporal relationship is not clearly understood. It has recently been suggested that loneliness may be both an antecedent and a consequence of paranoia, although these bi-directional dynamics were not often considered. In addition, negative schemas about self (e.g. 'I am weak') and others (e.g. 'Others are hostile'), which are theorized to drive the development and maintenance of both paranoia and loneliness, may contribute to these dynamics. As both paranoia and loneliness wax and wane over time, their fluctuations can be captured by repeated self-reports in daily life (i.e. experience sampling method, ESM). Using ESM, the present study examined the moment-to-moment dynamics between paranoia and loneliness in a sample of non-clinical young adults, who were at a life stage most vulnerable to paranoia. We also examined if negative-self and -other schemas were associated with the strength of these dynamics.
Methods: Participants aged 18–30 were recruited either from the subject pool of introductory psychology courses or campus mass email. Consented participants were screened with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-DSM-IV). Those without any psychiatric diagnosis completed a baseline survey, which included the Brief Core Schema Scale to assess their negative-self and -other schemas. They were then asked to fill in the same ESM questionnaire measuring levels of momentary paranoia and loneliness on an app installed on their mobile phone ten times per day over six days. Only participants who completed at least one-third of the ESM questionnaires were included in data analysis. Dynamic structural equation modeling with Bayesian estimation was applied to estimate the within-person cross-lagged effects from loneliness to paranoia and vice versa, taking into account their own carrying-over (or autoregressive) effects. The cross-lagged and autoregressive effects were

allowed to vary between individuals (i.e. random effects), which were correlated with individuals' levels of negative-self and -others schemas. The estimates of model parameters were considered as statistically significant if their 95% credible intervals (CI) exclude zero.
Results: The final sample consisted of 134 participants (58.2% female, mean age= 20.3 (SD= 2.91)). The mean compliance rate was 72.1% (SD = 0.16). There were significant autoregressive effects of paranoia (β= 0.49, 95% CI [0.28, 0.71]) and loneliness (β= 0.69, 95% CI [0.45, 0.95]). We found a significant within-person cross-lagged effect from loneliness to paranoia (β = 0.27, 95% CI [0.08, 0.47]), but not vice versa (β= 0.18, 95% CI [-0.03, 0.40]). Across individuals, negative-other schema was associated with the autoregressive effects of paranoia (r= 0.40, 95% CI [0.22, 0.56]) and loneliness (r= 0.24, 95% CI [0.03, 0.45]), whereas negative-self schema was associated with the autoregressive effect of paranoia (r= 0.28, 95% CI [0.08, 0.45]) only. Negative-self and -other schemas were not associated with any cross-lagged effects.
Discussion: We found that momentary loneliness precedes the increase in momentary paranoia in daily life, supporting loneliness as an antecedent (rather than consequence) of paranoia. Negative schema about others may contribute to the perpetuation of both paranoia and loneliness in daily life. These findings warrant future replication in clinical samples.

S144. ROUTINE CEREBROSPINAL FLUID PARAMETERS IN FIRST-EPISODE PSYCHOSIS: EFFECTS OF SEX AND FAMILY HISTORY OF PSYCHIATRIC DISORDERS

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Background: Previous studies have reported associations between cerebrospinal fluid (CSF) biomarkers that involve bioenergetics systems (e.g. lactate dehydrogenase [LDH], glucose) and the clinical expression of first episode psychosis. Our main aim was to conduct further exploratory analysis to assess whether sex and family history of psychiatric disorder are associated with different CSF concentrations of LDH, glucose and proteins.
Methods: We studied 95 inpatients (58.9% men, 41.1% women) with a first episode psychosis. All participants were informed about the nature of the study, which was approved by the local Ethics Committee, and signed a written informed consent. A lumbar puncture was performed at index admission (baseline) to study the CSF parameters (glucose, total proteins, lactate dehydrogenase [LDH]). The family history of psychiatric illness was assessed by semistructured interview by a psychiatrist. Statistical analyses were performed with SPSS v. 25.0. Total protein and LDH concentrations were log transformed (ln) for reducing skewness. General linear models (ANCOVA) were used for comparing CSF concentrations between groups. Gender and family history of psychiatric illness were considered fixed factors. Age and cannabis use were considered covariates. Significance was set at $p<0.05$.
Results: Of all patients, 58 (61.1%) had a positive family history of psychiatric disorders. Patients with a family history of psychiatric disorders reported more cannabis use (58.6% vs 25.1%, p= 0.026). There were no sex differences in the proportion of cannabis consumption nor a family history of psychiatric disorders. In the ANCOVA analyses, we found a significant interaction between sex and family psychiatric history (F= 4.002, p= 0.048): in men, those with a positive family psychiatric history reported lower CSF LDH concentrations (24.7 +- 13.2)

when compared to those without a family psychiatric history (33.2 +- 21.2); in contrast, women with a positive family psychiatric history had slightly higher CSF LDH concentrations (28.9 +- 12.0) than those without a family psychiatric history (25.7 +- 13.1). An interaction between sex and family psychiatric history was not found for CSF glucose or CSF total proteins.
Discussion: Our study suggests that family psychiatric history and sex are two variables that contribute to significant differences in CSF LDH concentrations in patients with a first episode psychosis. The more pronounced effect of family psychiatric history in men, with lower CSF LDH concentrations in men with a history of psychiatric disorders, suggest that there are sex differences in the risk of a dysregulation of LDH. Previous post-mortem studies have found a dysregulation of the LDH complex (LDHA/B) in the anterior cingulate cortex (ACC), cortex callosum (CC) and hippocampus of patients with schizophrenia. Our findings might indicate a greater vulnerability to a LDH dysregulation in men with a higher genetic loading for psychiatric disorders. Although speculative, there might be protective factors in women that counterbalance the risk observed in men.

S145. PREDICTING RELAPSE IN PSYCHOSIS USING SPEECH ANALYSIS

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Background: Risk of relapse after the first episode of psychosis is high, yet predicting relapse remains challenging. Recent developments in natural language processing have proven effective in a range of applications in psychosis, including early symptom recognition and (differential) diagnosis. It is not known whether this technology is also accurate in predicting relapse.
Methods: The current study uses a subset of patients enrolled in a Dutch nationwide randomized controlled trial of continuation versus discontinuation of antipsychotic medication in patients in remission after a first episode of psychosis. Patients were aged 16-55, native speakers of Dutch and were in remission for 3-6 months. Speech recordings were made at baseline, after 3 and 6 months, with a total follow-up of 24 months. Speech was analyzed for acoustic features using OpenSMILE. The main analysis was the prediction of relapse versus non-relapse within 3 months after a speech recording, based on the speech analyses. The analyses were done with random forest algorithms, using 10-fold cross-validation.
Results: Of 81 participants currently enrolled in the study, 21 patients relapsed within 3 months after a speech recording versus 24 patients who did not relapse within the follow-up period. 15 patients were lost to follow-up and 21 relapsed outside the 3 month time-window. The relapse versus non-relapse groups did not differ in age ($F(1,43)=.719$, $p=.401$), education level ($F(1,43)=.009$, $p=.927$), or gender ($\chi2=1.435$, $p=.231$). Based on the speech analyses, we identified a machine-learning classifier that had an 80.8% accuracy in predicting relapse.
Discussion: Psychosis relapse can be accurately predicted using an automated machine-learning speech classifier 3 months in advance.

S146. VISUAL FIXATION STABILITY: A SIMPLE TASK DETERMINES IMPAIRMENT IN ANTIPSYCHOTIC-NAïVE SCHIZOPHRENIA

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Background: Eye movement abnormalities are suggested neuro endophenotypes of schizophrenia (SCZ). Visual fixation stability measures the ability to maintain the gaze on a stationary object. It is one of the basic substrates of the visuoperceptual process with the involvement of a wider front-occipital-parietal neural network. We studied the comparative fixation stability and influence of the distance and laterality of distractor on it in antipsychotic-naïve/free SCZ, SCZ first-degree relatives (FDRs) and healthy controls (HC).

Methods: Monocular high-frequency eye tracking data (using Eyelink 1000, SR Research®, Canada) was recorded during the fixation stability task in 68 antipsychotic-naïve/free SCZ, 49 FDRs and 76 HCs. The task required maintenance of gaze on 0.50 central circular target for 5 seconds while ignoring the identical distractor at 1.430 (near) or 2.860 (far) on either of the sides. Using Quade's method, rank ANCOVA was performed over different fixation stability measures with age as a covariate followed by rank R-MANCOVA with posthoc Bonferroni tests. Laterality and distance of the distractors were used as with-in subject factors, and gender as a nuisance variable.

Results: There was a significant impairment in SCZ in all of the stability measures viz., frequency ($F=5.09$, $p<0.01$) and duration ($F=3.85$, $p=0.02$) of fixation, frequency ($F=3.35$, $p=0.04$) and amplitudes ($F=5.1$, $p<0.01$) of saccades, and scanpath length ($F=6.67$, $p<0.01$) compared to HC. There was a statistically significant Distance*Group interaction ($F=1.9$, Wilk's $\lambda= 0.9$, $p=0.04$, partial $\eta2=0.51$) controlling for age, but there was no significant effect of laterality ($F=1$, Wilk's $\lambda= 0.95$, $p=0.44$, partial $\eta2=0.03$) of the distractor.

Discussion: Fixation stability impairment seen in antipsychotic naïve/free SCZ but not FDRs reflects its close association as a marker of the disease process uncontaminated by the effects of medicines. Near distractors tend to elicit more impairment in fixation stability in SCZ compared to FDRs and HC, who had lesser fixation stability with far distractors. The fixation stability task is a promising, simple and ecologically valid experiment that can offer greater insights into the perceptual and neuropsychological processes in schizophrenia. Further studies on the specificity of the findings with SCZ, its neural basis and its response to treatments are needed.

S147. METABOLOMIC SIGNATURES IN ANTIPSYCHOTIC - NAïVE PATIENTS WITH PSYCHOSIS: A SYSTEMATIC REVIEW

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Background: The metabolome, or small molecule profile of biosamples, reflects the end Results: of genetic and environmental processes and can inform our understanding of schizophrenia spectrum disorders (SSDs). Applying metabolomics, or the study of the metabolome, to schizophrenia research could lead to the identification of biomarkers of illness and disease mechanisms. Although several reviews have examined metabolites in individuals with SSDs as compared to non-psychiatrically ill controls, existing reviews on the topic have included individuals treated with antipsychotics (APs), and or/ chronically ill patients. Given the potential confounding effects of illness-related lifestyle factors, which cumulate over illness

duration, as well as the effects of treatments (i.e., AP drugs) on metabolite signatures, the currently existing synopsis of this literature may not accurately represent metabolite differences inherent to SSDs. To address current gaps in knowledge, we conducted a systematic review of existing literature examining metabolomic signatures focusing on AP-naïve individuals. The objective of this systematic review was to identify the metabolomic signatures of AP-naïve individuals with SSDs in comparison to healthy controls (HCs).
Methods: A systematic search was conducted in the Ovid MEDLINE, Embase, PsycINFO, EBSCO's CINAHL, and Scopus databases. Only case-control studies were investigated, and no restriction regarding publication date was imposed for the search. Three conceptual domains, "psychotic spectrum disorders", "AP naïve status" and "metabolomics" were implemented into the search strategy.
Results: Several classes of metabolites were found to be significantly different between AP-naïve individuals with SSDs and HCs across included studies. Interestingly, the majority of metabolites which differentiated patients from controls were found to be downregulated in AP-naïve individuals, including fatty acids and steroids.
Discussion: Metabolomics appears to be a promising tool for identifying metabolic pathways that may be dysregulated in SSD AP-naïve individuals as compared to non-psychiatrically ill controls. Further research is needed to understand the relevance of perturbations in these pathways in relation to illness psychopathology and course in order to leverage these findings to help guide the development of disease biomarkers and potential targeted interventions.

S148. HOW IS CITY LIVING ASSOCIATED WITH PSYCHOSIS? FINDINGS FROM A NOVEL DATA LINKAGE OF 612,988 PEOPLE FROM AN URBAN AND ETHNICALLY DIVERSE AREA

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Background: Urban areas often show a higher incidence of psychotic disorders, but the underlying reasons are complex. Using a large-scale case-control design based on a novel data linkage between mental health records and the UK census sampled from a diverse urban area, we assessed the association between degrees of population density, urban social determinants, and affective/non-affective
Methods: The SocioEconomic Predictors of Mental Disorders (SEP-MD) project dataset comprises of data extracted from electronic health records (EHR) from the South London and Maudsley National Health Service Foundation Trust (SLaM). SLaM Trust is the principal provider of secondary mental healthcare to a catchment of 1.3 million people. In collaboration with King's College London, SLaM and the UK Office for National Statistics, these EHRs were individually linked to the 2011 UK census.
Cases with clinician-determined diagnoses of non-affective (schizophrenia spectrum) and affective psychoses (bipolar disorder and depression with psychosis) were identified. Population controls were sampled from the surrounding area. 45.38% of records were linked to census records and included in the analysis. We derived inverse probability weights based on age, sex and area deprivation to address potential non-linkage bias.

Urbanicity was assessed as persons per hectare at the smallest UK census administrative area level (1000-3000 residents). We also assessed individual-level socio-demographic factors derived from the census.

Logistic regression models were used to calculate weighted adjusted odds ratios (waOR) to assess the associations, with age and sex as a priori confounders. Robust standard errors were used to account for area-level clustering.

Results: 16,863 cases with psychoses (affective n=5,694; non-affective n=11,169) were identified alongside 596,125 population controls. Cases with psychosis were more likely to live in areas with the highest population density (waOR 1.17 (1.05, 1.30)) when comparing the lowest quintile to the highest. People living in the highest quintile of population density were more likely to have non-affective psychosis (waOR 1.35 (1.20, 1.53)) compared to those in the lowest quintile, while odds of having affective psychosis were lower in more dense areas (waOR 0.86 (0.76, 0.98)). We found that being of Mixed ethnicity (waOR 1.65(1.51-1.80)), Black Caribbean (waOR 1.71 (1.60-1.84)) or Black African (waOR 1.13 (1.05-1.22)) ethnicity was associated with a higher odds of non-affective psychosis (but not affective psychosis), while people of other ethnic minority groups were of lower or similar risk to White British participants. The risk of non-affective psychosis was lower in less deprived areas. Social isolation indicators were associated with higher odds of psychosis (living alone waOR 2.69 (2.57,2.82); divorced/separated/single waOR 3.00 (2.86,3.15)). Being born within the UK (waOR 1.76 (1.69,1.84)) was associated with a higher risk of psychosis, and migrants living in the country for > 10 years were at a significantly higher risk than those living in the country for < 2 years (waOR 4.37 (3.67,5.22).

Discussion: These early Results: highlight associations between urbanicity and psychosis risk in a large-scale urbanised catchment area and suggest the importance of social isolation. Findings relating to migration and ethnicity are generally consistent with previous work but require further exploration. The insight into individual determinants of psychosis provided by the linkage will allow us to explore associations previously only assessed using ecological or smaller studies within the UK.

S149. ASSOCIATION OF A CHILD'S PSYCHOTIC DISORDER WITH INCOME AND EMPLOYMENT OF THEIR PARENTS: A FINNISH REGISTER STUDY

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Background: Psychosis is associated with significant psychological, social and financial burden on the individual and may also affect their family members. Several studies suggest that family members of psychosis patients are particularly vulnerable to distress, depression and anxiety, but few nationally representative studies have attempted to quantify the socioeconomic consequences of a psychotic disorder for the family network. In this Finnish nationwide register study, we estimated associations of a child's psychotic disorder with their parents' annual income and employment status before and after the child's diagnosis.

Methods: We recorded all diagnoses of psychotic disorders (F20–29 based on ICD-10) received at ages 5–25 in Finland in 1994–2017. The first diagnosis of the first child diagnosed in each family was included. We used a pair matched cohort design, where each included child with a psychotic disorder was matched 1:1 to a child without a psychotic disorder and without siblings with a psychotic disorder based on birth year, birth month, geographical region, parents' history of a psychiatric disorder, and parents' educational attainment. Income and employment measures were based on registers gathered by Statistics Finland that cover all legal employment contracts in Finland. We estimated the associations of a child's psychotic disorder with their parents' annual earnings, social income transfers and employment status during a

follow-up of five years before and five years after the child's diagnosis using generalized estimating equations (GEE) with robust standard errors.
Results: In 1994–2017, 18 750 families had at least one child diagnosed with a psychotic disorder at ages 5–25 (n = 2 137 for schizophrenia, n = 16 613 for other psychotic disorders). The average age at diagnosis was 20.3 years (SD = 3.6). During the follow-up of five years before and after the diagnosis, a child's psychotic disorder was consistently associated with a lower level of annual earnings, greater annual amount of received social income transfers and a higher annual probability of unemployment among their parents. These associations were similar across time, suggesting no evidence of change in parents' annual income or employment status since the onset of their child's psychotic disorder. Results: were similar in analyses stratified by disorder type (schizophrenia vs. other psychotic disorders), the child's age at diagnosis (5–10 vs. 11–15 vs. 16–20 vs. 21–25), living situation (the child living with vs. without their parents), parents' history of a psychiatric disorder (psychiatric disorder vs. no psychiatric disorder) and parents' educational attainment (lower secondary or less vs. upper secondary vs. post-secondary or tertiary).
Discussion: The findings from this Finnish register-based study suggest that while parents whose child has a psychotic disorder have a lower annual income, receive more social income transfers and are more likely to be unemployed, the onset of the child's psychotic disorder does not affect the income or employment status of their parents. Further studies are needed to evaluate these associations in populations with different welfare systems and less universal access to health care services.

S150. SOCIAL ISOLATION, ETHNICITY AND ADVERSE OUTCOMES IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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Background: Severe mental illnesses, such as Schizophrenia and Bipolar affective disorder, are chronic conditions associated with high levels of disability, lower occupational functioning, and impaired relationships. Racialised minority groups diagnosed with these disorders may face even greater inequalities and consequently higher levels of social exclusion and impairment. Social and environmental factors are increasingly being recognised as important for modifying the course of illness. Comparative investigations with respect to ethnicity in terms of the distribution of environmental risk factors, and their association with outcomes of social functioning are nevertheless scarce and characterised by small sample sizes.
To address this issue, we utilised a uniquely diverse and large dataset consisting of clinical records linked to the 2011 UK Census. We examined within a cohort of individuals with severe mental disorders the association between social isolation, ethnicity, the interaction between the two, and multiple outcomes of functioning.

Methods: The South London and Maudsley (SLaM) mental health trust is the primary health care provider to 1.3 million individuals resident in a highly urban and ethnically diverse area. We used a dataset which linked patient records from SLaM to the 2011 UK Census, a rich source of individual level sociodemographic data typically absent from the patient record.

We identified 20,537 patient records in SLaM with an incident diagnosis of Schizophrenia or Bipolar Affective disorder prior to 2011, of which 8,930 (43.5%) matched the Census and were used for subsequent analysis. We utilised inverse probability weighting to account for potential biases introduced by clinical records from SLaM not matching the 2011 Census.

We examined social isolation, ethnicity, age of onset, diagnosis type (affective vs. non-affective), history of substance misuse, length of admission (0 days, 1-31 or 31+) as predictors for unemployment, disability and health status through logistic regression models. We fitted interaction terms to determine if the association between social isolation and outcomes varied by ethnicity.

Results: Unemployment (80.4%), disability (67.4%) and poor health (60.5%) were highly prevalent among cohort members. Social isolation was strongly associated with all outcomes after adjusting for all other variables: unemployment (OR 2.0 95% CI 1.7-2.5); poor health (OR 1.6, 1.4-1.8); and disability (OR 2.0, 1.7-2.4). We observed differences between ethnic groups with respect to all outcomes. Racially minoritised groups were more likely to be unemployed than the White British group, but this pattern was not consistent across the other outcomes. Compared to White British individuals, Black African and White Other cohort members less likely to experience poor health (OR 0.62, 0.52-0.75; OR 0.69, 0.55-0.86) or disability (OR 0.65, 0.54-0.78; OR 0.61, 0.49-0.76). We observed an interaction between ethnicity and social isolation for each outcome. Stratified analyses showed that the association between social isolation and each outcome was attenuated among the Black Caribbean (unemployment OR 1.2, 0.9-1.6; poor health: OR 1.2, 0.99-1.5; disability OR 1.5, 1.2-1.8) and African groups (unemployment: 1.3, 0.9-1.4; poor health: OR 1.0, 0.8-1.3; disability: 1.2, 0.9-1.6).

Discussion: Our results highlight the significant social and occupational morbidity experienced by this population and the potential importance of targeting social isolation in improving outcomes. They also suggest that outcomes among Black minority ethnic groups to a larger degree may be influenced by factors other than social isolation.

S151. CONSEQUENCES OF COVID-19 IN PSYCHOSIS SPECTRUM CONDITIONS: EXAMINING ASSOCIATIONS WITH PANDEMIC-RELATED STRESS AND CLINICAL AND FUNCTIONAL STATUS

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Background: The COVID-19 pandemic has led to widespread mental health challenges; however, populations with pre-existing psychiatric conditions may be particularly vulnerable to the impact of this global health crisis. Previous research has shown that individuals with severe mental illnesses display poorer coping abilities during times of disaster (Horan et al., 2007) and a higher likelihood of poor health and functional outcomes following catastrophic events (Franz et al., 2009). Lockdowns and social distancing measures have limited access to support systems, resulting in increased isolation and loneliness. Additionally, disrupted access to healthcare services for severe mental illnesses can further exacerbate psychiatric symptoms and marginalize individuals who already experience greater social and economic inequities. Therefore, the goal of the present study was to characterize the impact of the COVID-19 pandemic on individuals with psychosis spectrum conditions, and identify whether increased pandemic-related stress was associated with clinical and functional variables.

Methods: Study participants (N = 31) were outpatients with a primary psychosis spectrum diagnosis who were referred to a specialized outpatient CBT for Psychosis Service at the Centre for Addiction and Mental Health (Toronto, Ontario). The sample comprised of 17 females (55%) with a mean age of 42.1 (SD = 11.7). An assessment battery was administered over telephone between January and October 2021 and included the following clinician-rated and self-reported measures: depression (CDSS), anxiety (GAD-7), positive psychotic symptoms (PSYRATS), daily functioning (PSP), perceived stress (PSS), and CBT skills (CBTSQ). The Coronavirus Impact Scale (CIS; Stoddard et al., 2021) is a novel 12-item questionnaire that was also administered to assess the degree of change in multiple domains of daily life resulting from the pandemic on a 4-point Likert scale (none, mild, moderate and severe). A total impact score was derived by summing items 1-8 based on the acceptable internal consistency of these items (Stoddard et al., 2021).

Results: Based on individual items from the CIS, approximately two-thirds of participants (n=20) reported a change in their daily routines in two or more functional domains, and a quarter (n=8) experienced a loss of in-person and remote contact with their social supports. 68% of participants (n=21) endorsed worry or stress related to the COVID-19 pandemic, with 29% indicating stress-related symptoms in the moderate to severe range. Delays or cancellations in mental health treatments were identified in 16% of participants (n=5), and a subset (6.5%; (n=2)) reported being fully unable to access necessary medical care. 13% of participants (n=4) reported difficulty accessing food items or frequently going without enough food.

Exploratory correlations examined the relationship of pandemic-related stress with clinical and functional variables. Total CIS score was significantly correlated with anxiety symptoms, $r = .39$, $p = .036$ and functional difficulties resulting from anxiety symptoms, $r=.53$, $p = .003$. Though not statistically significant, a small correlation was found between total CIS and delusion symptom severity, $r = .32$, $p = .086$. No other relationships were identified between pandemic-related stress and other clinical and functional variables, $p > .10$.

Discussion: Results from the present study highlight the impact of the COVID-19 pandemic on individuals with psychosis spectrum conditions. More specifically, notable changes were reported in the daily routines, social networks and supports, and pandemic-related stress of participants, with a subset of individuals endorsing difficulty accessing necessary medical care and food. Collectively, these experiences were associated with symptom severity including anxiety and, to a lesser extent, delusions. These findings offer initial insight into the challenges faced by individuals with severe mental illness during the pandemic, and can inform future research and interventions aimed at addressing their mental health needs.

S152. OBSESSIVE AND CATATONIC SYMPTOMS IN THE EARLY STAGES OF PSYCHOSIS: ARE THEY RELATED?

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traditionally been associated with schizophrenia, although its presence has also been seen in other types of pathologies, such as affective disorders or obsessive-compulsive disorder.

The presence of obsessive symptomatology in schizophrenia is high, appearing in up to 60% of patients.

The aim of this study is to assess the presence of catatonic and obsessive symptoms in patients with initial stages of psychosis and to asses the possible correlations between catatonia and obsessivity in these patients.

Methods: The sample consisted of seventy patients (35 women and 35 men) with psychosis recruited from the Brief Psychiatric Inpatient Unit of the Virgen del Rocío University Hospital in Seville. The age of the subjects ranged from 18 to 55 years.
All subjects had recent-onset psychosis. 54 subjects (77%) had First Episode Psychosis (FEP) and had not received previous treatment, 16 (33%) had had their first psychotic episode less than five years ago (P5Y) and were receiving antipsychotic medication. All subjects were evaluated during the first 72 hours after admission.

We measure catatonic symptoms using the Bush Francis Catatonia Rating Scale (BFCR-S). Patients were also interviewed with the revised version of the Obsessive-Compulsive Inventory (OCI-R) and The Positive and Negative Syndrome Scale (PANSS).

Results: The mean score of OCI-R scale in our sample was 19,68. 28 patients (40% of the sample) reached or exceeded 21 in this score, that suggests of a comorbid obsessive-compulsive disorder.
The most frequent occurring obsessive-compulsive dimensions in our patients were ordering (with a mean of 4.6±2.9) and obsessing (with a mean of 4.2±3.2).

We observed that 51 patients (72.9% of the sample) scored positively for the catatonia screening. When applying all the scale to measure the severity of catatonic symptoms, the mean score is 12,29. The most frequent domain in our sample is retarded catatonia with an average score of 5,16. Inmobility/stupor and staring symptoms appear in more than 50% of the sample.

The mean score on the PANSS scale of the sample is 73,70.

There are significative correlations between catatonia total score and some OCI-R scale components: hoarding (Spearman 0.27, $p=0.02$), checking (Spearman 0.23, $p=0.05$), neutralizing (Spearman 0.826, $p<0.0001$), and washing (Spearman 0.803, $p<0.0001$).

There are also significative correlations among catatonia total score and several Marder factor of PANSS scale: specially the disorganization factor (Spearman 0.74, $p<0.0001$).

If we take into account those patients who present scores on the OCI-R scale ≥21 (cut-off point to consider OCD), we can establish an odds ratio of 5.12 to obtain a positive result in the screening performed with the BFCSI ($p=0.012$).

Discussion: The presence of symptoms of catatonia is very high in the sample. This finding suggests the need to measure the presence of these symptoms in psychotic disorders from the first episode.
We can observe in our study a high presence of obsessive symptoms in early phases of psychoses, reaching the possibility of suffering a comorbid obsessive compulsive disorder at least in 40% of patients.

We propose that the presence of obsessive symptomatology related to neutralization and washing/contamination causes important psychomotor alterations in patients, both due to excess and deficiency.

Obsessive symptomatology in initial phases of psychosis is high and acts as a risk factor for the presence of catatonic symptoms, being observed up to 5 times more in this sample.As far as we know, there is no description of this risk in the literature, so it would be interesting to take it into account for future studies.

S153. GENDER DIFFERENCES IN EMERGING PSYCHOSIS IN A SPECIALIZED EARLY DETECTION UNIT.

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Background: The Mutua Terrassa Early Detection of Psychosis Program offers clinical care to patients and their
families, with the team trying to adapt their care to the patients' circumstances.

The objective of the Program is to provide for each patient the most appropriate services, improve adherence to follow-up, improve self-awareness of the disorder and to prevent or avoid psychotic relapses.

In this study, we aimed to describe the main characteristics of the sample, clinical care that the patients received during 2022. Also we aimed set out for gender differences in substance use disorders, treatment adherence and antipsychotic required doses in patients with emerging psychosis.

Methods: One-year observational follow-up study including 148 adult patients who were recruited at the Early Detection of Psychosis Program (2022).
Patients were included if they experienced a FEP in the last 5 years or if they had a diagnosis of

Ultra-High Risk (UHR) for psychosis. Exclusion criteria: not having had psychotic symptoms orat least one relapse before inclusion.

At the time of the study inclusion, the following variables were recorded: sex, age, drug use, adherence to treatment. Assessment scales: Assessment of Functioning (GAF) scale for the measurement of functionality, Positive and Negative Syndrome Scale (PANSS), antipsychotic treatment with equivalent dose of risperidone.

Results: The mean GAF at baseline is 38.8 compared to the GAF after one year, which is 62, this difference being statistically significant.
The mean total PANSS at baseline is 71.2 while the total PANSS at one year of assessment is 38, this difference being found to be statistically significant.

Regarding drug use, statistically significant differences were also observed, with the female gender having the lowest percentage of drug use.

When analyzing adherence to treatment, statistically significant differences were also found between men and women, with the female gender being more adherent.

Discussion: Gender differences must be taken into account when prescribing pharmacological treatment for first psychotic episodes. In this study we find differences between men and women play a fundamental role in the course, the prescribed treatment and the outcomes obtained in patients with psychosis.

S154. INCIDENCE, CUMULATIVE INCIDENCE, AND STABILITY OF REMISSION IN INDIVIDUALS AT CLINICAL HIGH RISK FOR PSYCHOSIS

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Background: Clinical high risk for psychosis (CHR) research has primarily focused on predicting the transition to psychosis. However, the prediction of remission is also critical as it provides information about protective factors, which are essential for prognosis, mechanistic understanding, and stratification in clinical trials. Currently, there is no consensus regarding how to define remission, with most studies defining remission as not fulfilling CHR criteria at the last follow-up visit.
The present study aims to leverage data collected by the North American Prodromal Longitudinal Study 3 (NAPLS 3) to characterize the incidence, cumulative incidence, and stability of remission across several time points.

Methods: All data were downloaded from the NIH data archives, following a data share agreement. We included 698 individuals aged 12 to 30 who met the criteria for a psychosis risk syndrome as determined by the Scale of Prodromal Symptoms (SOPS) at baseline. We compared the two most commonly used remission definitions. The first was based on positive symptoms assessed by the SOPS, in which an individual was classified as remitted if each SOPS positive symptom rating was below three. We will refer to this definition as “symptoms only.” The second definition was based on the SOPS and social and occupational functioning assessed by the Global Assessment of Functioning (GAF). For this definition, an individual was classified as remitted if each SOPS positive symptom rating was below three and the GAF total score was above 60. We will refer to this definition as “symptoms and function.”
Based on the two definitions, we identified remission events for follow-up visits at months 2, 4, 6, 8, 12, 18, and 24. For each follow-up visit, we examined the incidence of having an initial remission event, the cumulative incidence of being in remission, and the percentage of individuals that remained remitted after an initial remission event.

Results: Using the “symptoms only” definition, the incidence of initial remission increased from 7% in month 2 to 18% in month 24. The cumulative incidence of being remitted increased from 7% in month 2 to 38% in month 24. Using the “symptoms and function” definition, the incidence of initial remission increased from 3% in month 2 to 10% in month 24. The cumulative incidence of being remitted increased from 3% in month 2 to 23% in month 24.

Using the "symptoms only" remission definition, 70% of initial remitters remained in remission for all subsequent visits with data available. Using the "symptoms and function" definition, 64% of initial remitters remained in remission for all subsequent visits with data available. This suggests that independent of definition criteria, sustained remission characterized more than half of those who met the criteria for initial remission.

Discussion: Our findings demonstrate that the incidence of remission increases with a longer follow-up period. Additionally, when using the "symptoms and function" definition, the incidence of remission was approximately half the incidence compared to the "symptoms only" definition. This difference highlights the importance of considering functioning in defining remission, as functional impairment can persist in individuals at CHR even with the remission of subthreshold psychotic symptoms. However, the stability of remission was relatively independent of the definition used. Findings indicate that after an initial remission visit, it is more likely than not to stay remitted in subsequent visits. It is essential to note that missing data for follow-up visits and unexplained dropouts may affect the reported incidence rates and evaluation of remission stability across visits.

S155. THE ROLE OF SEX AND NEGATIVE SYMPTOMS ON SOCIAL COGNITION AND FUNCTIONING IN PEOPLE WITH SCHIZOPHRENIA SPECTRUM DISORDERS

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Background: Social cognitive and functional impairments have been well documented in people with schizophrenia and related psychotic disorders (SSD), but individual differences can be observed in these impairments. Sex has been proposed as a potential factor supporting these differences. Previous studies on the differences between sex in social cognition and functioning in SSD remain scarce and are mainly heterogeneous regarding the samples and the measures used as well as the domains assessed. These mixed findings between sex could also be supported by other characteristics of SSD such as negative symptoms. The main objective of this study is to explore sex differences in social cognition and functioning in people with SSD and healthy controls (HC). A secondary objective is to explore the role of negative symptoms, in addition to sex, in social cognition and functioning in SSD.

Methods: A total of 296 participants with SSD and 186 HCs were included from the Social Processes Initiative in Neurobiology of the Schizophrenia(s) (SPINS). They were assessed with several objective and subjective measures of social cognition encompassing emotional processing, theory of mind and social perception. Functioning was estimated with the Birchwood Social Functioning Scale and negative symptoms with the Scale for the Assessment of Negative Symptoms using the total score as well as a two-solution factors (Experiential and Expressive factors). Women and men from the SSD and the HC groups were compared on composite scores as well as individual subdomains of social cognition and functioning using ANOVAs and MANOVAs. Further, in the SSD group, regression models including sex, negative symptoms and their interaction were computed for the composite scores of social cognition and functioning.

Results: For social cognition, women reported a higher overall score for the Interpersonal Reactivity Index ($F(1,382)=15.89$, $p<0.001$), as well as higher scores for the scales Personal

Distress (F(1,382)=7.14, p=0.008), Empathic Concern (F(1,382)=20.49, p<0.001) and Perspective Taking (F(1,382)=6.84, p=0.009) compared to men, both in the HC and the SSD group. For functioning, women in both groups presented with higher levels of functioning in Independence-Performance (F(1,419)=5.15, p=0.024), Social Engagement (F (1,419)=13.99, p<0.001) and Interpersonal Communication (F(1,419)=11.28, p=0.001). In addition, women in the HC group presented with higher performance in Recreation compared to men in the SSD group (F(1,419)=4.55, p=0.034). Regarding the role of negative symptoms, the regression models including sex and total negative symptoms revealed that more severe negative symptoms were associated with worse performance in social cognition (F(1,238)=13.156, p<0.001; B=-0.136) and functioning (F(1,260)=98.328, p<0.001; B=-0.312). In addition, a significant interaction of the Experiential factor and sex suggested that better social cognitive performance was observed when fewer men with severe experiential symptoms were included in the group (B=0.055, ES=0.027).

Discussion: The results of this study suggest a sex effect benefiting women in functioning, while the effect for social cognition appears to be limited to self-report measures. The significant effect of negative symptoms also suggests that these symptoms alone are better predictors of impairments in social cognition and functioning in people with SSD compared to sex.

S156. PREDICTING PSYCHOSIS FROM LARGE LANGUAGE MODELS (LLMS): DETECTING DISRUPTIONS OF THOUGHT AT THE DISCOURSE-LEVEL

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Background: Thought disorder (TD) is implied by the presence of disorganized speech (Andreasen, 1979). Natural Language Processing approaches to the analysis of speech have operationalized disorganization in terms of low levels of semantic similarity between adjacent sentences (Corcoran et al., 2018). However, high levels of semantic similarity need not imply coherence. If they did, redundancy would be a sign of health. Moreover, low levels of similarity need not indicate disorganization. Adjacent sentences often lack semantic overlap but are nevertheless well connected by means of entailment relations (e.g., The spider fell. The girl jumped up.) Here we investigate a novel approach to the assessment of TD. Rather than using similarity, we define coherence in terms of the degree to which words and sentences produced by a person can be generated similarly by an AI, specifically the Large Language Model (LLM) T0 (Sanh, et al., 2022). We predicted that the AI would be less able to predict the words and sentences of CHR individuals who converted to psychosis than those who did not.

Methods: Thirty CHR subjects were included from the second phase of the study North American Prodrome Longitudinal Study (NAPLS-2). The sample included seven individuals who converted to psychosis within the 2-year follow-up (Converters; CV). The remaining 23 subjects (Non-converters; NC) did not go on to develop psychosis within the follow-up period. Each subject was administered the Structured Interview for Psychosis-Risk Syndromes (SIPS) at their baseline visit and recordings were transcribed for analysis.

Word level analysis: LLMs are trained to predict missing or occluded words in a given context (a sentence, paragraph, etc.). We iteratively occluded each word in each sentence from the transcripts and asked the model to predict the missing word. We compared the generated list of 10 words to the one produced by the subject. A single match counted as a "hit."

LLMs can also generate sentences and paragraphs. We asked T0 to predict the answer to responses to questions. Critically, the model's ability to predict missing sentences was highest

when it was given the entire interview up until that point, seemingly allowing the AI to develop an overarching conceptualization of the subject. Performance was measured by assessing the semantic similarity of the sentence generated by T0 with the one produced by the subject based on the semantic textual similarity classifier in T5 (Raffel, 2022).

Results: As predicted, the T0 AI was less able to predict words generated by CVs than NCs, X2 (1), = 6.75, p = .009. In addition, the AI was less able to generate sentences produced by CVs than NCs, X2 (1), = 4.48, p = .034. Interestingly, the word and sentence predictions were associated with different pools as a variance. A model using both words and sentences as predictors accounted for a significantly greater amount of variance than one based on only words, X2 (1), = 3.38, p = .05, with the combined model predicting psychosis conversion with 83% accuracy.

Discussion: TD is a hallmark symptom of psychosis spectrum disorders. Sophisticated AIs may allow for a more accurate and objective measurement of this central illness feature, greatly improving upon more traditional approaches that have relied on clinicians' manual ratings. Interestingly, effects were found for both words and sentences. The effect associated with words might indicate disturbances associated with the production of language. On the other hand, the effect associated with sentences points to a deeper kind of disorganization, namely one instantiated across large swathes of text. This more discourse level of disorganization likely involves disruption at the level of ideas rather than language per se, taking us a step closer to measuring disturbances in thought through computational analyses of language.

S157. DEPRESSIVE SYMPTOMS ARE SPECIFICALLY RELATED TO SPEECH PAUSES IN SCHIZOPHRENIA SPECTRUM DISORDERS

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Background: Depression is a common and debilitating mental illness associated with sadness and negativity and is often comorbid with other psychiatric conditions, such as schizophrenia. Depressive symptoms are presently primarily assessed through clinical interviews, however there are other behavioural indicators being investigated as more objective methods of depressive symptom assessment. The present study aimed to evaluate the utility of assessing depression using quantitative speech parameters by comparing speech between schizophrenia spectrum disorder (SSD) patients with clinically significant depressive symptoms (DP), SSD patients without depressive symptoms (NDP) and 22 healthy controls with no psychiatric history (HC). Based on the speech-depression literature, it was hypothesised that DP patients would have significantly longer pauses in their speech and a reduced speaking rate compared to NDP patients. No specific hypotheses were made for utterance formulation errors and any differences for between/within utterance pause variables as these investigations were new and therefore exploratory.

Methods: Data from 64 participants (mean age=42.33, SD=10.91, range=20–64) were analysed – 42 with DSM-IV diagnosed SSD and 22 HCs with no personal/family history of psychiatric illness or medication use. All participants were screened for drug dependence, neurological illness, previous traumatic brain injury, English proficiency and developmental language impairments. Depressive symptoms were assessed using the Montgomery-Asberg Depression Rating Scale, with cutoffs of ≤6 for non-depressed and ≥7 for depressed. This resulted in 23 DP and 19 NDP patients. Participant speech recordings were transcribed and analyzed using the Systematic Analysis of Language Transcripts (SALT) software to extract

15 speech variables across five types: utterances, words, speaking rate, formulation errors and pauses.
Results: Total utterances were not significantly different between the DP and NDP groups, however they were both significantly higher than the HC group (vs DP d = 1.55; vs NDP d = 1.15). Consequently, relevant speech variables were corrected for total number of utterances. The results revealed that DP patients produced significantly more pauses within utterances, and had more utterances with pauses compared to NDP patients and HCs (p = <.05), who performed similarly to each other. Word, speaking rate and formulation errors variables were not significantly different between the patient groups (p > .05).
Discussion: The findings align with existing evidence of relationships between increased depressive symptoms and greater incidences of pauses, but not for duration of pauses. Critically, the observation of similar relationships in DP individuals here supports the transdiagnostic association between pauses and depressive symptomatology specifically. The findings thus support the potential future use of speech pause assessments as an alternative and objective depression rating and monitoring tool. Future studies should consider including more acoustic and temporal variables to contribute to a more comprehensive examination of speech patterns relating to depressive symptoms in SSD specifically.

S158. RELATIONSHIPS BETWEEN BRAIN STRUCTURE AND TREATMENT-RESISTANT SCHIZOPHRENIA: A GENETIC CORRELATION AND MENDELIAN RANDOMIZATION STUDY

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Background: Current antipsychotics fail to alleviate clinical symptoms in approximately one-third of patients with schizophrenia. This subtype is termed treatment-resistant schizophrenia (TRS). In order to identify potential treatment targets for the subtype, several neuroimaging studies have investigated brain structure, such as cortical thickness and surface area, in patients with TRS. However, there have been no robust findings and the causality between altered brain structure and TRS is still unclear. Therefore, this study aims to disentangle relationships and causality between brain structure and TRS using publicly available data of genome-wide association studies and genetics-based approaches.
Methods: Using the largest genome-wide association study data available of the phenotypes of interest (TRS, schizophrenia, cortical thickness, and surface area), we applied linkage disequilibrium score regression and bidirectional two-sample Mendelian randomization to investigate the potential role of brain structure for the risk of TRS.
Results: TRS is genetically correlated with global surface area (rg = -0.30, p = 0.041), but not with cortical thickness. In contrast, schizophrenia is not genetically correlated with both features. Furthermore, TRS is genetically correlated with regional surface area, including mainly frontal and temporal regions. However, two-sample Mendelian randomization reveals that there are no causal relationships between brain structure and TRS.
Discussion: We confirmed shared genetic etiology between TRS and surface area. Furthermore, the null findings of causality between them suggest that altered brain structure may not be neurobiological mechanisms underlying TRS and potential treatment targets.

S159. THE INTERRELATIONSHIPS BETWEEN EARLY ADVERSITY, NEUROCOGNITION, AND FUNCTIONING IN INDIVIDUALS AT CLINICAL HIGH RISK FOR DEVELOPING PSYCHOSIS

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Background: Growing evidence suggests that the clinical high risk for psychosis (CHR-P) syndrome is associated with an elevated risk of long-term impairments in social and role functioning, along with psychosis onset. Recent findings have demonstrated that processing speed and sustained attention deficits are strongly linked to poor social and role functioning, respectively, independent from clinical symptoms. However, while impaired neurocognition serves as an important risk factor, other external factors may contribute to neurocognitive performance, and in turn, to poor functioning in high-risk individuals. Early adversity, for example, is associated the development of neurocognitive dysfunction and poor functional outcomes in adult patients with psychosis. However, the interrelationships and impact of these variables on social and role functioning prior to the onset of the illness have not been examined. The current study used a structural equation modeling (SEM) approach to examine the interplay between adversity, neurocognition, and functioning among treatment-seeking CHR-P individuals.

Methods: Participants were 670 CHR individuals enrolled in the North American Prodrome Longitudinal Study (NAPLS2). CHR-P symptoms were assessed with the Scale of Prodromal Symptoms. The Global Functioning: Social and Role scales assessed social and role functioning. Two different types of adversity were examined and defined as Threat (physical and sexual abuse, bullying) and Deprivation (emotional neglect and poverty). Negative cognitive schemas about the self and others were also included. We evaluated several theoretically based models with pathways starting from adversity (threat and deprivation) to functioning. The intervening variables included neurocognition (processing speed and sustained attention), and negative cognitive schemas. Model estimation was performed using AMOS v16. Two separate models were constructed for social and role functioning.

Results: Adversity in the form of deprivation, but not threat, had a direct effect on social and role functioning. Deprivation also had direct effects on processing speed and sustained attention, which in turn, had significant connections to social and role functioning, respectively. While threat and deprivation were significantly related to negative self- and other-schemas, the direct effect from negative schemas to functioning were not significant. The final models accounted for 15% and 30% of the variance in social and role functioning, respectively.

Discussion: Our findings build upon previous work and reveal a complex relationship between specific types of adversity, neurocognition, negative schemas, and functioning in CHR-P youth. The present study demonstrates, to the best of our knowledge, for the first time that adversity has a direct impact on neurocognition (namely processing speed and sustained attention) and functioning in individuals at CHR-P. These findings shed some light on environmental factors that may contribute to neurocognitive dysfunction prior to the onset of psychosis. Early deprivation may impact neurodevelopment at a critical period and subsequently play a role in the association between neurocognition and functioning in at-risk youth. These results may have implications for early intervention strategies that aim to improve functional trajectories in young individuals at high risk of developing psychosis.

S160. AN EXPLORATORY STUDY OF THE RELEVANCE OF THE THERAPY CONTEXT IN COGNITIVE BEHAVIOURAL THERAPY FOR PSYCHOSIS (CBTP) - A COMPARISON BETWEEN TRADITIONAL SYMPTOM FOCUSED CBTP AND VOCATIONAL CBT.

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Background: Cognitive behavioural therapy for psychosis (CBTp) is an established evidence-based intervention, included in treatment guidelines. CBTp can be delivered in different formats and contexts from professional with different backgroundsuch as an integrated part of vocational rehabilitation (VR) programmes by employment specialists.
This is an exploratory study of the relevance of therapy context in CBTp. CBTp interventions from two different research projects delivered in two different contexts are compared on selected outcome measures, investigating potential differences in effects. One CBTp intervention was delivered in a traditional symptom focused therapy context. Here CBT was delivered by certified CBT therapists, i.e. psychologists or psychiatrists with a 2 year CBT training program. The other CBTp intervention was delivered as an add-on to a VR programme. In this setting, employment specialists undertook basic training (40 hours) in CBT and sessions were delivered both in vivo at the workplace, and at the employment specialists' office. To our knowledge, a comparison between a traditional CBTp intervention and a vocational CBTp intervention has not previously been done.

Methods: Data is sourced from two independent research projects; KATOslo and JUMP. The KATOslo study is a randomized controlled trial comparing CBT with treatment as usual (TAU) in individuals with early psychosis. The JUMP study is a VR programme, in which one intervention group received VR augmented with CBT, and the other group had VR augmented with cognitive remediation. Three repeated assessments were performed: at baseline, post-intervention (6-10 months) and follow-up (15-24 months). Our study includes 234 participants with a primary diagnosis of broad schizophrenia-spectrum disorders.
A secondary analysis of the data from the respective projects was carried out, assessing level of psychotic symptoms as measured by positive and negative symptom scale (PANSS). Additional outcome measures were global assessment of functioning (GAF-F and GAF-S), social functioning schedule (SFS) and Rosenberg self-esteem scale (RSES). Effects on depression, measured by Calgary depression scale for schizophrenia (CDSS), was also

investigated. Two series of mixed between-within subjects analyses of variance were conducted, adjusting for depression and IQ. Subsequently a series of exploratory analyses were conducted, adjusting for number of received therapy sessions.

Results: (A table of demographics for the participants will be displayed). Preliminary results in this study show that the average trajectories for all four groups exhibit a reduction in total PANSS score at post-intervention, and a subsequent smaller increase at follow-up. (A graph will be presented with values. Results for the additional outcome measures will also provided in the poster).

Discussion: This study indicates that CBT has effect in terms of reduction in PANSS total score in individuals with schizophrenia spectrum disorders in both data sets. There were no significant differences between the group where CBT was delivered by experienced CBT therapists in the KATOslo study compared the group where CBT was delivered by job specialist with limited training in CBT in the JUMP study. This may be due to the positive effect of employment focus in the JUMP study. However, this also emphasize that the effect of CBT for this group of individuals may not be correlated by the level of education for the health care professionals delivering the intervention. Additional research is needed investigate this relationship further.

S161. SEMANTIC COGNITION DEFICIENCIES IN EARLY PSYCHOSIS: EVIDENCE FOR A SELECTIVE IMPAIRMENT OF SEMANTIC CONTROL

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Background: Semantic processing anomalies, clinically reflected by disorganized speech, are core symptoms of schizophrenia. Semantic cognition relies on two principal interacting neural systems: one of representation and one of control.

Methods: Here, we used the DO80 picture naming task to assess general neuropsycholinguistic impairment. Semantic representation was examined using the multiple-choice word test (MWT-B). Control of semantic cognition was tested using a semantic verbal fluency task as well as by the Camel and Cactus Test (CCT), which requires matching an image with a matching image from a selection of four images based on their semantic association. We included three groups: A cohort of individuals with early psychosis (EP; target sample size N=50), a cohort of individuals with low schizotypy (target sample size N=50) and a cohort with high schizotypy (target sampl size N=50). Schizotypy was assessed based on the Multidimensional Schizotypy Scale (MSS) and the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE).

Results: Individuals with EP showed significantly more semantic and phonematic paraphasias in the DO80 than both schizotypy controls (RRR 1.58, 95% CI [1.13, 2.21], $p = 0.008$ and 6.20, [1.22,31.58], $p = 0.028$, respectively). With regard to semantic representation, there was no significant difference between individuals with EP and with schizotypy. By contrast, there were significant differences with regard to semantic control, where patients with EP named significantly fewer items within one minute than schizotypy controls (IRR 0.77, 95% CI [0.68, 0.87], $p < 0.001$). In the CCT, patients showed a significantly longer response latency than schizotypy controls (1.65, 95% CI [0.59, 2.70], $p = 0.002$). This increased response latency

was more pronounced compared with controls with low schizotypy (1.82, 95% CI [0.75, 2.89], p = 0.001).
Discussion: This study provided evidence for selective impairment of semantic control - and not semantic representation - in individuals with EP. Tract specific abnormal maturation and accelerated aging for the inferior fronto-occipital fasciculus (IFOF) (which forms part of the ventral language stream) were recently reported as compared to controls. Interestingly, the IFOF is considered a possible candidate for executive and semantic control over conceptual knowledge, thus providing a possible anatomical correlate for the results presented above. Related analyses on the described dataset will start shortly.

S162. CHANGES IN NEUROMELANIN CONTENT IN PEOPLE AT CLINICAL HIGH RISK FOR PSYCHOSIS AND PATIENTS WITH SCHIZOPHRENIA

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Background: Neuromelanin-sensitive MRI has gained increased interest in psychiatry as a surrogate marker for measuring catecholamine function in the substantia nigra, ventral tegmental area, and locus coeruleus. However, their characterization of youth at risk of psychosis (CHR) and those with schizophrenia (SCZ) remains unclear.
Methods: From the Psychosis Prospective Cohort Program, we recruited 33 CHR, 55 SCZ, and age- and sex-matched 61 healthy controls (HC). Subjects underwent 3 T MRI using T1-weighted and neuromelanin-sensitive imaging. Neuromelanin contents were segmented by a deep convolutional neural network-based approach. We compared the volume of segmentation, mean signal intensity, and intensity per unit volume of the neuromelanin between the groups.
Results: The volume of neuromelanin segmentation was significantly larger in SCZ than in CHR (
F = 96.1, p < 0.001) and HC (F = 69.0, p = 0.007). At the same time, there was no difference in the mean signal intensity of the neuromelanin between the groups. CHR showed higher neuromelanin intensity per unit volume than SCZ (F = -.0013, p = 0.037). No significant differences in neuromelanin contents were observed between CHR and HC.

Discussion: These results indicate that alterations in neuromelanin contents occur in SCZ. Furthermore, the functional alterations in the dopaminergic pathway may precede the prodromal phase of the disease.

S163. ACCEPTABILITY AND EFFECTIVENESS OF COGNITIVE REMEDIATION FOR PEOPLE WITH FIRST EPISODE PSYCHOSIS ATTENDING EARLY INTERVENTION SERVICES

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Background: Early intervention to reduce cognitive deficits in people experiencing first episode of psychosis (FEP) has the potential to impact recovery and quality of life; however, early intervention services (EIS) do not routinely incorporate cognitive remediation (CR) as an offered service. We trained teams from OnTrackNY, a network of EIS programs for people

with FEP, to offer two different CR dosing approaches and examined acceptability and pilot effectiveness.
Methods: Using a cluster randomized controlled trial design, 14 clinics were randomized to deliver A) TAU or B) 12 once-weekly clinician-led CR sessions combined with an additional 12 hours of independent cognitive practice or C) 24 twice-weekly clinician-led CR sessions. Acceptability was measured by rates of referrals to CR, drop out and satisfaction ratings, while pilot effectiveness was measured with change in cognition and functioning.
Results: Over 24 months, at the 11 clinics randomized to deliver CR, 112 people were referred to CR, 103 went on to receive a brief neurocognitive assessment and 88 commenced CR. Outcomes were analyzed from 65 CR initiators and 32 CR completers. OTNY clients presented with significant cognitive challenge, with a mean (SD) global cognitive T score of 36.27 (9.28). Referral rate was higher and drop out rate lower in the once-weekly approach. Across all CR sites, CR program completers expressed satisfaction with the service and made overall gains on neurocognition measures ($p<.01$) and on measures of functioning: MIRECC GAF Symptom Score ($p<.03$); MIRECC GAF Occupational Score ($p<.007$) MIRECC GAF Social functioning Score ($p<.004$). Controlling for site, demographics, baseline GAF scores, and time in program, participants who initiated CR+TAU showed significantly greater improvement in MIRECC GAF Social functioning Score 9 months after CR initiation compared to those who received TAU ($p=0.008$); participants who completed CR also showed significantly greater improvement at 9 months after initiation ($p=0.03$). Three months after CR initiation, those who initiated CR+TAU had significantly greater improvement in MIRECC GAF Symptom Score than TAU participants ($p=0.002$). Effect size differences between CR and TAU were in the medium range (0.35-0.50).
Discussion: In this network of EIS programs for people with FEP, a dosing schedule of 12 once weekly clinician run sessions with independent practice was more acceptable than 24 twice weekly clinician run sessions. Pilot effectiveness data indicated participation in cognitive remediation was associated with cognitive and functional improvement most noticeable in symptom and social domains.

S164. WHEN DO CONTRAST SENSITIVITY IMPAIRMENTS (OR ENHANCEMENTS) DEPEND ON SPATIAL FREQUENCY? TWO WAYS TO AVOID SPURIOUS INTERACTIONS

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Background: Contrast sensitivity (CS) corresponds to how much contrast energy is needed to identify a target reliably. Special population studies often report group differences in CS that are non-uniform across the spatial frequency spectrum. Such interactions have led to mechanistic speculations (e.g., magnocellular dysfunction). Here, we considered whether illness-specific non-uniform reductions in CS could be explained by the heteroscedasticity and rightward skew inherent to CS data. We further considered whether group differences in visual acuity might generate more of a deficit at higher spatial frequencies.

Methods: We leveraged a publicly available data set of 75 healthy controls and 68 schizophrenia/schizoaffective disorder patients with at least 20/32 acuity (Zemon et al. 2020). Participants attempted to locate briefly-appearing (33 ms, 500 ms), laterally-displaced

sinusoidal gratings in a staircase-controlled, two-alternative forced choice task. To maximize the chances of finding spatial frequency interactions, we analyzed data only from the two most extreme spatial frequency conditions (0.5 and 21 cpd). To consider the role of heteroscedasticity/skew on spatial frequency interactions, we conducted a 2 (spatial frequency) x 2 (subject group) ANOVA once on the raw (rightward skewed and heteroscedastic) CS data and once again on the log-transformed data. To confirm the log-transformed results, we additionally performed generalized estimating equations (GEEs) on the raw CS data with a log-link gamma distribution. To consider the role of visual acuity, we re-ran the above analyses with controls who had acuity no better than 20/20 (n=34) so that subject groups were approximately matched on this variable.

Results: For the short presentation condition, there was a significant interaction in the raw CS data such that patient deficits decreased with spatial frequency ($p<.001$, $\eta_p^2=.083$). Surprisingly, the interaction reversed in the log-transformed data ($p=.04$, $\eta_p^2 =.029$). GEEs yielded an interaction that agreed with the log-transformed results (Wald Chi-square(1)=4.87, $p=.027$). Matching groups on visual acuity abolished the significant interaction effect in the GEEs and log-transformed ANOVAs, although the main effect of group remained (all $p<.001$). Similar results emerged with the longer presentation time (500 ms). An important caveat is that matching groups on acuity is probably only defensible if the acuity differences arose from non-neural factors (e.g., refractive error).

Discussion: Our results reconcile seemingly inconsistent findings from past studies, which either applied or did not apply log transformations (e.g., Zemon et al., 2020; Butler et al., 2005). Our results also provide a possible alternative explanation for why some studies in the schizophrenia literature have found a worsening of CS at higher spatial frequencies (e.g., Keri et al., 2002). More generally, our results suggest that past studies may need to be revisited if not accounting for skew/heteroscedasticity or group differences in acuity.

S165. BIOMARKERS AS PROXIES FOR COGNITIVE RESERVE: THE ROLE OF HIGH DENSITY LIPOPROTEIN CHOLESTEROL IN FIRST EPISODE OF PSYCHOSIS

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Background: The proxies used to compose cognitive reserve (CR) in first episode of psychosis (FEP) have varied in the literature. The development of FEP is linked to the peripheral pathways of the central nervous system (Leboyer et al., 2016), but despite this knowledge, no research has considered the introduction of biomarkers as proxies for CR. Furthermore, we know that schizophrenia has been linked to the metabolic system, indicating

that alterations in the levels of biological parameters, in particular high-density lipoproteins (HDL), cause worse global functioning and cognitive impairment (Adamowicz and Kucharska-Mazur, 2020; Grover et al., 2019; Lindenmayer et al., 2012). For these reasons, the present study aimed to create a quantifiable and objective CR index that adjusts for the multifactorial nature of FEP.

Methods: We included 668 patients who had FEP and 217 healthy controls, who were assessed for sociodemographic information, years of education, employment status, premorbid IQ and levels of biological parameters: waist circumference, hypertension and levels of HDL, triglycerides and glucose. We performed Pearson correlations to explore whether there is a relationship between CR proxies and biological parameters. Subsequently, multiple regression analyses were performed to search for the causes of the relationships between CR and biological parameters at baseline. In the final step and in line with the methodology used in recent years in CR research, the following were carried out principal component analyses (PCA) and exploratory factor analysis (EFA) to create a "composite CR score" (Amoretti et al., 2018) for each participant, which we will refer to as biological CR.

Results: The findings suggest that the years of education proxy showed correlational and higher relationship with HDL levels for both FEP patients (r=0.23, b= 0.185) and controls (r= 0.31, b= 0.342). Specifically, the results of the regressions indicate that the Model 2 formed by the proxies years of education and unemployment had a higher predictive power explaining 5.4% of HDL levels and with a stronger F-statistic (F= 11.80). The next step in the analyses was to carry out PCA and EFA. After several attempts combining all possible components, exploratory analyses showed that the most optimal variables for the composite CR score were years of education and HDL levels. The variance results indicated that biological CR would have a greater explanatory power for the phenomenon than classical CR in both groups of participants. In the group of patients, classical CR explained 51.79% of the variance, while biological CR explained 59.06%. This percentage increase also occurred in the control group, where classical CR explained 51.04%, while biological CR increased to 67.12%. In both groups of participants the unemployment proxy in the classic CR had a degree of extraction lower than 0.30, which means that this proxy was not providing the necessary amount of information to be part of the CR. On the other hand, the years of education proxy was the one that provided the largest information to the CR (>0.70).

Discussion: The main objective of the present study was to explore a possible objective and quantifiable CR, taking into account endogenous and exogenous factors. Following this line of work, it is interesting to note that, in both groups of participants, the results found that the proposed biological CR has a greater explanatory value of the phenomenon than the classical CR consolidated by the literature. Therefore, we can affirm that introducing HDL levels, as a biological proxy, together with the years of education proxy, is a way of obtaining a CR adjusted to the multifactorial nature of psychosis.

S166. OLANZAPINE AND FECAL MICROBIOTA TRANSPLANTATION FROM ANTIPSYCHOTIC-NAÏVE SCHIZOPHRENIA PATIENTS ALTER METABOLIC PROFILES DIFFERENTIALLY IN MALE AND FEMALE MICE

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Background: Emerging evidence suggests that the gut microbiome (GMB) plays a role in the pathogenesis of schizophrenia (SCZ) and metabolic perturbations associated with antipsychotic (AP) treatment. In the present study, we investigated the role of GMB in metabolic alterations associated with SCZ and olanzapine (a prototype AP) treatment using human fecal microbiota transplantation (FMT) in mice.

Methods: FMT from AP-naïve SCZ patients (SCZ-FMT) and sex-BMI matched healthy controls (HC-FMT) were performed in 5-6 weeks old male and female germ-free C57BL/6 mice (n=8-10 per group). At the age of 10-12 weeks, mice were given an irradiated control high-fat diet (HFD) with or without olanzapine (50 mg/kg of the diet) for six weeks in a level-2 containment facility in individually ventilated cages. Weekly food intake and body weight were monitored. In the last week, animals were subjected to an intraperitoneal glucose tolerance test (IPGTT). Circulating concentrations of glucose, insulin and free fatty acid were also measured. Homeostatic model assessment for insulin resistance (HOMA-IR), and quantitative insulin sensitivity check index (QUICKI) were calculated for assessment of insulin sensitivity. Statistical analysis tested the effects of SCZ-FMT and olanzapine treatment on metabolic parameters.

Results: Neither SCZ-FMT nor olanzapine affected percentage weight change, adiposity index, and average daily food intake in males and females. However, olanzapine decreased distance travelled in male and female mice, regardless of the source of FMT. Distance travelled in open field test is indicative of locomotor activity. In male mice, neither SCZ-FMT nor olanzapine treatment had an effect on glucose tolerance, serum glucose levels, serum insulin levels, HOMA-IR and QUICKI. In contrast, female SCZ-FMT recipient mice showed decreased area under the curve in IPGTT compared to HC-FMT female mice, irrespective of olanzapine treatment. This was associated with an approximately five-fold increase in circulating insulin in female SCZ-FMT recipient mice. Significantly increased HOMA-IR and decreased QUICKI in olanzapine-treated female SCZ-FMT mice (vs. HC-FMT) suggested insulin resistance and decreased insulin sensitivity. Fasting circulating glucose concentrations were similar in both sexes.. Furthermore, SCZ-FMT recipient mice of both sexes showed significantly decreased serum FFA levels, which could be indicative of reduced lipolysis and/or increased uptake of serum FFA levels by tissues such as the liver. This effect was independent of olanzapine treatment.

Discussion: These preliminary findings suggest that in an obesogenic environment (i.e., HFD), olanzapine treatment and SCZ microbiota are associated with insulin resistance, but only in female mice. Glucose tolerance is not impaired in SCZ-FMT recipient female mice

likely due to substantial hyperinsulinemia, which is necessary to overcome the insulin resistance. Our results suggest that GMB could be a predisposing factor contributing to the intrinsic risk of developing type 2 diabetes associated with SCZ. Our ongoing molecular experiments, analysis of GMB composition, and associated metabolites could provide further explanation for these effects.

S167. SCOPING THE LITERATURE ON CARE MODELS FOR PEOPLE WITH COEXISTING SCHIZOPHRENIA AND DIABETES

Birgitte Lerbæk*[1], Peter Vestergaard[2], René Ernst Nielsen[3], Hanne Ravn Larsen[4], Rikke Jørgensen[5]
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Background: Managing coexisting diabetes and schizophrenia is complex. Even though the prevalence of coexisting diabetes and schizophrenia is well established, knowledge about what can be done to provide optimal support and treatment to this population is sparse. There is a need to gain insight into beneficial aspects of existing outpatient care and treatment models targeted people experiencing coexisting diabetes and schizophrenia.

The aim of the review was to identify and summarise the range and nature of the existing literature describing outpatient diabetes care and treatment delivered to people diagnosed with coexisting diabetes and schizophrenia.

Methods: A systematic search was conducted in PubMed, CINAHL and PsycInfo. A scoping review as described by Arksey and O'Malley (2005) was performed. To build an overview of the range and nature of the existing literature, characteristics of the selected studies were charted. Information reported specifically about outpatient care was extracted from the studies. The review process included consultation with clinical specialist stakeholders to determine the scope and translate findings of the review.

Results: The systematic search resulted in 580 references. After removing duplicates (n = 151), 401 references were excluded during screening of title and abstract. Additional 26 references were excluded during full text screening, resulting in two publications being included in the review. Hand-search in reference lists provided no additional references.

The outpatient care models described in this review represent two different strategies to support people with coexisting diabetes and severe mental illness (including schizophrenia) in managing these conditions by; 1) integrating diabetes care into an existing mental health care service and increasing accessibility to a primary health care person, who has the possibility of engaging with the mental health care team, an endocrinologist and a psychiatric specialist consultant, and 2) offering targeted training in illness management. They both represent initiatives with potentially beneficial effects in relation to management of coexisting diabetes and schizophrenia in everyday life.

Discussion: Current state of physical health and reports of unmet health care needs among people with severe mental illness underlines the urgency of exploring management and self-management of coexisting diabetes and schizophrenia among this vulnerable population.

This scoping review included two studies on outpatient care models for people with coexisting diabetes and schizophrenia, pointing to a lack of research describing and evaluating this area of clinical practice. In order to plan and provide beneficial, evidence-based care and treatment to this particular group, there is a need for further research examining beneficial treatment or consultation opportunities targeted people experiencing coexisting diabetes and schizophrenia. Future research should explore service user needs and experiences as well as evaluate potentially beneficial care model solutions. Studies exploring potential effect of integrated care models should make sure to describe how integration is achieved and the specific circumstances that might limit or support integration of care.

S168. FUNCTIONAL CONNECTIVITY OF THE DEFAULT MODE NETWORK WAS ASSOCIATED WITH AUTISTIC TRAITS IN SCHIZOPHRENIA

Miki Ishizuka*[1], Syuraku Son[2], Yukako Nakagami[3], Takahiko Kawashima[2], Yuko Kobayashi[2], Manabu Kubota[2], Yujiro Yoshihara[2], Toshiya Murai[2], Jun Miyata[2]
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Background: Patients with schizophrenia often have problems with social functioning, which is associated with impaired social skills including social cognition. Schizophrenia and autism spectrum disorders share similarities in that both have impaired social cognition and problems with social functioning, and recent studies have reported biological overlap between them such as functional connectivity (Yoshihara et al., 2020). Autism Spectrum Quotient (AQ, Baron-Cohen et al., 2001) is a measure of autistic traits consisting of items about social cognitive and behavioral characteristics. In this study, we aimed to identify background factors of social functioning in schizophrenia by using AQ and functional connectivity (FC) between brain regions.

Methods: 20 patients with schizophrenia (SCZ) and 25 healthy controls (HC) were included in the study. AQ was employed that consists of 50 items and has indices of Total AQ and 5 subscales (Social Skills, Attention to Change, Attention to Detail, Communication, Imagination). The higher the score, the greater autistic tendency. All subjects underwent magnetic resonance imaging (MRI) on a Simens 3T scanner to obtain resting functional MRI data. After preprocessing (realignment, slice timing correction, spatial normalization, and denoising), FC between each cortical and subcortical region of interest (ROI) was calculated by Pearson's correlation using CONN Toolbox. We first identified significantly different FCs between groups, and then examined the correlation between significant FCs and total/five subscales of AQ using Spearman's rank correlation. The study plan was approved by the Ethics Committee of the Graduate School of Medicine and Faculty of Medicine, Kyoto University. After receiving a description of the study, all participants provided written informed consent.

Results: Total AQ was significantly higher in SCZ than in HC ($p< 0.05$). We found significantly lower but not higher FCs in SCZ ($p<0.05$, false discovery rate (FDR) corrected at seed level). FC between the precuneous and posterior cingulate cortex (PCC) was significantly correlated with total AQ ($r=-0.74$, $p<0.05$), Attention subscale ($r=-0.77$, $p<0.05$), and Communication subscale ($r=-0.71$, $p <0.05$). FC between the lateral occipital cortex and left inferior lateral visual was correlated with Communication subscale ($r=0.62$, $p<0.05$).

Discussion: We found that impaired social cognitive and behavioral functioning in schizophrenia was associated with functional connectivity of the cortical regions included in the DMN. Since the DMN is associated with reflective/introspective process, our findings indicate importance of introspective process for an extrospective process such as social functioning.

Poster Session III

12:00 p.m. - 2:00 p.m.

S1. META-ANALYSIS AND SYSTEMATIC REVIEW OF THE RELATIONSHIP BETWEEN NEGATIVE SYMPTOMS AND NEUROCOGNITIVE FUNCTIONING

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Background: Negative symptoms (NS) are a core symptom domain in schizophrenia spectrum disorders and have been associated with poorer social and vocational functioning, and with increased likelihood and durations of hospital admission. The underlying mechanisms of NS are not well known. However, one promising area is understanding the relationship NS have with neurocognition as both represent trait-like entities. Numerous studies have examined associations between cognitive measures and NS severity revealing significant associations, notably with verbal memory and processing speed. Considering multiple cognitive domains are significantly impaired, as work from the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus attests, there is a need to systematically examine these domains within samples and to investigate their association with NS severity. The cognitive domains identified by MATRICS include processing speed, attention, working memory, verbal learning and memory, visual learning and memory, and problem-solving and reasoning. The aim of the current quantitative review was to determine whether the relationship between neurocognition and NS in schizophrenia spectrum disorders is driven by specific neurocognitive domains (e.g. verbal memory) or a general neurocognitive factor. To that end, we compared the strength of correlations between negative symptoms and the six MATRICS neurocognitive domains from studies using a battery that captured all six domains of interest.

Methods: This review was registered on PROSPERO (CRD42022328828). Ovid PsycINFO, Ovid MEDLINE and Web of Science were searched for articles from January 2005 (year of MATRICS Consensus release) through May 12, 2022. The initial search yielded 4,127 texts. After removing duplicates, 4,119 abstracts were screened, 1,599 full texts were subsequently reviewed. Inclusion criteria included texts written in English; participants with schizophrenia spectrum disorders or first episode psychosis; assessed all six neurocognitive domains of interest using a single battery comprised of valid neuropsychological tests; assessed NS; and reported a statistical measure of the relationship between all six neurocognitive domains and NS. Articles that were theses/ dissertations were excluded. Authors were contacted for additional information if not all data on the relationship between neurocognition and NS were reported. An independent reviewer extracted the data and assessed for study quality using the Mixed Methods Appraisal Tool, 25% of extracted data underwent a quality control process by an independent reviewer and 50% of the quality assessment ratings were completed by an independent reviewer. A random effects three-level meta-analysis was performed using RStudio to aggregate effect sizes within and between studies.

Results: We included 17 eligible studies (N=3001 participants) in the analyses. Most individuals in the studies had diagnoses of schizophrenia and schizoaffective disorder, <1% of the study population had diagnoses of affective psychosis and other psychotic disorders. All neurocognitive

domains had small significant relationships with global negative symptoms (r = -0.16 to -0.21, ps <0.0005) with poorer cognitive performance being associated with greater negative symptoms severity across all cognitive domains. Analyses on the moderating effects of sociodemographic characteristics, positive symptoms, depression, functioning, antipsychotic medication, type of negative symptom scale, type of neuropsychological scale and study quality are pending.
Discussion: Our results confirm the relationship between negative symptoms and neurocognition, suggesting that the association is generalizable to all domains. This may be taken as evidence for a general neurocognitive factor driving the relationship with global negative symptoms. These findings have important implications on understanding the relationship between neurocognition and negative symptoms and the development of cognitive treatments to target negative symptoms.

S2. CANNABIS USE MOTIVES AND IMPULSIVITY FACETS MODERATE ASSOCIATIONS BETWEEN PROBLEMATIC CANNABIS USE AND PSYCHOTIC-LIKE EXPERIENCES

Samantha Johnstone*[1], Cassandra Wong[1], Todd Girard[1], Hyoun Kim[1]

[1]Toronto Metropolitan University

Background: Problematic cannabis use is associated with endorsement of psychotic-like experiences (PLEs) in non-clinical samples. However, little is known in regard to potential moderators of this relationship. In the present research, we investigated whether cannabis use motives and impulsivity moderate the relationship between problematic cannabis use and PLEs.
Methods: We assessed endorsement of psychotic-like experiences using the Community Assessment of Psychic Experiences (CAPE), problematic cannabis use with the Cannabis Use Disorder Identification Test (CUDIT), motivations for using cannabis with the Substance Use Motives Measure, and impulsivity using the urgency, premeditation, perseverance, sensation seeking, and positive urgency scale.
Results: Greater positive and depressive subscales on the CAPE were associated with significantly higher scores on the CUDIT. The relation amongst greater CUDIT scores and negative symptoms was greater in individuals endorsing depression coping motives and sensation seeking impulsivity. Furthermore, the relation amongst greater CUDIT scores and positive symptoms was greater in individuals endorsing depression coping motives and lack of premeditation. Finally, the relation between depressive symptoms and greater CUDIT scores was moderated by greater depression coping motives and lack of perseverance.
Discussion: In line with the broader substance use and psychosis-spectrum literature, our results support a role of coping motivations for cannabis use and higher impulsivity in negative mental health outcomes.

S3. SCHIZOPHRENIA PATIENTS PERFORM AS WELL AS HEALTHY CONTROLS ON CREATIVE PROBLEM SOLVING WHEN MATCHED ON FLUID INTELLIGENCE

Hanna Kucwaj*[1], Zdzisław Gajewski[2], Adam Chuderski[1]

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Background: On the one hand, schizophrenia is related to loose conceptual boundaries and overinclusive thinking that may help to reach unobvious solutions. On the other hand, cognitive

deficits present in schizophrenia may hinder creative thinking. We aimed to verify three hypotheses: (H1) schizophrenia patients differ from healthy controls in the accuracy of creative problem solving; (H2) schizophrenia patients are less effective at evaluating and rejecting incorrect associations compared to controls; and (H3) schizophrenia patients have a more idiosyncratic way of searching for semantic associations compared to controls.
Methods: The Remote Associates Test (RAT) and three insight problems were applied to 62 schizophrenia patients and 62 matched healthy controls. We compared groups on the overall accuracy in the tasks to verify H1. We developed a novel method of comparing the patterns of errors in the RAT to verify H2 and H3. Importantly, the groups were matched on fluid intelligence to eliminate this significant source of variation, as typically creativity and intelligence are significantly related.
Results: We conducted Bayesian factor analysis to verify the hypotheses. Firstly, we found that schizophrenia patients scored as high as the healthy controls on creative problem solving tasks (H1). Secondly, we found that the groups did not differ in the pattern of errors. Both the patients and the healthy controls tended to produce a similar amount of incorrect responses (H2). Finally, in both groups the majority of errors committed in the task were identical within the group. In other words, when participants were incorrect, they usually produced dominant associations (H3).
Discussion: The patients performed as well as the controls on both tasks when matched on fluid intelligence. We think that if no differences were found after such a precise matching, then it is highly unlikely that schizophrenia patients might benefit from their diagnosis during creative problem solving. The analysis of errors suggests that the process of searching semantic and associative networks takes a similar course in both groups.

S4. ADOLESCENT CANNABIS VAPOUR EXPOSURE INDUCES LEARNING DEFICITS AND CHANGES BRAIN CONNECTIVITY DURING ADULTHOOD IN RATS

Jaiden Smith[1], Hakan Kayir*[1], Patrick McCunn[2], Pedro Marinho[2], Yu Gu[1], Ron Johnson[1], Jibran Khokhar[2]

[1]University of Guelph, [2]University of Western Ontario

Background: Adolescence is a critical time for brain development. Cannabis use, especially during adolescence, is associated with a greater risk for schizophrenia (SCH). However, the causal basis of this association, and the relative contribution of various cannabis constituents, remains unknown. The present study recognized the recent increases in cannabis vaping in adolescents, and aimed to determine the long-term effects of adolescent cannabis vapour exposure rats. The behavioural tests focused on cognitive domains and further MRI analysis was performed to show altered structural and functional connectivity in the brain.
Methods: Male Sprague-Dawley pups (n=7/group) were exposed to three different vapourized cannabis flower types (High-THC, high-CBD, and balanced THC-CBD) daily for 14 days starting from postnatal day (PND) 28. The control group was exposed to air alone. Exposure to the cannabis vapour was confirmed with the tetrad test and blood THC, CBD and 11-OH concentration measurements at the end of treatment. Starting from PND56 the rats went through a battery of tasks including: Pavlovian autoshaping, prepulse inhibition and active avoidance. All the rats underwent brain MRI scans after PND122.
Results: Blood concentrations of THC and CBD were in accordance with the high-THC and high-CBD cannabis grouping. The high-THC treated group also had higher concentrations of the active

metabolite, 11-OH-THC. Rats exposed to high-THC or high-CBD cannabis vapour during adolescence had significantly lower lever-directed behaviour after the 3rd session in the autoshaping procedure compared to the control group. Unlike the control and balanced groups, their Pavlovian conditioned approach (PCA) scores remained at intermediate levels until the end of 12 days of autoshaping protocol. All of the treatment groups had intact prepulse inhibition (PPI). However, all three treatment groups showed impaired learning in the active avoidance test. Network-based statistics indicated that the functional connectivity between the left primary somatosensory cortex and several nodes such as interhemispheric retrosplenial granular cortex, left primary and secondary visual cortex, right retrosplenial system, and right pontine reticular nucleus (RPRN) were altered in high-CBD cannabis treated group compared to the control group. Diffusion MRI analyses revealed all three treatment groups had decreased anatomical connectivity between the following nodes: Left striatum-endo/piriform cortex, left striatum-interhemispheric ventral thalamus (IVT), and right insular cortex-IVT. The same analyses indicated increased connectivity in the treatment groups between the following nodes: RPRN-interhemispheric interpeduncular nucleus, RPRN-interhemispheric pontine nuclei (IPN), and IPN-right intermedial entorhinal cortex.
Discussion: The present study indicated that cannabis vapour exposure during adolescence induces learning deficits during adulthood without disrupting PPI, as well as brain-wide changes in functional and structural connectivity across networks previously implicated in schizophrenia. Future studies will assess how adolescent cannabis vapour exposure interacts with genetic or developmental risks for schizophrenia.

S5. THE ASSOCIATION BETWEEN NATURE CONNECTEDNESS AND MINDFULNESS-BASED INTERVENTIONS IN THE TREATMENT OF INDIVIDUALS WITH A SCHIZOPHRENIA SPECTRUM DISORDER

Marco Zierhut*[1], Inge Hahne[1], Niklas Bergmann[1], Nina Hartter[1], Josefa Wohlthan[1], Thi Minh Tam Ta[1], Malek Bajbouj[1], Eric Hahn[1], Kerem Boege[1]

[1]Charité – Universitätsmedizin Berlin, Campus Benjamin Franklin, Berlin

Background: Evidence of positive effects of nature on mental and physical health is accumulating in the general population, which has led to a surge in the development of nature-based interventions. The level of feeling of being connected to nature is conceptualized as nature connectedness and has been associated with a reduction in stress and a positive impact on affect in healthy individuals in recent studies. Research indicates a reciprocal relationship between mindfulness and nature connectedness, suggesting benefits from interventions that combine these two aspects. At the same time a growing body of literature indicates therapeutic effectiveness of mindfulness-based interventions for schizophrenia spectrum disorders (SSD). In the present study, we sought to combine the positive effects of mindfulness and nature connectedness in patients with SSD in an established mindfulness-based group therapy (MBGT) focusing on nature components, respectively. It was hypothesized that individuals with SSD would have lower scores on stress and negative affect and higher scores on positive affect following the MBGT sessions. In addition, it was hypothesized that changes in affect and across both conditions would be related to increases in nature connectedness.
Methods: For this pilot study recruitment took place at the Charité - Universitätsmedizin, Berlin. A total of 41 individuals with SSD participated in two MBGT sessions in a group of six patients

each and led by two psychotherapists over a period of one week with a focus on nature. Before and after the treatment, questionnaires for nature connectedness (Connectedness to Nature Scale, CNS), affect (Positive and Negative Affect Schedule, PANAS), and stress using visual analog scales were administered. The mentioned outcome variables were controlled for corresponding baseline scores.
Results: Analysis of covariance (ANCOVA) revealed significant increases in nature connectedness and significant decreases in negative affect, general stress, and symptom-related stress after the two MBGT sessions. In addition increases in nature connectedness were significantly associated with decreases in stress and negative affect. No severe adverse events or side effects were reported.
Discussion: This pilot study provides preliminary evidence of the positive effects of MBGT with a nature component. They provide the basis for future research to disentangle the effects of mindfulness and nature in larger samples and further investigate the benefits of this combination in the treatment of people with SSD.

S6. EXPERIENTIAL NEGATIVE SYMPTOMS AND SELF-RELIANCE PREDICT WORK

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Background: Social function and psychiatric symptoms were prominent factors in predicting work outcomes in patients with schizophrenia (Sumiyoshi et al., 2018). A recent cross-regional study reported a two-factor negative symptoms structure consisting of Expression deficits and Experience deficits (Khan et al., 2017). Likewise, social functioning is characterized as Social domain (e.g. social participation, recreation) and Self-reliance domain (e.g. self-care, everyday skills) (Okada et al., 2021). Specifically, Experience deficits factor and the Self-reliance-reliance execution domain were associated with work outcome in patients with schizophrenia (Okada et al., 2021; Llerena, et al., 2018; Harvey et al., 2017). Therefore, the aims of this study were 1) to conform the two-dimensional structure, and 2) to improve our previous model for predicting work outcome in patients with schizophrenia. Specifically, sub-domains of negative symptoms and social function were considered in the analyses.
Methods: Participants: Data were obtained from 293 patients with schizophrenia. 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.
Assessment: The following variables were assessed: 1) the Positive and Negative Syndrome Scale (psychotic symptoms); 2) the Wechsler Adult Intelligence Scale-Third Edition (intellectual or cognitive ability); 3) the Social Functioning Scale Individuals' version Modified for MATRICS-PASS (social function); 4) the Social Activity Assessment (work status, as measured by hours worked per week).

Analyses: Confirmatory factor analysis (CFA) was conducted designating two factors (Expression deficits factor: N1, N3, N6, G7, Experience deficits factor: N2, N4, G16). Four separate logistic regression analyses were conducted with work hours dichotomized by four criteria (0, 10, 20, or 30 hours per week) as dependent variables Two factor scores (Expression deficits and Experience deficits) and domain scores from the SFS, as well as intellectual, demographic, and clinical characteristics, were entered as independent variables.

Results: Fit measures in the CFA were sufficient enough to validate the two-factor structure. Logistic regression analyses revealed that the Self-reliance execution domain was the strongest factor in all the regression models. Similarly, the Experience deficit factor was significant in all models except the model with the 0 hours per week criterion.

Discussion: This study confirmed the dimensional structure of negative symptoms in Japanese patients with schizophrenia. Furthermore, we demonstrated the Experience deficits factor in negative symptoms and the ability of Self-reliance execution to predict work outcome in this disorder. Our study suggests significance of the bio (alleviation of negative symptoms)-psycho (rehabilitation in Self-reliance domain)-social model approach to support work outcome in patients with schizophrenia.

References:

Khan, A et al. Innov Clin Neurosci. 2017: 14, 30-40

Harvey et al., Innov Clin Neurosci. 2017: 14, 18-22

Llerena, K. et al. Schizophr Res. 2018: 192, 148-153

Sumiyoshi, C., et al. Schizophr Res. 2018: 201, 172-179

Okada, H., et al. Schizophr Res Cogn. 2021:23, 1001911162

S7. EMOTION RECOGNITION TRAINING IN YOUTH AT FAMILIAL HIGH RISK OF SCHIZOPHRENIA

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Background: Individuals living with schizophrenia and their first-degree relatives (individuals at familial high risk (FHR)) experience difficulties in many social cognitive domains, including emotion recognition. These deficits can negatively impact social interactions, thus impacting well-being. Recent research indicates that emotion recognition training can improve emotion recognition performance in individuals with schizophrenia. Similar training programs could also benefit individuals at FHR, but it remains to be tested. In our study, we aim to determine the initial feasibility and efficacy of an emotion recognition training program in individuals at FHR.

Methods: In this ongoing randomized controlled trial (NCT: 04681807), thirty-six young healthy controls and thirty-six individuals at FHR will be recruited. At baseline, all participants are administered a social-cognitive battery and an fMRI scan. Individuals at a FHR also complete a second fMRI scan and emotion recognition assessments one-week post-training. After the baseline assessment, individuals at FHR are randomized into one of two groups (Group A and Group B). All participants receive four hours of training delivered over a two-week period. In the intervention

group condition, participants complete emotion recognition exercises while individuals in the active control group condition complete exercises that does not specifically target emotion recognition.

Results: Seven individuals at FHR have been enrolled, and four participants have completed the training program (2 participants in each group). At baseline, Group A had a mean emotion recognition accuracy of 76.25 % (SD = 5.30%) while Group B had a mean emotion recognition accuracy of 83.75% (SD = 1.77%). One-week post-training, both groups experienced a trending increase in accuracy in identifying emotions. Group A experienced an 8.20% increase (SD = 10.61%), with a large effect size (d = 0.79). Group B experienced an average 1.49 % increase (SD = 7.07%), with a small effect size (d = 0.24). At the end of the training, all participants were asked how much they agreed to this statement: "I think I was assigned to the active training group" on a Likert scale of 1 (totally disagree) to 5 (totally agree). In group A, participants agreed with a level of certainty of 3/5 and in Group B, participants agreed with a level of certainty of 5/5.

Our current sample is very small, but more participants will be completing the training in the coming months. As social cognition, especially emotion recognition, is impaired in individuals at FHR of schizophrenia, it is important to conduct more research in this field to better understand how we can improve this ability. Thereby, it may help individuals at FHR to improve their prognosis. With a larger number of participants enrolled, this study may contribute to the understanding and future development of evidence-based preventative care in psychiatry.

S8. UNDERSTANDING OTHERS AND BEING UNDERSTOOD IN SOCIAL INTERACTIONS: THE ROLE OF THEORY OF MIND AND CLINICAL SYMPTOMS IN PEOPLE WITH SCHIZOPHRENIA SPECTRUM DISORDERS

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Background: Language production is often affected in schizophrenia spectrum disorders (SSD), yet a limited number of prior studies relied on joint tasks performed with a real interaction partner. The Storytelling in Sequence Task (STST) is a recently developed joint task based on the referential communication paradigm (Fossard et al., 2018). The task is performed between the participant and an interaction partner and has never yet been used to study language production in SSD. While the verbal productions from this task can be analyzed in several different ways, the current study aimed to determine whether individuals with SSD are judged to make it less easy or less interesting to perform the joint task with them, relative to a healthy control group. A second objective was to examine the link between these judgements and clinical symptoms as well as theory of mind (ToM).

Methods: The sample includes 51 stable outpatients with a diagnosis of SSD (SSD group; 34.8 years, 37 men) and 69 healthy controls (HC group; 28.4 years 34 men). All the participants performed the STST and the verbal interactions were audio recorded. For each of the nine trials from the STST, the participants' task is to tell a cartoon story to his interaction partner, so the partner can place the images of the stories in the right order. The complexity of the story is manipulated, with three stories per level of complexity. Four raters listened to the anonymized

audio recordings from the STST and were asked to score how easy participants made it to understand them (Facility ratings), how interesting they were to listen to (Interest ratings) and how expressive they were (Expressivity ratings). Clinical symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) five-factor version. ToM was assessed using the Combined Stories Test (COST).

Results: For the Facility ratings, a significant main effect of group emerged ($F(1,116) = 13.36$, $p < .001$), whereas the main effect of complexity of the stories and the interaction with group were not significant. For the Interest ratings, a significant main effect also emerged ($F(1,116) = 46.50$, $p < .001$), with no main effect of complexity or interaction with group. For the Expressivity ratings, there was a significant main effect of group ($F(1,116) = 53.46$, $p < .001$), as well as a significant main effect of referential complexity ($F(2,232) = 5.25$, $p = .006$), but no interaction.

In the SSD group, the Facility ratings were significantly associated with the Interest ratings ($r = .47$, $p < 0.001$), ToM performance ($r = .41$, $p = 0.003$), Positive symptoms ($r = -.34$, $p = 0.016$), Negative symptoms ($r = -.45$, $p < 0.001$), Cognitive/Disorganization symptoms ($r = -.61$, $p < 0.001$) and Excitability/hostility symptoms ($r = -.31$, $p = 0.026$). The Interest ratings were significantly associated with the Expressivity ratings ($r = .89$, $p < 0.001$), ToM performance ($r = .31$, $p = 0.026$) and Negative symptoms ($r = -.58$, $p < 0.001$). The Expressivity ratings were significantly associated with Negative symptoms ($r = -.53$, $p < 0.001$).

Discussion: The results of the current study replicate and extend those from a previous study by Achim et al. (2022) using a different joint task. Notably, these results include the strong association between Interest and Expressivity ratings. Finally, the results highlight that people with SSD who experienced ToM difficulties also have more difficulty making themselves understood by others.

S9. CROSS-CULTURAL MEASUREMENT OF SOCIAL COGNITION IN U.S. LATINXS WITH A SCHIZOPHRENIA DIAGNOSIS

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Background: Because social cognition (SC) reliably predicts functional outcomes in schizophrenia, psychosocial interventions targeting SC are crucial. However, most SC data has been collected from primarily White samples in the U.S. and in Western cultures, potentially resulting in culturally incongruent SC interventions and limited functional improvements for minoritized groups. Given that Latinxs are the largest ethnoracial minoritized group in the U.S. and evidence suggests significant differences in SC task performance when compared to their white peers, the current study aims to evaluate validated measures of SC for use with U.S. Latinxs living with schizophrenia. Culturally appropriate measurement during clinical trials is critical for developing equitable and inclusive treatments.

Methods: Using participant data from the Social Cognition Psychometric Evaluation (SCOPE) study, this secondary data analysis examines the psychometric properties of SC tasks in a sample of Latinxs with schizophrenia (N = 73). A comparison group of non-Latinx white individuals (N = 115) was drawn from the SCOPE dataset and matched to the Latinx group based on age, gender, and educational attainment. SC tasks included the Bell Lysaker Emotion Recognition Task (BLERT), Penn Emotion Recognition Task (ER-40), Hinting Task, and The Awareness of Social Inferences Test (TASIT). Tasks were evaluated by characteristics of their distributions, test-retest

reliability, internal consistency, utility as a repeated measure, relationship to functional outcome, and practicality and tolerability. Mean scores were compared using t-tests. Step-wise regression models examined the associations between SC and key domains of functional outcome, including functional capacity, social skills competence, and real-world functional outcome. The regression models first account for variation attributed to a neurocognition composite score (MATRICS) while SC tasks are entered into a second block to examine incremental validity. All analyses were completed in R 4.2.1.

Results: Cross-cultural comparisons demonstrated mixed psychometric results Promising properties included acceptable internal consistency of SC tasks in the Latinx group (Pearson's r between 0.66 - 0.83) and were similar to that of non-Latinxs. While the white group performed adequately on test-retest reliability, the Latinx group fell slightly below (e.g., Pearson's r of .56 for ER-40 and .59 for TASIT). Significant mean differences were present for the Hinting Task (Latinx M = 12.95; white M = 14.25; $t(184) = 2.5$, $p < .05$) and TASIT (Latinx M = 45.40; white M = 47.75; $t(185) = 2.14$, $p < .05$), with Latinxs performing more poorly. Regarding predictability, SC tasks consistently predicted functional outcomes beyond neurocognition for the white group but were inconsistent for the Latinx group. Specific patterns will be discussed. Latinxs tended to rate SC tasks significantly more tolerable than their white peers but took significantly longer to complete the Hinting Task and TASIT.

Discussion: The results of the current study suggest the differential performance of SC tasks between Latinx and white groups, most pronounced in the predictability of the tasks on key measures of functional outcomes. Researchers should critically consider differential properties of these tasks for Latinxs with schizophrenia. These findings are an important first step in assessing SC tasks for Latinxs. Further research should intentionally recruit a Latinx sample large enough to perform sophisticated tests of measurement invariance (i.e., IRT). Qualitative research will also be important for identifying the nature of measurement bias in terms of sociocultural factors that influence SC.

S10. THE INFLUENCE OF SCHIZOTYPY ON THE RELATIONSHIP BETWEEN DEPRESSION AND QUALITY OF LIFE

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Background: Depressive symptoms negatively impact quality of life. While this relationship is well-established, we have yet to develop an understanding of how the relationship might differ based on one's level of schizotypy. Schizotypy is a personality trait that can indicate risk for schizophrenia-spectrum disorders when found in very high levels. Schizotypy is independently related to both depression and quality of life, yet few studies have investigated the intersection of these three variables. Further, no study to date has investigated these relationships separately in women and men. This is important, as women experience high rates of depression, and literature suggests that depressive symptoms in women may be more strongly linked to both mental and physical quality of life. This study aims to examine the relationship between depression and quality of life separately in women and men to fill this gap in the literature. We hypothesize that 1) higher depression will be correlated with lower quality of life across the sample; and 2) schizotypy will moderate the relationship between depression and quality of life such that for people higher levels

of schizotypy, depression will have a weaker relationship to quality of life, while for people with lower schizotypy, depression will be more strongly related to quality of life. Lastly, we aim to differentially explore these relationships in men and women separately.
Methods: We collected data from 856 undergraduate students (710 women, 146 men; mean age=21.8) who completed self-report questionnaires assessing depression, quality of life, and schizotypy. Correlations informed bivariate relationships among variables, while moderation analyses were used to investigate whether there was an interaction between depression and schizotypy in the prediction of quality of life. Parallel models were run in women and men.
Results: Resultsindicated that, as expected, greater depression is related to worse quality of life ($p<.001$), and higher schizotypy was related to higher depression ($p<.001$) and lower quality of life ($p<.001$). Moderation analyses revealed that schizotypy significantly moderates the relationship between depression and quality of life for women ($f(1,669)=7.07$, $p=.008$), but not men ($f(1,133)=1.02$, $p=.32$). Interestingly, the nature of the relationship between depression and quality of life in women remains the same across all levels of schizotypy (i.e., higher depression significantly predicts lower quality of life), but the strength of the relationship varies such that for those with very high or very low levels of schizotypy, the relationship is weaker.
Discussion: Our findings indicate that depression is most strongly related to quality of life for women with moderate levels of schizotypy, while schizotypy does not impact this relationship in men. With replication, findings suggest that women with moderate levels of schizotypy may experience the most detrimental impact of depressive symptoms on quality of life. This investigation highlights the importance of investigating the unique female experience, especially with regard to schizotypy as a moderator. Future work should explore whether schizotypy subtypes (e.g., positive, negative) differentially influence these relationships and whether interventions relating to schizotypy may be worth considering as possible adjunct treatments to improve quality of life for women experiencing depressive symptoms.

S11. COGNITIVE MODEL OF NEGATIVE SYMPTOMS: META-ANALYTIC REVIEW

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Background: According to the cognitive model, negative symptoms can be conceptualized, in part, as maladaptive behavioural and emotional responses to dysfunctional beliefs. Specifically, six distinct cognitions have been proposed to contribute to the development, expression, and maintenance of negative symptoms: defeatist performance beliefs; asocial beliefs; low expectancies for success; low expectancies for pleasure; internalized stigma; and perception of limited resources. In order to integrate and synthesize the extant research from this growing body of literature, the present study conducted a comprehensive meta-analysis of the relationships between negative symptoms and each of these six dysfunctional belief systems among patients with schizophrenia-spectrum disorders.
Methods: A broad search of potential studies for inclusion was conducted in MEDLINE and PsychINFO, and supplemented by manual searches of reference lists and Google Scholar. Abstracts were independently analyzed by two raters, and full text-articles were inspected against the inclusion criteria, which required studies to include measures of negative symptoms and at

least one of the relevant belief systems. In the event that a direct test of association was not reported, study authors were contacted with this request. Effect sizes were represented by z-transformed Pearson's r correlations and random-effects models were used to pool effect size estimates to account for expected heterogeneity. Sub-group analyses were also conducted to examine differential relations among the diminished motivation and diminished emotional experience subdomains of negative symptoms. When sufficiently powered, meta-regression analyses were carried out to examine the moderating role of age, sex, and illness duration.
Results: The meta-analysis for the relationships between overall negative symptoms and defeatist performance beliefs, asocial beliefs, low expectancies for success, low expectancies for pleasure, and internalized stigma revealed small significant effects; however, the relationship between negative symptoms and perception of limited resources (k = 10) was non-significant. For defeatist performance beliefs, data was pooled from 29 studies with 2282 participants (effect size (r) = 0.22, 95% confidence interval (CI) = 0.16, 0.28, $p < 0.0001$). Subdomain analyses revealed similarly small significant effects for diminished motivation (k = 24, effect size (r) = 0.20, 95% CI = 0.15, 0.24, $p < 0.0001$) and diminished emotional expression (k = 19, effect size (r) = 0.17, 95% CI = 0.09, 0.24, $p < 0.0001$). Data for asocial beliefs was pooled from 6 studies with 511 participants (effect size (r) = 0.20, 95% confidence interval (CI) = 0.11, 0.28, $p < 0.0001$). Subdomain analyses for diminished motivation (k = 4) and diminished emotional expression (k = 3) were non-significant. For low expectancies of success, data was pooled from 39 studies with 4511 participants (effect size (r) = -0.20, 95% confidence interval (CI) = -0.14, -0.25, $p < 0.0001$). Subdomain analyses indicated small significant effects for diminished motivation (k = 11, effect size (r) = -0.27, 95% CI = -0.18, -0.35, $p < 0.0001$) and diminished emotional expression (k = 8, effect size (r) = -0.16, 95% CI = -0.03, -0.28, $p = 0.02$). The analysis for low expectancies for pleasure consisted of 4 studies with 213 participants (effect size (r) = -0.23, 95% confidence interval (CI) = -0.09, -0.35, $p = 0.001$). For internalized stigma, data was pooled from 58 studies with 7240 participants (effect size (r) = 0.17, 95% CI = 0.11, 0.23, $p < 0.0001$). The subdomain analysis revealed a significant relationship for diminished motivation only (k = 16, effect size (r) = 0.25, 95% CI = 0.18, 0.33, $p < 0.0001$). Across all analyses, there were no significant moderating effects of age, sex, or illness duration.
Discussion: Advancing our understanding of the cognitive model of negative symptoms represents an essential next step to the development of more optimized and precision-based cognitive-behavioural interventions for negative symptoms in schizophrenia. The results of this meta-analysis underscore the importance of specifically targeting defeatist beliefs, asocial beliefs, low expectancies for success, low expectancies for pleasure, and internalized stigma as dysfunctional belief systems contributing to the manifestation of negative symptoms.

S12. EXPLAINING INDIVIDUAL DIFFERENCES IN COGNITION FROM SYMPTOMS OF SCHIZOPHRENIA

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Background: Neurocognitive impairment is a critical feature of schizophrenia spectrum disorder (SSD). The relationship between cognition and symptoms in SSD is a well-researched topic. The dominant position is that episodic memory is associated with negative symptom scales, but the

specific aspects of negative (or positive) symptoms that dominate this relationship are unknown. The present study aims to clarify this by analyzing the individual symptoms overlapping with performance on various cognitive tests in a large sample of SSD patients.

Methods: We introduced a novel multivariate analysis method that allowed the overlap between symptoms and cognition to be explored at the level of individual items while still avoiding concern over the risk of Type I errors. Cross-Validation Constrained Principal Component Analysis (CPCA) was carried out on a sample of SSD patients in the early stages of psychiatric treatment (n = 213). Components optimized to overlap with symptoms measured by the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS) were formed from measures of attention, processing speed, verbal and visual memory, learning, working and spatial memory, planning, and executive functions.

CPCA allows variance in criterion variables (cognition) to be constrained to that predictable from the predictors (schizophrenia symptoms) prior to dimension reduction of the criterion variables. CPCA was carried out on 17 cognitive measures as the criterion variables and 59 SANS and SAPS questionnaire items as the predictor variables. CPCA is a supervised dimensionality reduction technique that combines the variance constraints of multivariate multiple regression and the dimension reduction of PCA into a unified framework. The current application of CPCA involves the extraction of dimensions from the criterion variables (cognitive measures) that are optimized to be predictable from a set of predictor variables (i.e., symptom rating scale items). Exploration of the items which dominate this overlap without increased concern over Type I errors is achieved using variance constraints, dimension reduction, split-half cross-validation, and permutation tests.

Results: We discovered three components of cognitive functions that optimally overlap with symptoms. The first one was dominated by cognitive measures of sustained attention and processing speed and was predicted by the SANS item ‘serial 7s’, measuring attention and working memory skills. The second component was characterized by verbal memory and learning. It was mainly dominated by items related to reduced nonverbal communication of emotion perception (e.g., poor eye contact), disordered verbal communication (e.g., alogia and derailment), disengagement (e.g., long pauses for replies, avolition-apathy, and social inattentiveness), and odd behaviour (e.g., ritualistic and bizarre behaviour). The third component focused on visual memory and learning and working memory, negatively predicted by items measuring inattention, reduced nonverbal communication of actions (paucity of expressive gestures, spontaneous movements and reactive smile and laughter), and the ‘serial 7s’ item.

Discussion: The aim of this study was to investigate the components of cognitive domains that optimally overlap with symptom items on the SANS and SAPS in SSD patients in the early stages of psychosis treatment.

We differentiated between several symptoms: reduced nonverbal communication of emotion and action, disordered verbal communication, disengagement, odd behaviours, inattention, and working verbal memory impairment having specific relationships with cognitive decline in verbal and non-verbal memory and attention. In particular, we discovered that reduced nonverbal communication of emotion and disordered verbal communication, disengagement, and odd behaviours predicted verbal memory processing, whereas nonverbal communication of action was related to non-verbal cognitive processing.

S13. NEGATIVE MOOD STATES AS A CORRELATE OF COGNITIVE PERFORMANCE AND SELF-ASSESSMENT OF COGNITIVE PERFORMANCE IN BIPOLAR DISORDER VERSUS SCHIZOPHRENIA

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Background: Mood states have been reported to manifest a cross-sectional correlation with self-assessment accuracy across functional domains and psychiatric conditions. Ecological momentary assessment (EMA) provides a strategy to examine the momentary course and correlates of mood states. This study tested the association of moods assessed longitudinally with accuracy of immediate self-assessments of cognitive test performance in participants with schizophrenia and bipolar disorder.
Methods: 240 well-diagnosed participants with schizophrenia and bipolar disorder completed a subset of tests from the MATRICS Consensus Cognitive Battery and an immediate self-assessment of cognitive performance. Differences between actual and self-reported performance were used to index the accuracy of self-assessment. Daily smartphone EMA, 3x per day for 30 days, sampled participants´ momentary moods (sad, happy, relaxed, anxious), aggregated into positive affect and negative affect (NA).
Results: Bipolar participants had better cognitive performance, but both samples had equivalent mis-estimation. Repeated-measures analyses found that NA did not manifest significant variability over time either between or within participants in the two diagnostic groups. Within-group analyses found that higher average NA was associated with greater inaccuracy and poorer cognitive performance in participants with bipolar disorder, but not in those with schizophrenia.
Discussion: Predominant negative mood had a significant association with impairments in self-assessment of cognitive performance in participants with bipolar disorder. Our study did not confirm previous cross-sectional findings of more accurate self-assessment associated with greater NA in schizophrenia. These findings suggest that cross-sectional assessments, particularly self-reports, may lead to different results than aggregated data from longitudinal evaluations.

S14. SEX DIFFERENCES IN COGNITION, INDIVIDUAL BRAIN CONNECTIVITY, AND FUNCTIONAL OUTCOMES: A TRANSDIAGNOSTIC ANALYSIS OF 4000+ PATIENTS WITH PSYCHIATRIC DIAGNOSES AND HEALTHY CONTROLS FROM THE UK BIOBANK

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Background: Functional outcomes for individuals living with psychiatric disorders can be defined as the ability to function in areas of everyday life that may be affected by one's illness, including employment, relationships, and general well-being. Well-documented cognitive deficits, including verbal memory (VM), spatial memory (SM), processing speed (PS) and executive functioning (EF), are shared by a wide range of psychiatric disorders and have been found to predict poorer functional outcomes. VM in particular has been associated with functioning, most notably in schizophrenia.

Sex differences in domain-specific cognition have also been reliably found in the general population. Specifically, females tend to demonstrate an advantage for VM, while males show an advantage in SM performance. However, less is known about how normative sex differences in cognition extend to clinical populations, and their impact on functional outcomes. Furthermore, as brain connectivity underlies cognition, investigating differences in overall connectivity is informative for understanding sex and/or clinical differences in cognition.

Methods: In this study, we used the UK BioBank (UKBB) dataset to examine the cognitive performance and functional outcomes of a transdiagnostic sample of patients diagnosed with mental disorders (n = 1429; schizophrenia spectrum disorders n = 43; mood disorders n = 911; anxiety disorders n = 727; obsessive-compulsive disorder n = 8, post-traumatic stress disorder n = 10). We compared patients to a sample of healthy controls (n = 2858) matched on age, sex, and handedness, examining sex differences as well as group interaction effects with sex.

To investigate differences in cognitive performance, we used measures available from the UKBB, including the pairs learning task (VM), the pairs matching task (SM), and the numeric and alphanumeric trail-making tasks (PS and EF). We used multiple measures to holistically assess individual functioning, including the employment score on the Index of Multiple Deprivation (IMD), social support (number of visits from family and friends), and the self-report measures of loneliness, health satisfaction, overall health, and happiness. Finally, using T1-weighted magnetic resonance imaging (MRI) scans and regional cortical thickness values, we generated individualized structural covariance matrices through a jackknife procedure and obtained subject-specific measures of global efficiency, or overall connectivity.

In our statistical analyses, we ran multiple ANOVAs for each of these 11 dependent variables, covarying for age as it significantly differed by sex in our sample. To control for bias due to multiple comparisons, we applied the Benjamini-Hochberg correction, choosing an initial p value of .05. If results were significant, we would conduct an exploratory moderated mediation analysis to see if sex- or patient-related differences in cognitive performance contributed to differences in functioning. Specifically, we would include patient status as our predictor, functional outcomes as the dependent variable, cognition as a mediator, and sex as a moderator of the effect of patient status on cognition.

Results: Consistent with the literature, patients showed poorer SM, PS, and EF, males showed an advantage in SM, and females had better VM. Interestingly, there was an interaction of sex and patient status on VM, such that male patients demonstrated poorer performance on this task ($B = -0.57$, $t(2674) = -2.62$, $p = .009$), with no observed difference between patients and controls overall. Furthermore, we found a small but significant sex difference in global efficiency ($B = 0.07$, $t(4282) = 5.58$, $p < .001$), such that males had greater overall connectivity.

In functional outcomes, patients had poorer employment, more self-reported loneliness, decreased health satisfaction, lower self-rated health, and greater unhappiness. Compared with females,

males in our sample had poorer self-rated health and less social support. No interaction effects were found for sex and patient status, suggesting that observed sex differences appear similarly in patients and healthy controls.

Further, we found that VM mediated poorer functional outcomes in male but not female patients when compared to controls, representing a moderation by sex. Specifically, we found these effects to be significant for employment ($R2 = 0.03$, $F(5,2415) = 17.71$, $p < .001$, 95% CI [0.004, 0.002]), loneliness ($R2 = 0.07$, $F(3,2633) = 49.93$, $p < .001$, 95% CI [0.0133, 0.0997]), health satisfaction ($R2 = 0.05$, $F(3,911) = 15.26$, $p < .001$, 95% CI [0.000, 0.05]), and self-rated health ($R2 = 0.07$, $F(3, 2664) = 71.64$, $p < .001$, 95% CI [0.003, 0.027]).

Discussion: In this study, we found patients to show poorer SM, PS, and EF compared to controls, and we recreated well-established sex differences in cognition. Additionally, overall brain structural connectivity differed by sex, such that it was higher in males. Importantly, male sex moderated poorer VM in patients, and this was predictive of poorer functional outcomes. Findings will contribute to an improved understanding of how differences in cognition related to sex and mental illness are linked to functional outcomes in both healthy and clinical populations.

S15. ADAPTING GROUP COMMUNITY REINFORCEMENT APPROACH AND FAMILY TRAINING TO TARGET SUBSTANCE USE IN EARLY PSYCHOSIS INTERVENTION (CRAFT-EPI): A PILOT STUDY

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Background: Patients with substance use disorders often struggle with treatment-seeking motivation, whereas their family members are typically highly motivated to get help for them. Community Reinforcement Approach and Family Training (CRAFT) is an evidence-based intervention delivered to family members of people who use substances with the aim of increasing their treatment-seeking motivation. Despite research supporting CRAFT's efficacy across diverse populations, and evidence that substance use is both highly prevalent in early psychosis and can negatively impact outcomes, CRAFT had never been studied in early psychosis until a recent pilot study found it to be a feasible and acceptable intervention when delivered to family members individually. Because group interventions can be associated with additional benefit and provide services more efficiently, we adapted the individual intervention for study as a group treatment. Given the profound impact of substance use on psychosis and lack of specialized interventions in this population, we aimed to pilot CRAFT in an early psychosis intervention (EPI) program in a group format for the first time.

Methods: This is a proof-of-concept pre-post single-arm pilot study for family members concerned about the substance use of their 16-to-29-year-old patient receiving EPI services. Family members participated in an individual orientation, 6 weekly sessions, and a booster session 12 weeks later, all held virtually. Family members and their corresponding identified patients were invited to complete assessments at baseline, post-intervention, and 12 weeks, and a focus group at

12 weeks. We assessed feasibility of a larger trial with recruitment, retention, and assessment completion metrics. We evaluated patients' engagement in substance use treatment, readiness to change, and substance use, and families' depression, anxiety, perceived stress, and happiness.
Results: Of 13 potential family member participants assessed for eligibility, 10 consented to participation, and 8 completed the intervention, while 2 were lost to follow-up. We were only able to recruit 4 identified patients. Consented family member participants attended 81% of sessions, and completed 90% of outcome measures. Family members experienced improvements in depression, anxiety, and perceived stress with medium effect sizes (d=-0.39 to -0.52 from baseline to 12-week follow-up). We did not calculate identified patient changes over time due to small cells related to our low recruitment. In the focus groups, participants valued the group format and new skills they learned. Family members expressed desire for more resource handouts at the end of treatment.
Discussion: We found evidence of feasibility for a larger definitive trial based on family member recruitment and intervention delivery, as well as high intervention acceptability, but recruitment of identified patients will require a different approach. At 12-week follow-up, improvement was sustained in most measures. It will be important to determine how to sustain this response over the longer term, and if there are particular characteristics associated with differences in improvement (e.g., primary substance of concern). This study supports further examination of the application of CRAFT to EPI.

S16. BRAIN SUBCORTICAL AND CORTICAL FUNCTIONAL HIERARCHY IN FIRST-EPISODE SCHIZOPHRENIA AND THE TREATMENT EFFECTS AFTER ANTIPSYCHOTICS

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Background: Identifying biomarkers indicative of treatment response in patients with schizophrenia has been a sustained area of research over the past two decades. Commonly used antipsychotics are thought to improve symptoms via the blockade of dopamine D2 receptors which are abundant mainly in subcortical regions. Though the development of neuroimaging acquisition and analysis techniques has led to major progress in investigating the local subcortical changes including striatum in anatomy, function and chemistry before and after antipsychotic treatment, the subcortical-cortical interaction and related biological measures have yet to show consistency in relation to treatment response. Here, a novel gradient-based approach has been introduced to define a non-linear decomposition of high-dimensional resting-state functional connectivity (FC).The concept of gradient focuses on connectomes where voxels with similar connectivity patterns are located close to one another along a given connectivity gradient. Leveraging this method to examine the synchronous measure of subcortical and cortical FC architecture in untreated schizophrenia patients and after treatment further in relation to symptom improvement might providing novel insight of illness- and treatment-related effects on subcortical and cortical interaction.
Methods: Fifty-seven patients (FES0W) and 64 healthy controls (HC) at baseline, and patients after 12-month (FES12M) treatment were recruited. Resting-state functional MRI (rs-fMRI) data

and high-resolution T1-weighted images (T1WI) were obtained for all participants in 3.0T scanner. After functional data preprocessing with conventional steps, the individual subcortical-cortical/cortical-subcortical FC matrix was constructed using Pearson's correlation between the time courses of each voxel. Gradient metrics were calculated using BrainSpace Toolbox. Voxel-based gradient values were generated and group-averaged gradient values were further extracted across all voxels (global), three systems (thalamus, limbic and striatum) in subcortex and 7 networks in cortex. The group comparisons of principal gradient alterations at global and network level were conducted separately between FES0W and HC for investigating illness effects, and between FES12M and FES0W for treatment effects. Correlational analyses were then conducted between the longitudinal gradient alterations and the improvement of clinical ratings, including the Positive and Negative Syndrome Scale (PANSS) and the Global Assessment of Functioning (GAF) scores. False discovery rate (FDR) corrections were used to correct for multiple comparisons and the statistical significance threshold was set at $p < 0.05$ with FDR correction.

Results: In HC group, the gradient values were distributed along the axis from high to low in subcortex with thalamic-striatal-libmic systems and in cortex with primary to transmodal networks, while the gradient maps were consistent with previous characterizations of the spatial distribution of human. We further identified that before treatment, schizophrenia patients exhibited functional segregation in subcortical gradient with expanded global gradient scores involving increased gradient in limbic system and decreased gradient in thalamic and striatal systems compared to HC. While the baseline patients showed functional integration in cortical gradient with compressed global gradient scores including increased gradient in primary visual/sensorimotor networks (VIS/SMN) and decreased gradient in transmodal default mode network (DMN). More importantly, these disruptions were normalized after treatment, and the longitudinal changes of subcortical gradient scores in limbic system were significantly associated with symptom improvement (negatively correlated with increase of GAF scores ($r = -0.376$, $p = 0.018$) and positively correlated with reduction of PANSS total scores ($r = 0.419$, $p = 0.006$) and subscales (disorganization scores: $r = 0.416$, $p = 0.030$ and excitement scores: $r = 0.424$, $p = 0.030$), all results were corrected with FDR corrections). However, there were no significant results: in clinical relation to longitudinal cortical gradient alterations.

Discussion: A novel functional connectome gradient algorithm calculating the spatial representation of subcortical and cortical functional hierarchy was performed by capturing the similarity of whole brain FC profiles between two voxels. The main finding was that the distinct alterations of gradient scores in subcortex and cortex in drug-naïve FES patients and were normalized after antipsychotic treatment. What's more, the longitudinal changes of the subcortical gradients in the limbic system were highly associated with improvements in clinical symptoms. The baseline different gradient patterns of subcortex and cortex may be explained their different roles in the processing perception, motor and cognition, and the gradient-based characterization may represent a more sensitive approach to study treatment effects which reflect their interaction and normalization. The findings also highlighted the subcortical hierarchy could represent a more robust indicator of treatment response than cortical hierarchy.

S17. DOES CULTURE ALTER THE EFFECT OF SCHIZOTYPAL TRAITS ON AUTOBIOGRAPHICAL SPEECH?

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Background: To date, the evidence of whether culture has a meaningful effect on schizotypy presentation remains heavily mixed. There is recent evidence that schizophrenia-like experiences, often conceptualized as lending to a reduced sense of self, influence autobiographical speech and social behavior (Minor et al., 2015; Minor et al., 2017). The current study sought to clarify the effect of culture on schizotypy, and whether culture interacts with schizotypy traits to effect autobiographical speech.
Methods: 121 undergraduate students enrolled in a psychology course at the University of Illinois at Chicago completed a demographics questionnaire, the Schizotypal Personality Questionnaire-Brief Revised Updated (SPQ), and a semi-structed interview assessing autobiographical speech. Of these participants, 57 Hispanic, 39 Asian, and 26 White/Caucasian individuals were included in the statistical analysis, as all other cultural groups did not reach sufficient power. Interviews were coded using the Linguistic Inquiry Word Count (LIWC; Pennebaker et al., 2007) and data was analyzed in R (4.0.2) using linear regression analysis.
Results: The current study found consistent evidence of a main effect of schizotypy traits (i.e., total SPQ score and the four SPQ factors) on autobiographical word use. No significant effect of culture on autobiographical word use nor any significant interaction with schizotypy traits was found.
Discussion: Cultural differences may shape expectations for individuals across phases of life, which may in term alter goal-related retrospection, self-concept, and perceived self-actualization. Further research should continue to assess whether culture has a significant effect on sense of self, autobiographical speech, and schizotypy among diverse groups.

S18. THE GOAL-DIRECTED MOTOR CONTROL, SENSITIVITY TO SELF-CONTROL AND SELF-ATTRIBUTION JUDGEMENT IN SCHIZOPHRENIA: TOWARD UNDERSTANDING HIERARCHICAL PATHOPHYSIOLOGY OF ABERRANT SENSE OF AGENCY

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Background: Sense of agency refers to the feeling of controlling one's own actions and their effects in the outside world. Abnormal sense of agency has been widely reported in patients with schizophrenia. Patients with schizophrenia are considered to have dysfunction in producing sensory predictions of their actions and often make inaccurate self-attribution judgments. However, previous studies found both the behavioral evidences of excess self-attribution and the opposite, diminution of the ability to detect self-control. It remains unclear what specific abnormalities exist from lower to higher levels in the process of emergence of the sense of agency in patients with schizophrenia.
Methods: The present study used three motor-control tasks to systematically assess the goal-directed motor control, active sensing of control, and self-attribution of control, respectively. In all the three tasks, participants' real-time mouse movements were combined with pre-recorded other's motion and introduced an angular bias of 0- or 90-degree. In the reaching task, participants moved a dot to touch a target on the screen as much as they can. This task was conducted to measure the goal-directed motor control performance under a spatial distortion. In the control

detection task, participants identified one target dot whose motion contained a certain level of the participants' real-time mouse movements, among three moving dots. This task measures the ability of sensing one's control via voluntary actions. In the control judgment task, participants made a yes/no binary response to whether they felt that they had a control over the moving dot on the screen. This task reflects the self-attribution judgment based on cognitive inference processes which relies on contextual information and individual criterion.

Results: The results showed that patients with schizophrenia performed significantly worse in the reaching and the control detection tasks than healthy subjects, but their self-attribution judgment did not differ from healthy subjects in the control judgment task. The ability to actively sense their control in the environment via voluntary actions and the ability of goal-directed control are impaired. Furthermore, our classification analyses using clustering and machine learning provided a distinguish accuracy at approximately 90% between patients with schizophrenia and healthy controls.

Discussion: Taking together, the results from the present study showed that patients with schizophrenia perform poorly on goal-directed motor control and have low sensitivity to their control in the environment. Moreover, the assessment of abnormalities in the goal-directed motor control and sensitivity to self-control may be useful for the development of diagnostic support tools based on behavioral tests in the future.

S19. SINGLE-TRIAL READOUT OF MOVEMENT CONTROL IN SCHIZOPHRENIA: STOPPING DURING THE LATE STAGE OF MOVEMENT EXECUTION

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Background: Executive functions, including processing speed, working memory, inhibition, interference control, and mental flexibility are known to be affected in several ways in schizophrenia. Assessment and stratification of these functions rely on extensive and standardized protocols, and they are highly relevant for comorbidity and risk factors in familiarity with schizophrenia. However, long-lasting repeated testing and highly demanding tasks can poorly reveal small but often essential variations in these functions during the course of their life in not fully collaborating or lower educated patients, as well as in younger adults, leading to a suboptimal description of effective status, future potentials, response to treatments and changes in that single patient, since his/her behavior is not completely caught by those protocols.

Moreover, specific importance of fine movement control and inhibition has been recognized in schizophrenic patients, but it is still underused. However, we know that movement execution/inhibition tasks require lower cognitive engagement and collaboration, nevertheless preserving the possibility to reveal underling executive functions features, even at higher levels (go/no go tasks, countermanding tasks, flakner task, stroop test etc).

Recently (Hannah, Aron, Behav Res Methods, 2022), a version of the stop signal task that required participants to respond by making reaching movements with a computer mouse and used movement kinematics to provide single-trial readouts of key performance metrics has been developed, enriching and increasing our possibility to understand (in less time as possible, namely at single-trial level) the ability of a patient to engage in an executive function test. This method can be performed anywhere using a computer and a mouse, since it does not require special

equipment to collect data. They contrasted for the first time kinematic and model-based estimates of inhibitory performance, producing valuable results in healthy patients that needed to be validated in a population of patients.

Methods: We tested this single-trial movement control in schizophrenic patients (n=12) and compared the results to their neuropsychological assessments. Some patients (n=3) were already able to be tested twice, producing a comparison between different time span.
Patients made motor responses by moving a computer mouse from a starting position to targets on the monitor with a single smooth movement to be as fast and as accurate as possible. In 25% of trials a stop signal was present, visible at variables delays.

Results: Our results show that the ability to stop properly can be captured with kinematics at a single-trial level and correlates with the general neuropsychological assessment of the patient at a group level. At a single subject level, however, the performance can be highly affected by the status of the patient at that specific moment, inducing an increased or reduced capability to properly inhibit a movement, in particular in the late stage of the execution.
Discussion: We aim at repeating this task over time, to produce a longitudinal (>12 months) study of the variations, improvements, responses to treatments, and possible correlations with more severe psychotic episodes for each single patient.
Furthermore, this approach can be useful for single-trial neurophysiological correlates of inhibitory behavior for psychiatric patients while used in combination with electroencephalography (EEG) and transcranial magnetic stimulation (TMS) allowing also to probe in real time the effects of the application of repetitive TMS treatments over the executive functions network by reading the inhibitory behavioral patter with a single-trials test.

S20. IMPAIRED NONVERBAL PERCEPTION AFFECTS PSYCHOMOTOR SLOWING AND FUNCTIONING IN CHRONIC SCHIZOPHRENIA

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Background: Psychomotor slowing is the most frequent motor abnormality in schizophrenia, affecting both processing speed and movement. Deficits in nonverbal social perception refer to patients' difficulty to interpret others' facial expressions, hand gestures, and prosody (i.e. intonation when speaking). Impaired nonverbal social perception is linked to motor abnormalities and poor use of hand gestures in schizophrenia. Hence, patients are impaired in the perception, as well as, the production of nonverbal communication, which may hamper their daily social interactions and reduce their quality of life. Both psychomotor slowing and impaired nonverbal social perception are directly associated with poor functioning in schizophrenia. To date, the nature of the relationship between slowing, social perception and functioning in schizophrenia is not clear. Therefore, we investigate whether the relationship between psychomotor slowing and functional capacity/social functioning is mediated by nonverbal social perception deficits in schizophrenia patients. In addition, we compare psychomotor slowing and nonverbal social perception in chronic patients with schizophrenia and healthy controls.

Methods: We included 58 chronic patients with schizophrenia spectrum disorders (mean age = 39.9 ± 12.0 years; 50.0% female; mean education = 13.9 ± 3.3 years) and 31 healthy controls (mean age = 41.4 ± 11.9 years; 51.6% female; mean education = 16.2 ± 2.6 years). All but 7 patients were on antipsychotic medication at the time of testing (mean olanzapine equivalents in mg/d = 11.6 ± 10.5). The mean duration of illness was 15.7 ± 12.5 years. Patients had moderate symptom severity, which was assessed with the Positive and Negative Syndrome Scale (PANSS, mean = 63.8 ± 21.5) and the Brief Negative Symptom Scale (BNSS, mean = 29.2 ± 15.9). In addition, we used the Salpêtrière Retardation Rating Scale (SRRS) to assess psychomotor slowing, and the Mini-Profile of Nonverbal Sensitivity (Mini-PONS) task to assess nonverbal social perception. Functional capacity and social functioning were assessed using the University of California San Diego Performance-Based Assessment (UPSA-brief) and the Specific Level of Functioning scale (SLOF), respectively. Both functional capacity and social functioning were poorer in patients with schizophrenia (UPSA-brief, mean = 78.2 ± 16.9; SLOF mean = 180.4 ± 18.8) than in healthy controls (UPSA-brief mean = 90.4 ± 7.5; SLOF mean = 213.4 ± 3.9). We ran a series of linear regression analyses and used bootstrapping estimates to test mediation effects of nonverbal social perception on the association between psychomotor slowing and functional capacity/social functioning.
Results: After controlling for education, chronic schizophrenia patients displayed more psychomotor slowing and poorer nonverbal social perception than controls (all $F(1, 87) > 8.5$; $p < .01$). In patients, psychomotor slowing predicted poor functional capacity and impaired social functioning (both $\beta = -.9$, $p < .001$). This relationship remained significant after adding nonverbal social perception as a mediator in the models (both $\beta = -.7$, $p < .05$). The bootstrapping estimate indicated that psychomotor slowing is linked to functional capacity/social functioning through nonverbal social perception, thereby supporting indirect effects of the mediation models, both $\beta < -.3$, 95% CI [-.6, -.04]. After controlling for medication, the mediation models accounted for 38% of the total variance on functional capacity ($R2 = .38$, $F(3, 54) = 13.0$, $p < .001$) and 27% of the total variance on social functioning ($R2 = .27$, $F(3, 54) = 7.3$, $p < .001$) in patients with schizophrenia.
Discussion: These findings suggest that psychomotor slowing predisposes people with schizophrenia to worse functional capacity and reduced social functioning, partially through the impairment of nonverbal social perception. This emphasizes the importance of alleviating both psychomotor slowing and nonverbal social perception deficits to improve community functioning in schizophrenia. This study provides insight into a functional model of schizophrenia that could guide the development of novel treatment effects, through the use of brain stimulation, cognitive remediation therapy and virtual reality.

S21. EFFECTS OF METACOGNITIVE TRAINING (MCT) IN SOCIAL COGNITION FOR SCHIZOPHRENIA SPECTRUM AND RELATED PSYCHOTIC DISORDERS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Individuals with schizophrenia spectrum and related psychotic disorders (SSD) experience significant impairments in social cognition that impede functioning, close relationships and parenting. Social cognition is a multidimensional construct consisting of four domains: 1. theory of mind, 2. emotion processing, 3. social perception and 4. attributional style. Metacognitive training (MCT) is an intervention designed to target cognitive biases in psychosis containing two modules addressing social cognition. The aim of this project was to investigate the effects of MCT on social cognition and two of its domains: theory of mind and emotion processing.
Methods: A systematic review and meta-analysis was conducted. Ten electronic databases were searched from 2007 to February 1, 2022 for MCT studies reporting at least one social cognition outcome for people with SSD (1045 identified, 282 assessed). Effect sizes were calculated using Cohen's d in R.
Results: Nine studies were included in the meta-analysis (nMCT= 212, ncontrol = 194). MCT had a small but positive effect on global social cognition (d = .21 [95% CI = .04 – .37]) and theory of mind (d = .29 [95% CI = .07 – .51]). MCT showed no evidence of an effect on emotion processing (d = 0.1 [95% CI = –.26 – .28]). Similar results were obtained in three sensitivity analyses examining the effects of sample size, study design and correction for nested effect sizes.
Discussion: MCT has a small but significant effect on social cognition outcomes for people with SSD. Effect sizes may have been underpowered by small sample sizes and high-quality active control conditions. Our results add to other recent meta-analyses showing significant effects of MCT on clinically relevant outcomes such as positive symptoms, cognitive biases and cognitive insight. Within the current context of the economic recession and the global mental healthcare crisis, MCT stands as a valuable intervention that is cost-effective, accessible, culturally sensitive and adaptable to other psychopathologies. Thus, even if our effect sizes are modest at present, other benefits of MCT make this intervention a worthwhile and clinically relevant contribution to the treatment of psychosis.

S22. RELIABILITY AND VALIDITY OF TWO MEASURES TO ASSESS ROMANTIC AND SEXUAL FUNCTIONS OF PEOPLE WITH PSYCHOSIS

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Background: Psychotic disorders are often linked to poorer social functioning, which encompasses many facets of one's life, including intimate relationships and sexuality. Although healthy romantic relationships have been found to promote recovery from mental illness, romantic relationship functioning is rarely addressed by health professionals and few tools are currently available to adequately evaluate the romantic and sexual functioning of people diagnosed with a psychotic disorder. Most psychometrics instruments currently available are limited to assessing sexual dysfunctions on a physical level (e.g., arousal, penile erection/vaginal lubrication, ejaculatory volume, etc.) or through medication-induced side effects. They fail to assess psychological factors that might influence respondents' overall sexual functioning. The use of a self-report questionnaire that considers several psychological aspects of human sexual experience, such as the Multidimensional Sexuality Questionnaire (MSQ), may be better suited for identifying specific targets for psychological intervention. Indeed, the MSQ includes questions about confidence, self-awareness, and the ability to communicate one's needs during sexual encounters, as well as distress linked to sexual experiences. However, the MSQ has never been empirically

validated in this population. While romantic relationship functioning is severely impaired among people with psychotic disorders, no psychometric instrument for assessing this social ability in this population has been validated yet. Only the Romantic Relationship Functioning Scale (RRFS) has been specifically developed for use with people with serious mental illness, but its psychometric properties have never been evaluated in a sample of individuals with psychotic disorders. There is a clear need for valid tools that can be used to evaluate this population's romantic and sexual functioning, and consequentially, offer corresponding services and support to improve their intimate relationships. Given the potential research and clinical utility of the MSQ and the RRFS, the goal of the present study was to conduct a preliminary validation (i.e., construct validity, internal consistency, convergent validity, test-retest reliability) of these two instruments among persons with psychosis.

Methods: A total of 196 participants were recruited. Individuals were included if they were 18 years of age or older and had reported having been formally diagnosed with a schizophrenia-spectrum disorder (e.g., schizophrenia, schizoaffective disorder, schizophreniform disorder, etc.) or a mood disorder with psychotic features.

A sociodemographic questionnaire was used to collect descriptive data. Convergent validity was assessed using the Intimacy subscale of the First-Episode Social Functioning Scale (FESFS; Lecomte et al., 2014), the Self-Esteem Rating Scale – Short Form (SERS-SF; Lecomte et al., 2006), and the Anxiety and Depression subscales of the Brief Symptom Inventory (BSI; Derogatis and Melisaratos, 1983). The MSQ and the RRFS were the primary measures of interest for this study. The MSQ is a 60-item self-report questionnaire that measures several tendencies associated with human sexuality across 12 subscales. The MSQ's 12 subscales can be divided into two dimensions : positive score (i.e. positive sexual aspects) and negative score (i.e. negative sexual aspects). The RRFS is a 22-item questionnaire assessing various aspects of romantic competence.

After providing informed consent, participants completed each of the above measures online through the Qualtrics platform. In addition, a subset of participants (n = 40) agreed to complete the MSQ and the RRFS twice to measure test-retest reliability, with the second administration occurring two weeks after the first.

Results: Confirmatory factor analyses were performed using R version 4.0.0 to evaluate the construct validity of the MSQ and the RRFS subscales as originally conceptualized. Internal consistency calculations (Cronbach's alpha) were also computed in SPSS version 27, as were correlational analyses in order to assess convergent validity and test re-test reliability.

The original factor structures of the MSQ and the RRFS were found to be acceptable, with alphas ranging from 0.68 to 0.94 and 0.74 to 0.86, respectively.

MSQ Positive and Negative scores were significantly correlated with FESFS Intimacy and SERS-SF scores. MSQ Negative scores were also correlated with BSI Anxiety and Depression scores, although MSQ Positive scores were not. Meanwhile, RRFS scores were significantly correlated with all convergent measures.

Test-retest reliability was high for both MSQ Positive ($r = .90$, $p < .001$) and Negative ($r = .93$, $p < .001$) scores, as well as RRFS scores ($r = .90$, $p < .001$).

Discussion: Given that both measures were found to be valid and reliable when used with individuals with a psychotic disorder, researchers and clinicians may benefit from employing these

tools to better understand the romantic and sexual functioning of this population. By taking interest in the intimacy and sexuality needs of this population beyond concerns with sexual dysfunction, we can move away from pathological models of mental illness towards recovery-oriented care.

S23. EVALUATING THE SOCIAL FUNCTIONING SCALE MODIFIED FOR USE IN INDIVIDUALS AT CLINICAL HIGH-RISK FOR PSYCHOSIS

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Background: Social functioning deficits occur prior to the onset of psychosis and predict conversion to psychosis in clinical high-risk (CHR) populations. The Social Functioning Scale (SFS), a self-report measure of social functioning, is widely used in adults with psychosis but has not been tailored to CHR individuals. CHR syndromes overlap with the adolescent/young-adult developmental period, a time with unique social demands and contexts. The current study evaluates a modified version of the SFS in CHR individuals.

Methods: Two independent samples of CHR participants (n=84 and n=45) and non-CHR participants (n=312 and n=42) completed the SFS and a psychosis-risk interview. Resulting factors were compared across diagnostic categories (CHR, Major Depressive Disorder, Generalized Anxiety Disorder) and community controls (CC) who were not excluded for any psychopathology except psychosis, depression, and anxiety. CHR participants completed scales of negative symptoms, global social and role functioning, cognition, and finger tapping as measures of convergent and divergent validity.

Results: Exploratory factor analysis identified three SFS factors (RMSEA=0.05) which demonstrated reliability in a confirmatory analysis in an independent sample: Recreation (α=0.82), Nightlife (α=0.85), and Interpersonal (α=0.69). Factors and their composite score demonstrated increased social deficits in CHR compared to CC and depression groups and showed expected convergent (r's=0.30-0.54) and divergent (r's=-0.004-0.26) validity with appropriate measures.

Discussion: These findings suggest that there are reliable, valid, and developmentally relevant categories of social behavior within the SFS that differentiate between CHR and MDD or CC individuals. Recommendations for future work with CHR populations are included.

S24. NEUTROPHIL EXTRACELLULAR TRAPS (NETS): A NOVEL CELLULAR MECHANISM IN SCHIZOPHRENIA AND THE IMPLICATIONS OF EARLY-LIFE ADVERSITIES

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Background: Neutrophil Extracellular Traps (NETs) are web-like structures involved in the killing of bacteria, fungi, parasites, and viruses. It is becoming increasingly apparent that the

release of NETs from functionally activated neutrophils is central to both the initiation and chronicity of autoimmune and inflammatory diseases and COVID-19. In experimental studies, NETs inhibitors limit peripheral and central inflammation and associated behavioural changes in mice. Previous studies using blood cytokines to stratify patients with schizophrenia suggest that only a subset presents a low-grade inflammatory state. However, these studies have not addressed whether environmental factors such as childhood maltreatment contributed to identifying inflammatory clusters. Moreover, a neutrophil-related mechanism (NETs) has never been investigated in the field. We investigated NETs as a novel biological mechanism in early schizophrenia and their role together with interleukin-(IL-6) and childhood maltreatment in identifying cluster subgroups.

Methods: Clinical study: We used data available from the STREAM study, a case-sibling-control investigation conducted in the Ribeirão Preto catchment area (São Paulo, Brazil). The sample included individuals with early-stage schizophrenia spectrum (n=78), sex- and age-matched controls (n=78), and available unaffected siblings of patients with early schizophrenia spectrum (n=25). A history of childhood maltreatment was evaluated using the Childhood Trauma Questionnaire. NETs and IL-6 were evaluated in the plasma using the Quant-iT PicoGreen kit and multiplex, respectively. Fresh neutrophils were isolated from healthy donors to test the effect of antipsychotic drugs (haloperidol or risperidone) on NETs release after activation with phorbol myristate acetate in vitro. To evaluate group differences on NETs and IL-6, we used general linear models with Bonferroni post-hoc, adjusted for sex, body mass index (BMI), tobacco smoking, and psychoactive substance use. We used two-way ANOVA with Bonferroni post-hoc to test the effect of antipsychotics on NETs in vitro.

To identify clusters, we applied unsupervised two-step clustering analyses with Bayesian Criterion to estimate the maximum number of clusters after integrating values of NETs, IL-6, and childhood maltreatment scores. Rodent model: Juvenile male Sprague-Dawley rats (postnatal day, PND 24) were exposed to an adolescent early stress protocol (a combination of daily inescapable footshock from PD31-40, and three restraint stress sessions, PD31, 32, and 40) or left undisturbed (controls). At PN51, NETs and IL-6 were evaluated in serum. We also measured levels of NETs released from fresh neutrophils isolated from rats' bone marrow.

Results: We found increased NETs in the plasma of patients with early schizophrenia, compared to both their unaffected siblings and community controls (n=78), irrespective of sex, body mass index, psychoactive drug use, or tobacco smoking ($F=50.79, df=2, p<0.001$). Increased NETs in patients were unrelated to duration of antipsychotic treatment ($p>0.05$). This was further discarded using an in vitro assay in which both haloperidol and risperidone inhibited NETs release from stimulated neutrophils. By applying unsupervised two-step clustering analysis, we identified two main clusters; childhood maltreatment scores and NETs were the most important variables contributing to cluster separation (high-CL1 and low-CL2). Patients with high-CL1 (61.5%) had significantly higher childhood maltreatment scores ($F=26.23, df=5, p<0.001$), NETs ($F=25.17,5, p<0.001$), and IL-6 ($F=3.87, df=5, p<0.002$) levels than the remaining groups. Using a rat model based on stress exposure, we found that adolescent stressed rats had higher NETs ($t16=5.18$, $p<0.001$) and IL-6 ($t10=6.33$, $p<0.001$) levels in serum compared to non-stressed rats, with a tendency to produce more NETs from the bone marrow.

Discussion: The participation of peripheral cellular immunity, related mechanisms, and their association withlow-grade inflammation in schizophrenia is fairly unexplored. The release of NETs from

neutrophils is crucial to immune defence and autoimmunity. However, exacerbated NETs foster

chronic inflammation, and controlling NETs has become a relevant therapeutical target for various non-infectious and autoimmune diseases and COVID-19. Most of the NETs-associated diseases, such as psoriasis, diabetes, and cardio-metabolic disorders, are comorbidities for psychosis and schizophrenia that contribute to a substantial reduction in life expectancy. Our study demonstrates for the first time a novel cellular-based mechanism in schizophrenia that suggests neutrophils are in an active and functional state. We further suggest that NETs and early stress should be considered in future studies attempting to identify immune biological subgroups for more personalised treatments to improve quality of life and life expectancy in these individuals.

S25. STRESSFUL LIFE EVENTS MODERATE THE ASSOCIATION BETWEEN THE DURATION OF UNTREATED PSYCHOSIS AND CEREBROSPINAL FLUID LACTATE DEHYDROGENASE IN FIRST EPISODE PSYCHOSIS

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Background: Previous studies have reported associations between cerebrospinal fluid (CSF) biomarkers that involve bioenergetics systems (e.g. lactate dehydrogenase [LDH], glucose) and the clinical expression of first episode psychosis, including an association between LDH and prodromal symptoms. We aimed to study whether there is a relationship between the duration of untreated psychosis (DUP) and CSF biomarkers in first episode psychosis, and whether stressful life events could moderate the association.

Methods: We studied 95 inpatients (58.9% men, 41.1% women) with a first episode psychosis. All participants were informed about the nature of the study, which was approved by the local Ethics Committee, and signed a written informed consent. A lumbar puncture was performed at index admission (baseline) to study the CSF parameters (glucose, total proteins, lactate dehydrogenase [LDH]). The DUP was assessed with the Quick Psychosis Onset and Prodromal Symptoms Inventory (Q-POPSI). Stressful life events (SLEs) in the previous 6 months were assessed with the List of Threatening Experiences. We used a dichotomous variable for SLEs, defined as having experienced at least one SLE. Statistical analyses were performed with SPSS v. 25.0. Total protein and LDH concentrations were log transformed (ln) for reducing skewness. Multiple linear regression analyses were conducted for exploring the association between DUP and CSF parameters (CSF parameters were considered the dependent variable). Age, gender, DUP and SLEs were considered independent variables. We tested the interaction DUP by SLEs. Significant interactions were included in the final model. Significance was defined as $p<0.05$.

Results: Fifty-four patients (56.8%) reported an SLE in the previous 6 months. There were no significant differences in DUP between patients with or without SLEs (40.2 +- 60.6 vs 34.9 +- 37.5, p= 0.625). There were no significant differences in CSF biomarkers between SLE groups. In the multiple linear regression analyses we found a significant interaction between DUP by SLEs in relation to CSF LDH concentrations (standardized beta= -0.320, t= -2.084, p= 0.040). In those patients with SLEs, the shorter DUP was associated with higher CSF LDH concentrations whereas those with longer DUP and SLEs had lowered CSF LDH concentrations. No significant associations were found between the DUP or SLEs and other CSF biomarkers (glucose, total proteins).

Discussion: Our study suggest that SLEs moderate the relationship between the DUP and CSF LDH concentrations. These results are in accordance with the allostatic load model which suggests that chronic stress contributes to a disbalance of stress-related biomarkers that might be preserved with acute stress. An important limitation of our study is the cross-sectional design with the retrospective assessment of the DUP. Therefore, we cannot infer causality, and future longitudinal studies conducted in cohorts of people at risk for psychosis might explore whether stressful life events moderate the relationship between psychotic symptoms and CSF biomarkers that involve bioenergetics systems.

S26. ANTIPSYCHOTIC MEDICATION AFFECTS SPEECH QUALITY IN A SAMPLE OF FIRST EPISODE PATIENTS

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Background: The quantification of language and speech in schizophrenia-spectrum disorders (SSD) has shown promise as biosocial marker for diagnosis, symptomatology and prognosis. However, antipsychotic medication also changes speech characteristics. Antipsychotic use is associated with speech deficiencies such as slower speech or impaired quality of voice. In this study, we evaluated the impact of dosage and type of antipsychotic medication on acoustic measures of speech in persons with first-episode psychosis (FEP). Because of presumed gender differences in both speech characteristics and medication effects, subgroup analyses were performed.

Methods: In total, 102 subjects were selected from baseline assessments of the HAMLETT study, a large ongoing antipsychotic dose-reduction trial. Subjects were 3-6 months in remission after FEP, >18 years of age and native Dutch speakers. A semi-structured interview was recorded using a digital audio recorder. After preprocessing and selecting only patient speech, a subset of the eGEMAPS acoustic feature set was extracted from the acoustic signal, focusing on measures of voice quality. Antipsychotic dosage was recalculated to olanzapine dose equivalents. The Dopamine 2 receptor occupancy (D2RO) was calculated per medication, according to a mathematical model. In addition, antipsychotics were divided into categories of either strongly binding or weakly binding, based on D2 receptor affinities. Correlational analyses were performed for jitter, shimmer and temporal characteristics of speech. Regression analysis for voice quality and medication dosage were performed, for both men and women separately.

Results: D2RO correlated significantly with jitter and the standard deviation (SD) of jitter, in men and women separately as well as both groups combined (all $p<0.05$). A regression analysis on jitter SD showed a significant effect of a dosage * binding affinity, $p = 0.003$, $F(1,96)=9.53$, $R2 = 0.15$. In men (n=71), D2RO was no longer significantly correlated with shimmer, while for women (n=31) the effect remained. In order to investigate possible effects within medication types, analyses were repeated for high and low dopaminergic affinity; for the high dopaminergic affinity group, dosage olanzapine equivalent was significantly correlated with more fragmented speech, while this effect was absent in the low affinity group.

Discussion: Our findings show that both type and dosage of antipsychotic medication affect voice quality measures of jitter and shimmer. Voice characteristics are important for social and daily

functioning, with impairments possibly leading to increased social isolation. Our finding of gender-specific effects argue for further investigation of the relation between speech and medication, with gender as a confounder next to dosage and medication type
While we show mainly correlational effects here, the subjects in this sample are followed longitudinally, with a substantial percentage eventually reducing their antipsychotic medication. This would allow us to move closer toward causal investigation as well as reversibility of effects on an intra-individual level. Our findings support taking dosage and type of medication into account for acoustic analysis, although not all measures are impacted.

S27. RETINAL DEGENERATION AS A POTENTIAL BIOMARKER OF ACCELERATED AGING IN SCHIZOPHRENIA

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Background: Schizophrenia (SZ) is associated with reduced retinal layer thickness (Silverstein et al., 2020). Because retinal neurodegeneration occurs as part of the normal aging process, differences in retinal structure in SZ may reflect markers of accelerated aging. Therefore, the aim of this study was to examine the relationship between age and thickness of the inner retinal layers and macular volume, in both individuals with SZ and controls without psychopathology. We hypothesized that retinal tissue loss would be more strongly associated with age in the SZ group. An exploratory analysis was also done to investigate whether SZ diagnosis accounted for a unique portion of variance over and above the presence of diabetes or hypertension, which are known to affect retinal health, and are present at elevated rates in SZ (Lee et al., 2019; Liao et al., 2011; van Dijk et al., 2012).
Methods: Patients with SZ (n = 60) and psychiatrically healthy control (CON) participants (n = 69) received spectral domain optical coherence tomography (OCT) scans to examine the following variables in both eyes: Retinal nerve fiber layer (RNFL) thickness, macula central subfield (CSF) thickness, macula volume, ganglion cell layer-inner plexiform layer (GCL-IPL) thickness, optic cup volume, and cup-to-disc ratio at the optic nerve head. 11 participants in each group had documented diabetes or hypertension.
Results: Negative correlations between age and right eye RNFL thickness ($r_s = -.42$, $p < .001$), macula cube volume ($r_s = -.35$, $p = .007$), and GCL-IPL thickness ($r_s = -.51$, $p < .001$) were observed in the SZ group, indicating that older age corresponded to reductions in retinal layer thickness and macula cube volume. Values were nearly identical for the left eye. No significant correlations were found between age and cup-to-disc ratio, optic cup volume, and macula CSF thickness in the SZ group (all ps > .248). In the CON group, correlations were in the same direction as for patients, but none reached statistical significance (all ps > .05). Correlations between age and RNFL and GCL-IPL thickness in the CON group were consistent with those in a prior study (all ps > .25; Wei et al., 2017). Both left eye ($z = -1.95$, $p = .026$) and right eye macula volume ($z = -1.70$, $p = .044$) and age correlations in the SZ group were significantly larger than those in the CON group. The correlation between GCL-IPL thickness and age in the SZ group was significantly higher than in the CON group for right eye data ($z = -2.60$, $p = .005$), and at a trend-level difference for the left eye ($z = -1.53$, $p = .063$). Trend-level findings suggested that the SZ group had larger

correlations than controls between age and RNFL thickness, in both eyes (left: z = -1.45, p = .073; right: z = -1.37, p = .085).
Linear regression analyses indicated that group status (SZ vs. non-SZ) moderated the relationship between age and macula cube volume reduction, in both eyes (left: $\Delta R2 = .03$, p = .042; right: $\Delta R2 = .03$, p = .055). Lastly, SZ diagnosis accounted for additional variance in macula cube volume reduction over and above the presence of diabetes or hypertension (left: $\Delta R2 = .06$, p = .002; right: $\Delta R2 = .05$, p = .007).

Discussion: These findings provide converging evidence across eyes, regions of the retina, and 2D and 3D measurements, that retinal atrophy occurs at an increased rate in SZ. Importantly, SZ diagnosis explained a unique portion of the variance in macula cube volume reduction over and above the presence of systemic disease. Because OCT is a rapid, non-invasive technique that acquires all relevant data over a span of only several seconds, and is well-tolerated by patients, it holds promise as a useful biomarker of CNS integrity and accelerated aging that can be used in patient evaluation and monitoring efforts.

S28. ODOR DISCRIMINATION AS A MARKER IN CHRONIC SCHIZOPHRENIA: RELATIONSHIP TO MRNA IN LYMPHOCYTES AND MATRCIS BATTERY SCORES.

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Background: Patients with schizophrenic have been reported to show deficits in various measures odor perception but odor discrimination has not been regularly assessed in most studies. DNA methylation and GABAergic input have been implicated in biochemical process controlling odor in animal studies, but this has not been investigated in human studies. Some studies have related cognitive deficits in schizophrenia to odor deficits but none have used the MATRICS battery to investigate this question.
Methods: In a study of DNA methylation and GABAergic mRNAs in lymphocytes we also measured odor identification and discrimination with the Sniff and Sticks battery in 58 patients with chronic schizophrenia (CSZ) and 48 non-psychiatric controls (NPC). mRNAs in lymphocytes were assessed by qPCR using TaQMan probes. Cognition was assessed by the MATRICS battery in CSZ and NPC and symptoms in CSZ were assessed by PANSS scale. The relationship of odor deficits to mRNA levels and MATRICS scores and symptoms was explored by correlation analysis.
Results: CSZ showed significant deficits compared to NPC in odor identification (P = 0.011, Cohen's d=0.50)), but much larger deficits in discrimination (P<0.001, d=1.01). In logistic regression analysis odor discrimination but not odor identification had significant Wald $\chi 2$ for classifying patients into the CSZ vs NPC group. Odor discrimination significantly(P=0.0002) predicted a subject's group member in chronic schizophrenia vs controls group with a Sensitivity of 0.78 and Specificity of 0.75. There were significant negative correlations (r=-33 to -.68) of odor identification with DNMT1 mRNAs, and significant negative correlations with odor discrimination and GABAergic mRNAs in CSZ subjects (-.38 to -.42). Odor discrimination scores

correlated significantly (P=.02 to P=.009) with several Matrics Domain scores in CSZ subjects but not NPC; there was a sex effect and these correlations were stronger in female than male CSZ.
Discussion: Odor discrimination deficits, which has not been consistently evaluated in schizophrenia studies, showed the strongest differentiation between patients with chronic schizophrenia and controls. This is the first study to report relationship between odor deficits and DNMT and GABAergic mRNAs in human subjects. However, the negative correlations of odor scores with lymphocyte mRNA levels may not necessarily reflect neuronal processes.

S29. PLASMA LEVELS OF THE EPIDERMAL GROWTH FACTOR SYSTEM LIGAND BETACELLULIN DIFFERENTIATES TREATMENT RESISTANT SCHIZOPHRENIA FROM TREATMENT RESPONSIVE SCHIZOPHRENIA AND OTHER PSYCHOTIC DISORDERS

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Background: Symptom based diagnostic ambiguity plagues clinical and research endeavours to improve outcomes for people with psychotic disorders. Reliable pragmatic biomarkers to assist with differential diagnosis or treatment outcome prediction may provide substantive improvements to current care. One example is the earlier introduction of the atypical antipsychotic drug (APD) clozapine for people non-responsive to conventional APD treatment, so termed treatment resistant schizophrenia (TRS). Understanding why this group shows efficacy for clozapine but not conventional APDs may aid in identifying biomarkers of TRS. We previously identified clozapine alone transactivated the epidermal growth factor (EGF) system which may be involved in its unique effectiveness in TRS. Reasoning that signalling augmentation by clozapine may indicate a hypofunctioning EGF system, we investigated peripheral levels of the EGF ligand, betacellulin (BTC), in a range of psychotic disorders and healthy controls.
Methods: Peripheral venous blood was collected from three separate cohorts and plasma assayed for betacellulin using commercial and custom ELISA systems. Cohort 1 comprised patients with TRS who were assayed prior to and 26 weeks after commencing clozapine treatment and healthy controls; cohort 2 was a cross sectional sample of patients who were stably treated on clozapine >6 months; and cohort 3 was a cross sectional sample from multiple patient groups from a large previously conducted Australian national study, the Survey of High Impact Psychosis (SHIP). Parametric and non-parametric statistics were used to compare between groups with post-hoc tests as appropriate.

Results: There was a highly significant main effect (p=0.0005) between healthy controls (median BTC 2385pg/ml, 95%CI 1652-2657; n=28), people with schizophrenia (1502pg/ml, 1332-1717; n=288), schizoaffective disorder (1981pg/ml, 1575-2901; n=71), mood disorders (2131pg/ml, 1780-2796; n=121) and other psychoses (2324pg/ml, 1693-2643; n=44) with levels in schizophrenia significantly lower than in mood disorder. When schizophrenia was divided into TRS (clozapine treated) (1166pg/ml, 1005-1294; n=161) and non-TRS (2247pg/ml, 1729-2672; n=127) groups there was a highly significant overall effect (p<0.0001). Dunn's post-hoc multiple comparison tests showed levels in the TRS group were significantly lower than healthy controls (p=0.006), non-TRS, schizoaffective and mood disorders (all p<0.0001) and other psychoses (p=0.001).
Discussion: We used a reasoned clinical and bench-based approach to identify putative biomarkers to test in the clinic. Markedly decreased plasma BTC levels in people with TRS compared to healthy controls, other diagnostic and non-TRS groups indicate its potential as a diagnostic and treatment biomarker. Moreover, inspection of the data identified a minor proportion of participants from each of the other patient group also demonstrated BTC values below the range of healthy controls. This suggests possible transdiagnostic alignment of pathological mechanisms and more importantly, a mechanism for the potential role of clozapine outside schizophrenia in these patients.

S30. IDENTIFICATION OF INFLAMMATORY SUBTYPES IN SCHIZOPHRENIA: A MACHINE LEARNING APPROACH

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Background: Inflammation has been associated with grey matter volume deficits, reduced cognitive function and increased symptom severity within schizophrenia. However, recent findings have been disparate, with anti-inflammatory interventions yielding mixed outcomes. Heterogeneity in Results: may be evidence of an immune-active subgroup, identification of which may provide novel treatment targets and is vital for progressing forward within the study of immune-psychiatry. Using advanced clustering techniques and support vector machine (SVM) classification models, we aim to identify inflammatory subgroups within a schizophrenia cohort.
Methods: HYDRA (HeterogeneitY through DiscRiminant Analysis), a semi-supervised machine learning tool was used to separate patients (n=250) from healthy controls (n=42) and define disease-related subgroups based on 4 cytokines (IL-6, CRP, TNF-a and IFN-y), in a combined dataset from the Benefit of Minocycline Study (BeneMin) and The Study of Psychosis and the Role of Inflammation and GABA/Glutamate (SPRING). Further SVM models were built using a repeated nested pooled cross-validation strategy. Two classification models were built; one of neurocognitive and clinical data and one of grey matter volume (GMV) data.
Results: The optimal clustering solution demonstrated 4 schizophrenia-specific clusters: Increased CRP (N=29), Increased IL-6 (N=50), Increased TNF-a (N=40) and Non-inflamed (N=110), (ARI=0.83). Each of these subgroups presented with unique patterns of grey matter volume and neurocognitive/clinical symptoms, as identified by the SVM models. The CRP cluster presented with the greatest neurocognitive deficits and the most widespread GMV decreases. The IL-6 cluster demonstrated greater negative/anxiodepressive clinical scores, with notable GMV

increases in a number of basal ganglia structures, alongside bilateral decreases in the cerebellum. The TNF-a cluster also demonstrated increases in negative symptoms, but GMV decreases in the pallidum. Finally, the noninflamed cluster presented with the greatest positive symptoms, fewest negative symptoms and best performance on neurocognitive tasks, alongside the fewest differences in GMV compared to HCs, with the SVM model performing worst out of the HC comparisons.
Discussion: Identification of these inflammatory subtypes can help aid our understanding of the pathogenesis of schizophrenia and may provide novel treatment targets, especially focused on alleviating negative symptoms. Immune-focused treatment in schizophrenia has yielded mixed results some studies have reported moderate success and others have found no beneficial effect. Results such as ours may present a solution - identifying valid, reproducible, clusters of patients with altered inflammatory levels who may respond differently to anti-inflammatory treatment.

S31. SEX AND GENDER ASSOCIATIONS WITH NEURODEVELOPMENTAL RISK MARKERS IN FIRST-EPISODE PSYCHOSIS

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Background: Sex and gender differences have been associated with risk factors for schizophrenia such as childhood trauma and earlier age of onset, consistent with the neurodevelopmental model of the disorder. In this study, we examined the associations of biological sex and gender role endorsement with putative indicators of neurodevelopmental compromise.
Methods: We used the Bem Sex Role Inventory to calculate masculinity scores in patients with a first episode of a schizophrenia spectrum disorder (n = 77) in Cape Town South Africa, and selected the following indicators of neurodevelopmental compromise: family history of schizophrenia, obstetric complications, premorbid functioning, neurological soft signs, and cognitive function. Secondary objectives included the moderating effects of age of onset of illness, substance use, and negative symptoms on these associations.
Results: There were no significant sex differences in any of our indicators of neurodevelopmental compromise. However, lower masculinity scores correlated significantly with poorer premorbid adjustment, sensory integration deficits, and worse overall cognitive performance. Stepwise linear regression identified poorer premorbid adjustment in early adolescence (beta = -1.74, T = -2.92, p = 0.005) and lower verbal learning scores (beta = 0.026, T = 2.17, p = 0.034) as independent predictors of lower masculinity scores.
Discussion: In contrast to sex, gender showed several associations with indicators of neurodevelopmental compromise. Lower masculinity scores may represent part of a phenotype for a neurodevelopmental anomaly that places some individuals on a pathway to schizophrenia.

S32. THE HETEROGENEITY OF CORTICAL MORPHOLOGICAL AND ITS RELATIONSHIP WITH GLUTAMATERGIC RECEPTOR VARIATIONS IN SCHIZOPHRENIA

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Background: Recently, many studies have been conducted to dissect the heterogeneity of schizophrenia in symptomatology, neurocognition, genetics and neuroimaging. Among them, the use of brain morphology has been the most promising, and reasonably replicated subtyping approach to date. Brain morphological features are more stable, with low within-subject fluctuations than symptom rating scores and functional readouts. Previous studies found cortical thickness and gyrification are reduced in schizophrenia, but only a subgroup of patients exhibits such structural deficits. Besides, recent genetic evidence strongly implicates glutamatergic-receptor variations in schizophrenia. Glutamatergic excess during early life may affect brain structure through excitotoxicity. We delineate the neuroanatomical variation among unaffected siblings and patients with schizophrenia to study the role of key glutamate-receptor polymorphisms on the neuroanatomical variations of schizophrenia.

Methods: Patients (n=114) with a diagnosis of schizophrenia (based on DSM-5), healthy controls (n=112) and their siblings (n=42) were recruited in this study. Gaussian Mixture Model clustering was applied to cortical thickness and gyrification data to identify subgroups. In addition, we studied the distribution of glutamate-receptor (GRM3, GRIN2A, and GRIA1) and voltage-gated calcium channel (CACNA1C) variations across the MRI-based subgroups.

Results: We observed the 'hypogyric', 'impoverished-thickness' and 'supra-normal' subgroups of patients, with higher negative symptom burden and poorer verbal fluency in the hypogyric subgroup and notable functional deterioration in impoverished-thickness subgroup. Compared to healthy subjects, the hypogyric subgroup had significant GRIN2A and GRM3 variations, the impoverished-thickness subgroup had CACNA1C variations while supra-normal group had no differences. But the unaffected siblings showed no difference from healthy controls. Additionally, the current study also found an interaction effect between two risk SNVs of GRIN2A and heterogeneous group on cortical gyrification of left parstriangularis, which showed that the effect of risk SNVs in supranormal cluster was similar to healthy controls: the homozygous subjects without mutation exhibited higher gyrification in left parstriangularis than the homozygous subjects with mutation.

Discussion: We report 3 major findings: 1) three morphologically distinguishable clusters of patients are identifiable (reduced gyrification, reduced thickness and higher thickness subgroups); 2) the subgroups are phenotypically similar, but have varying burden of negative symptoms, cognitive deficits and functional deterioration 3) the subgroup membership influences illness-related variation in glutamatergic receptor polymorphisms. By linking MRI-derived cortical morphological patterns to glutamatergic and calcium channel variations, we highlight the potential to select patients with certain neuroanatomical features when studying interventions that regulate glutamate/calcium channels in schizophrenia.

S33. MULTI-MODAL NEUROIMAGING TO QUANTIFY BRAIN ACTIVATION MEDIATES THE ASSOCIATION BETWEEN STRUCTURAL ABNORMALITY AND COGNITION ACROSS CLINICAL STAGES OF PSYCHOSIS

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Background: Structural and functional deficits associated with schizophrenia are observed prior to the onset of psychosis and differ according to the stages of illness. Severity of psychosis correlates with decreased grey matter volume and cortical activation during language tasks. However, most previous studies concentrated on a limited period during the illness, and the relationship between loss of grey matter and decreased brain activation remains unclear. The present study aimed to clarify the association between functional and structural abnormalities in subjects with clinical high risk of psychosis (CHR), those with first-episode schizophrenia (FES) and healthy controls(HCs).

Methods: A total of 285 participants (120CHR/ 54FES /111HC) were recruited. They all finished cortical activity measurement using function near-infrared spectroscopy(fNIRS) while performing a letter version verbal fluency test (VFT). Meanwhile, 140 subjects (64CHR /28FES /55HC) also finished structural magnetic resonance imaging (MRI) scanning. Bilateral prefrontal and temporal cortical hemodynamic changes on Oxy-Hb during VFT were compared among the three groups. Gray matter volume (GMV) were compared among the three groups using FreeSurfer. A mediation model was tested using a four-step multiple regression approach incorporating cortical volume, functional activation and cognition.

Results: Significantly reduced brain activation in left pre-motor and supplementary motor cortex($F=15.79$, $p<0.001$), left supramariginal gyrus($F=11.98$, $p<0.001$), left dorsolateral prefrontal cortex($F=12.59$, $p<0.001$), left pars opercularis($F=11.89$, $p<0.001$), left subcentral area($F=11.42$, $p<0.001$), left pars triangularis($F=11.34$, $p<0.001$) and inferior prefrontal gyrus ($F=9.74$, $p<0.001$), right middle temporal gyrus ($F=11.51$, $p<0.001$), right temporopolar gyrus ($F=9.72$, $p<0.001$) and right inferior prefrontal gyrus ($F=11.54$, $p<0.001$) (Bonferroni correction) compared to HC. Pronounced GMV decline was observed in right frontal pole ($F=11.54$, $p<0.001$, FDR correction). GMV within the right frontal pole significantly correlate with Oxy-Hb ($r=-0.2$, $p=0.02$). The mediation result indicate that the association between brain activation and cognition is partially mediated by GMV.

Discussion: Task-related brain activation and anatomical deficits were observed in different brain regions, indicating that anatomical and function brain abnormalities are dissociated in the early stages of schizophrenia. The relationship between neural activity and GMV in the right frontal pole may reflect a specific pathophysiology related to the cognition deterioration of schizophrenia.

S34. A FUNCTIONAL CONNECTOME-BASED NEURAL SIGNATURE FOR INDIVIDUALIZED PREDICTION OF ANTIPSYCHOTIC RESPONSE IN FIRST-EPISODE PSYCHOSIS

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Background: Identification of robust biomarkers that predict individualized response to antipsychotic treatment at the early stage of psychosis remains a challenge in precision psychiatry.

This study aimed to investigate if any functional connectome-based neural traits could serve as such a biomarker.
Methods: In a discovery sample, 49 first-episode patients with psychosis received multi-paradigm fMRI scans at baseline and were clinically followed up for 12 weeks under antipsychotic monotherapies (either risperidone or aripiprazole). Treatment response was evaluated at the individual level based on the psychosis scores of the Brief Psychiatric Rating Scale (BPRS). Cross-Paradigm Connectivity was applied to extract individualized "trait" connectomes across different fMRI paradigms. Connectome-based Predictive Modeling was subsequently employed to train a predictive model that uses baseline connectomic trait measures to predict individualized change rates of psychosis scores. The model performance was evaluated as the Pearson correlations between the predicted change rates and the observed change rates, based on cross validation. The generalizability of the prediction model was further examined in an independent validation sample of 24 first-episode patients with a similar design. Significance of prediction performance in both samples was determined by 5000 permutations.
Results: The results revealed a paradigm-independent connectomic trait that significantly predicted individualized treatment outcome in both the discovery sample (r[predicted vs observed] = 0.44, P = 0.007) and the validation sample (r[predicted vs observed] = 0.50, P = 0.005). This neural trait involved connections predominantly linking the cerebellum (especially crus 1) and multiple sensory (e.g. sensorimotor, auditory, visual) and cognitive (e.g. default-mode, frontoparietal, cingular-opercular) systems in the cerebral cortex.
Discussion: This study discovers and validates a connectome-based functional signature as a promising early predictor for individualized response to antipsychotic treatment in first-episode psychosis, thereby highlighting the potential clinical value of this biomarker in precision psychiatry.

S35. FINGERTIP ADVANCED GLYCATION END PRODUCTS AND TRAJECTORY OF PSYCHOTIC SYMPTOMS AMONG DRUG NAïVE ADOLESCENTS

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Background: Advanced glycation end products (AGEs) are yielded during glycation stress, and are well known as harmful molecules due to enhancement of inflammation and oxidative stress. Prior case control studies have suggested that increase of AGEs was associated with chronic schizophrenia, and pilot clinical trial dta showed that AGEs inhibitor improved the psychotic symptoms of patients with schizophrenia. However, there has been no study investigating the role of AGEs in the mental health of adolescents, including whether accumulation of AGEs is involved in the development of psychosis.
Methods: This study examined the association between AGEs and the trajectory of psychotic symptoms in drug naïve adolescents using data from prospective population-based biomarker subsample study of the Tokyo Teen Cohort. The sample consisted of 277 community-dwelling adolescents aged 13 years without neuroleptic mecidations. AGEs were non-invasively measured

by AGEs sensor, in which the middle fingertip of the nondominant hand of adolescents was used. The operation of the measurement was quite easy, so that almost all subjects quickly completed the measurement within 3 min. The trajectory of psychotic symptoms in a one-year follow-up was evaluated by using a brief self-report questionnaire including the Adolescent Psychotic-Like Symptom Screener (APSS) followed by semi-structured interview by experienced psychiatrists.
Results: Of the 277 participants, 13 (4.7%) were determined as having an experience of persistent psychotic symptoms (psychotic symptoms at baseline and follow-up) Among the rest of the sample, 199 (71.8 %) had no experience of psychotic symptoms and 65 (23.5 %) experienced transient psychotic symptoms (psychotic symptoms at baseline or follow-up), respectively. Multinomial logistic regression analysis adjusted for age and sex showed that baseline AGEs were significantly associated with persistent psychotic symptoms (odds ratio = 1.68; 95% confidence interval, 1.05-2.69; P = 0.03).
Discussion: Our findings suggest that fingertip AGEs could identify adolescents at psychosis risk, that is persistent psychotic symptoms, implying that AGEs is involved in the development of early psychosis independent of anti-psychotic medication. Further validation will be required, and development of strategies to reduce the AGEs in adolescent, which may include diet, exercise, or inhibition of AGEs, may contribute to preventing the onset of psychosis.

S36. SOCIOECONOMIC FACTORS ASSOCIATED WITH PHYSICAL ACTIVITY IN YOUTH AT CLINICAL HIGH RISK FOR PSYCHOSIS

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Background: There is increasing evidence of the health benefits associated with engaging in physical activity (PA) in youth at clinical high risk for psychosis (CHR-P). Additionally, it has been observed that youth of higher SES background are more physically active than youth of lower SES, and researchers have called for additional exploration of factors associated with PA in youth. Given the potential health benefits of PA, the present study aimed to identify SES factors associated with participation in PA in CHR-P youth. Additionally, we aimed to explore interest in engaging in a health behavior promotion intervention.
Methods: Sixty-one individuals meeting CHR-P criteria (57.9% female; M=16, SD=3.8) participating in a randomized trial of family focused therapy across seven sites in North America were included in this study (see Miklowitz et al., 2022 for details). PA was assessed via a questionnaire developed for CHR-P youth (Deighton and Addington, 2015), symptoms were measured via the Structured Interview for Psychosis-Risk Syndromes (SIPS; McGlashan et al., 2010), and psychosocial functioning was assessed via the Global Function Scales: Role and Social (Cornblatt et al., 2007). Household income and parental years of education were used as proxies for SES. Kendall's Rank correlation coefficient was used to assess associations between PA, physical health, positive and negative symptoms, and psychosocial functioning.

Results: Overall, 61.4% of participants reported engaging in PA at least 2-3 times per week, whereas 9.8% reported not engaging in any PA. PA behaviors (frequency, intensity, and time spent exercising) were not significantly associated with household income. However, parental education and frequency and time spent exercising were positively correlated and approached significance ($r=0.2$, $p=0.07$; $r=0.19$, $p=0.07$, respectively). Additionally, frequency of PA was associated with better social functioning ($r=0.25$, $p<0.05$). More than half of participants (55.8%) reported interest in learning health behavior strategies to improve mental health. There was a trend towards an inverse relationship between interest in learning health behavior strategies and household income ($r= -0.22$, $p =0.07$), but no association with parental education ($r=-0.05$, $p=0.7$).
Discussion: Future research should further examine differences in rates of PA and other health behaviors across SES among CHR-P youth. Findings suggest health behavior strategies may be an amenable intervention for CHR-P youth across SES levels.

S37. METABOLIC AND HEPATIC FUNCTION BEFORE AND DURING CLOZAPINE TREATMENT BY ACKR1 GENOTYPE

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Background: People with schizophrenia experience metabolic abnormalities prior to medication treatment and in association with antipsychotic use, including weight gain, insulin resistance, non-alcoholic fatty liver disease (NAFLD), and development of metabolic syndrome (MetS). These abnormalities may be related to underlying genetic differences and treatment-related changes in inflammatory cytokine profiles. There is evidence that polymorphisms on the ACKR1 gene also impact levels of chemokines and cytokines that play a role in MetS, particularly monocyte chemotactic protein-1 (MCP-1). The Duffy-null (CC) genotype at rs2814778 on the ACKR1 gene is notably associated with reduced neutrophil counts during treatment with clozapine, but less is known about its potential effects on metabolism and risk of developing MetS while on clozapine. Given the high risk of MetS in schizophrenia and in association with clozapine treatment, it is important to understand the role of ACKR1 genotype on metabolic measures and related cytokines.
Methods: This is a secondary data analysis of a 6-month open-label trial of clozapine in patients of African descent with schizophrenia spectrum disorder who had ACKR1 genotype of either CC (Duffy-null) or CT/TT. We examined baseline differences by genotype and changes by genotype over time during 24 weeks of clozapine treatment in metabolic parameters (weight, BMI, fasting glucose, and cholesterol measures), liver function (albumin, protein, alkaline phosphatase, ALT,

AST, bilirubin, and NAFLD Fibrosis Score [NFS]), and two associated cytokines (MCP-1 and IL-1RA). We also examined relationships between cytokines, genotype, and metabolic and liver function at baseline.

Results: There were 274 total enrolled participants. Of those, 138 had available data to calculate NFS and 61 had available cytokine data. At baseline, the CC genotype group had significantly lower weight (p=0.000), BMI (p=0.000), triglycerides (p=0.001), and MCP-1 (p=0.000), but significantly higher bilirubin (p=0.000). Although baseline difference in mean NFS were not significant between groups, 33.72% of the CC genotype groups had an NFS above -1.46, the cutoff score used to exclude advanced fibrosis, whereas none of the CT/TT group had a score above -1.46. Baseline MCP-1 was negatively correlated with AST in the CC group (r=–0.369, p=0.016). BMI (b=0.460, p<0.001), age (b=0.466, p<0.001), and MCP-1 level (b=0.304, p=0.026) were predictors of baseline NFS. Over the course of treatment, there was a significant increase in weight (F=14.25, df=1,237, p<0.0001), BMI (F=12.59, df=24,3828, p<0.0001) and albumin (F=2.47, df=6,610, p=0.0227), but no genotype by time effects on any measures of metabolism or liver function. There was a small and non-significant increase in NFS over the course of treatment in both genotypes.

Discussion: There are baseline differences in measures of metabolism and liver function by ACKR1 genotype. Notably, CC genotype participants had higher indicators of NAFLD despite lower BMI and more favorable cholesterol profile. Given the role of MCP-1 in hepatic inflammation, it is possible that differences in MCP-1 levels or pharmacokinetics driven by ACKR1 genotype impact liver and metabolic function. The current study did not suggest any differences in the effects of clozapine on metabolic or liver function by genotype.

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S38. A BIOEQUIVALENCE COMPARISON AT STEADY STATE BETWEEN A NEWLY DEVELOPED ONCE-DAILY EXTENDED-RELEASE TABLET FORMULATION AND THE APPROVED TWICE-DAILY TABLET FORMULATION OF DEUTETRABENAZINE

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Background: Deutetrabenazine (Austedo, Teva) in a twice-daily (BID) formulation is an approved treatment for tardive dyskinesia and chorea associated with Huntington disease. A newly developed once-daily (QD) extended-release formulation of deutetrabenazine has been developed with the aim to improve patient convenience and adherence. The study objective was to assess the bioequivalence (BE) and relative bioavailability (BA) between the QD formulation and the approved BID formulation at steady state under fed conditions.

Methods: In a phase 1 study (TV50717-BE-10179) using a randomized cross-over design, healthy adult males and females (n = 262) received 24 mg QD formulation (test) as a once-daily administration and 12 mg BID formulation (reference) as a twice-daily administration, each for 7 days in fed state. Safety was assessed throughout the study and pharmacokinetic (PK) blood

sample collection occurred on days 4-7 for the determination of deutetrabenazine and active metabolites, i.e deuterated α-HTBZ and β-HTBZ. Exposure PK parameters (area under the plasma concentration curve over 24 hours at steady-state [AUC0-24h,ss] and maximum plasma concentration at steady-state [Cmax,ss]) were calculated and test-to-reference geometric mean ratios (GMRs) and 90% CI for BE acceptance limits (80.00% to 125.00%) were computed to determine relative exposure. Relative BA was assessed for Cmax,ss of the active metabolites (individually and as a total sum).

Results: The GMRs (90%CIs) for AUC0-24h,ss were 115.15% (110.38–120.14%) for deutetrabenazine, 95.40% (94.13–96.69%) for α-HTBZ, 94.13% (92.35–95.94%) for β-HTBZ, and 95.05% (93.67–96.46%) for total (α+β)-HTBZ. GMRs of Cmax,ss were 95.09% (90.60-99.80%) for deutetrabenazine, 79.56% (78.21-80.94%) for α-HTBZ, 74.85% (73.13-76.60%) for β-HTBZ and 77.71% (76.26-79.16%) for total (α+β)-HTBZ. No new safety findings emerged in this study.

Discussion: At steady state, deutetrabenazine administered once-daily as the QD extended-release formulation was shown to be bioequivalent to the twice-daily administration of approved BID formulation for both AUC0-24h,ss and Cmax,ss. The active metabolites at steady state were also bioequivalent with regard to AUC0-24h,ss comparing the QD to the BID formulation. The relative bioavailability of Cmax,ss for the active metabolites was slightly lower at steady state after repeated doses of the QD formulation compared with the BID formulation.

S39. IS THERE A DIFFERENCE IN VESTIBULAR SYSTEM REACTIVITY BETWEEN PATIENTS WITH SCHIZOPHRENIA AND HEALTHY CONTROL PARTICIPANTS?

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Background: Conventional caloric vestibular stimulation (CVS), which involves the irrigation of cold or warm water into the external ear canal induces a temperature gradient across the semicircular canals of the vestibular apparatus stimulating the vestibular nerve and eliciting the vestibulo-ocular reflex. It is commonly used in both otolaryngology to assess vestibular function and neurology to test brain stem function. In schizophrenia, there is no conclusive link between psychopathology and vestibular dysfunction. Initial data from another CVS study from our group suggests individuals with schizophrenia may have greater reactivity to body temperature (37°C) CVS, as measured by the peak slow phase velocity of the resulting nystagmus (PSPV), than would be expected for healthy participants. However, we are unaware of any studies that have investigated the differential effects of CVS temperature gradients on individuals with schizophrenia versus healthy control (HC) participants. As such, we aimed to examine if individuals with schizophrenia have greater reactivity to caloric vestibular stimulation than HC participants.

Methods: Patients with schizophrenia and HC participants received three conditions bilaterally: (1) body temperature CVS (37°C); (2) warm CVS (44°C), and (3) cold CVS (30°C). All conditions were performed by an audiologist. The physiological response of vestibular stimulation was

assessed with electronystagmography, which provides a measure of the intensity of the nystagmus via PSPV. Independent sample t-tests were conducted to compare vestibular reactivity (i.e., nystagmus) between patients and HC participants for each CVS condition.
Results: A total of 17 patients (mean age 40.4, SD=11.7, 12% female) and 15 HC participants (mean age 36.4, SD=10.3; 13% female) completed the study. There was no statistically significant difference between patients and HC participants in body temperature, warm or cold CVS ($p>0.05$).
Discussion: In schizophrenia, there is no conclusive link between psychopathology and vestibular dysfunction, and we are not aware of any data that exists on the range of responses to CVS in persons with schizophrenia.
We did not find any differences in vestibular reactivity between patients with schizophrenia and HC participants in response to CVS.

S40. ALLYL ISOTHIOCYANATE (TRPA1 AGONIST) PROTECTED AGAINST OLANZAPINE-INDUCED METABOLIC ALTERATIONS IN MICE

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Background: Olanzapine is one of the commonly prescribed atypical antipsychotics but has a higher propensity of inducing severe metabolic adverse effects such as obesity and type 2 diabetes. Allyl isothiocyanate (AITC) is an agonist of transient receptor potential ankyrin 1 (TRPA1) channel and has been reported to have antidiabetic and antiobesity potential in rodents as well as in humans. The present study was aimed to investigate the role of TRPA1 channels in olanzapine-induced metabolic alterations in mice.
Methods: Female BALB/c mice were treated with olanzapine, AITC, and HC-030031 (TRPA1 antagonist) for 6 weeks. Locomotor activity in open field test, weekly body temperature, and feed intake were measured. Biochemical/molecular metabolic parameters were estimated in serum, liver and hypothalamus.
Results: AITC co-treatment protected against chronic olanzapine-induced metabolic alterations mainly by restoring reduced locomotion and body temperature, increased serum glucose, lipids, insulin, proinflammatory cytokines, and liver glycogen levels. AITC treatment protected against olanzapine induced insulin resistance and glucose intolerance in the oral glucose tolerance test. These peripheral changes were associated with altered mRNA expression of hypothalamic appetite-regulating, nutrient-sensing and inflammatory markers, which were reversed by AITC treatment. Interestingly, olanzapine treatment reduced TRPA1 mRNA expression in the hypothalamus indicating its role in inducing metabolic alterations. Furthermore, antidiabetic and antiobesity effects of AITC were differentially abolished in the presence of HC-030031.

Discussion: Our preliminary results suggested the protective effects of AITC against olanzapine-induced metabolic alterations, which were likely to be TRPA1 dependent. Further studies are needed to investigate the molecular interactions between TRPA1 channels and antipsychotics.

S41. EFFECT OF CARIPRAZINE ON QUALITY OF LIFE AND ATTENTION IN PATIENTS WITH PERSISTENT NEGATIVE SYMPTOMS OF SCHIZOPHRENIA: A POST-HOC ANALYSIS

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Background: Cariprazine (CAR) is a dopamine D3-preferring D3/D2 receptor and serotonin 5-HT1A receptor partial agonist, approved to treat schizophrenia in US, Europe and Canada. The D3-receptor may play a role in treating negative symptoms, depression, and cognitive impairment. This work aims to evaluate short-term changes on QoL and attention in schizophrenia patients treated with CAR versus PBO and further evaluate these changes within a subgroup of patients presenting with persistent negative symptoms (PNS).

Methods: Data were pooled from two 6-week phase 3 trials evaluating the efficacy, safety and tolerability of CAR in patients with schizophrenia. One study included a 10mg/d aripiprazole (ARI) active-control group. The primary efficacy outcome was Positive and Negative Syndrome Scale (PANSS) total score change (baseline to week 6). Additional efficacy measures were QoL, via Schizophrenia Quality of Life Scale–Revision 4 (SQLS-R4), and attention, evaluated using composite scores from the Cognitive Drug Research Attentional Battery - Power of Attention (CDR-PoA; focused attention) and -Continuity of Attention (CDR-CoA; sustained attention).

Data were analyzed from the ITT-population and a PNS subgroup (PNS-population). CAR dose groups were pooled, and least-squares mean change (LSMC; baseline to week 6) and least-square mean difference (LSMD; CAR vs PBO and ARI vs PBO) were determined for SQLS-R4, CDR-PoA and CDR-CoA, PANSS total score, PANSS factor score for negative symptoms (PANSS-FSNS) and PANSS factor score for positive symptoms (PANSS-FSPS). PNS was defined as: PANSS-FSNS≥24, PANSS-FSPS≤19, and scores of ≥4 on ≥2 of 3 PANSS items (N1, N4, N6).

Results: The pooled ITT-population represented data from 1055 patients [CAR-ITT, n=603, ARI-ITT, n=150, PBO-ITT, n=299]; 219 patients met criteria for PNS [CAR-PNS, n=110, ARI-PNS, n=42, PBO-PNS, n=67]. Baseline demographics were similar between ITT- and PNS-populations. In the ITT-population, differences were significant (*$p<0.05$) in favor of CAR versus PBO for SQLS-R4 and CDR-CoA at week 6 [SQLS-R4 (LSMD = -6.12, p=0.0004)*, CDR-PoA (LSMD = -141.68; p=0.0628), CDR-CoA (LSMD = 3.01; p=0.0039)*]. In a post-hoc analysis of the PNS-population, patients treated with CAR showed statistically significant improvement in SQLS-R4, CDR-PoA and CDR-CoA at week 6 [SQLS-R4 (LSMD = -10.27; p=0.0027)*, CDR-PoA (LSMD = -308.98; p=0.0193)*, CDR-CoA (LSMD = 6.84; p=0.0012)*].

In the ITT-population, differences were significant in favor of ARI versus PBO for SQLS-R4 at week 6 [SQLS-R4 (LSMD = -9.51; p <0.0001)*, CDR-PoA (LSMD = 22.36; p=0.8309), CDR-CoA (LSMD = 1.55; p=0.2951)]. In a post-hoc analysis of the PNS-population, patients treated with ARI showed statistically significant improvement in SQLS-R4, and CDR-CoA at week 6 [SQLS-R4 (LSMD = -13.2; p=0.0023)*, CDR-PoA (LSMD = -115.91; p=0.5719), CDR-CoA (LSMD = 5.72; p=0.0268)*].

Discussion: Patients in the ITT population treated with CAR showed improvement in QoL- and sustained attention. An enriched sample of schizophrenia patients with PNS improved in QoL, focused- and sustained-attention after 6-weeks of CAR treatment; LSMD values for CDR-PoA (focused-attention) only reach significance for the PNS-population treated with CAR. Patients in the ITT population treated with ARI showed improvement in QoL. An enriched sample of schizophrenia patients with PNS improved in QoL and sustained-attention after 6-weeks of ARI treatment. Results further implicate the D3-receptor as a potential target for treating negative and cognitive symptoms1,2. In patients with increased negative symptom burden, treatment selection may be important in optimizing attention related cognitive outcomes.

S42. TV-46000, A LONG-ACTING SUBCUTANEOUS ANTIPSYCHOTIC (LASCA) FORMULATION OF RISPERIDONE, MAINTAINED AND PROVIDED CONTINUED PSYCHOPATHOLOGICAL SYMPTOM IMPROVEMENT IN PATIENTS WITH SCHIZOPHRENIA (SHINE)

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Background: The Safety in Humans of TV-46000 subcutaneous INjection Evaluation (SHINE) study (NCT03893825) was a multicenter, double-blind study that evaluated the long-term safety, tolerability, and effectiveness of TV-46000 in adults and adolescents with schizophrenia. TV-46000 is a long-acting subcutaneous antipsychotic (LASCA) that combines risperidone and an innovative copolymer-based drug delivery technology.

Methods: Adults and adolescents with schizophrenia, including patients who completed the RIsperidone Subcutaneous Extended-release (RISE) study (NCT03503318) without relapse (rollover) and patients who had not participated in RISE (de novo), were eligible to participate in the SHINE study. After stabilization on oral risperidone for 12 weeks (completed in RISE for patients who rolled over, or in SHINE for those newly enrolled), patients were randomized to TV-46000 once monthly (q1m) or once every 2 months (q2m) for up to 56 weeks. Psychopathological symptom severity and improvement were evaluated using Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression-Severity (CGI-S), and Clinical Global Impression-Improvement (CGI-I).

Results: 336 patients (109 de novo and 227 rollover [172 from TV-46000, 55 from placebo]) were randomized to TV-46000 q1m (n=174) or q2m (n=162). 6 patients (4 de novo, 2 rollover) did not complete the study because of relapse (CGI-I ≥5 and any key PANSS item [conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content] score >4 with an absolute increase of ≥2 on the item or ≥4 on the combined score of the 4 key PANSS items; hospitalization because of worsening symptoms; suicidality; or violent behavior). Mean PANSS total scores for TV-46000 overall decreased from baseline (indicating improvement) to the last assessment (mean change [SE], −1.6 [0.47]), with an overall percent reduction of 2.1% (SE, 2.27). The reduction was numerically larger for TV-46000 q2m (least-squares [LS] mean change from baseline [SE], −1.59 [0.68]) than for q1m (−0.45 [0.66]). At baseline/randomization, mean total PANSS scores were higher in the de novo group (59.3 [0.84]) than in the TV-46000 rollover (56.1 [0.89]) and placebo rollover (56.2 [1.52]) groups. At the last assessment, changes from baseline were also smaller in the TV-46000 rollover groups (q1m, 0.50 [0.77]; q2m, −0.71 [0.81]) than in the de novo (−1.54 [1.47]; 2.67 [1.49]) and placebo rollover (1.64 [1.21], −2.28 [1.18]) groups. LS mean CGI-I score (SE) at the last assessment for TV-46000 q1m was 3.41 (0.08) and 3.29 (0.08) for q2m, indicating a perception of minimal improvement (score of 3) to no change (score of 4). Overall symptom reduction (lower scores) was numerically greater in the de novo group (q1m, 3.22 [0.17]; q2m, 3.05 [0.18]) than in the TV-46000 rollover (3.52 [0.10]; 3.41 [0.10]) and placebo rollover (3.36 [0.17]; 3.40 [0.17]) groups, with better (lower) scores in the respective q2m groups. Mean (SE) CGI-S scores for TV-46000 overall decreased numerically from 3.1 (0.04) at baseline to 3.0 (0.04) at the last assessment. Similarly, scores decreased numerically in the de novo group from 3.2 (0.05) at baseline to 3.0 (0.08) at last assessment but remained stable in the TV-46000 rollover (3.0 [0.05]; 3.0 [0.05]) and placebo rollover (2.9 [0.09]; 2.9 [0.09]) groups.
Discussion: Numerical improvements in psychopathological symptoms were observed for both dose regimens, with general stability maintained during subcutaneous TV-46000 treatment. Patients in the de novo and placebo rollover groups benefited slightly more from TV-46000 (based on PANSS scores) compared with patients with prior TV-46000 exposure.

S43. LONG-TERM SAFETY, TOLERABILITY, AND EFFECTIVENESS OF A LONG-ACTING SUBCUTANEOUS ANTIPSYCHOTIC (LASCA) AGENT (TV-46000) IN PATIENTS WITH SCHIZOPHRENIA: A PHASE 3, RANDOMIZED, DOUBLE-BLIND STUDY (SHINE)

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Background: TV-46000 is a long-acting subcutaneous antipsychotic (LASCA) agent that combines risperidone and an innovative copolymer-based drug delivery technology. In the

RIsperidone Subcutaneous Extended-release (RISE; NCT03503318) study, TV-46000 once monthly (q1m) and once every two months (q2m) significantly extended the time to impending relapse (5-fold [q1m] and 2.7-fold [q2m]) compared with placebo. The Safety in Humans of TV-46000 subcutaneous INjection Evaluation (SHINE; NCT03893825) study was designed to evaluate the long-term safety, tolerability, and effectiveness of TV-46000 q1m and q2m in adults and adolescents with schizophrenia.

Methods: Patients who completed RISE without relapse (rollover) or who were newly recruited (de novo) were eligible. Patients were initially stabilized on oral risperidone for 12 weeks (completed in RISE for rollover, or in SHINE for de novo). Patients in the de novo group and patients who received placebo in RISE (placebo rollover) were randomized 1:1 in SHINE to receive TV-46000 q1m or q2m for up to 56 weeks; patients who received TV 46000 in RISE (TV-46000 rollover) continued their assigned dosing regimen. The primary endpoint for SHINE was the frequency of adverse events (AEs). An exploratory endpoint was the proportion of patients who experienced impending relapse (defined by ≥1 of the following: Clinical Global Impression-Improvement score ≥5 and any key Positive and Negative Syndrome Scale item [conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content] score >4 with ≥2-point increase in any key item or ≥4-point increase in total of key items; hospitalization because of worsening of symptoms; suicidality; and violent behavior).

Results: 336 patients were randomized: 109 de novo and 227 rollover (172 from active treatment, 55 from placebo); 334 were evaluated for safety. Patients received TV 46000 q1m (n=172; patient-years [PY]=97.8) or q2m (n=162; PY=104.5). The most frequently reported treatment-emergent AEs (TEAEs; reported for ≥5% of patients in either group) were injection site pain (event rate [ER]/100 PY, n [%]: q1m, 24.54, n=9 [5%]; q2m, 22.01, n=7 [4%]), injection site nodule (6.14, n=3 [2%]; 12.44, n=9 [6%]), and headache (q1m, 4.09, n=4 [2%]; q2m, 7.66, n=8 [5%]). The most frequently reported TEAEs for the de novo group were injection site pain (58.95, n=6 [11%]; 53.51, n=5 [9%]), injection site nodule (11.23, 2 [4%]; 20.39, 4 [7%]), urinary tract infection (11.23, n=3 [5%]; 10.19, n=4 [7%]), blood creatine phosphokinase increased (8.42, n=2 [4%]; 22.93, n=6 [11%]), blood triglycerides increased (0; 10.19, n=3 [6%]), weight increased (11.23, n=4 [7%]; 0), increased appetite (8.42, n=3 [5%]; 0), sedation (11.23, n=3 [5%]; 2.55, n=1 [2%]), and dizziness (8.42, n=3 [5%]; 0); for the placebo rollover group, it was tremor (8.59, n=1 [4%]; 26.00, n=4 [15%]); and for the TV-46000 rollover group, they were injection site nodule (3.96, n=1 [1%]; 8.02, n=4 [5%]) and headache (3.96, n=2 [2%]; 12.03, n=6 [7%]). Serious AEs reported for ≥2 patients overall were worsening schizophrenia (1.02, n=1 [<1%]; 1.91, n=2 [1%]), hyperglycemia (1.02, n=1 [<1%]; 0.96, n=1 (<1%), and myocardial infarction (1.02, n=1 [<1%]; 0.96, n=1 [<1%]). Of 3 reported deaths, none were related to treatment. 6 relapses were reported (q1m, n=3 [2%]; q2m, n=3 [2%]). Kaplan-Meier estimates of patients remaining relapse-free by week 56 were 0.98 (2% risk) for q1m and 0.88 (12% risk) for q2m.

Discussion: In the SHINE study, TV-46000 q1m or q2m had a favorable benefit-risk profile, consistent with other formulations of risperidone and previous studies with TV 46000. The total number of relapses in SHINE were similar for TV-46000 q1m and q2m.

S44. SAFETY AND EFFECTIVENESS OF TV-46000, A LONG-ACTING SUBCUTANEOUS ANTIPSYCHOTIC (LASCA), BY INJECTION SITE (UPPER ARM OR ABDOMEN): A POST HOC ANALYSIS OF THE SHINE STUDY

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Background: TV-46000 is a long-acting subcutaneous antipsychotic (LASCA) that combines risperidone and an innovative copolymer-based drug delivery technology. In the RIsperidone Subcutaneous Extended-release (RISE; NCT03503318) study, TV-46000 once monthly (q1m) and once every two months (q2m) significantly extended the time to impending relapse (5-fold [q1m] and 2.7-fold [q2m]), compared with placebo. The Safety in Humans of TV-46000 subcutaneous INjection Evaluation (SHINE; NCT03893825) study was designed to evaluate long-term safety, tolerability, and effectiveness of TV-46000 q1m and q2m in adults and adolescents with schizophrenia.

Methods: Patients who completed RISE without relapse (rollover) or who were newly recruited (de novo) were eligible. Patients were initially stabilized on oral risperidone for 12 weeks (completed in RISE [rollover] or in SHINE [de novo]). Patients in the de novo group and patients who received placebo in RISE (placebo rollover) were randomized 1:1 to receive TV 46000 q1m or q2m for up to 56 weeks; patients who received TV-46000 in RISE (TV-46000 rollover) continued their assigned dosing regimen. The primary endpoint for SHINE was the frequency of adverse events (AEs). Each trial site was assigned to administer either only abdomen or only upper-arm injections; most sites were assigned abdominal administration. Injection site remained consistent throughout the study, alternating sides with each administration. Post hoc analysis of AEs per injection site were performed.

Results: 336 patients were randomized, and 334 were evaluated for safety: 109 de novo (74.9 patient-years [PY]) and 225 roll over (172 from TV-46000 [100.4 PY], 53 from placebo [27.0]). AEs (including injection site AEs) were reported at greater rates for patients who received TV-46000 via abdominal vs upper-arm injection across patient groups: de novo+placebo rollover group, abdominal (n=129; PY=176.7) vs upper arm (33; 54.1), 50% (event rate/100 PY [ER], 244.47) vs 45% (134.91); TV 46000 rollover group, abdominal (n=109; PY=127.2) vs upper arm (63; 73.6), 39% (ER, 125.81) vs 27% (70.62). General disorders and administration site (ie, injection site) conditions AEs were reported at greater rates for the de novo+placebo rollover group (q1m, 17% [ER, 74.04]; q2m, 10% [65.90]) than the TV 46000 rollover group (9% [27.71]; 11% [20.05]). The most frequently reported injection site AEs for both q1m or q2m regimens in the de novo+placebo rollover group were injection site pain (q1m, 17% [ER, 74.04]; q2m, 10% [65.90]) and injection site nodule (2% [8.46]; 6% [16.47]), with lower rates in the TV-46000 rollover group for both pain (3% [5.94]; 1%, [2.00]) and nodule (1% [3.96]; 5% [8.02]). Most injection site AEs were mild; no patients had severe reactions. In the de novo+placebo rollover and TV 46000 rollover group, ≤6% (upper arm) and ≤10% (abdomen) of patients reported an AE after the 7th injection, regardless of dosing regimen. Injection site AEs led to <1% of patients discontinuing treatment. There were 6 relapses during the study (3 each for q1m and q2m); given this low number of events, analysis of relapse rate by injection site was not feasible.

Discussion: In the SHINE study, TV-46000 q1m or q2m showed a favorable benefit-risk profile, regardless of injection site, consistent with the RISE study and other formulations of risperidone. Instances of injection site reactions, including injection site pain, were minimal, and there were no clinically meaningful differences across dosing regimens or injection sites. These data provide support for the safety of TV-46000 in patients with schizophrenia, whether administered in the upper arm or abdomen.

S45. THE PARKWOOD INSTITUTE PSYCHOSIS PATHWAY: ADAPTING COGNITIVE BEHAVIORAL THERAPY INPATIENT GROUPS FOR PSYCHOSIS

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Background: In line with Health Quality Ontario standards for the treatment of psychosis, an interdisciplinary team at St. Joseph's Health Care London - Parkwood Institute Mental Health's Adult Treatment and Rehabilitation Service adapted a cognitive behavioural therapy for psychosis (CBT) group therapy program. The feasibility, acceptability, and preliminary efficacy of CBTp groups for inpatients has been scarcely researched. However, extant studies have yielded promising results such as fewer psychiatric readmissions, improved recovery, and increases in self-efficacy.

Methods: Our revised protocol retains principles from third wave CBT in the original protocol, entitled "What is real and what is not?", including a focus on mindfulness. Changes were made for cultural relevancy. Additionally, we adapted the protocol to improve accommodations for variability in cognition, such as shorter attention span, concrete thinking, learning disabilities, and/or intellectual disabilities.

Using a pilot treatment-outcome design with a waitlist control group, we hypothesized that CBTp will be feasible and acceptable to inpatients. We predicted that participants will report greater reductions in distress and greater progress in recovery than those receiving treatment as usual. Data will be collected at three time points: Time 1 (Pre-Program/Waitlist1); Time 2 (Post-Program/Waitlist2); Time 3 (One-month follow-up)

Inclusion criteria include distress related to positive symptoms of psychosis (i.e., hearing voices, having visions, paranoia, and/or strong uncommon beliefs). Exclusion criteria include the inability to read or understand English or the inability to tolerate sessions due to acute distress.

Feasibility will be measured by attendance and attrition rates. Acceptability will be assessed through session feedback forms and a program satisfaction survey. Psychological distress was measured using the Clinical Outcome in Routine Evaluation (CORE-10) self-report survey. Recovery from mental illness was measured using the Process of Recovery Questionnaire), which is another self-report survey. As a secondary outcome, we will capture positive symptoms of psychosis using a portion of the Positive and Negative Syndrome Scale, to be completed by nursing.

For between-groups effects, a series of two-way 2 (group: treatment and waitlist) x 2 (time: baseline and post-treatment) mixed ANOVAs will be conducted. For within-group changes, one-way repeated measures ANOVAs will be conducted on the treatment group to determine whether

there are significant changes in each of the outcome variables over three time points (pre, post, and one-month follow-up).

Results: In our pilot trial, participant attendance across four sessions was 100%, with overwhelmingly positive feedback. We are in the process of revising our ethics submission and will collect data for research, offering one course of CBTp group to 4-7 inpatients per month. Additionally, we are building capacity across nursing, psychiatry, psychology, and social work to implement the groups.

Discussion: Practical considerations to implementing the CBTp group and research study will be reviewed. Recruitment and retention are historically difficult in psychosis populations due to the lack of insight, cognitive impairment, and complex presentations. Team challenges include balancing clinical and research tasks, in addition to training frontline staff.

S46. HAPPY THOUGHTS: IS THERE ANY ASSOCIATION BETWEEN EMOTIONAL CONTENT AND THE FLOW OF THOUGHT?

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Background: Formal thought disorders are associated with psychosis since initial descriptions of schizophrenia, as well as the lack of emotional recognition and expression. Both aspects can impact social interactions and interfere with sociability and mental health rehabilitation. During the past decade, the representation of spontaneous narratives as a word graph allowed for the quantification of aberrant signs of the flow of thoughts associated with negative symptomatology in different stages of psychosis. The results were mostly informative, using emotional narratives like dream reports or affective picture descriptions.

Methods: We analyzed a speech elicitation protocol based on dream reports and affective picture descriptions applied to first-episode psychosis (FEP) and a clinical high-risk (CHR) cohort. Word-graph connectedness was calculated by representing the spontaneous narrative as a word graph. The proportion of positive and negative emotional words was estimated using the Linguistic Inquiry and Word Count tool based on a Brazilian dictionary.

Results: We will discuss the interaction between emotional content and word trajectories connectedness in spontaneous narratives in different stages of psychosis (FEP, CHR, and controls) and the differences in speech elicitation protocol (dreams and affective picture reports). In the FEP sample, the association between congruent emotional expression and connectedness occurs in the presence of negative symptomatology mediated by formal education. While in the CHR sample, the association between connectedness and emotional expression shows a weaker association in different directions.

Discussion: Considering a pathological trajectory in the developmental stages of psychosis, understanding cognitive/emotional aspects revealed by computational analysis can help us understand protective factors like formal education. Implications for social recovery and mental health prevention and promotion will be discussed especially considering the earlier stages of psychosis.

S47. ANHEDONIA SYMPTOMS SELECTIVELY MODULATE THE COMPUTATION UNDERLYING THE TRADE-OFF BETWEEN SOCIAL REWARD AND PHYSICAL EFFORT

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Background: Anhedonia, one of the core negative symptoms of many psychiatric disorders, is related to the lack of interest and motivation to participate in social activities. Previous research has shown impaired effort-based decision-making in individuals with anhedonia. However, it remains unclear the computational mechanism underlying the trade-off between effort-taking and different types of rewards, and how this links to anhedonia. The present study aimed to apply computational modelling to explore how individuals with different anhedonia levels pit effort against social or non-social reward using a novel effort-based decision-making task.

Methods: We recruited 100 college students (72 F; age: 18-26) to complete a novel effort-based decision-making task. Specifically, participants were asked to decide whether to accept or reject the chance of interacting with an opposite-sex partner (the social condition) or obtaining an office goods (the non-social condition), at the cost of paying certain physical effort (i.e., perform keystrokes repeatedly). Both the reward (i.e., attractiveness of the partner or the good) and physical effort were independently varied in a parametric manner (6 levels) based on the individualized subjective rating. The Dimensional Anhedonia Rating Scale (DARS) was administrated to participants, with lower scores indicating higher level of anhedonia.

Results: The mixed-effect logistic regression on choice showed that individuals' sensitivity to attractiveness and physical effort was significantly modulated by the reward type. In particular, individuals were more sensitive to the attractiveness in the social (vs. non-social) condition ($z = 5.965$, $p < .001$), whereas their sensitivity to the physical effort was stronger in the non-social (vs. social) condition ($z = 4.270$, $p < .001$). To more rigorously examine the value computation underlying decision-making, we established a series of computational models and fitted them to choices. A hierarchical Bayesian approach was adopted to estimate the model parameters. Bayesian model comparison suggests that the model assuming a trade-off between reward and physical effort (denoted by a parameter k) with a default response bias that vary across conditions outperforms other candidate models. We found that individuals indeed biased the weight on social (vs. non-social) reward in the reward-effort trade-off (khuman vs. kobject: 0.57 ± 0.13 vs. 0.47 ± 0.15; $t99 = 6.635$, $p < .001$), which is consistent with the results of regression analyses. More importantly, the relationship between levels of anhedonia (measured by the total score of DARS) and k varied across types of reward (DARS ~ Δk = khuman vs. kobject; Pearson $r = 0.313$, $p = .002$), which was mainly driven by a positive correlation in the social (DARS ~ khuman; Pearson $r = 0.204$, $p = .042$) rather than the nonsocial condition (DARS ~ kobject; Pearson $r = -0.110$, $p = .277$).

Discussion: The above findings suggest that elevated level of anhedonia is characterized by the selective devaluation of social reward, rather than non-social reward, in a reward-effort trade-off. To our knowledge, our study provides the first empirical evidence that shed light on the potential

mechanisms underlying the social dysfunction of ahhedonia, which supports the social deafferentation hypothesis positing the developmental psychopathology of schizophrenia.

S48. NEUROPHYSIOLOGICAL ASSESSMENT AND OCULOMOTOR COMPUTATIONAL MODELING OF FLUENT READING DEFICITS IN SCHIZOPHRENIA

Heather Sheridan*[1], Andriana Christofalos[1], Nicole Arco[1], Madison Laks[1], Anna Beloborodova[2], Shayna Herszage[3], Maria Belen Aburto[4], Daniel C. Javitt[4]

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Background: Deficits in fluent reading ability contribute to impaired social and occupational function in schizophrenia (Sz) and may permit early detection of at-risk individuals during the late adolescent period. Both fixation-related potentials (FRP) obtained from concurrent EEG recording and eye-tracking, and computational modeling of eye movements during passage reading can be used to evaluate both lower- and higher-level contributions to reading impairments. We have previously reported significant correlations between impaired generation of the P1 FRP component and impaired reading ability in Sz along with group level differences in oculomotor control (Dias et al., 2021). Here, we evaluate these processes in an additional sample using expanded reading measures, and we also conduct model fits at the individual level using previously reported data.

Methods: We collected detailed reading measures in a new sample of 28 Sz individuals (including 5 first-episode), 19 clinical high risk and 16 healthy volunteers using the Woodcock-Johnson reading battery, along with FRP responses during passage reading. In addition, we conducted single-subject simulations on a previous dataset that included 26 Sz and 26 control individuals using the E-Z Reader model of eye-movement control. Specific measures used for modeling included: 1) first-fixation duration, 2) single-fixation duration, 3) gaze duration, 4) probability of making a single fixation, 5) probability of making multiple fixations, and 6) probability of skipping. Specific model parameters of interest include $\alpha 1$ (reflecting lexical processing speed); ε (reflecting effects of visual acuity); and λ (reflecting probability of making a refixation). For the individual model fits, we excluded outliers higher than 1.5*IQR above the upper quartile for each group.

Results: In the updated data set, as expected, we observed significant impairments in P1 FRP generation during reading in individuals with established Sz relative to the other groups ($p = .001$). We also observed significant reductions in reading fluency and comprehension (main effect $p < .001$) along with a significant group by task interaction ($p = .017$) reflecting a differential deficit in fluency versus comprehension. Impaired reading fluency correlated with impaired P1 generation ($p = .05$). In individual model fits, between-group differences were observed in the $\alpha 1$ ($p = .001$) and λ ($p = .003$) parameters, along with a significant correlation between the P1 reduction and the λ ($p = .02$).

Discussion: These findings continue to highlight the importance of reading fluency impairments in Sz both as a cause of psychosocial dysfunction and as a method to investigate underlying neural processes. The greater impairment in fluency vs. comprehension along with the consistent reduction in fixation-induced phase reset highlights the importance of lower-level deficits within the early visual system. These findings are emphasized by single-subject computational modeling showing impaired processing at both the lexical and parafoveal levels of processing. The findings

add to the growing body of literature demonstrating bottom-up contributions to impaired cognitive function in Sz.

S49. COMPUTATIONAL SPEECH AND LANGUAGE BIOMARKERS FOR PSYCHOSIS SYMPTOMS DURING ACUTE HOSPITALIZATION

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Background: The goal of acute psychiatric hospitalization during psychosis exacerbations is to quickly stabilize dangerous or distressing symptoms while avoiding overmedication and adverse effects. The development of sensitive, cost-effective and objective markers for changes in psychosis symptoms would be invaluable for assessing medication response and informing optimal titration. This study evaluated computational speech and language features derived from acoustic and linguistic analyses as potential biomarkers for changes in psychosis symptoms. Specifically, we used computational features to track changes in positive symptoms, negative symptoms, and thought disorder from initial treatment to discharge.

Methods: This was a prospective, longitudinal cohort study which recruited inpatients hospitalized with acute psychosis exacerbations. Fifty-four participants were assessed at two timepoints: the initial timepoint (T1) as soon after admission as possible, and the second timepoint (T2) just before discharge or within 1 week after discharge. At both timepoints, positive and negative psychosis symptoms were assessed with the Brief Psychiatric Rating Scale, and thought disorder was rated on the Scale for the Assessment of Thought, Language, and Communication.

Speech was elicited and recorded using the Winterlight Labs iOS app, including open-ended narrative tasks, picture descriptions, category and phonemic fluency tasks, and paragraph reading. Recorded speech underwent transcription and automated extraction of computational features relating to acoustics, timing, content units, lexical characteristics, sentiment, local coherence, syntax, and discourse-level variables. Initially, 1147 features were generated. After dropping covaried features (Pearson coefficient > 0.90), we had a final set of 511 computational speech and language features. To further reduce the feature space, we performed a principal component analysis (PCA) using the promax rotation, identifying 3 components.

To evaluate the longitudinal relationships between speech features and psychosis symptoms dimensions, we constructed linear mixed models with the relevant psychosis rating score as the dependent variable, timepoint and a speech features component score as the fixed effects, and participant as the random effect. Correction for multiple comparisons for the 3 components was done using the FDR method.

Results: The PCA resulted in 3 components: Component 1 accounted for 8% of the total variance, and represented features measuring local semantic similarities, size and organization of speech graphs, and type-token ration; Component 2 accounted for 5% of the variance and represented features measuring syntax, use of pronouns and nouns, and the commonness of the words used; Component 3 accounted for 3% of the variance and represented features measuring the quantity of detail identified in picture description tasks, pause frequency, pause duration, word duration, and

determiner-noun constructions. Change in positive symptoms was significantly predicted by change in Component 2 score (Beta = -0.08, adjusted p=0.005), change in negative symptoms was significantly predicted by change in Component 3 score (Beta = 0.03, adjusted p=0.03), and change in thought disorder was significantly predicted by change in Component 1 score (Beta=0.10, adjusted p=0.008) as well as Component 3 score (Beta=-0.13, adjusted p=0.01).
Discussion: We calculated 3 principal components based on 511 speech and language features. Each component tracked symptom changes for a major dimension of psychosis symptoms: positive symptoms, negative symptoms, and thought disorder. Our findings suggest that computational speech and language features may provide sensitive, efficient, and objective markers for changes in psychosis symptoms during acute psychiatric hospitalization. Future studies should examine these changes on a more fine-grained time-scale.

S50. DETECTING AT-RISK MENTAL STATES FOR PSYCHOSIS (ARMS) IN GENERAL POPULATION INDIVIDUALS USING MACHINE LEARNING ENSEMBLES AND FACIAL FEATURES

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Background: At Risk Mental State (ARMS) is a preclinical stage that might indicate conversion into psychosis or schizophrenia. This preclinical stage motivates a series of studies in the last years, but despite current advances, identification of ARMS amongst control participants still lacks methods that are not time consuming and with good accuracy. Our work aims to ease ARMS recognition employing machine learning ensembles combined with facial and head movement features extracted from brief video-recordings.
Methods: 58 ARMS and 69 Control participants were interviewed with the Structured Interview for Prodromal Syndromes while being recorded. We used these videos to extract 68 facial keypoints at each frame of the videos, these keypoints are summarized with median absolute deviation, their interquartile ranges and their correlations alone or with each other, we also employ them to create facial features for each participant (eg.: head angle, distance between two points or the aspect ratio of the eyes or the mouth) that are later summarized as well. The aftermath of this step is a 649 dimension vector for each participant that is lately augmented with feature interaction, creating 210925 new features from the repeated combination of them.

In possession of these features, we employ different types of machine learning ensembles for feature selection and classification of ARMS individuals. Firstly, Gradient Boosting Machines are used to select the best 0.05% (110) features, and then a combination of AdaBoost and Random Forests is trained on these selected features added with sociodemographic information (gender, age and scholarity) to obtain our final classifier.

Results: The final classifier reached averages of 82%, 84% and 93% of F1 Score, Balanced Accuracy and AUC respectively after 100 hundred leave-group-out training sessions. Moreover, 73 of the selected features showed significant p-values when comparing their distribution with the absence (diagnosis of 0 or 1) or presence (diagnosis equal or greater than 2) of 16 prodromal symptoms with Wilcoxon's Ranksum test, highlighting: the interquartile range of the angle between the tip and one midpoint of the nose multiplied by the median absolute deviation of the sum of the head pose angles with the absence or presence of Avolition (pvalue: 3.99e-5) and the interquartile range of the angle between the tip and one upper point of the nose multiplied by the Spearman's correlation coefficient of each corner of the mouth on the Y axis with Ideational Richness (pvalue: 0.0032).
Discussion: Our methodology of feature engineering and selection resulted in independent variables effectively able to classify ARMS and healthy participants from the general population. These variables show significant correlations with prodromal symptoms diagnosed with the SIPS as well and might indicate a path towards the use of facial landmarks to early detect ARMS with video interviews alone, since the final metrics were obtained without any clinical information.

S51. COMPARING THE VALIDITY OF VARIOUS NATURAL LANGUAGE PROCESSING TOOLS IN PSYCHOSIS ASSESSMENT

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Background: Natural language processing (NLP) has been shown as highly promising in differentiating patients from nonpatients, predicting transition to psychosis in individuals at clinical high risk, and identifying psychotic symptoms, such as disorganized speech. Research in the area has been blooming over the past few years; however, progress has been limited by small sample sizes and unstandardized methods in both linguistic analysis and speech elicitation techniques. These issues render comparisons of the various NLP programs or the identification of the best suited approach impossible. The present study utilizes 2 popularly researched NLP programs on a larger inpatient sample, allowing for a comparison of the different tools. As recent studies conducted with standardized speech elicitation measures suggest this method is more reliable, the speech analyses will be based on verbatim responses from R-PAS protocols. The Rorschach Performance Assessment System (R-PAS) provides a standardized procedure for gathering speech samples to 10 inkblots and has meta-analytic support for its reliability and validity in assessing disordered thinking.
Methods: 91 patients, 19-80 years old (M = 40) and predominantly male (89%), were recruited from a maximum-security inpatient forensic hospital. R-PAS protocols were coded for thought disturbance using the R-PAS language and reasoning Cognitive Codes (WSumCog, DR2). The patient's primary clinician and psychiatrist provided ratings of conceptual disorganization (P2) on the Positive and Negative Syndrome Scale (PANSS) for schizophrenia.
First, we evaluate the magnitude of relationships between the traditional measures of disorganized thinking on R-PAS (WSumCog, DR2) and the PANSS (P2). Subsequently, the NLP tools – RoBERTa and GloVe – will be used to compute the cosine similarity (CoS) of the raw data of the R-PAS protocols (i.e., the verbal responses) and compared to each other regarding clinical utility. To assess whether NLP scores provide incremental validity over R-PAS scores of disordered

thinking (WSumCog, DR2) in predicting PANSS P2 ratings, hierarchical regression analyses will be used.
Results: Rater agreement was excellent for the R-PAS WSumCog (ICC = 0.76) and good for the PANSS P2 Conceptual Disorganization ratings (ICC = 0.70). The R-PAS WSumCog and DR2 variables were significantly correlated with PANSS Conceptual Disorganization ratings ($r = 0.39$, $r = 0.41$, respectively). RoBERTa but not GloVe was significantly correlated with DR2 ($r = -0.44$, $p < 0.001$), WSumCog ($r = -0.39$, $p < 0.001$), and PANSS P2 ($r = -0.35$, $p < 0.001$). The hierarchical regression analyses showed that RoBERTa did not provide incremental validity over the R-PAS DR2 ratings in predicting the clinician ratings on the PANSS P2 ($\Delta R2 = 0.02$, $p = 0.106$). However, RoBERTa did add a small amount of predictive validity to R-PAS WSumCog in predicting PANSS P2 ratigns ($\Delta R2 = 0.05$, $p = 0.028$).
Discussion: While GloVe CoS does not correlate with any of the clinical ratings of disorganized speech, RoBERTa CoS appears to measure positive formal thought disorder. Although RoBERTa did not provide incremental validity over R-PAS DR2 in predicting PANSS P2 ratings, it may offer a quick- and easy-to-administer screening tool for psychosis. We plan to replicate these findings in additional archival samples and compute Word2Vec CoS. Our results further aim to contribute to the creation of an overarching framework for the use of NLP, as a novel objective and highly efficient assessment tool, in the clinical assessment of emerging psychosis.

S52. THE IMPORTANCE OF TRANSDIAGNOSTIC PSYCHOTIC SYMPTOMS IN SUICIDE RISK ASSESSMENTS - RESULTS FROM 7000 ACUTELY ADMITTED PSYCHIATRIC INPATIENTS AND DEATH BY SUICIDE AT FOLLOW UP

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Background: Psychotic symptoms are understudied as a short-term predictor of suicide
Objective: To prospectively investigate the predictive relationship of psychotic symptoms for short-term risk of suicide death.

Methods: Prospective study of a representative and diagnostically mixed sample of 7000 acutely hospitalized psychiatric patients between 2005 and 2014 in a Norwegian catchment area of 400 000 inhabitants. Suicide deaths were registered at one and two weeks, and at one, six and twelve months following admission. Survival analyses were used to estimate the regression coefficients of psychotic symptoms, severe depressive symptoms and substance use regardless of diagnosis. Assessments were conducted at admission, and included ICD-10 diagnosis; clinical interview in the form of the Health of the Nation Outcome Scales and qualitative assessments of suicidal ideation and suicide attempts over the past week.
Results: After one year follow-up, 101 (1.4%) patients died by suicide, of whom almost 70% were men. The relationship between psychotic symptoms and suicide deaths at 1 and 2 weeks and at 1, 6, and 12 months following admission will be reported. Psychotic experiences were far more prevalent than psychotic disorders.

Discussion: When assessing short-term suicide risk, we recommend thoroughly examining psychotic symptoms and experiences. Routinely assessing severity of symptoms in dimensions as psychosis, severity of depressive symptoms and severity of substance use may bring us closer to a transdiagnostic clinical tool for assessing suicide risk, which could aid us in our risk assessment.

S53. DEVELOPMENT AND VALIDATION OF THE COMPLEX VOICES SCALE IN A SAMPLE OF INPATIENTS WITH SCHIZOPHRENIA SPECTRUM DISORDERS

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Background: Auditory verbal hallucinations, the experiences of hearing voices without external stimuli, are common in individuals with schizophrenia spectrum disorders. Recent models of auditory verbal hallucinations highlight dissociative processes in the psychopathology of voices, as there is evidence indicating a similar or even higher prevalence of voices in individuals with dissociative disorders, as well as the robust association between voices and dissociation. A key phenomenological feature of voices is the personification of one or more identities in interaction with the self, indicating the interpersonal and dialogical nature of voices. Therefore, it has been proposed that (some types of) voices reflect disintegrated and disowned aspects of self, which are dissociative in nature. Recently, Ross (2020) proposed the concept of "complex voices" to represent voices that have thoughts, emotions, and personalities, and display interactive relationships with other voices experienced as coming from the outside of the self. The development of a psychometrically sound measure to assess complex voices is crucial for the assessment of this phenomenon in clinical settings and research. The current study aimed to develop and validate the Complex Voices Scale (CVS) as a measure of complex voices, in a sample of inpatients with schizophrenia spectrum disorders.

Methods: A panel of researchers and mental health professionals generated a pool of 33 items based on a range of phenomenology of auditory verbal hallucinations. Nine items were agreed upon for capturing the concept of complex voices and subjected to psychometric analyses. Firstly, item discrimination analysis was conducted. Secondly, the factor structure was examined with exploratory factor analysis and then confirmed with confirmatory factor analysis. Thirdly, convergent validity was tested with correlations of the CVS with measures of auditory hallucinations (i.e. the auditory hallucinations subscale of the Psychotic Symptom Rating Scales) and dissociation (i.e. Dissociative Experience Scale- Taxon). Lastly, Cronbach's alpha of the CVS was computed as an index of internal consistency. The validation sample consisted of 100 inpatients with schizophrenia spectrum disorders in Taiwan (45% females, age range 36-71, 54% met the diagnostic criteria of a dissociative disorder).

Results: Item discrimination analysis of the initial nine items suggested the removal of one item due to poor discrimination power. Exploratory factor analysis recommended the one-factor structure, with one item further removed due to low factor loading (< 0.40). The one-factor structure of the 7-item CVS was confirmed (CFI= 0.96, TLI= 0.94, RMSEA= 0.07, SMRS= 0.06). The convergent validity of the CVS was supported by its association with auditory hallucinations ($r= 0.90$, $p< .001$) and dissociation ($r= 0.89$, $p< .001$). In addition, there was evidence supporting

complex voices, auditory hallucinations and dissociation as non-overlapping constructs (CFI= 0.96, TLI= 0.95, RMSEA= 0.05, SMRS= 0.04). The internal consistency of the CVS was satisfactory (α= 0.78). Furthermore, the severity of dissociation was independently predicted by complex voices (β= 0.89, p< .001) and auditory hallucinations (β= 0.80, p< .001).
Discussion: The CVS demonstrated sound psychometric properties and may be useful for assessing complex voices in clinical populations. The CVS may supplement existing measures of auditory hallucinations and dissociation, allowing investigation of the relationship between voices and dissociation. Future studies should examine the psychometric properties of CVS in individuals in early stage of their illness and also in non-clinical populations.

S54. AUTISTIC SYMPTOMS IN PATIENTS WITH RECENT-ONSET PSYCHOSIS: CLINICAL, COGNITIVE, PSYCHOSOCIAL AND FUNCTIONAL CHARACTERISTICS

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Background: Although autism and schizophrenia have been classified as distinct illnesses, a number of studies have investigated the similarities between them. Also, patients with schizophrenia with prominent autistic symptoms were known to generally have lower neurocognitive and functional level of life. We intended to investigate the differences in clinical, cognitive, psychosocial and functional characteristics according to the severity of autistic symptoms in patients with recent-onset psychosis.
Methods: : The participants were 671 patients with recent-onset psychosis enrolled in the Korean Early Psychosis Cohort Study (KEPS). To evaluate the severity of autism symptoms, PANSS Autism Severity Score (PAUSS) was used, dividing the subjects into three different groups: “Autistic group” (PAUSS≥30), “Non-autistic group” (PAUSS≤10) and “Moderate group” (10<PAUSS<30). The baseline sociodemographic and clinical characteristics, cognitive functions and emotional recognition were compared by group. The relationship between the two-factor model of Clinician-Rated Dimensions of Psychosis Symptom Severity (CRDPSS) and the severity of autism was also analyzed. Additionally, changes in the longitudinal clinical course in the three different groups of patients were monitored for 2 years.
Results: In the group with more severe autistic symptoms, non-autistic symptoms also worsened, leading to a worsening of overall symptom severity. Neurocognitive function and emotional recognition also showed that the more severe the autistic symptoms, the more severe the impairment. Non-autistic group showed better social functioning than autistic group. As for the presence of comorbid psychiatric disorders, lowest incidence was shown in the autistic group, suggesting the diagnosis of pure psychosis. Also, the rate of diagnosis of schizophrenia was the highest in the autistic group. Comparing with CRDPSS factor group, no difference was shown between the autistic and non-autistic group. As a result of follow-up assessment for 2 years, significant differences in overall symptom severity were maintained by group, and so was the difference in autistic symptoms.
Discussion: Autistic symptoms have a significant impact on overall symptoms and functions on patients with recent-onset psychosis. Furthermore, in the longitudinal perspective, autistic symptoms and their impact also persisted, suggesting that autism may be a trait rather than a simple state variable.

S55. VALIDATION OF A NEW SCREENING QUESTIONNAIRE TO DISCRIMINATE SCHIZOTYPAL DISORDER (SD) FROM AUTISM SPECTRUM DISORDER (ASD) IN ADULTS: SCIZOTYPY AUTISM QUESTIONNAIRE (ZAQ)

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Background: Autism Spectrum Disorder: ASD and SD historically and practically have been grounded in two different scientific traditions,
which has had a significant impact on the way clinicians assess patients and how the diagnostic criteria have developed. ASD has its roots in the relatively young field of child and adolescent psychiatry, whereas SD comes out of a more than 100-year-old tradition and is primarily based on clinical presentations in adults. Consequently, professionals involved in assessment of ASD and SD often come from different backgrounds and make use of different diagnostic methods The prevalence estimates of ASD display a high variability across nations worldwide. In most western countries the prevalence is estimated to be 1-2% [3]. Danish data suggest a prevalence of 1.65% or approximately 95,000 persons in Denmark [4]. The case identification and assessment of ASD is challenged by a high rate of comorbidity with depression (50%), anxiety (40%) and ADHD/ADD (40-60%) [5,6]. The prevalence of comorbidity with SD has to our knowledge not been established. Nevertheless, some indications of the relation between ASD and SD can be estimated by looking at studies comparing ASD with psychosis or schizophrenia spectrum disorders (SSD). Sub-clinical psychotic symptoms occur frequently in ASD patients [7–9], and the prevalence of SSD in adults with ASD are in the range of 4-12% [5].

To aid in case identification of ASD, several screening questionnaires have been developed, AQ, RAADS-R and SRS. None differentiate well between autistic individuals and individuals with SSD [13,14].

Schizotypal Disorder: SD is also a heterogeneous disorder with an estimated prevalence of 4.6% and a high rate of comorbidity [15, 16]. The diagnosis can be made if at least 4 out of 9 ICD-10 criteria are met (see Figure 1). Although debated [17], SD is considered a crucial construct in the development of SSD [18]. Thus, early diagnosis is important for prognosis, as 25-48% of SD patients are prodromal and go on to develop SSD [17,19]. The prevalence of comorbidity between ASD and SD, which is the main focus of this study, has to our knowledge not been described in any detail. However, the prevalence of ASD in individuals with SSD seems to be substantially increased relative to the general population, although estimates vary widely [20].

Several psychometrically robust questionnaires are available to assess features of and screen for SD. None have differential diagnostic properties.

Given significant difficulties in discriminating between ASD and SD and the serious consequences that case misclassification can have for treatment and prognosis, we have sought to develop the schiZotypy Autism Questionnaire (ZAQ) to aid clinicians in the assessment of and discrimination

between ASD and SD in adults at the case identification stage. A pilot version of this novel screening questionnaire ZAQ, containing 130 questions, has been developed at the Mental Health Centre, Capital Region of Copenhagen. This will be tested in 400 psychiatric patients and 200 healthy controls from May 2022 – April 2023, which constitutes Phase 1 of this study. Psychometric data analysis from this study will constitute the empirical foundation for the development of the final version of ZAQ. This final version, which pending statistical recommendations is expected to contain approximately 60 questions, will undergo subsequent validation in an independent sample (Phase 2).

Methods: We aim to test 200 autistic patients and 100 schizotypy patients recruited from specialised psychiatric clinics and 100 controls from the a general psychiatric population (Phase 1). The results from ZAQ will be compared to the clinical diagnoses from interdisciplinary teams at specialised psychiatric clinics. After this initial testing phase, the ZAQ will be validated in an independent sample (Phase 2).

Results: We are performing psychometrical analysis as we complete our data collection. The Inclusion I scheduled to be completed April 2023, and the preliminary data will be presented at the SIRS conference, for the first time.

We hypothesize that the ZAQ will provide acceptable discrimination between ASD and SD, as indicated by an AUC $\geq$ 0.7. The ZAQ will retain a clinically meaningful factor structure, instructing further research on distinct sub-constructs. Lastly, the positive predictive value of the cut-off score will have strong clinical power regarding the selection of which patients need further diagnostic examination.

Discussion: The main incentive to conduct this study has arisen from a clinical need to improve case identification of patients before referring to either ASD or SD assessment. Wrong initial case identification can lead to unacceptable clinical trajectories for the patients. An overlooked prodromal SSD in an autism clinic can delay onset of necessary treatment. A misdiagnosis of a patient in a unit for assessment of SSD can lead to treatment with antipsychotics when not warranted. Thus, incorrect referral can have severe negative consequences for the patient and is cost inefficient. ZAQ is designed to help avoid these unsatisfying trajectories and is primarily developed to alleviate difficulties in the initial case identifying phase of clinical assessment.

S56. UNDERSTANDING PATTERNS OF COMORBIDITY WITHIN INDIVIDUALS AT CLINICAL HIGH RISK FOR PSYCHOSIS THROUGH THE HIERARCHICAL TAXONOMY OF PSYCHOPATHOLOGY

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Background: The Hierachical Taxonomy of Psychopathology (HiTOP) consortium's transdiagnostic dimensional model of psychopathology has considerable support; however, this

model has been under-researched in individuals at clinical high risk (CHR) for psychosis, a population that may advance the model. CHR individuals have attenuated psychotic symptoms that vary in severity, but also have many comorbid diagnoses, including disorders with uncertain placement in HiTOP (e.g., obsessive-compulsive disorder).
Methods: The present study will use confirmatory factor analysis in the North American Prodrome Longitudinal Study-3 consortium dataset (710 CHR, 96 controls) to replicate the HiTOP model and test specific hypotheses regarding disorders with uncertain placement. The final model will be examined in relation to functioning and conversion to psychosis. Items and diagnoses from the Structured Clinical Interview for DSM-5, Structured Interview of Prodromal Symptoms, and Structured Assessment of Violence Risk in Youth will be used to represent HiTOP dimensions. Specific predictions were pre-registered (osf.io/uh9fr) and analyses included examinations of factor structure, competing models for specific diagnoses, correlations with functioning, and prediction of conversion to psychosis.
Results: Both a 3 correlated factors model (emotional dysfunction, externalizing, and psychosis) and 3 level hierarchical factor model (general factor, 3 super spectra, and 7 subfactors) provided nearly adequate fit (CFI > .87, RMSEA < .06) and, with limited modifications, fit well (CFI > .90, RMSEA < .05) . Diagnoses with unclear placement within HiTOP were tested in the context of these two models, with some diagnoses being easily placed within the 3 factor model (e.g., avoidant personality disorder) and others requiring the more fine-grained perspective of the hierarchical model (e.g., obsessive compulsive disorder; OCD). Notable findings included clear evidence that bipolar spectrum disorders load exclusively on psychosis (standardized loading = .39) and the more complex finding that OCD loads on both fear and reality distortion subfactors. All HiTOP dimensions were related to poor global, social, and role functioning (rs = -.26 to -.76); however, the psychosis spectrum subfactors of reality distortion and detachment showed the strongest unique relations to functioning. Finally, the P-factor, psychosis superspectrum, and reality distortion factors all significantly predicted conversion to psychosis, with predictive accuracy increasing with more specific factors.
Discussion: Overall, the present findings suggest the utility of the HiTOP model for understanding psychosis risk and, furthermore, demonstrate the ability of CHR samples to inform the HiTOP model. Comorbidity is an important area of CHR research and the present study suggests that the HiTOP model can organize and simplify these efforts, through focusing efforts on transdiagnostic dimensions rather than single diagnoses. In turn, the unique complexities of CHR samples allow for stronger tests of the HiTOP model, with the present study notably advancing debates regarding the placement of OCD and bipolar spectrum disorders.

S57. CLINICAL AND COGNITIVE FEATURES ASSOCIATED WITH AUDITORY HALLUCINATIONS IN CLINICAL AND NONCLINICAL VOICE HEARERS

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Background: Auditory verbal hallucinations (AVH) are a central symptom observed in people with schizophrenia (PSZ). However, recent research has shown that a small percentage of the general population report AVH in the absence of other evidence of illness (termed nonclinical voice hearers, NCVH). Here we sought to examine the phenomenology of AVH in these two

groups as well as examine broader indices of psychopathology and cognitive performance to determine the degree to which NCVH demonstrate an extended psychosis phenotype.
Methods: : We studied 76 PSZ, 51 Healthy volunteers, and 33 NCVH, most of whom reported being psychic mediums. We administered the Wechsler Test of Adult Reading and the Working Memory, Verbal Learning, and Processing Speed measures from the MCCB. We administered the Brief Psychiatric Rating Scale (BPRS), Chicago Hallucination Assessment Tool (CHAT), Peters Delusion Inventory (PDI), Launay Slade Hallucination Scale (LSHS), Clinical Assessment Interview for Negative Symptoms (CAINS),Positive and Negative Affect Scale (PANAS) and the Childhood Trauma Questionnaire (CTQ). Our analyses used three or four group ANOVAS followed by post-hoc t-tests.
Results: The NCVH and HCs did not differ from one another, and both scored significantly higher than the SZ groups on all of the cognitive performance measures. On the BPRS, both H+ and H- PSZ had higher total scores than NCVH (p's <.001). However, the PSZH+ and NCVH had very similar hallucination severity ratings (4.7 vs 4.3 respectively). The NCVH had significantly higher Grandiosity ratings than both patient groups (p<.001), while both patient groups had significantly higher ratings on suspiciousness (p's<.001). On the CHAT, the NCVH reported very similar sensory features (loudness, frequency, etc) for their AVH as seen in PSZ H+ (9.3 vs 9.8) . However, PSZH+ reported significantly less ability to control their AVH (p<.001), and their AVH had more negative content and resulted in more distress than seen in NCVH (p<.001) . Both PSZH+ and NCVH had significantly higher scores on the Launay Slade Hallucination Scale (23.4, 25.4) than seen in PSZ H- (17.9) and HCs (9.8). NCVH (9.5) and both groups of PSZ (9.7, 7.0 in H+ and H-) had significantly higher total PDI scores than did HCs (1.9). The PSZH+ had significantly higher ratings on paranoia items than did NCVH and PSZ H-). Both SZ groups had much more severe negative symptoms than NCVH on the CAINS. On the PANAS both patient groups experienced significantly more negative, and less positive affect than in NCVH. NCVH reported more emotional abuse than did HC on the CTQ (p<.01); both patient groups reported more emotional abuse than seen in HC but these differences were not significant.
Discussion: NCVH lack the cognitive impairments and negative symptoms seen in PSZ. They share AVH with very similar sensory features as in PSZ. PSZ report less ability to control their AVHs and report more distress associated with AVH than seen in NCVH. While NCVH endorse a number of unusual beliefs, they do not experience the degree of suspiciousness and paranoia that is common in PSZ. It is likely that the distress associate with psychotic symptoms is reflected in global ratings of reduced positive and increased negative affect seen in PSZ relative to NCVH. These data suggest that the experience of AVH, by itself, does not result in a need for care. It appears that lack of ability to control the onset and offset of AVH, the negative content that characterizes the AVH of PSZ, and paranoid/suspicious beliefs are the critical features that are associated with clinical morbidity. NCVH appear to share only the AVH and unusual beliefs seen in PSZ, lacking negative symptoms and cognitive impairment.

S58. EXPLORING THE CONCEPTUALISATION, MEASUREMENT, CLINICAL UTILITY AND TREATMENT OF FORMAL THOUGHT DISORDER IN PSYCHOSIS: A DELPHI STUDY

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Background: Disorganised speech is considered as one of the core features of psychosis, however, the concept, measurement, clinical utility and treatment of disorganised speech, traditionally referred to as Formal Thought Disorder (FTD), remains much debated.

Methods: This study adopted the Delphi technique to investigate expert opinion towards improving clarity in how the concept, measurement, clinical utility and treatment of FTD is understood among researchers and clinicians. Potential participants were identified via relevant international and national organisations and publications, and recruited based on their expertise in FTD and relevant experience working with adult psychosis cohorts. Across three rounds, these experts were asked how they defined FTD, what methods they used to assess and measure FTD, and whether assessing FTD had any clinical utility. Panellists were also surveyed on treatment options for FTD.

Results: Three hundred potential participants were identified and contacted. A total of 56 discrete responses were obtained from clinicians (n = 25), researchers (n = 9), and individuals who held dual roles with varying research loads (n = 22). This consisted of 48 participants in Round One, with 30 participants returning to participate in Round Two, as well as 8 new participants, and 34 of these participants returning to participate in Round Three.

Overall, consensus (>80%) endorsement was infrequent, and the conceptualisation, measurement, clinical utility and treatment of FTD appeared to have a multitude of interpretations. With regards to the concept of FTD, no consensus was obtained with regards to terminology (FTD= 34.21%, thought disorder = 18.42%, disorganised speech = 15.79%, disagreement of all terms = 31.58%), or the number and nature of dimensions represented within the construct. Consensus was achieved with regards to the definition of FTD, in that it was multidimensional (100%), distinct from aphasia (100%) and associated with psychosis (93.37%). Possible aetiological mechanisms identified were diverse (e.g. language/linguistic processes, developmental factors and cognition).

Results also suggested that 78.86% of panellists perceived the assessment of FTD to be important in both clinical and research settings, but that the appropriateness of an assessment depended on the context of its use. The top three perceived difficulties with measuring FTD included poor or limited training of clinicians and researchers, poor understanding of the concept between professionals, and inadequate or lack of consensus regarding measures. The top three recommendations to improve the measurement of FTD included improve training of clinicians, develop easy to use assessment criteria and improve methods of objective assessment.

Overall, panellists generally agreed that it was clinically useful to assess FTD in terms of the presence, severity, and impact of, though no single reason as to why reached agreement. Agreement amongst panellists was also low regarding the treatment of FTD, with the most common interventions identified as antipsychotics, cognitive remediation therapy and cognitive behavioural therapy.

Discussion: The findings of this first-ever FTD Delphi study provide an appreciation of the state-of-play of the field. Areas of consensus provide a platform for the expansion of future work along avenues of FTD conceptualisation, measurement, clinical utility and treatment, where agreement is still lacking. The intertwined nature of these four facets of FTD is also a ubiquitous challenge. A coordinated international and multidisciplinary approach is needed to achieve and maintain progress in characterising and engaging with this major psychiatric phenomenon.

S59. THE EFFECTS OF AN EARLY DETECTION CAMPAIGN AND THE DURATION OF THE UNTREATED PSYCHOSIS ON CLINICAL AND FUNCTIONAL PRESENTATION

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Background: The aim of the current paper is to examine the effects of an early detection (ED) campaign and the duration of untreated psychosis (DUP) on clinical and functional presentation at baseline. We hypothesized that the shorting of DUP at the ED site would result in recruiting patients who are less sick, that is, with a better clinical and functional presentation at admission compared with No-ED–area patients.
Methods: Data were collected between 2015-2019 during a pragmatic trial conducted at two clinics of first episodes of psychosis (FES) in (STEP, n = 147) or outside (PREP, n =75) an ED campaign. We first evaluated the effect of ED on clinical outcomes by comparing the pre and post-campaign change between two clinics using linear regression for continuous variables and logistic regression for binary outcomes. Further mediation analysis was conducted to explore the role of DUP reduction in the campaign effect on clinical outcomes in the STEP site. If the regression coefficient changes by more than 5%, a formal Sobel test is conducted.
Results: Contrary to our hypothesis, symptom severity (PANSS scores), global functioning (GAF score), cannabis use, suicidality, childhood pre-morbid adjustment, and aggression level, did not significantly differ between sites and the ED period. The level DUP explained the difference in positive scores pre vs. post-ED within STEP.
Discussion: ED does not seem to change presentation despite reducing DUP. Participants of both ED and No-ED sites had a similar clinical and functional presentation at baseline.

S60. VALUES AND PRINCIPLES OF EARLY INTERVENTION SERVICES FOR PSYCHOSIS: WHAT DO WE KNOW AND WHERE DO WE GO NEXT?

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Background: Early intervention for psychosis, with its origins in the early 1980s, continues to rapidly evolve, nationally, and internationally. Despite early intervention originating as a movement founded in philosophical shifts away from nihilism and towards hope, few attempts have been made to systematically examine its underpinning principles and values. Furthermore,

there have been key recent shifts in the field towards values and principles such as recovery-oriented, preference-based, patient-centered, family-centered, measurement-based, etc. These principles offer both a philosophy of care and a set of practices to guide research, training, and service delivery. As we near half a century of providing early intervention for psychosis, it is an appropriate time to examine early intervention from a principles-and values-based standpoint. Values are embedded in and expressed by principles. Principles express values in a way that makes them actionable. Clinical Practice Guidelines (CPGs) and other guidance documents provide recommendations for optimal treatment for a health condition, e.g., psychosis, and guide teams' and clinicians' decision-making. Our goal was to synthesize and explore values and principles of EIP from existing clinical guidance documents.

Methods: A systematic scoping review was conducted of grey and peer-reviewed literature (published between January 2000 and June 2022) providing clinical guidance focused on early intervention for psychosis (e.g., guidelines, standards, etc.). Two reviewers independently searched 58 websites (e.g., government, organizational, academic, non-profit, health, etc.) using ten keywords. The peer-reviewed scoping review search was conducted by a librarian on MEDLINE, EMBASE, PsycINFO, CINAHL, Cochrane Trials, and ProQuest Dissertations and Theses. Documents were included based on consensus. Two raters later independently extracted data on values and principles and other aspects (e.g., stakeholders involved in developing CPGs). Conflicts were resolved through team consensus. Data were analyzed using the iterative process of deductive and inductive qualitative thematic analysis.

Results: A total of 58 documents were included, of which only 21 (36%) explicitly mentioned EIP principles and/or values. Preliminary analysis identified 32 themes under which values and principles were categorized. Common themes (endorsed in more than 10 documents) among endorsed principles and values consisted of provision of service that is age/developmentally appropriate, culturally sensitive, individualized/personalized, recovery-oriented, family-focused, and that promoted shared decision-making or partnership-based care. Themes that were less frequently (1-2 documents) identified were ultra-high-risk identification/treatment, early detection, outreach/community education, transparency, accountability, trust, hope/optimism, autonomy, and self-management. Various gaps were identified around equity, diversity and inclusion (e.g., gender or 2SLGBTQI+ inclusive language and perspectives); the lack of recommendations of concrete practices aligned with values and principles; and the limited involvement of service users and families in guidelines development.

Discussion: Given that early intervention was founded as a philosophical or values-based movement around optimism and hope, it is striking that less than half of the documents explicitly outlined values and principles. While there was convergence around some values and principles, this was not always the case with some values/principles being articulated only in select documents. At times, activities or practices (e.g., outreach) were framed as values. That service users and families were rarely or inadequately involved in guidance development may have also contributed to the neglect of values and principles, often central to lived experience experts. We recommend that future clinical guidance development in early psychosis involve all key stakeholders, especially service users and families, and explicitly articulate values and principles and evidence-informed practices that align with these.

S61. MOTIVATIONAL VARIABLES PREDICT COGNITIVE AND FUNCTIONAL GAINS DURING COORDINATED SPECIALTY CARE

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Background: Coordinated specialty care (CSC), or comprehensive early intervention encompassing psychotherapeutic, medication, and supportive components, provided in the early course of psychosis can reduce the short-term and potentially long-term dysfunction associated with schizophrenia-spectrum psychotic disorders. While CSC can be effective in improving various outcomes such as cognitive performance and functioning, there is considerable variability in treatment responsiveness. A critical research endeavor is to identify modifiable personal factors that can be targeted to enhance the likelihood of successful treatment outcomes. Motivation, a broad multi-faceted construct that includes both intrinsic motivation and extrinsic motivation, has emerged as a key determinant of treatment efficacy. Intrinsic motivation refers to the willingness to exert effort because a task is inherently meaning or interesting, while extrinsic motivation refers to externally regulated behavior that is motivated by rewards or punishments and compelled by feelings of the need to comply. Surprisingly, relatively little research has considered the roles of these aspects of motivation with treatment responsiveness in first-episode schizophrenia. This study investigated early intrinsic and extrinsic motivation as a potential predictor of cognitive and functional gains within CSC.

Methods: Forty participants with first-episode schizophrenia from the UCLA Aftercare Research Program were administered baseline measures of intrinsic/extrinsic motivation, one for group psychotherapy (The Situational Motivation Scale) and one for work/school (Work Preference Inventory), as well as 6- and 12-month measures of cognition (MATRICS Consensus Cognitive Battery) and functioning (Global Functioning Scale). Participants completed 12 months of CSC that included medication management by a psychiatrist, weekly case management and individual supportive therapy provided by a psychologist, family education, and Individual Placement and Support services. Participants were also enrolled in a simultaneous randomized controlled trial comparing group-based cognitive training and group-based healthy behavior training. Partial Spearman correlations (rs), controlling for the randomized treatment arms, were used to examine predictive relationships due to the non-normal distribution for treatment gain indices.

Results: Results indicated that higher baseline scores of extrinsic motivation for group psychotherapies, and, interestingly, intrinsic motivation for work/school were predictive of greater cognitive gains at 6 months ($rs > .34$, $p < .05$). Higher baseline scores of intrinsic motivation for group psychotherapies were predictive of greater cognitive gains at 12 months ($rs = .49$, $p < .01$). For functional gains, higher baseline scores of intrinsic motivation for work/school predicted both role and social functioning gains at 6 months ($rs's > .37$, $p < .05$), while baseline extrinsic motivation for work/school predicted social functioning gains at 12 months ($rs = .39$, $p < .05$). These medium to large predictive relationships did not substantially change even when covarying for baseline cognitive and functional scores.

Discussion: Thus, both early intrinsic and extrinsic motivation are important predictors of cognitive and functional treatment responsiveness. This study provides support for monitoring and enhancing motivation early during service delivery to maximize treatment response in first-episode schizophrenia.

S62. EXPLORING THE PRODROME OF SEVERE MENTAL DISORDERS: AN ELECTRONIC HEALTH RECORD STUDY

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Background: Preventive approaches in psychiatry rely on accurate knowledge of the specific types and timing of prodromal features preceding the onset of severe mental disorders (SMD), such as psychotic disorders, major depressive disorder and bipolar disorder. The prodromal phase has mostly been investigated in “look-back” studies which have several limitations including the use of interviews that are not integrated into clinical practice, the small sample sizes and substantial recall biases. Moreover, it is unclear to what extent SMD may display diagnostic-specific or transdiagnostic prodromal symptoms. To address these limitations, we will take advantage of Electronic Health Records (EHRs) routinely employed in secondary mental healthcare, constituting an extensive pool of untapped real-world information.
We aim to describe and compare the (1) incidence and duration of the first prodromal clusters, (2) total number of occurrences of prodromal features, and (3) mean number of occurrences of prodromal clusters between SMD diagnostic groups and prodromal years.

Methods: Clinical register-based EHR cohort including all individuals accessing the South London and the Maudsley (SLaM) services (2008-2021) and receiving a primary (i.e. not comorbid) diagnosis of any ICD-10 mental disorder that falls under SMD will be included. These diagnoses were then clustered into diagnostic groups: non-bipolar mood disorders (NBMD), bipolar disorders (BD), and psychotic disorders (PSY). We extracted 52 prodromal features (symptom and substance use variables) through NLP algorithms that are pooled in 8 broader prodromal clusters (depressive, disorganised, catatonic, manic, negative, positive, substance use and other symptoms). Prodromal features and clusters were extracted monthly from the index date of diagnosis until their first occurrence.
All analyses were conducted in R version 4.1.3. For aim 1, the proportion of individuals who experienced each first prodromal cluster and durations of prodromal period and clusters are described and compared between index diagnostic groups with the Welch ANOVA test. For aim 2, the mean number of prodromal features are described with radar plots. Cohen’s D effect sizes are calculated to assess how specific each prodromal feature is within each SMD group. For aim 3, the mean number of occurrences for each prodromal cluster (total of constituent feature occurrences within each cluster in each prodromal year) between index diagnostic groups over time (prodromal years) are analysed using a linear mixed effects model.

Results: 63,519 patients received an SMD index diagnosis (NBMD=36,190; BD=5,509; PSY=21,820) and had NLP-derived data before their index date. The prodromal period in NBMD (median [IQR]= 25 months[42]) was shorter than BD (44[47]) and PSY (44[48]). The number of feature occurrences across the prodromal period showed small discriminability effects between SMD groups (overall d=0.27), suggesting that most features remained transdiagnostic throughout the prodrome. Overall, the features discriminated NBMD-PSY the most (d=-0.34), followed by NBMD-BD (d=0.25) and BD-PSY (d=-0.13). Finally, we found that the mean number of symptom

occurrences within positive, negative, depressive, manic and other symptom clusters increased as patients became closer to their index date.
Discussion: These findings suggest that there are some differences in the length and presentation of the prodromal period between NBMD, BD and PSY. However, all SMD groups follow a similar time-dependent build-up of prodromal features, with most presenting as transdiagnostic. Feature-level approaches can help to better understand the clinical presentation of SMD to refine at-risk assessments and inform future prediction models.

S63. SUPPORTING THE DELIVERY OF COORDINATED CARE FOR EARLY PSYCHOSIS INTERVENTION USING THE ECHO MODEL

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Background: Early psychosis intervention (EPI) programs were introduced to reduce barriers to treatment and improve recovery from first-episode psychosis (FEP). However across programs in Ontario there has been variability in how services are delivered. NAVIGATE is an evidence-based manualized model of coordinated care for FEP consisting of four key interventions: individualized medication management, psychoeducation and resiliency training, supported employment and education, and family education. NAVIGATE operationalises EPI standards and has been implemented in the Centre for Addiction and Mental Health (CAMH) EPI program.
Project Extension for Community Healthcare Outcomes (ECHO) is an educational model that uses videoconferencing to connect a specialist (hub) team with multiple learner (spoke) teams. The ECHO model provides an opportunity to create a community of practice, and to share knowledge of best practices through didactic and case-based learning. In August 2019 a team at CAMH launched Early Psychosis Intervention-Spreading Evidence-Based Treatment (EPI-SET) ECHO, where the ECHO model is being used as a tool to guide implementation of new practices and support the delivery of NAVIGATE in geographically diverse EPI programs across Ontario. EPI-SET ECHO is aimed at creating a community of practice among EPI programs, and at building provider capacity to deliver the different components of NAVIGATE.

Methods: We examined 3 cycles of EPI-SET ECHO. Participants completed satisfaction surveys after each session, and practice change was assessed. Participants rated their satisfaction using a five-point Likert scale. Participants completed a questionnaire post cycle regarding the impact of ECHO on practice change.
Results: 86 providers from 6 EPI programs participated, including 22 occupational therapists, 15 social workers, 15 nurses, 10 clinic directors and care coordinators, 4 mental health clinicians and therapists, 3 peer coaches, 3 child youth workers, 2 psychiatrists, and 12 from unspecified disciplines. Satisfaction domains were highly rated including: enhancing clinical practice (3.90/5), reducing social isolation (3.83/5), addressing learning needs (3.99/5), overall satisfaction (4.14/5), and would recommend to others (4.08/5). 60% of participants indicated that EPI-SET ECHO resulted in a change in their practice.
Discussion: These findings would suggest high participant engagement and satisfaction with EPI-SET ECHO. It also suggests that participation translated into practice change for a majority of the

participants. ECHO may therefore be a practical model to support the learning of new practices, and to support capacity building in providers delivering a manualized model of coordinated care across EPI programs in Ontario.

S64. SUICIDALITY AND PERSISTENT NEGATIVE SYMPTOMS FOLLOWING A FIRST EPISODE OF PSYCHOSIS

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Background: Negative symptoms are a core feature of psychotic disorders and can be primary to the illness or secondary to the disease process. The construct of Persistent Negative Symptoms (PNS) captures idiopathic negative symptoms that result from the psychotic illness itself, while secondary PNS (sPNS) identifies a subgroup of patients whose negative symptoms result from different comorbid symptoms, such as positive, depressive, or extrapyramidal symptoms. While previous studies have shown that individuals with higher negative symptoms have a lower risk of suicide, the distinction between the different subgroups of negative symptoms, such as PNS and sPNS, is unclear. Because negative symptoms in sPNS are associated with secondary symptoms that are conducive to suicide risk (i.e., depressive and positive symptoms), this subgroup might demonstrate a different suicidality profile than those with PNS. In the present work, we examined the severity of suicidality between the different PNS groups in patients with a first episode of psychosis (FEP).

Methods: FEP patients admitted to an early intervention service were categorized into three different PNS groups at 1-year follow-up. Consistent with our earlier work, patients were classified as PNS if they had a moderate global rating or higher on at least one of the negative symptom dimensions of the Scale for the Assessment of Negative Symptoms (SANS), but no more than mild global ratings of positive, depressive, and extrapyramidal symptoms. This level of symptomatology had to persist for 6 months during the first year of follow-up, specifically from 6 to 12 months after admission. Patients with moderate negative symptoms or higher who also exhibited threshold positive, depressive, or extrapyramidal symptoms were classified as sPNS. The rest of the patients were classified as non-PNS. Because PNS groups were classified at month 12, we used BPRS suicidality at month 12 rated on a 7-point Likert scale (1=not present; 7=extremely severe). We conducted an ANCOVA using PNS group membership as our independent variable and BPRS suicidality as our dependent variable, controlling for age and sex. We subsequently added BPRS depression at month 12 as an additional covariate to control for the possibility that depressive symptoms might be contributing to the difference in suicidality between groups.

Results: Suicidality was examined in 113 PNS, 89 sPNS, and 235 non-PNS patients. Controlling for age and sex, we found a significant difference across PNS groups on suicidality ratings ($F(4, 432) = 9.285$, $p < .001$). Specifically, Bonferroni corrected pairwise comparisons revealed a significant difference between PNS and sPNS on suicidality ($p < .001$), with sPNS patients having higher suicidality ratings than PNS patients. Similarly, we found a significant difference between sPNS and non-PNS ($p < .001$) on suicidality, whereby sPNS patients had higher suicidality ratings

than non-PNS patients. However, we found no significant difference between PNS and non-PNS patients on suicidality ratings ($p>.05$). When controlling for overall depression, the difference between PNS and sPNS was maintained ($p<.05$) but sPNS and non-PNS no longer differed on suicidality ($p>.05$).

Discussion: While previous studies indicate that patients with higher negative symptom severity are at a lower risk of suicide, our findings suggest that suicidality differs between negative symptom subgroups, with sPNS patients displaying higher suicidality than PNS patients, even after controlling for overall depression. This suggests that depressive symptoms alone do not account for the elevated suicide risk observed in sPNS patients. Importantly, these results highlight the need to differentiate PNS and sPNS patients to appropriately capture suicide risk and offer tailored and targeted intervention based on negative symptom profiles. Future work should differentiate between suicidal ideation and suicide attempts for a more complete picture of the relationship between suicidality and PNS.

S65. IDENTIFYING LATENT TRAJECTORIES OF COGNITIVE FUNCTIONING AMONG CLINICAL HIGH RISK FOR PSYCHOSIS

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Background: Cohort studies demonstrate that people who later develop schizophrenia, on average, present with mild cognitive deficits in childhood and endure a decline in adolescence and adulthood. Yet, tremendous heterogeneity exists during the course of psychotic disorders, including the prodromal period. Individuals thought to be in this period (known as CHR-P) are at heightened risk for developing psychosis (~35%) and begin to exhibit cognitive deficits. Cognitive impairments in CHR-P (as a singular group) appear to be relatively stable or ameliorate over time. A sizeable proportion has been described to decline on measures related to processing speed or verbal learning. The purpose of this analysis is to use data-driven approaches to identify latent subgroups among CHR-P based on cognitive trajectories. This will yield a clearer understanding of the timing and presentation of both general and domain-specific deficits.

Methods: Participants included 684 young people at CHR-P (ages 12-35) from the second cohort of the North American Prodromal Longitudinal Study. Performance on the MATRICS Consensus Cognitive Battery (MCCB) and the Wechsler Abbreviated Scale of Intelligence (WASI) was assessed at baseline, 12-, and 24-months. Tested MCCB domains include verbal learning, speed of processing, working memory, and reasoning and problem-solving. Sex- and age-based norms were utilized. The Oral Reading subtest on the Wide Range Achievement Test (WRAT3) indexed pre-morbid IQ at baseline. Latent class mixture models were used to identify distinct trajectories of cognitive performance across two years. One- to 5-class solutions were compared to decide the best solution. This determination depended on goodness-of-fit metrics, interpretability of latent trajectories, and proportion of subgroup membership (>5%).

Results: A one-class solution was found for WASI Full-Scale IQ, as people at CHR-P predominantly demonstrated an average IQ that increased gradually over time. For individual domains, one-class solutions also best fit the trajectories for speed of processing, verbal learning, and working memory domains. Two distinct subgroups were identified on one of the executive functioning domains, reasoning and problem-solving (NAB Mazes). The sample divided into unimpaired performance with mild improvement over time (Class I, 74%) and persistent performance two standard deviations below average (Class II, 26%). Between these classes, no significant differences were found for biological sex, age, years of education, or likelihood of conversion to psychosis (OR = 1.68, 95% CI 0.86 to 3.14). Individuals assigned to Class II did demonstrate a lower WASI IQ at baseline (96.3 vs. 106.3) and a lower premorbid WRAT3 IQ (100.8 vs. 106.2).
Discussion: Youth at CHR-P demonstrate relatively homogeneous trajectories across time in terms of general cognition and most individual domains. In contrast, two distinct subgroups were observed with higher cognitive skills involving planning and foresight, and they notably exist independent of conversion outcome. Overall, these findings replicate and extend results from a recently published latent class analysis that examined 12-month trajectories among CHR-P using a different cognitive battery (Allott et al., 2022). Findings inform which individuals at CHR-P may be most likely to benefit from cognitive remediation and can inform about the substrates of deficits by establishing meaningful subtypes.

S66. INVESTIGATING SUICIDE THOUGHTS AND BEHAVIOURS WITH CLINICAL AND PRODROMAL LATENT PROFILES IN YOUTH

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Background: Suicide accounts for 5–10% of deaths in psychotic patients. As many as 21.6% of youth at high risk for psychosis will attempt suicide, with youth at the early stages of the disease at an 8-fold increase in risk of suicide compared to healthy controls. In a separate literature, a dysregulated profile (DP) of clinical symptoms is postulated to be a marker for persistent psychopathology and suicidality in youth and adults found across 34 countries. DP comprises of elevated scores on anxious-depressed, attention, and aggression subscales, and thus reflects substantial difficulties in self-regulation of mood, cognition, and behaviour. No studies have investigated whether suicidal thoughts and behaviours vary with different clinical profiles of psychosis risk and/or DP.
Methods: The CAMH TAY Cohort Study is recruiting 3000 youth ages of 11 to 24 seeking treatment for mental health concerns over five years. Using early data (N=265), latent profile analyses were conducted with psychosis risk (PRIME Screen—Revised), prodromal symptoms (Prodromal Questionnaire Brief), and syndromes scales (Youth/Adult Self-Report) to examine profiles characterized by high psychosis risk (HPR) and/or DP. Profiles were compared based on suicidal ideation (Suicidal Ideation Questionnaire-Junior/Adult), non-suicidal self-injury (NSSI; Nock's Self-Injurious Thoughts and Behaviors Interview), and lifetime suicide attempt (Columbia Suicide Severity Rating Scale). Profiles were conducted separately for youth and young adults.

Results: In line with theoretical considerations, the model fit (AIC = 2817, BIC = 2994, Entropy= .91) for youth 11 to 18 (Mage = 14.86; SD = 1.75) favored five profiles: "Normative"; "Moderate Externalizing"; "HPR"; "Moderate Internalizing"; "DP and HPR". The "DP and HPR" had the highest levels of dysregulation, prodromal symptoms, and psychosis risk compared to other groups. Bayesian one-way ANOVA showed overwhelming evidence for main effect of profiles predicting suicidal ideation (P[M|data] = 1.00; BFM= 5.4x108; R2=.37 [.25;.46]) and "DP and HPR" demonstrated the highest levels of suicidal ideation compared to other groups (BF10 >90 all groups). The "HPR", "Moderate Internalizing", and "DP and HPR" profiles endorsed 81%, 73%, and 67% of lifetime NSSI, respectively (BF10 Independent Multinomial [IM]= 56.03). In contrast, 32%, 16%, and 70% of "HPR", "Moderate Internalizing", and "DP and HPR" endorsed a previous suicide attempt, respectively (BF10 IM = 3.89).
Amongst young adults 18 to 25 (Mage = 21.26; SD = 2.26), the best fitting model (AIC = 3078; BIC = 3262; Entropy = .92) was a five-profile solution: "Normative", "HPR, High Psychopathology"; "Moderate Symptoms"; "DP"; "HPR, Low Psychopathology". Evidence supported profiles predicting suicidal ideation (P[M|data] = 1.00; BFM = 7.7x1010; R2=.40[.29, .48]). Suicidal ideation was highest in DP compared to other groups (BF10>50 all comparisons). For NSSI, 100% of "DP", 83% of "HPR, High Psychopathology", and 46% "HPR, Low Psychopathology" had a history of self-harm (BF10 IM = 9.26). A total of 79% of "DP", 61% of "HPR, High Psychopathology", and 33% of "HPR, Low Psychopathology" had a previous suicide attempt (BF10 IM = 4.15).

Discussion: Youth with DP and HPR were observed in a single group whereas adults show two distinct groups of DP and HPR. Youth with DP and HPR had the highest suicidal ideation and lifetime suicide attempt prevalence, but not NSSI. In young adults, DP was linked with high risk for suicide. HPR, when combined with other symptoms of psychopathology, was associated with enhanced risk for NSSI and suicide attempt. Recognition of these profiles may guide the detection of suicide risk in the early phases of psychosis.

S67. POST-TRAUMATIC STRESS DISORDER IN PEOPLE WITH FIRST-EPISODE PSYCHOSIS IN A SOUTH AFRICAN SETTING

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Background: The association between psychosis, childhood and life-course trauma, and post-traumatic stress disorder (PTSD) sequelae has been shown in populations with psychosis. Approximately two-thirds of South Africans, including those accessing mental healthcare services, report at least one traumatic life experience; however, the epidemiology of PTSD in early psychosis has not been explored. The study aimed to determine the prevalence of PTSD associated factors in people with first episode psychosis.
Methods: Recruitment in this study started in 2019 to date. In- and outpatients with first-episode psychosis were enrolled in five hospitals that provide psychiatry services in Kwa-Zulu Natal, South Africa. Participants were included in the study if they were 18 – 45 years old, had psychosis according to the MINI interview for psychosis, and had received less than six weeks of antipsychotics. Participants were included in this sub-analysis if they had attended an initial

enrolment visit and a follow-up visit at three months. At baseline, data was collected using the Childhood Trauma Questionnaire (CTQ), Positive and Negative Symptoms Scale (PANSS) for psychosis symptom severity and Patient Health Questionnaire (PHQ-9) for depression screening. Three months after enrolment, PTSD Checklist for DSM-5 (PCL) the Zulu Culture-Specific Trauma Experience Questionnaire (Z-CTEQ) were used to assesses for PTSD.
Results: A total of 51 participants were included in the sample. 36 (71%) were male, 41 (80%) had achieved a grade school education, and 33 (65%) were unemployed. Total PANSS mean scores were 80.2 (SD 19.2). At median scores of 6.0 (IQR 4.0, 7.0) and 3.5 (IQR 3.0, 5.0) for females and males respectively, females had significantly higher scores in the anxiety domains of the PANSS (p=0.005). 34 (67%) scored positive for one or more domains of childhood trauma. For childhood trauma, a significantly higher proportion of females had experienced emotional, physical and sexual trauma compared to males ($p<0.05$). Females scored significantly higher depression scores (median 14, IQR 9-21), compared to males (median 5, IQR 1-15) (p=0.009). Females had also experienced a significantly higher number of lifetime trauma events (median 2, IQR 1-2) compared to males (median 1, IQR 0-2; p=0.026). In the cohort 14 (30%) scored positive for PTSD on the PCL, and an additional 2 (4%) scored positive on the Z-CTEQ.
Discussion: The prevalence of PTSD in populations with psychosis is high. Females are disproportionately affected by childhood and lifetime trauma exposure. A proportion of patients with PTSD may be missed if culturally congruent tools are not used for assessments. There is evidence for the need of interventions, including culturally appropriate intervention, for vulnerable populations with psychosis.

S68. PERCEIVED DETERMINANTS TO OVERALL WELL-BEING AMONG BLACK SERVICE USERS WITH EARLY PSYCHOSIS AND THEIR FAMILY MEMBERS: PRELIMINARY FINDINGS

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Background: Few studies have adopted a qualitative approach to understanding the meaning of well-being and what supports are needed to maintain or improve well-being among service users in the early stages of psychosis and of those, none of which have focused on Black/African families. The purpose of this study is to understand determinants that support or hinder the well-being of Black/African American service users who have experienced psychosis and their family members/support persons.
Methods: Semi-structured qualitative interviews were conducted with 17 self-identified Black/African American services users and family members/support persons recruited from coordinated specialty care for early psychosis in the Pacific Northwest, United States. Completed interviews in this on-going study were transcribed verbatim and analyzed using a content analysis approach. Codes identified from completed interviews were categorized into four overarching themes informed by a socio-ecological framework: individual, interpersonal, community, and societal.
Results: The mean age of services users (n=6) was 21.8 years (SD= 3.5; age range: 19-28 years) and the majority were male (83%). The majority of family members (n=11) were parents, and the mean age was 43.2 years (SD= 11.23; age range: 25-58 years). Several participants emphasized individual-level factors that would support their overall well-being such as the need to improve

social skills and expressed hesitation disclosing experiences or diagnosis with old and potentially new friends. At the interpersonal-level, developing supportive relationships with providers and staff were considered paramount to navigating various systems of care. Family dynamics (e.g., mental health concerns with other family members, communication) had a positive or negative impact. At the community-level, engaging in activities and with organizations that stimulated community connectedness. Familiarity with resources and services (e.g., housing, transportation, employment) were vital to achieving basic needs and supporting goals. However, community-level supports that were missing were the lack of community advocacy and representation of Black providers. At the societal-level, participants described the lack of public awareness and education and limited access to services.

Discussion: Preliminary findings from this ongoing qualitative study, highlights determinants at various levels that support, would support, or a barrier to the overall well-being of Black/African American families. These findings potentially identify mechanisms associated with mental health outcomes and further stresses the need for the development of multi-level strategies/interventions that address well-being and not only mental health outcomes. Supported by NIMH K01MH117457.

S69. SATISFACTION WITH COGNITIVE REMEDIATION THERAPY: ITS EFFECTS ON IMPLEMENTATION AND OUTCOMES USING THE COGNITIVE REMEDIATION SATISFACTION SCALE

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Background: Cognitive Remediation (CR) is effective but implemented in a variety of ways. We do not know whether service users find these implementation methods acceptable, or whether satisfaction with CR influences outcomes.

Methods: Mixed participatory methods including focus groups, produced a co-developed CR satisfaction scale. We applied three psychometric criteria (Cronbach's alpha, item discrimination, test-retest agreement) to select items and used factor analysis to explore potential substructures. Using secondary analysis data from a randomised controlled trial,
structural equation joint models were used on the CR scale to detect whether satisfaction: (1) is associated with CR implementation methods (One-to-One, Group, Independent), (2) is affected by treatment engagement, or (3) influences the Goal Attainment Scale (GAS) recovery outcome.

Results: The 31-item Cognitive Remediation Satisfaction scale (CRS) reduced to 18 Likert items, which had good internal consistency (Alpha=.814), test-retest reliability (r= .763), and concurrent validity using the Working Alliance Inventory (r=.56). A 2-factor solution divided items into therapy engagement and therapy effects. Satisfaction was not related to any implementation method (Independent: Group, p=0.312; One-to-One: Group, p=0.847; Independent: One-to-One, p=0.402); but was significantly associated with CR engagement (therapy hours completed, p=0.001). Therapy hours were also significantly associated with recovery at 15-weeks post-treatment (GAS; p=0.002), however there was no direct effect of satisfaction on recovery (p=0.373).

Discussion: Although satisfaction is important to therapy engagement, it has no direct effect on outcome. It is the number of hours of CR therapy which directly affects outcome, irrespective of implementation model.

S70. ALTERED ASSOCIATIONS BETWEEN TASK ABILITY AND DORSOLATERAL PREFRONTAL ACTIVATION DURING A COGNITIVE CONTROL TASK IN SCHIZOPHRENIA

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Background: The contributions of disrupted brain activity to altered behavior during cognitive control in schizophrenia (SZ) are poorly understood. Using the drift diffusion model (DDM), we examined relationships between the drift rate (DR) parameter as an index of evidence accumulation and task ability with dorsolateral prefrontal cortex (DLPFC) activation during the AX Continuous Performance Task (AX-CPT), a task designed to measure proactive cognitive control (CC), in SZ.
Methods: 1.5 and 3T fMRI AX-CPT data were analyzed from 118 healthy controls (HCs) and 151 people with recent onset schizophrenia (SZ). Individual performance was fit using a DDM, allowing the DR (a parameter that depends on both accuracy and reaction time) to vary between task conditions. Association between left and right DLPFC activation with DR (with field strength and sex as covariates) were examined using mixed effects models.
Results: Across all participants, significant positive relationships were observed between CC-associated activation and DR for both the left ($F=11.34$, $p<.001$) and right ($F=6.55$, $p=.011$) DLPFC. Furthermore, significant activation*DR interactions were observed for both the left ($F=8.77$, $p=.003$) and right ($F=5.37$, $p=.021$) DLPFC, in which greater positive associations were observed between activation and DR in HCs vs. people with SZ.
Discussion: These findings suggest that task ability and CC-associated DLPFC activation are less well-linked in SZ and have important implications for understanding the neurobiology of CC deficits in the illness.

S71. YOUNG ADULT PERSPECTIVES ON COMMUNICATION WITH FAMILY AND CLINICAL PROVIDERS DURING FIRST EPISODE PSYCHOSIS TREATMENT

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Background: Treatment non-adherence among individuals who experience first-episode psychosis (FEP) is highly prevalent. Reducing duration of untreated psychosis and preventing dropout may be achieved by promoting family involvement in psychosis treatment and positive relationships with treatment providers. Understanding young adults' preferences regarding communication with family and providers may help to facilitate positive therapeutic alliance and deter disengagement from care (Browne et al., 2019; McFarlane et al., 2003; Pharoah et al., 2010).

Methods: Young adults were recruited who had an onset of psychosis within the past 5 years and were between 18-35 years of age. Using a semi-structured interview, participants were asked questions about what treatment they were involved in, how much their family is involved with treatment and their opinions on communication with their treatment team and their family. Research staff then coded to find important themes. The team coded transcripts by using thematic analysis.
Results: The analysis of the interviews revealed (1) a robust engagement with treatment is influenced positively by therapeutic alliance and clinical benefit and negatively by structural barriers and interpersonal barriers; (2) expectations from family include a deeper understanding of psychosis and the current psychological condition of the individual with psychosis; and (3) the quality of communication with family is impacted by the caregiver's response to the individual's varying needs for respect, privacy, autonomy, and care.
Discussion: Listening to young adults' opinions on their experiences can provide insight into what type of support best facilitates treatment alliance and open communication. The results: suggest that family-focused interventions that target enhancing communication and interpersonal dynamics between caregivers and young adults might support treatment engagement and the general well-being of the youth. The results also revealed that positive patient-provider relationships, prioritizing therapeutic alliance with a crucial focus on a non-judgmental, caring, and respectful approach, are another key element of treatment engagement.

S72. A RETROSPECTIVE DATABASE STUDY ON TWO-YEAR WEIGHT TRAJECTORIES IN FIRST-EPISODE PSYCHOSIS

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Background: It has been established that people with psychosis are at risk of developing metabolic syndrome and cardiovascular diseases during the course of antipsychotic treatment. However, while there has been literature examining antipsychotic-induced weight gain, it is also critical to focus on individual weight profiles in line with efforts to tailor treatment, given the heterogeneous nature of the clinical population. Weight interventions are too costly to be implemented program-wide, and are usually the most effective for those at-risk for or already with severe weight gain. The current study thus aims to identify and describe two-year weight trajectories among patients accepted to the Early Psychosis Intervention Programme (EPIP) in Singapore, and to highlight sociodemographic differences, if any, between those with complete two years of weight data and those without.
Methods: De-identified data was extracted from EPIP's standing database for patients accepted from 2014 to 2018 with a schizophrenia spectrum disorder. Data collected at fixed time-points (baseline, 1-year, and 2-year) included anthropometric measures (height and weight), and sociodemographic (age, sex, highest education level, and vocational status) and clinical (duration of untreated psychosis, number of inpatient admissions, and Positive and Negative Syndrome Scale [PANSS] and Global Assessment of Functioning [GAF] scores) information.

Baseline sociodemographic characteristics between those who did and did not have complete weight data for the first two years was compared using t-tests and chi-square tests. For complete data sets, each was assigned a profile according to weight change across the first two years: (1) super high risk (eg. increase severe [weight gain ≥7%] across two years); (2) high risk mitigated

(increase severe then decrease [weight loss >1%]); (3) at risk (eg. increase mild [gain <7% and >1%] across two years); (4) delayed risk (eg. maintain [gain ≤1% and loss ≤1%] then increase severe); and (5) low risk (eg. maintain across two years).

Results: A total of 686 data sets were included for the study; however, only 445 (64.9%) had complete weight data for the first two years. Those with missing data were more likely to be males, older at baseline, have a baseline highest educational level of tertiary and above, and have a longer duration of untreated psychosis. Of these, 391 (87.9%) had complete clinical data and were included for the main analyses. The weight change across two years resulted in the following membership breakdown: 151 (38.6%) in super high risk; 133 (34.0%) in high risk mitigated; 17 (4.3%) in at risk; 34 (8.8%) in delayed risk; and 56 (14.4%) in low risk. Chi-square tests and one-way ANOVAs were conducted as part of secondary exploratory analyses to elucidate differences in outcomes among the groups. It was found that there were no significant differences in two-year vocational outcome (meaningfully engaged in an age-appropriate role versus unemployed) between the weight trajectory groups. In terms of clinical outcomes, the delayed risk group was consistently scoring higher on the PANSS positive and general psychopathology subscales and scoring lower on the GAF disability scores as compared to the other groups.

Discussion: The lack of pharmacological and physical activity data is a significant limitation in this study. However, the results still prove illuminating; the weight data not missing at random suggests that there exists a gap in existing weight monitoring procedures that should be looked into. These findings also provide justification for future studies to prospectively capture and examine the influence of pharmacological and physical activity, with the aim of early detection and weight intervention for high risk groups.

S73. LIFETIME ANTIPSYCHOTIC EXPOSURE IS ASSOCIATED WITH THINNER CORTEX AND SMALLER SUBCORTICAL GRAY MATTER VOLUME IN FIRST-EPISODE PSYCHOSIS AND CLINICAL HIGH-RISK INDIVIDUALS

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Background: Several studies have investigated the effects of antipsychotics on brain morphology in early course psychosis. Yet, there is a lack of consensus on the magnitude or location of these effects. Here, we studied the effects of lifetime antipsychotic exposure on brain morphology in individuals either at clinical high-risk for psychosis or during their first-episode psychosis.

Methods: Eighty-two individuals with first-episode psychosis (47 males, age = 26.8 ± 5.98) and 49 individuals at clinical high-risk for psychosis (28 males, age = 25.8 ± 6.09) were included in this study. Lifetime antipsychotic exposure was assessed retrospectively from electronic medical records. A T1-weighted MRI was acquired from all participants and used to estimate cortical thickness and subcortical gray matter volume using Freesurfer v7.1.1.

Results: Higher lifetime antipsychotic exposure was associated with thinner cortex ($t = -4.159$, $p < 0.001$) and less subcortical gray matter volume ($t = -2.157$, $p = 0.033$). Vertex-wise analysis revealed regional heterogeneity in the effect of cortical thinning, which was statistically significant

in the prefrontal, cingulate and parietal cortices (pperm < 0.05). Subcortically the effect of volume reduction remained statistically significant (pFDR < 0.05) in the left amygdala, left caudate, right caudate and right accumbens area after false discovery rate correction.
Discussion: These data suggest that lifetime antipsychotic exposure has a heterogenous impact on cortical thickness and subcortical gray matter volume. Mechanisms by which antipsychotic leads to thinner cortex and reduced gray matter are not fully understood. Investigating reasons why some regions may be more susceptible for antipsychotic induced cortical thinning may help to reveal the underlying mechanisms.

S74. FREQUENCY OF CANNABIS-USE AND BASELINE NEUROCOGNITIVE AND FUNCTIONAL PROFILES AMONG INDIVIDUALS AT CLINICAL HIGH-RISK (CHR) FOR PSYCHOSIS: FINDINGS FROM THE NORTH AMERICAN PRODROMAL LONGITUDINAL STUDY-3 (NAPLS-3)

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Background: Deficits in distinct neurocognitive domains have been identified in clinical high-risk psychosis (CHR) populations relative to controls and as indicators of increased risk for developing psychosis. Additionally, rates of cannabis-use are high in this population, with robust findings demonstrating the association between cannabis-use and severity of positive symptoms, impaired psychosocial functioning, and an increased risk for conversion to a psychotic disorder. Notably, deficits in psychosocial functioning have been attributed to poorer neurocognitive performance in this population. We hypothesized that moderate to severe cannabis-use at baseline among a large CHR cohort would be associated with poorer neurocognitive functioning as well as associated functional deficits.
Methods: CHR participants ages 12-30 from the North American Prodromal Longitudinal Study (NAPLS-3) (N=652) completed the Cannabis Use Questionnaire (CAQ) to assess for current cannabis-use. CHR participants were grouped according to frequency of cannabis use: never or a few times – "minimal" (n=329), monthly to yearly use – "moderate" (n=72), or daily to weekly use – "heavy" (n=93). All individuals completed three subtests from the MATRICS-MCCB Battery: Letter-Number Sequence to assess working memory, Brief Assessment of Cognition in Schizophrenia Symbol Coding to assess processing speed, and the Hopkins Verbal Learning Test - Revised to assess verbal learning. The Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II; 2-subtest version) was used to estimate general intellectual functioning for all participants. An estimate of premorbid IQ was also attained, using the Wide Range Achievement Task, Fourth Edition. Current social, role and global functioning was measured at baseline using the Global Functioning Social Scale, Role Scale and Global Assessment of Functioning.
Results: Multivariate analysis (MANCOVA) was used to assess the effect of cannabis-use frequency (independent variable) on neurocognitive raw scores (dependent variables), controlling

for sex and age. There was a statistically significant cannabis-use frequency group effect on the combined dependent neurocognitive variables ($F(24, 952)=1.80$, $p=.011$). Specifically, there was a significant effect of cannabis-use frequency on working memory ($F(2, 494)=3.26$, $p=.04$), estimated premorbid IQ ($F(2,494)=5.44$, $p=.005$) and WASI-II-IQ ($F(2,494)=4.23$, $p=.02$). Post-hoc analyses revealed that moderate cannabis-users had better neurocognitive performance ($p<0.05$) than those with minimal or heavy use. An additional MANOVA revealed a significant effect of cannabis use-frequency on global and social functioning ($F(6,984)=3.67$, $p=.001$) also driven by CHR participants with moderate use displaying better functioning ($p<0.05$) relative to the other groups. Partial correlations revealed all neurocognitive measures were positively correlated with social, role and global functioning ($p<.001$). Analyses of clinical symptoms and risk of conversion to psychosis did not differ across use-groups.

Discussion: Better neurocognitive and psychosocial functioning in moderate cannabis-users, also observed in schizophrenia cohorts, may indicate the presence of a distinct subgroup of CHR youth. These individuals may not present with typical neurocognitive and functional deficits often observed in the CHR population but may still be at increased risk for psychosis based on a combination of moderate cannabis-use and attenuated positive psychosis symptoms. Future studies should evaluate the relationship between cannabis-use frequency, neurocognition and functioning longitudinally.

S75. THE CHANGES IN HIPPOCAMPAL VOLUME AFTER INITIAL ANTIPSYCHOTIC MEDICATIONS WERE DIFFERENT BETWEEN YOUNGER AND OLDER FIRST-EPISODE SCHIZOPHRENIA PATIENTS

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Background: Hippocampus is involved in the pathological process of schizophrenia, and its volume alterations after initial antipsychotic treatment are reported in first-episode schizophrenia (FES). However, whether they interact with age is still unclear.

Methods: The present study included 120 medication naïve FES patients (age range 15-) and 110 matched healthy controls (HC). Patients took MRI scans before and after weeks of antipsychotic treatment, while HC took MRI scans at baseline. Volumes of hippocampus and subfields were measured by FreeSurfer 7. Liner mixed models (LMM) and repeated measures analysis of variance (RM-ANOVA) were mainly used for statistical analyses.

Results: The volume of the hippocampus and subfields were comparable between FES and HC before treatment. LMM showed a significant main effect of time($\beta=62.486$,$t= 2.571$, $p=0.011$), as well as a significant age-by-timepoint interaction effect ($\beta=-1.964$,$t= -2.048$, $p=0.043$) on the left hippocampal volume in FES. Implying that the left hippocampus atrophied from pre to post-treatment as age in baseline decreased. While PANSS score decreased from pre to post-treatment as age increased, for a significant main effect of time($\beta=19.691$, $t= 4.057$, $p < 0.001$), and a significant age by timepoint interaction effect ($\beta=0.419$, $t=2.185$, $p=0.031$). To further analyze the longitudinal change, the whole sample was divided into two subgroups by age 24. RM-ANOVA revealed a significant group-by-time interaction for the left whole hippocampus ($F= 5.395$, $p = 0.022$, $\eta^2=0.046$), and post hoc ANOVA exhibited a significant volume decrease in the left whole

hippocampus (F= 10.291, p = 0.002, η^2=0.085)among the younger FES. On the subfield level, the interaction effects existed in left granule cells in the molecular layer of the dentate gyrus (GC-ML-DG) (F=8.499, p = 0.044, η^2=0.071, FDR corrected) and left cornu ammonis 4 (CA4) (F=8.231, p = 0.028, η^2=0.069, FDR corrected), and significant volume decrease also exhibited in the left GC-ML-DG (F= 14.484, p ＜0.001, η^2=0.115) and left CA4 (F=12.648, p =0.001, η^2=0.102) of the younger FES (age＜24 y, n=60) after antipsychotic medications. However, older FES (age ≥24 y, n=60) showed insignificant longitudinal change, though the pre-treatment left hippocampus was smaller than matched HC. The difference in longitudinal changes of volume in the two subgroups still existed after controlling their respective baseline volumes. Exploratory analyses revealed a partial correlation between negative score reduction rate and volume decrease in left GC-ML-DG (pre-post) (r=-0.275, p = 0.045) among older FES controlling for age, sex, education years, duration of untreated psychosis, chlorpromazine equivalents and intracranial volume.

Discussion: The smaller left whole hippocampus in older FES pre-treatment was in line with the mainstream findings and reflected the hippocampal injury in the early stage of schizophrenia.

The severe longitudinal hippocampal atrophy in the younger FES could be a reflection that the immature hippocampus is more vulnerable in the psychotic attack stage and more sensitive to being affected by the toxic effects of antipsychotics. While the unshrink hippocampal volume in the older FES may possibly reflect the neuroprotective effect of atypical antipsychotics.

The antipsychotic treatment in the acute stage failed to improve hippocampal atrophy of FES, while the correlation between the volume shrinkage and negative symptom reduction in the older FES may suggest that the preservation of hippocampal volume is beneficial to the prognosis.

Our findings suggest that age affects the hippocampal volume changes after initial antipsychotics of FES, with the younger showing a more pronounced volume reduction in the left hippocampus.

S76. NON-LINEAR VARIATIONS IN GLUTAMATE DYNAMICS DURING A COGNITIVE TASK ENGAGEMENT IN SCHIZOPHRENIA

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Background: To investigate the role of glutamate in psychosis, we employ functional magnetic resonance spectroscopy at an ultra-high magnetic field (7T) and employ fuzzy-approximate entropy(F-ApEn) and Hurst Exponent (HE) to capture time-varying nature of glutamate signalling during a cognitive task.

Methods: We recruited thirty first-episode psychosis patients (FEP) with age- and gender-matched healthy controls (HC) and administered the Color-Word Stroop paradigm, providing 128 raw MRS time-points per subject over a period of 16 minutes. We then performed metabolite quantification of glutamate in the dorsal anterior cingulate cortex, a region reliably activated during the Stroop task. Symptoms/cognitive functioning was measured using Positive and Negative Syndrome Scale-8 score, Social and Occupational Functioning (SOFAS) score, digit symbol) coding score, and Stroop accuracy.

Results: Patients with FEP had significantly higher HE compared to HC, with individuals displaying significantly higher HE having lower functional performance (SOFAS) in both HC and FEP groups. Among healthy individuals, higher HE also indicated significantly lower cognitive function through Stroop accuracy and DSST scores. F-ApEn had an inverse Pearson correlation with HE, and tracked diagnosis, cognition and function as expected, but with lower effect sizes not reaching statistical significance.
Discussion: We demonstrate notable diagnostic differences in the temporal course of glutamate signaling during a cognitive task in schizophrenia.

S77. AUDITORY N100 EVENT-RELATED POTENTIALS ARE MORE RELIABLE AND BEST DIFFERENTIATE EARLY PSYCHOSIS FROM HEALTHY CONTROLS IN A PAIRED-CLICK PARADIGM

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Background: Early sensory processing deficits recorded by EEG are well-established in the schizophrenia spectrum. Despite findings in P50 and N100 event-related potential (ERP) amplitude and percent suppression in the auditory paired-click paradigm reported in translational and genetic association studies, the validity and reliability of this paradigm as a schizophrenia biomarker has been questioned. Moreover, in a preliminary report, individuals putatively in the prodromal phase of psychotic illness had P50 sensory gating deficits, potentially identifying a subgroup at risk for psychosis. In this longitudinal observational study of the prodrome and first episode (FE) of psychosis, we expand these findings to determine which early ERP components—amplitude/area, difference, and/or percent suppression—are most reliable and best differentiate healthy controls (HC) from individuals at clinical high risk (CHR) for psychosis and those experiencing FE of psychosis.
Methods: CHR individuals (N = 77), FE patients (N = 52), and healthy controls (N = 65) between the ages of 12-30 were recruited for the study. Participants were assessed at baseline and over nine data collection time points over two years of follow-up. Among CHR participants, a sub-cohort of individuals converted to FE psychosis (CHR-C; N = 8) while another sub-cohort did not convert (CHR-NC; N = 39) within the first 24 months of follow-up. EEG data were gathered using the paired click ERP paradigm, and symptom and demographics data were collected by structured interviews and self-report, respectively. Test-retest reliability of ERP indices was assessed by intraclass correlation coefficients using a two-way mixed effects model for absolute agreement of single measurements. Side-by-side boxplots were used to visualize group differences for each of the ERP components. In addition to one-way ANOVA and post-hoc Fisher's least significant difference (LSD) tests, Hedges g values were calculated to determine effect size between groups.
Results: With respect to P50, S1 amplitude was the most reliable measure among HC (ICC = 0.60, $p < 0.001$) and CHR (ICC = 0.71, $p < 0.001$) participants, but not in FE individuals (ICC < 0.01, NS). Regarding N100, area measures were more reliable than amplitude measures overall, particularly S1 area (HC: ICC = 0.62, $p < 0.001$; CHR: ICC = 0.73, $p < 0.001$; FE: ICC = 0.69, $p < 0.001$) and area difference (HC: ICC = 0.73, $p < 0.001$; CHR: 0.61, $p < 0.001$; FE: ICC = 0.63, $p < 0.001$). Both percent suppression of P50 and N100 amplitude were the least reliable measures among all groups. When comparing ERP components between three groups (HC, CHR, FE), mean

differences in N100 S1 amplitude (p = 0.0489; HC vs. FE), N100 S1 area (p = 0.0127; HC vs. CHR, HC vs. FE), and N100 area difference (p = 0.022; LSD: HC vs. FE) reached statistical significance. Furthermore, upon comparison of four groups (HC, CHR-NC, CHR-C, FE), N100 S1 area (p = 0.00457; HC vs. CHR-NC, HC vs. FE) and N100 area difference (p = 0.00447; HC vs. CHR-C, HC vs. FE) reached statistical significance. Hedges g between HC versus CHR-C (N100 area difference: g = 0.916) and HC versus FE (N100 S1 area: g = 0.539; N100 area difference: g = 0.528) demonstrated moderate to large effect sizes.
Discussion: N100 S1 amplitude, S1 area, and area difference were moderately reliable across all groups and had greater test-retest reliability compared to P50 components. N100 measures of early auditory processing and sensory gating—in particular, N100 S1 area and area difference—best differentiated individuals in the early phase of psychosis from healthy controls. To better evaluate whether N100 indices are indicators of psychosis risk among CHR participants, a larger sample is required.

S78. GLUTAMATE LEVELS IN THE MEDIAL PREFRONTAL CORTEX IN FIRST-EPISODE PSYCHOSIS AND HIGH RISK OF SCHIZOPHRENIA

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Background: Schizophrenia is an illness where glutamatergic dysfunction in medial prefrontal cortex has been long suspected; but in vivo studies of glutamate in very early stages of this illness (high-risk states) has been inconclusive. In particular, recent evidence (Adams et al, 2021) has implicated pyramidal dysfunction (reduced glutamate tone) as the primary pathophysiology, with a secondary disinhibition effect (higher glutamate tone) resulting in emergence of symptoms later. In this study, we investigate if genetic high risk (GHR) for schizophrenia is associated with reduced glutamatergic tone in medial prefrontal cortex (mPFC), when compared to clinical high risk (CHR) state and state of first episode schizophrenia (FES) where symptoms are already prominent.
Methods: We recruited 322 individuals (CHR,n=68; GHR,n=83; FES,n=100;healthy control [HC],n=71） and obtained proton magnetic resonance spectroscopy (MRS) of glutamatergic metabolites at 3-Tesla (Glx and Glu). We used a General Linear Model with mPFC metabolites as independent variables and assessed the effect of group membership (CHR, GHR, FES, HC), with age as a covariate. We also related Glx levels to positive, negative and disorganization symptoms from SIPS scale, to detect the symptom group that varied most with the Glx levels across all High risk(UHR,GHR) individuals.
Results: Individuals with GHR had lower Glx in mPFC compared to UHR and FES ($F(3,317)=2.97$, $p= 0.032$ mean(SD) in GHR =1.85(0.26); FES =1.95(0.26); CHR =1.96(0.26); HC=1.90(0.26)). Glu values did not vary significantly across groups ($F(3,317)=2.17$, $p=0.091$). Regression analysis with symptom dimensions indicated that lower Glx in mPFC was predicted by higher disorganization but lower positive symptoms.
Discussion: Our results indicate that there is likely to be a primary glutamatergic dysfunction in the medial prefrontal cortex in very early stages of this illness, influenced by genetic risk. The reduction in glutamatergic tone in GHR supports the case for a pyramidal dysfunction contributing to higher disorganization. In turn, the burden of positive symptoms is low across all high-risk subjects when the state of reduced glutamatergic tone prevails, indirectly supporting the need for

a secondary disinhibition effect (higher glutamate tone) for the development of a full-blown psychotic or subthreshold state.

S79. N400 EVENT-RELATED BRAIN POTENTIAL INDEX OF SEMANTIC PROCESSING AND TWO-YEAR CLINICAL OUTCOMES IN PERSONS AT HIGH RISK FOR PSYCHOSIS

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Background: The N400 event-related brain potential (ERP) semantic priming effect reflects greater activation of contextually related versus unrelated concepts in long-term semantic memory. Deficits in this ERP measure have been found in patients with schizophrenia and those at clinical high risk (CHR) for this disorder. We tested the hypothesis that in patients at high risk for schizophrenia or a related psychotic disorder, N400 semantic priming deficits at baseline would predict greater psychotic symptom severity after two years.
Methods: We measured N400 semantic priming at baseline in CHR patients (n = 47) who viewed prime words each followed by a related or unrelated target word, at stimulus-onset asynchronies (SOAs) of 300 or 750 ms. We measured psychosis-spectrum symptoms using the Structured Interview for Prodromal Symptoms, at baseline, one year (n=30) and two years (n=29). Linear mixed effect models for repeated-measures were used to test whether N400 priming effects at each SOA (300 ms and 750 ms) were associated with changes in positive symptoms over the two-year follow-up period. SOPS total Positive subscale scores were specified as dependent variables. The N400 at each SOA was specified as a continuous fixed effect, in separate models; time (baseline, one year, and two years) was entered as categorical fixed effect; and the interaction between N400 and time was the fixed effect of interest. Subjects had their intercepts modeled as random effects.
Results: Baseline N400 effects at the 300-ms SOA were not significantly associated with psychosis-spectrum symptoms over two years. Although larger baseline N400 effects at the 750-ms SOA were associated with numerically greater improvement in Ptotal scores from year 1 to year 2, this interaction was also not statistically significant (p=0.09).
Discussion: CHR patients' N400 effects did not significantly predict clinical outcomes over two years. The results suggest that this ERP measure is not a clinical prognostic predictor for psychotic symptom severity.

S80. MULTISENSORY INTEGRATION IMPAIRMENT IN FAMILIAL HIGH-RISK OFFSPRING FOR MAJOR PSYCHIATRIC DISORDERS: TOWARDS A POTENTIAL EARLY MARKER OF VULNERABILITY

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Background: Major psychiatric disorders (MPDs) such as schizophrenia, bipolar disorder, and recurrent major depression disorder all have a common neurodevelopmental vulnerability due to early neuronal and sensory abnormalities. Several evidence supports that a harmonious development of the self, - known to be disturbed early in MPDs - requires a synchronized and well-integrated perception of the sensory afferences coming from the self and the world which surrounds us (e.g. tactile, visual, auditory and proprio/interoception). An early impairment of audio-visual multisensory integration (MSI) would impede the development of the self and of a stable and unified representation of the world, leading to a MPD susceptibility. MSI might be measured during a simple reaction time task when multisensory facilitation is observed with a shorter reaction time for audio-visual (AV) multisensory stimuli, compared to stimuli presented in a single auditory (A) or visual (V) modality. This project aims to explore whether MSI sensory abnormalities in Familial High-Risk offspring for MPD (FHR-MPD) could be considered as a marker of developmental vulnerability to MPD using a computerized task. This task is designed to be easily administered with participants starting 9 y/o, speaking any language and that may live in remote communities.

Methods: Fifty-two FHR-MPD for schizophrenia, bipolar disorder or recurrent major depressive disorder (28 girls, mean age = 12.13 years) were recruited within the INTERCEPT cohort study recruiting itself into the HoPE program of the CIUSSS de la Capitale-Nationale. Thirty-nine controls with no family history of MPD (CTL, 27 girls, mean age = 12.64 years) were recruited using advertisements or a control bank. All participants were aged between 9 and 15 and had no personal history of affective or psychotic disorder at DSM-V according to KIDDIE-SADS-PL interview.

The multisensory integration task is a shortened version of a simple reaction time (RT) task used by Williams et al. (2010) to demonstrate MSI impairment in schizophrenia consisting of 2 blocks of 70 trials (total 140 trials) as follow per block: 10 catch trials (trial without stimulus to prevent commissions); 20 auditory (A) alone trials; 20 visual (V) alone trials; 20 multimodal (AV) trials.

Trials were presented randomly between A-V-AV modalities. Based upon measured both A and V RTs, RACE model calculates the probability of response for RTs percentiles assuming that A and V are separated channels (no MSI). Gathering faster AV RTs than those predicted by RACE (RTs AV<RACE) indicate RACE model violation and stand for AV facilitation meaning actual MSI.

For each percentile of RTs distribution, when a faster AV RTs than what predicted by the RACE model was observed, then there was indeed an AV facilitating effect (i.e. MSI) on subject's RTs otherwise than a simple additive effect due to the presentation of two stimuli. We calculated both AV RTs and RACE RTs means for percentiles 0 to 1 both for FHR-MPD and CTL groups and used t-test (with Bonferroni corrections) to detect MSI within groups for relevant percentiles. Still to prevent type I error, the percentiles with MSI in CTL groups were then compared to FHR-MPD using t-test (with Bonferroni) to size any group difference in MSI.

Results: A preliminary analysis of raw RTs according both to the mode of stimulus presentation (A-V-AV) and groups does not show major significant differences between groups with regard to the mean RTs and their variability excepted slower RTs in AV for FHR. While CTL group showed

sensory facilitation from the 25th to the 35th percentile, FHR-MPD showed no sensory facilitation (RTs AV>RACE) in their RTs for the percentiles where CTLs showed it, demonstrating an absence of MSI for this group and even a pattern of deleterious effect of multisensory stimuli To compare MSI between FHR-MPD group and the control group, we calculated the difference in mean RTs between RACE and AV for each percentile. Positive difference is presumably reflecting AV facilitation whereas negative difference echoes for a deleterious effect of AV stimuli presentation. AV facilitation (positive difference) was observed in control groups for percentiles 0.15 to 0.65 with significant difference with FHR-MPD ($p<.05$ with Bonferroni correction) for percentile 25th to the 35th. FHR-MPD showed no AV facilitation for any percentile.
Discussion: Lack of AV facilitation in FHR-MPD group highlights that patient's offspring fail to integrate the multisensory stimuli and to benefit from multimodal stimuli presentation to improve their RTs as controls do. These results are consistent with the hypothesis that MSI difficulties in high-risk youth could provide fertile ground for the development of MPDs in adulthood. Developmentally, FHR-MPD are reported to exhibit significant MSI impairment that are indicators of neurodevelopmental sensory dysfunction, or risk endophenotypes, that manifest in both FHR-MPD and MPD patients. In definitive, the task developed for this study demonstrated to be valid and sensitive to early sensory alterations of the development of the self. The task easily performed by children on the computer is brief, achievable in ambulatory settings, without verbal response, which makes it easy to use for the screening of MPDs in any population.

S81. CO-SPEECH GESTURES AND SELF-STIMULATING MOVEMENTS DURING SPEECH TASKS IN BRAZILIAN INDIVIDUALS WITH AT-RISK MENTAL STATES

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Background: Nonverbal communication (NVC) is a complex behavior that involves several modalities that are impaired in schizophrenia spectrum, such as gesticulation. However, there are few studies that evaluate it in the so-called at-risk mental states (ARMS) for psychosis and most of them are performed in North American or European cultures. Given the reduced movement observed for ARMS during speech in our previous findings, here we aimed to investigate if it would be a result of gestures behaviors.
Methods: Fifty-six medication-naïve ARMS and sixty-nine healthy controls were video recorded while performing different speech tasks: subject overview (SO) and memory report (MR) based on recent dream, old dream report and memory report based on positively affective pictures. The frequency of self-stimulating movements and four gestures categories performed were coded and correlated with symptoms of the Structured Interview for Prodromal Syndromes (SIPS).

Results: Independent-samples tests – Mann-Whitney U and t Student - were used to analyze differences between ARMS and control group. No significant differences between the ARMS and control groups were observed for any category of gesticulation or self-stimulatory movement in SO or MR videos. However, using Kendall's Tau-B correlation and also significant using Generalized Linear Model by negative binomial distribution (GLM-NB), deictic gestures made during both videos (SO: $\tau = -0.206$, $p<0.001$; MR: $\tau = -0.119$, $p<0.05$) and metaphoric gestures made during MR task ($\tau = -0.188$, $p<0.01$) were inversely correlated with total negative symptoms. For the specific expression of emotion symptom, this correlation was seen for beats in MR ($\tau = -0.161$, $p<0.05$) and deictic gestures in both videos (SO: $\tau = -0.248$, $p<0.001$; MR: $\tau = -0.163$, $p<0.05$). For positive symptoms significant negative correlations were only seen by Kendall's Tau-B correlation for beats ($\tau = -0.127$, $p=0.048$) and deictic ($\tau = -0.194$, $p=0.002$) in SO. For other SIPS categories, only GLM-NB found that total disorganization was significant estimated by deictic in MR ($z=-2.193$, $p<0.05$) and total general symptoms by metaphoric in MR ($z=-2.471$, $p<0.05$).
Discussion: These results contrast the few studies published on the issue, concerning gesture difference between ARMS and controls. While our previous study with this sample found a reduced movement and an increased erraticism of movements in ARMS, the present results show that these movement abnormalities are probably not associated with gestures or with self-stimulating movements and other variables—such as postural sway—might have accounted for that. The correlation observed between gesture categories and SIPS symptoms show the importance of analyzing NVC in ARMS and of considering different cultural and sociodemographic contexts in the search for markers of these states.

S82. PARSING HETEROGENEITY IN THE CLINICAL HIGH RISK FOR PSYCHOSIS PARADIGM

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Background: The Clinical High Risk for Psychosis (CHR-P) paradigm demonstrates high variability in outcomes and clinical profiles, which may be indicative of meaningful variation in underlying pathophysiology. As such, deconstructing heterogeneity in the CHR-P paradigm is an essential step to progress towards precision psychiatry. Indeed, identifying sources of meaningful heterogeneity may offer viable candidate features for stratification in therapeutic trials. Existing research in this field typically examines heterogeneity in-depth across just one modality, such as cognition or neuroanatomy. Therefore, this research aimed to elucidate and quantify heterogeneity across twenty-two clinical, cognitive and environmental parameters in the same sample of individuals.
Methods: We applied the Bonferroni-corrected log-variability ratio (VR) and the coefficient of variation (CV) ratio as indexes of group-level heterogeneity in a large, international sample (CHR-P N = 344; Control N = 67) across twenty-two parameters. The parameters covered non-psychotic symptomatology, aspects of cognitive function, and environmental experiences of childhood trauma (including abuse and neglect). We assessed heterogeneity across three between-group analyses: i) individuals at CHR-P compared with healthy controls, ii) individuals experiencing attenuated psychotic symptoms (APS) compared with individuals experiencing brief limited intermittent symptoms (BLIPS), and iii) individuals at CHR-P who subsequently transitioned to psychosis compared with those who did not transition to psychosis.
Results: We observed greater environmental heterogeneity in CHR-P compared with controls across childhood physical abuse (VR = 2.13, CV = 1.66) and childhood sexual abuse (VR = 2.18, CV = 1.70), as well as greater cognitive heterogeneity in visual attention performance, notwithstanding application of the CV (VR = 1.42). Those who transitioned to psychosis demonstrated increased homogeneity in baseline depressive symptom scores (VR = 0.62), and greater heterogeneity in baseline mania symptom scores (VR = 1.46) compared with those who did not transition to psychosis, notwithstanding further interrogation with the CV. APS-allocated individuals demonstrated greater heterogeneity in both physical abuse (VR = 1.85), and baseline obsessive-compulsive symptom scores (VR = 1.76) compared with BLIPS-allocated individuals, suggesting that those experiencing brief intermittent symptoms present as a more homogenous group.
Discussion: These findings highlight the inherent variability in the CHR-P paradigm and call for a shift away from a one-size-fits-all approach to care and towards more targeted, precision care. The significantly greater homogeneity in depressive symptoms observed in those who subsequently transition to psychosis may present baseline depressive symptoms as an interesting candidate for stratification purposes. Further research is required to deconstruct heterogeneity in the CHR-P paradigm, representing an essential step towards precision psychiatry.

S83. OBSTETRIC COMPLICATIONS AND CLINICAL PRESENTATION IN FIRST EPISODE OF PSYCHOSIS

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Background: First episode of psychosis (FEP) can be the initial event of a wide variety of diagnoses and eventually lead to schizophrenia, bipolar disorder, major depression disorder and other clinical entities. Regardless of diagnostic heterogeneity, genetic and environmental factors interact on the risk pathway. Among the environmental factors, obstetric complications (OCs) have been historically described as major risk contributors. However, current evidence suggests that OCs in psychosis are a risk factor not only for the later development of psychosis but also for other effects that range from neuroanatomical, neurocognitive, metabolic abnormalities and clinical psychopathology. The study of OCs, particularly pregnancy difficulties and birth asphyxia, and its relationship with clinical presentation in psychiatric patients has received less attention in recent years. A recent cross-sectional study in patients with chronic-schizophrenia with predominant negative symptomatology described an association between difficulties during delivery assessed with the Lewis-Murray scale and measures of anxiety, guilt feelings, and unusual thought content. In another study of patients with chronic schizophrenia and early onset in adolescence, OCs taken as a whole were associated with more prominent negative symptoms and abnormalities in delivery evaluated with the Apgar score were also associated with negative symptomatology. Notably, sex differences also apply to OCs, in a large schizophrenia hospital cohort, OCs were associated with negative symptomatology only in females. Built on the rationale described above, we aimed to evaluate the clinical presentation characteristics of a cohort of FEP according to their profile of obstetric complications.

Methods: This study is part of the multicentre Project 'Phenotype–genotype interaction: application of a predictive model in first psychotic episodes', the PEPs study, which is a longitudinal cohort study examining GxE interactions on the pathway to psychosis. 335 FEP patients were recruited in the PEPs Project between 2009 and 2011 at 16 Spanish hospitals that participated in the Biomedical Research Networking Center for Mental Health (CIBERSAM) OCs were assessed using the Lewis-Murray scale through familiar interview

The scale groups OCs in three categories, A, B and C according to the type of complication defined as follows:

A. Complications of pregnancy (syphilis or rubella, rhesus isoimmunization/Rh incompatibility, severe preeclampsia, requiring hospitalization or induction of labor, and bleeding before delivery of threatened abortion);

B. Abnormal fetal growth and development (twin delivery, preterm birth week less than 37 weeks, or long-term birth week of more than 42 weeks, weight at birth less than 2500 g, and any important physical abnormality);

C. Difficulties in delivery (which is composed by premature rupture of membranes, duration of delivery more than 36 hours or less than 3 hours, umbilical cord prolapse, complicated cesarean delivery, abnormal fetal presentation, use of forceps, and being in an incubator for more than 4 weeks).

To assess differences among patients with or without OCs in terms of psychopathology, independent t-test analyses of the PANSS and its subscales between the groups studied (OCs and their subtypes) were performed. Then, analyses of covariance (one-way ANCOVA) were performed to remove possible confounding factors in the association between OCs and psychopathology. In the model, PANSS subscales (positive, negative, or general psychopathology) or total PANSS score were included as the dependent variable, OCs and their subtypes as the independent variables, while age, sex, cannabis use, childhood adversity and chlorpromazine dosage were included as the covariates.

Results: Overall patients with abnormalities in the perinatal period displayed a more severe psychopathological profile than patients who did not suffer from them. Lewis AB was associated with worse general psychopathology, LewisC with worse general psychopathology and total score while Lewis T was associated with worse positive, general psychopathology and total score.
Discussion: The findings from our study show a worse psychopathological profile in FEP with difficulties during the perinatal period compared with patients who were not exposed to them. These results confirm the association of OCs in the presentation of clinical symptomatology in a cohort of FEP.
Our approach to differentiating the events according to the timing of the event, distinguished the effect of difficulties during pregnancy and difficulties during delivery into different clinical areas. Our results highlight the need of describing the timing of the event during the perinatal period to better understand its impact on the clinical presentation at onset.

S84. RELIGIOUSNESS AND PSYCHOTIC EXPERIENCES AMONG COLLEGE STUDENTS IN THE UNITED STATES

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Background: Religiousness and psychotic experiences have been related, though findings have been mixed, with little attention paid to specific religious affiliations and religious importance.
Methods: We analyzed data from the Healthy Minds Study (2020-2021), which was an online survey administered at 140 college campuses across the United States. We used multivariable logistic regression to examine the associations between religiousness (affiliation and importance) and 12-month psychotic experiences, adjusting for age, gender, and race/ethnicity.

Results: Only Christian religious affiliation was associated with lower odds of psychotic experiences (aOR: 0.79; 95% CI: 0.75, 0.84), while Non-Christian religious affiliation (aOR: 1.34; 95% CI: 1.19, 1.50) and Multiple religious affiliation had greater odds (aOR: 1.28; 95% CI: 1.15, 1.42). Overall, increased religious importance was associated with lower odds of psychotic experiences (aOR: 0.96; 95% CI: 0.94-0.99). After stratifying by affiliation, religious importance was only associated with lower odds of psychotic experiences among people who identified as Other Christian, Mormon, and Other World Religion. Religious importance was associated with greater odds of psychotic experiences among Atheists, Agnostics, Buddhists, Nothing in Particular, and Multiple Religions.
Discussion: Religious affiliation and importance had varying associations with psychotic experiences, depending on type of religious affiliation. More research is needed to explore the modifying effects of religiousness. Responsiveness to religious beliefs and practices may be critical when assessing risk for psychosis.

S85. ALTERED DYNAMIC FUNCTIONAL BRAIN PROPERTIES AND THEIR RELATIONSHIP TO SYMPTOMS IN ACUTELY ILL, FIRST-EPISODE, DRUG-NAIVE PATIENTS WITH SCHIZOPHRENIA

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Background: Studies of dynamic functional connectivity (dFC) and topology can provide novel insights into the pathophysiology in schizophrenia and its relation to core symptoms of psychosis. Limited investigations of these disturbances have been conducted in drug-naïve, first-episode patients to avoid the confounds of treatment or chronic illness. Therefore, we recruited acutely ill, first-episode, drug-naive patients with schizophrenia and examined brain dFC patterns relative to healthy controls using resting-state functional magnetic resonance imaging (rs-fMRI).
Methods: Ninety-five acutely ill, first-episode, never-treated schizophrenia patients and 100 healthy controls (HCs) matched by age, sex, and head motion were recruited and underwent brain rs-fMRI. The sliding-window approach (22 time of repetition [TR] window size with a step of 1TR) was applied to obtain a series of dFC matrices for characterizing state characteristics (mean dwell time and fractional time), and the dynamic topological properties (global efficiency, clustering coefficient, nodal efficiency, and nodal eigenvector centrality [EC]) were calculated. We compared these dynamic attributes at the group level and identified dynamic attributes associated with symptoms. A linear support vector classifier was used to identify the profile of dynamic attributes that best distinguished patients from HCs at the individual level.
Results: Compared to controls, patients spent more time in the hypoconnected state (patients 75.6 ± 25.1%, HCs 67.2 ± 27.0%, FDR-P = 0.017, fractional time of patients is almost 1.125 longer than that of controls) and correspondingly less time in the hyperconnected state (patients 24.4 ± 25.1%, HC 32.8 ± 27.0%, FDR-P = 0.017). Patients with schizophrenia also showed longer mean dwell time of the hypoconnected state (patients 61.5 ± 52.7, HCs 41.0 ± 35.0, FDR-P = 0.002). Analysis of dynamic topological properties indicated that patients had decreased dynamics of nodal efficiency and EC in the right medial prefrontal cortex (mPFC), which was associated with the total ratings (r = -0.29, P = 0.005) and general symptom ratings (r = -0.21, P = 0.048) from the Positive and Negative Syndrome Scale. In contrast, we observed increased dynamics of EC in

temporal and sensorimotor regions. These findings were successfully replicated in the validation analysis (30TR window size with a step of 2TR). Selected features for case-control classification were highly aligned with the properties demonstrating significant between-group differences.
Discussion: Our findings provide novel neuroimaging evidence about dynamic characteristics of brain physiology in acute schizophrenia without confounding effects of medication treatments or long illness duration. Schizophrenia patients tended to remain in a weakly connected state, which suggests that previously observed static FC deficits in schizophrenia may reflect a reduced rate of shifting into the actively connected brain state as was observed in the present study. The correlation between dynamic mPFC nodal centrality and psychotic symptom severity highlight the clinical importance of dynamic functional alterations in mPFC in relation to whole brain topological organization. These clinically relevant atypical pattern of dynamics in schizophrenia may represent a critical aspect of illness pathophysiology underpinning its defining cognitive, behavioral, and affective features. Further research on other stages of schizophrenia is needed to explore these altered dynamics with course of disease, especially the relationship with symptoms.

S86. 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. Patients that meet criteria for treatment resistance demonstrate poor antipsychotic medication response from the onset of illness; this poor response to dopamine blocking medications may be due to an inherent lack of dopaminergic elevation. It has been speculated that treatment resistance may be associated with elevated glutamatergic metabolites. There are currently no objective biomarkers available to support clinicians in accurately identifying individuals who may benefit from a clozapine trial, and subsequently clozapine initiation is frequently delayed, despite individuals meeting criteria. We hypothesized that elevated glutamate in the Anterior Cingulate Cortex (ACC) would be associated with clozapine eligibility in an early psychosis sample.
Methods: The present study will compare glutamate levels in the ACC between clozapine eligible (CE) patients with early phase psychosis, and those who have responded to traditional treatment (treatment responders, TR) using 3T proton magnetic resonance spectroscopy (1H-MRS). Clozapine eligible patients continued to have psychotic symptoms after two antipsychotic medication trials, while treatment responders had minimal symptoms and were taking a single antipsychotic medication. The sample consisted of individuals with non-affective psychotic disorders who were followed by the Nova Scotia Early Psychosis Program (NSEPP) and were within the first five years of their initial presentation of psychotic symptoms.
Results: While this study is ongoing, at the time of writing we have a completed sample size of 27 (TR= 16 and CE= 11). The TR group (M=12, F=4) has an average age of 26 and PANSS score of 36.75 with an average duration of untreated psychosis (DUP) of 9 weeks. The CE group (M=8, F=3), has an average age of 26 and PANSS score of 69.40 with an average DUP of 19 weeks. To date, the average glutamate levels are 10.34 (SD= 0.80) and 10.04 (SD= 0.60) for the TR and CE groups respectively. Up to date results: will be presented at the conference.

Discussion: This is the first study to investigate the association of brain glutamate with clozapine eligibility in an early psychosis sample. While elevated ACC glutamate has been associated with poor antipsychotic response, it is unclear whether elevated glutamate is associated with clozapine eligibility, a clinically meaningful outcome. The ability to prospectively identify clozapine eligibility could lead to reformulation of current guidelines regarding clozapine use and may inform the development of additional treatment options for individuals with treatment resistant schizophrenia.

S87. TREATMENT RESISTANCE IN SCHIZOPHRENIA INDEXED BY HIGHER POLYGENIC RISK SCORES

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Background: Treatment-resistant schizophrenia (TRS) occurs in approximately one-third of individuals who fail to show adequate response to antipsychotic medications, with variability in symptoms severity. Clozapine demonstrates clear clinical benefits in TRS and is the only antipsychotic specifically indicated for use. Unfortunately, barriers to clozapine use exist, leading to its delay, resulting in poorer outcomes. This study aims to examine the association between the genetic liability of schizophrenia and TRS.
Methods: Individuals diagnosed with schizophrenia (N = 876) were categorised as TRS (n = 150) and non-TRS (n = 726); TRS in this study comprised of individuals with schizophrenia who were prescribed clozapine after the failure of two antipsychotic trials. Schizophrenia polygenic risk score (PRS) was calculated using PRSice-2 as the weighted sum of risk alleles using GWAS summary statistics from the PGC East-Asian schizophrenia analysis as the discovery sample (Lam et al., 2019). Logistic regression analyses were conducted to discriminate TRS and non-TRS.
Results: The TRS group was significantly younger with more severe symptoms compared to the non-TRS group. Schizophrenia PRS discriminated TRS and non-TRS (R2 = 3.04%, p = 2.27 x 10-5, 0R = 1.55), with higher PRS observed in the TRS group, compared with non-TRS.
Discussion: The common risk variants for schizophrenia are associated with TRS status. Findings suggest that the genetic burden of schizophrenia may in part explain treatment resistance status in schizophrenia, and indexes treatment outcomes. This raises the attractive proposition for genetic risk to be employed in early identification of TRS and for early access to clozapine.

S88. POLYGENIC RISK FOR SCHIZOPHRENIA IS ASSOCIATED WITH VARIATION IN CARDIAC STRUCTURE AND FUNCTION

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Background: Cardiovascular disease (CVD) is a major cause of excess mortality in people with schizophrenia. Several factors are responsible, including lifestyle and metabolic effects of antipsychotics. However, variations in cardiac structure and function are seen in people with schizophrenia in the absence of CVD risk factors and after accounting for lifestyle and medication. It is not known if shared genetic aetiology is contributing to these cardiac variations.
Methods: Cardiac phenotypes were measured using MRI. First, we examined the relationship between polygenic risk score for schizophrenia (PRS-SCZ) and cardiac phenotype using principal component analysis (PCA) and regression. Second, we explored the relationship between PRS-SCZ and individual cardiac phenotypes using robust regression. Third, we repeated analyses with fibro-inflammatory pathway-specific PRS-SCZs. Fourth, we investigated genome-wide sharing of common variants between schizophrenia and cardiac phenotypes using linkage disequilibrium (LD) score regression.
Results: Data were available for 33,353 participants; complete cardiac MRI data were available for 32,279 people. A model regressing PRS-SCZ onto the first 5 cardiac principal components (PCs) of the PCA was significant (F=5.09; P=0.0001). PC1 captured a pattern of increased cardiac volumes, reduced myocardial stiffness and reduced ejection fractions; there was a negative relationship between PRS-SCZ and PC1 (beta(SE)= -0.01(0.003); P=0.02). In keeping with the PCA results, for individual cardiac phonotypes, we observed negative associations between PRS-SCZ and indexed right ventricular end-systolic volume (beta(SE)= -0.14(0.04); P=0.001; PFDR=0.01), indexed right ventricular end-diastolic volume (beta(SE)= -0.17(0.08); P=0.03; PFDR=0.0975), and longitudinal peak diastolic strain rate (beta(SE)= -0.01(0.003); P=0.002; PFDR=0.01), and a positive association between PRS-SCZ and right ventricular ejection fraction (beta(SE)= 0.09(0.03); P=0.004; PFDR=0.02). Models examining TGFbeta and acute inflammation specific PRS-SCZ were significant. Using LD score regression, we observed genetic overlap with schizophrenia for right ventricular end-systolic volume (P=0.009) and right ventricular ejection fraction (P=0.008).
Discussion: Higher PRS-SCZ is associated with smaller cardiac volumes, increased ejection fractions, and smaller absolute peak diastolic strain rates. TGFbeta and inflammatory pathways may be implicated, and there is evidence of genetic overlap for some cardiac phenotypes. Smaller absolute peak diastolic strain rates indicate increased myocardial stiffness and diastolic dysfunction, which increases risk of cardiac disease. Thus, genetic risk for schizophrenia is associated with cardiac structural changes that worsen cardiac outcomes.

S89. ASSOCIATION OF SCHIZOPHRENIA-SPECTRUM DISORDER AND PRENATAL ANTIPSYCHOTIC EXPOSURE WITH THE RISK OF OBSTETRIC AND NEONATAL COMPLICATIONS: A POPULATION-BASED COHORT STUDY

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Background: Literature generally indicates the association between schizophrenia-spectrum disorder (SSD) and increased risk of obstetric and neonatal complications. Yet, many earlier studies did not take into consideration confounding effect of illicit substance use and physical comorbidity. There is some evidence suggesting associations between prenatal exposure to

antipsychotics and adverse birth and neonatal outcomes. of SSD per se and antipsychotic treatment to elevated risk of adverse pregnancy outcomes are understudied. We aimed to examine the risks of adverse obstetric and neonatal outcomes in pregnant women with SSD relative to those without SSD, as well as comparison between antipsychotic-treated and untreated SSD women.

Methods: This population-based cohort study comprised 466,358 pregnant women (of which 804 were women with SSD) aged 15–50 years who gave a singleton livebirth or stillbirth between January 2003 and December 2018, using a territory-wide medical-record database of public healthcare services in Hong Kong. SSD women were subdivided into women treated (n=519) and untreated with (n=285) antipsychotic medications during pregnancy. Propensity-score weighting was applied to minimize potential confounding between SSD patients and non-SSD controls (two-group comparison), as well as among women with treated and untreated SSD and non-SSD controls (three-group comparison). Logistic regression models weighted by propensity score were used to estimate the risk of obstetric and neonatal complications in the two-group and three-group comparisons.

Results: Women with SSD showed significantly elevated risk of caesarean delivery (OR=1.22 [95% CI: 1.04–1.42]), index delivery hospitalization ≥7 days (1.66 [1.38–1.99]), psychiatric (192.75 [151.83–244.70]) and non-psychiatric (2.48 [1.98–3.11]) admission ≤90 days after discharge for index delivery but lower likelihood of labor prolongation (0.73 [0.57–0.93]) than controls. Infants born to mothers with SSD demonstrated higher rates of preterm birth (1.84 [1.51–2.24]), small for gestational age (1.87 [1.26–2.77]), large for gestational age (1.56 [1.10–2.22]), low birth weight (1.52 [1.22–1.90]) and admission to special care baby unit (SCBU; 2.57 [2.23–2.97]) than those born to mothers without SSD. With untreated SSD women as the reference, controls had lower likelihood of psychiatric admission ≤90 days after discharge from index pregnancy (0.36 [0.12–0.97]). Treated SSD women exhibited increased rate of psychiatric admission ≤90 days after discharge from index pregnancy (3.05 [1.59–6.13]) than their untreated counterparts. Infants born to controls displayed lower rates of admission to SCBU (0.63 [0.44–0.88]) than those born to untreated SSD women. Infants born to treated SSD women had increased admission rate to SCBU (1.64 [1.15–2.34]) relative to those born to untreated SSD women.

Discussion: Our data revealed excess risk of obstetric and neonatal complications in SSD women. SSD per se conferred increased risk of some complications, whereas prenatal antipsychotic treatment did not appear to have significant impact on obstetric and neonatal complications. More future studies should be conducted on risk-benefit evaluation of prenatal use of antipsychotics to facilitate optimal management of SSD women during pregnancy and to minimize risk of negative obstetric and neonatal outcomes.

S90. CANNABIS USE AS A POTENTIAL MODERATOR BETWEEN CHILDHOOD TRAUMA AND PARANOIA

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Background: Up to 10% of the general population reports minor psychotic symptoms, paranoia in particular, which is associated with significant distress, leading to social avoidance and disruption to the person's life. Substance use (e.g., cannabis use) is one of the most consistently replicated environmental risk factors associated with psychosis. Childhood trauma (CT), namely

anything that presents a moderate to severe threat to a child's physical or psychological well-being (e.g., abuse, neglect, household discord or bullying), is another environmental risk factor consistently reported to increase up to a 3-fold the risk of psychosis. Furthermore, evidence suggests that CT may determine a range of negative social outcomes, including substance related problems. Hence, some authors have hypothesized a 'double hit' theory of the psychosis pathogenesis, suggesting that an early exposure to CT may produce a latent vulnerability to a second impact, such as cannabis use during adolescence or early adulthood. Therefore, this study aims to investigate the moderating effect of harmful patterns of cannabis use in the relationship between CT and psychotic like experiences, such as paranoia, in a non-clinical population sample.
Methods: The Cannabis and me study (CAMe) aims to recruit online n = 3000 (age above 18 years) current cannabis users and n = 3000 (age above 18 years) subjects who never used cannabis or stopped at least a year before. Retrospective measures of CT (e.g., emotional and physical neglect; emotional, physical and sexual abuse; household discord; and bullying) were collected through a brief trauma online questionnaire. Composite measures of neglect, abuse, and total trauma were derived. An updated version of the modified Cannabis Experience Questionnaire was used to collect a detailed history of cannabis us, including frequency of use. Paranoia levels were measured with the Green et al. Paranoid Thoughts Scale (GPTS). The following background variables were used as covariates: sex, age, years of education, ethnicity, and socio-economic status. To date n = 1930 respondents completed the online survey.
Results: Among the 1930 subjects recruited so far, approximately two third are male (n = 1293) and of white ethnic background (n = 1244), the mean age is 29.1 (SD 8.57). In regard to socio-economic status and educational attainment, participants studied on average 15.5 years (SD 3.88) and are more often employed (n = 1582). A vast majority are frequent cannabis users (n = 1259, 65.23%) and only 97 participants (5.03%) who completed the online survey are non-users/past users. Frequent cannabis use vs occasional / never use was associated with higher paranoia scores (coeff. 1.2905, SE 0.5965 – p-value = 0.031). Similarly, all the associations between the cumulative trauma variables (e.g., neglect, abuse, and total) and paranoia were statistically significant (coeff. 13.1801, SE 1.7356; coeff. 10.7832, SE 1.001; coeff. 8.3902, SE 0.7390, all p-values < 0.5x10-6). When testing interaction, only the effect of cumulative abuse on paranoia was negatively moderated by frequency of cannabis use (coeff. -3.0499, SE 1.1933 – p-value = 0.011).
Discussion: Preliminary findings from the CAMe study confirmed the negative effect of both cannabis use and CT in affecting vulnerability to develop paranoia. However, when looking at the interaction between these two environmental risk factors, frequent cannabis use seemed to negatively moderate the association between cumulative abuse (i.e., emotional, physical and sexual) and paranoia, suggesting a protective role. A better understanding of the relationship between CT and cannabis use with psychosis may have important implications at a clinical level. For instance, this would help clinicians at evaluating adversity and cannabis related risk predicting those more likely to develop psychosis who can ultimately benefit from specific preventive and/or therapeutic interventions.

S91. INCREASING RISK OF PSYCHOTIC EXPERIENCES DURING THE COVID-19 PANDEMIC

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Background: Psychotic experiences (PEs), including sub-clinical hallucination- and delusion-like symptoms, are commonly self-reported by adolescents. Epidemiological data has broadly supported a negative correlation between age and PE prevalence, with PEs gradually becoming less common (but potentially more clinically/functionally impactful) as children age. However, the COVID-19 pandemic greatly disrupted typical developmental trajectories and contributed to social isolation for most adolescents. Further, many youth were directly affected by COVID-19 infection itself, either through their own illness or the illness/mortality of friends or family members. Given that social isolation, prolonged stress, and COVID-19 infection itself have all been linked to increased odds of reporting psychotic experiences, we hypothesized that the steady decline of PE prevalence across adolescence may have been altered by the pandemic. To test this hypothesis, we tested whether the prevalence of PE among adolescents in the Tokyo Teen Cohort increased following the beginning of the COVID-19 pandemic.

Methods: The Tokyo Teen Cohort is an ongoing prospective cohort study of youth residing in the greater metropolitan area of Tokyo, Japan. While data are collected in waves (i.e., age 10, 12, 14, and 16 years), data are effectively collected continuously due to staggered data collection dates at the individual participant level. Therefore, we were able to treat "time since COVID-19 pandemic" as a continuous variable, seeding March 1, 2020 as the starting date of the pandemic in Tokyo. PEs are self-reported at each wave using the items derived from the schizophrenia section of the Diagnostic Interview Schedule for Children (DISC-C), with one additional question on visual hallucinations and are coded as a continuous variable, indicating the number of endorsed PEs. The effects of the COVID-19 pandemic on PEs were examined by analyzing within-person changes in PE scores and its association with the pandemic employing mixed effects regression models. As an exploratory analysis, all analyses were repeated with stratification by gender.

Results: PE prevalence was found to decline linearly from the beginning of the study, approximately eight years prior to the COVID-19 pandemic when participants were on average 10 years old, up until the onset of the pandemic. This trend reversed following the beginning of the COVID-19 pandemic ($p<0.001$). Exploratory analyses revealed that this reversal was more pronounced for boys than girls.

Discussion: The COVID-19 pandemic appears to have altered the trajectory of PE prevalence across adolescence. Rates of PEs rapidly increased with the onset of the pandemic, particularly for boys. While COVID-19 infection itself has been associated with PEs, there is no prior evidence that this association varies by gender. Findings therefore may be more consistent with socioenvironmental explanations (e.g., social isolation) that may have differential implications and clinical effects for adolescent boys and girls in Tokyo.

S92. IDENTIFYING THE TREATMENT GAP OF UNDIAGNOSED TARDIVE DYSKINESIA: AN ANALYSIS OF UNSTRUCTURED ELECTRONIC HEALTH RECORD DATA

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Background: Tardive dyskinesia (TD) is a severe and persistent involuntary movement disorder, which is commonly associated with prolonged antipsychotic treatment. TD is likely underreported and misdiagnosed in real-world clinical practice[1,2], and there is a need to understand the proportion of patients who may experience TD but receive no formal diagnosis. This information could support the characterisation of patient populations that may benefit from novel therapeutic interventions, such as vesicular monoamine transporter type 2 (VMAT2) inhibitors. Electronic health records (EHRs) can be used to assemble large, naturalistic cohorts of patients who are representative of those receiving routine mental healthcare. EHRs typically include structured data on demographics, diagnoses and prescribed medication, but the majority of clinical information is stored in unstructured data fields that comprise documentation of clinical assessments and treatment plans. This study aimed to identify and describe the number of patients with a history of antipsychotic treatment who had 1) a recorded diagnosis of TD in structured EHR data, and 2) no recorded diagnosis of TD, but evidence of clinical features of TD documented in unstructured EHR data.

Methods: A retrospective study was conducted using de-identified EHR data recorded between 1999 and 2021 across 25 US mental healthcare sites. The NeuroBlu platform[3] was used to assemble a dataset of 363,043 adults (>18 years) treated with antipsychotics. Patients with a recorded diagnosis of TD were identified based on the presence of the following ICD codes within structured portions of medical records: ICD-9: 333.85; ICD-10: G24.01, G24.4. Clinical features of TD documented within unstructured EHR data were extracted through manual review. Features of TD were defined using key words manually derived from the Abnormal Involuntary Movement Scale[4] and independently validated by a trained psychiatrist. 25,376 unique text-strings describing psychomotor function as part of the mental state examination were reviewed. Strings containing relevant key words were categorised as indicating a likely diagnosis of TD.

Results: Across the whole cohort (n=363,043), 4,243 patients (mean [SD] age = 39.1 years [14.9], 41% male) had features of TD recorded within the unstructured portions of the EHR. Of those, 54 (1.3%) had an ICD diagnosis of TD within the structured portion of the EHR. The most frequently clinician-recorded TD features were extremity movements (n = 3,329, 78.5%) such as “wringing of hands”, and unspecified symptoms (n = 685, 16.1%), such as “tardive dyskinesia present”. Trunkal movements such as “rocking back and forth” and “hip gyrations” were documented in 247 (5.8%) patients. Facial/oral movements such as “oral buccal smacking/puckering/chewing” were documented in 135 (3.2%) patients.

Discussion: Presence of movements that could be associated with TD may be frequently recorded by clinicians in unstructured EHR data but may not be formally recorded as a diagnosis in structured fields. The lack of recording of a structured TD diagnosis in 99% of patients with evidence of TD recorded in unstructured fields could represent a substantial missed opportunity for treatment. While involuntary facial and oral movements may account for up to 60-80% of TD cases[5,6] our data suggest that broader features of a “tardive syndrome” may be frequently documented during clinical assessment. Alternatively, other motor symptoms, such as akathisia, Parkinsonian symptoms or tremor, could have been misattributed. The present study highlights a pressing need for clinicians to better recognise and diagnose TD to close the treatment gap and increase access to treatments for affected patients.

References:

1. Brown P, Funk SC. Tardive dyskinesia: Barriers to the professional recognition of an iatrogenic disease. Journal of Health and Social Behavior. 1986 Jun 1:116-32.

2. Weiden PJ, Mann JJ, Haas G, Mattson M, Frances A. Clinical nonrecognition of neuroleptic-induced movement disorders: a cautionary study. Am J Psychiatry. 1987 Sep 1;144(9):1148-53.

3. Patel R, Wee SN, Ramaswamy R, Thadani S, Tandi J, Garg R, Calvanese N, Valko M, Rush AJ, Rentería ME, Sarkar J. NeuroBlu, an electronic health record (EHR) trusted research environment (TRE) to support mental healthcare analytics with real-world data. BMJ open. 2022 Apr 1;12(4):e057227.

4. Lane, R. D., Glazer, W. M., Hansen, T. E., Berman, W. H., and Kramer, S. I. (1985). Assessment of tardive dyskinesia using the Abnormal Involuntary Movement Scale. Journal of Nervous and Mental Disease.

5. Hauser RA, Meyer JM, Factor SA, Comella CL, Tanner CM, Xavier RM, Caroff SN, Lundt L. Differentiating tardive dyskinesia: a video-based review of antipsychotic-induced movement disorders in clinical practice. CNS spectrums. 2022 Apr;27(2):208-17.

6. Frei K, Truong DD, Fahn S, Jankovic J, Hauser RA. The nosology of tardive syndromes. Journal of the Neurological Sciences. 2018 Jun 15;389:10-6.

S93. ANTIPSYCHOTIC MEDICATION ADHERENCE AT THE EARLY PERIOD OF SCHIZOPHRENIA DIAGNOSIS AND ITS ASSOCIATION WITH PSYCHIATRIC HOSPITALIZATIONS: A NATIONWIDE POPULATION-BASED STUDY

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Background: In most cases of patients afflicted with schizophrenia, pharmacotherapy including antipsychotic drugs is considered as a necessary component of initial treatment. However, nonadherence to antipsychotic drugs is common among patients, which leads to increased medical service use and economic burden, such as relapse, emergency room visits, and hospitalizations. In this study, we investigated the effect of medication adherence early at diagnosis of schizophrenia on the later psychiatric hospitalizations.

Methods: Data were obtained from the Health Insurance Review and Assessment Service database between July 2009 and August 2021 in South Korea. A total of 71,792 patients were included in an incident cohort of schizophrenia. The adherence to antipsychotic medication was estimated by medication possession ratio (MPR) and the poor adherence was defined as MPR < 0.6.

Results: The mean value of the MPR was 0.93, and the proportion of patients with poor adherence (MPR < 0.6) was 13.8%. In the poor adherence group, the proportion of patients who experienced psychiatric hospitalization between 1 and 2 years after diagnosis of schizophrenia was 33.0%, which was higher than 27.0% in the adherence group (MPR ≥ 0.6).

Discussion: Our results suggest that encouraging antipsychotic medication adherence early at the time of schizophrenia diagnosis can reduce the possibility of later psychiatric hospitalization. Considering the clinical situation, further research investigating the determinants of early medication adherence would be needed.

S94. INEQUALITY AND BARRIERS IN PSYCHOSIS PREVENTION: A SYSTEMATIC REVIEW ON CLINICAL HIGH-RISK FOR PSYCHOSIS STUDIES FROM DEVELOPING COUNTRIES

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Background: The clinical high-risk for psychosis (CHR) paradigm is one of the best studied preventive paradigms in psychiatry. However, most studies have been conducted in high-income countries. It is unclear if knowledge from such countries applies to low and middle-income countries (LAMIC), and if there are specific limitations hindering CHR research there. Thus, our aim is to systematically review studies on CHR from LAMIC.

Methods: A multistep PRISMA-compliant literature search was performed in PubMed and Web of Science for articles published until 1/03/2022, conducted in LAMIC, addressing the concept and correlates of CHR. Study characteristics as well as studies' main limitations as described in the articles were reported. Corresponding authors of the included studies were invited to answer an online poll with 5 questions on their published study. Quality assessment was done with the MMAT. Study protocol was registered in PROSPERO: CRD42022316816.

Results: 109 studies were included in the review: none from low-income countries, 8 from lower middle-income countries, and 101 from upper middle-income countries. The most frequent limitations were small sample size (47.9%), cross-sectional design (27.1%), and follow-up issues (20.8%). Mean quality of included studies was of 4.4. Out of the 43 corresponding authors, 12 (27.9%) completed the online poll. They cited further limitations as few financial resources (66.7%), no involvement of population (58.2%) and cultural barriers (41.7%). 75% researchers reported that CHR research should be conducted differently in LAMIC compared to high-income countries, due to structural and cultural issues. Stigma as a problem was mentioned in three out of five sections of the poll.

Discussion: Results show the discrepancy of available evidence on CHR in LAMIC, given the shortage of resources in such countries. Besides the disparity in data and funding, findings could be summarized into two other topics: difficulties in gathering longitudinal data, and cultural barriers and stigma hampering CHR research. Future directions should aim to increase funding and increase the knowledge on individuals at high-risk for psychosis in such settings. Also, stigma and cultural factors that play a major role in the pathways toward care in psychosis should be addressed, as they vary according to country's income level.

S95. PSYCHOTIC EXPERIENCES AMONG MEDICAL RESIDENTS OF QUéBEC, CANADA: PREVALENCE AND RISK FACTORS

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Background: Medical training is associated with sociodemographic, mental health, and lifestyle factors that may increase physicians' risk of psychotic experiences. Yet, no study has investigated psychotic experiences in physicians, let alone in medical residents. This cross-sectional study aimed to examine the prevalence of psychotic experiences and their potential risk factors in medical residents.
Methods: Recruitment and data collection were conducted between September and November 2022. Medical residents in the province of Québec, Canada were recruited by email via their residency programs and on social media. Participants completed an online questionnaire measuring their psychotic experiences in the past 3 months using the 15-item Community Assessment of Psychic Experiences (CAPE-15). Three categories of potential risk factors were measured: (1) sociodemographic factors; (2) mental health, including depression and anxiety; and (3) lifestyle factors, including digital media use, sleep, physical activity, and cannabis use. Negative binomial regressions were used to examine the associations between these potential risk factors and the count of psychotic experiences, adjusted for age and gender.
Results: Of 3906 medical residents in Québec, 564 (14.4%) individuals from 42 residency programs participated in the study (mean age=27.71 years, 33% men). Among participants, 52.7% endorsed having at least one putative psychotic experience in the past 3 months, and 1.6% of the sample met the clinical cut-off for at-risk mental state. By large, persecutory ideations were the most endorsed psychotic experiences (reported by 51.8% of the total sample), followed by bizarre experiences (7.6%) and perceptual abnormalities (1.2%). Demographic factors that were associated with higher risk of psychotic experiences included older age in years (relative risk [RR]=1.05, 95% confidence interval [CI]: 1.02, 1.09), non-White ethnicity (RR=1.97, 95% CI: 1.48, 2.63), and using English instead of French as preferred language, French being the majority language in Québec (RR=2.06, 95% CI: 1.31, 3.26). Psychiatry residents endorsed lower levels of psychotic experiences than other residents (RR=0.56, 95% CI: 0.36, 0.86), while gender was not associated with psychotic experiences. Higher levels of depression (RR=1.10, 95% CI: 1.07, 1.13) and anxiety (RR=1.13, 95% CI: 1.11, 1.16) were both associated with higher risk of psychotic experiences. Lifestyle factors that were associated with higher risk of psychotic experiences included greater time spent on digital media (RR=1.12, 95% CI: 1.04, 1.20), greater number of nights affected by clinical duties (RR=1.03, 95% CI: 1.01, 1.05), and fewer hours of sleep on average (RR=1.19, 95% CI: 1.06, 1.35). Cannabis use and physical activity were not associated with psychotic experiences.
Discussion: Psychotic experiences, particularly persecutory ideations, were commonly reported by medical residents and were associated with higher levels of depression and anxiety. Social adversity seems to be a risk factor for psychotic experiences in this population, as suggested by the associations of psychotic experiences with ethnic and linguistic minority status. Lower endorsement of psychotic experiences among psychiatry residents could reflect favorable differences in their working conditions, or bias in their responses due to greater familiarity with measures of psychosis. Future research should consider whether digital media use and sleep disruptions are effective targets for preventing psychotic experiences in medical residents.

S96. ALL-CAUSE MORTALITY IN MEDICAL INPATIENTS WITH SCHIZOPHRENIA BY SMOKING EXPOSURE

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Background: Current meta-analyses on persons with schizophrenia (PWS) and mortality supports an aggregated relative-risk of 2.54 for death relative to controls without schizophrenia (Correll 2022) with the largest discrepancy for natural-death between control and PWS being attributable to pneumonia, at a RR for death due to Pneumonia of 7.0 (Correll 2022). This is in addition to significant disparities that exist related to COPD and smoking-related cancers (Olfson 2015). Despite convincing epidemiological data pointing to disproportionate smoking rates in persons with psychotic disorders (Lasser 2000), there exists scant data quantifying the role cigarette smoking plays in accounting for the discrepancy in mortality between persons with schizophrenia and controls. What is more, current epidemiological data largely compares healthy controls or population figures to calculate relative-risk of all-cause mortality in persons with schizophrenia (Correll 2022, Olfson 2015) despite established data acknowledging the robust effect of socioeconomic status on all-cause mortality (Stringhini 2017) and the population-level association between psychotic illness and differences in socio-economic status (Luo 2019) . Methodological barriers complicate our ability to assess the magnitude of the effect of smoking in persons with schizophrenia as it is unethical to randomize one group to receive the morbidity/mortality incurred by smoking. Using a retrospective case-control design, we were able to calculate the relative risk of smoking in the setting of Schizophrenia relative to matched smoking and non-smoking controls as well as compare the existing data on relative risk of all-cause mortality to data that controls for socio-economic status.

Methods: Patient observations were pulled from October 2012 to October 2022. All persons with both a medicine inpatient admission within the observation window and an ICD-10 or ICD-9 code in the window indicative of a diagnosis of schizophrenia or schizoaffective disorder were included in the study. This group was then pair-matched to medicine-admitted controls without psychotic illness based on age, gender, race and public insurance usage to come up with the sample for investigation. The resultant sample was analyzed to produce relative risk values for all-cause mortality related to diagnosis and smoking status.

Results: Persons with schizophrenia (PWS) were 20% more likely to die during the observation window than matched controls without schizophrenia - when matched for age, race, sex and public insurance usage.

PWS whom ever-smoked cigarettes were only 9% more likely to die during the observation window, relative to matched ever-smoking controls.

Discussion: A RR of all-cause mortality of 1.2 is significantly lower than other data-sets comparing PWS to population-level or healthy controls. A number of factors are possibly at play: Public-insurance usage seem to influence mortality in schizophrenia with steep reductions in relative mortality when patients are matched on this variable. Previous data often failed to elucidate the importance of proxy-variables for socio-economic status and resource availability.

Natural control of inpatient medicine admit with mortality risk may also be impacting lower relative risk. Future research would work to standardize medical-illness severity and match on relative severity.

Further controlling for ever-smoking status causes all-cause mortality to fail to separate from control similar to existing data on the disproportionate causes of mortality in schizophrenia, these data are suggestive of a robust effect for smoking cigarettes.

S97. PREDICTORS OF MORTALITY: EVIDENCE FROM THE 20-YEAR FOLLOW-UP OF THE OPUS STUDY INVESTIGATING SPECIALIZED EARLY INTERVENTION VS TREATMENT AS USUAL FOR PATIENTS WITH A SCHIZOPHRENIA SPECTRUM DISORDER

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Background: Schizophrenia is one of the most debilitating mental illnesses worldwide. The life expectancy of patients diagnosed with schizophrenia is about 15 years lower than in the general population and the mortality gap seems to be worsening. Some of these deaths can be attributed to suicides, drug overdoses, violence, and accidents, and many are due to natural causes. Many of these deaths might be avoidable.
The aim of this study was to determine mortality rates and causes of death in a schizophrenia spectrum population 20 years after the first diagnosis. We also examined if any baseline characteristics predicted increased mortality, and if any clinical characteristics later in the course of illness could predict mortality.

Methods: The OPUS I was a randomized controlled trial that included 578 patients first diagnosed with a schizophrenia spectrum disorder between 1998 to 2000 578. Patients were randomized to early specialized intervention treatment or treatment as usual. All participants were invited to participate in follow-up assessments 2, 5,10 and 20 years after inclusion. Symptom level, cognitive function, global level of functioning, sociodemographic factors such as employment and family life, suicidal ideation and substance use among other things were reassessed.
We collected data from the national Danish registers on all former participants regarding the use of psychiatric and general healthcare services, medication, supported housing or homelessness, and employment status. We obtained information about the time and cause of death from the Danish cause of death register. Using Cox Regression models we determined risk factors for mortality at baseline or during the follow-up period.

Results: 178 people participated in the 20-year follow-up. 82 people had died (14,4%) In comparison the mortality rate of a matched background population was 4,4% . Approximately half died of unnatural causes and half died of natural causes. The most common cause of unnatural death was suicide, which accounted for 27,5% of the total deaths, and the most common causes of natural death were cardiovascular disease and cancer both representing 8,3 % of the total number of deaths.
Substance use increased the risk of overall mortality while employment, being diagnosed with a psychotic disorder other than schizophrenia, and having a shorter duration of untreated psychosis all decreased the risk of mortality. Substance use and older age increased the risk of death due to natural causes. Male sex increased the risk while being employed decreased the risk of death due to unnatural causes.

Looking at clinical predictors at later assessments, symptom remission without the use of antipsychotic medication and recovery significantly decreased the risk for overall mortality while

substance use and chronic illness prior to death increased it. Substance use in the later course of illness also increased the risk of natural cause mortality and unnatural cause mortality separately.

Discussion: In our study, the extensive interviews combined with the data collected from Danish registers gave us a unique opportunity to look at long-term mortality outcomes after a schizophrenia spectrum diagnosis.

We showed that suicide remains a vital problem in the schizophrenia population, even many years after diagnosis. As age increases, so does the incidence of natural death, but this happens too early in this population. Substance use was the strongest and most consistent predictor of mortality. Patients die at an alarmingly high rate, and new efforts are needed to implement and finance initiatives that can treat substance use, promote a healthy lifestyle, screen for physical comorbidities and guarantee the better treatment of patients.

S98. TARDIVE DYSKINESIA: EPIDEMIOLOGICAL TRENDS IN US POPULATIONS BASED ON CROSS-SECTIONAL ANALYSES OF RETROSPECTIVE CLAIMS DATA

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Background: Tardive dyskinesia (TD) is an iatrogenic movement disorder associated with antipsychotic agent (AP) use. The global prevalence of TD is predicted to increase in the near future, but real-world data are lacking.

Methods: TD prevalence by year, payer type, AP type, and underlying condition (schizophrenia [SCZ], bipolar disorder [BD], or mood disorders [MDs]) was calculated. Data from patients aged ≥18 years that were collected from 2016 through 2020 were retrieved from the All-Payer Claims Database (APCD).

Results: Of the 278,679,590 individuals whose data were included in the APCD, 103,739 were adults diagnosed with TD, resulting in an overall TD prevalence of 37.23/100,000. Among these individuals with TD, 60.9% were female, 41.8% were white, and 55.1% were aged between 55 and 74 years. TD prevalence increased consistently over time from 6.88/100,000 (2016) to 7.60/100,000 (2017), 8.90/100,000 (2018), 10.70/100,000 (2019), and 11.53/100,000 (2020). TD prevalence was highest among patients with Medicare (78.79/100,000) or Medicaid (38.27/100,000) insurance. Among patients with ≥2 AP claims, TD prevalence was highest for those who submitted claims for both typical and atypical APs (2690.7/100,000), followed by those who submitted claims for only typical APs (1576.1/100,000) and only atypical APs (619.0/100,000). When data from patients with ≥2 AP claims were analyzed by underlying condition, TD prevalence was highest among those with recorded diagnoses of SCZ (2899.3/100,000), followed by BD (883.9/100,000) and MDs (453.7/100,000).

Discussion: TD prevalence increased consistently per year from 2016 through 2020. This could possibly be a result of new TD-specific treatments that were made available in 2017 leading to increased TD awareness and diagnosis rates. TD prevalence was greatest for Medicare and Medicaid beneficiaries, patients who submitted claims for both typical and atypical APs, and patients with underlying SCZ. However, TD may still be underdiagnosed, and additional research is needed to further elaborate on these findings.

S99. MODELLING PRENATAL HYPOXIA IN A CEREBRAL ORGANOID MODEL OF SCHIZOPHRENIA

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Background: Prenatal hypoxia during fetal development is a significant environmental risk factor linked to schizophrenia (SZ) vulnerability. However, hypoxia's impacts on human brain development at the cellular level remain unclear. In addition, how hypoxia may increase schizophrenia vulnerability for individuals already at genetic risk for schizophrenia is not well understood. Cerebral organoids are a complex in vitro 3D model that recapitulates many aspects of a developing human brain.

Methods: To address these questions, our laboratory has developed cerebral organoids derived from induced pluripotent stem cells (iPSCs) from six healthy control and six SZ patient cell lines. This creates a platform that allows for the investigation into the pathophysiology of SZ and hypoxia in tandem. Our model exposes differentiated organoids to oxygen deprivation after 1 month of development, mimicking the early stages of cortical growth in the human foetus. We are presently examining the impact of hypoxia and the genetic basis of SZ at the protein and RNA levels using immunofluorescence imaging, western blot protein expression analyses and quantitative PCR. We are also investigating the transcriptomic profiles of the organoids through RNA sequencing.

Results: Preliminary characterization demonstrates the organoids express expected neuronal molecular markers (MAP2, FZD9, PROX1, mGluR2/3, CTIP2, VGLUT1, NMDA receptor 2A and 2B, etc.) at various stages of development. Additionally, hypoxia-exposed organoids express the expected molecular responses to oxygen deprivation both immediately following the insult, 1-month-old, and after a period of recovery, 3 months old. Hypoxia impacts the expression of proteins relating to the mitochondrial electron transport chain (cytochrome c reductase, ATP synthase) within schizophrenia and control organoids immediately following the insult. Mitochondrial dysfunction is common in post-mortem analyses of SZ patient samples with differences in mitochondria morphology, cell respiration, and oxidative stress responses; this is reflected in our initial results within the organoid model. Additionally, depletion of various neuronal factors has been shown in previous SZ organoid models, which reflects what we detect in our semi-mature 3-month-old organoids. Using qPCR, we have observed clear differences in the expression of various neuronal markers (PAX6, EOMES, TBR1, CTIP2, TUJ1, SOX1, etc.) with higher mRNA levels in the control versus schizophrenia organoids. We will also present comprehensive RNA sequencing data comparing experimental organoid treatment groups.

Discussion: Our findings thus far highlight critical differences in the expression of several key neuronal populations between healthy vs. schizophrenia populations, and highlight hypoxia's further impacts on neurodevelopmental pathophysiology related to schizophrenia risk.

S100. ASSOCIATION OF SUBSTANTIA NIGRA NEUROMELANIN WITH SALIENCE NETWORK CONNECTIVITY IN FIRST EPISODE PSYCHOSIS

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Background: Basic cognitive processes, such as working memory and attention, are notably impaired in those with schizophrenia. There is a strong association between cognitive impairment and a reduction in quality of life; however, there is a lack of effective interventions to reverse this impaired cognition. Emerging evidence points to two putative mechanisms for cognitive deficits in schizophrenia: (1) disruptions of a brain network called the salience network, which includes the anterior insula and the anterior cingulate cortex (ACC); and (2) increased dopamine turnover, implicated in the positive symptoms of schizophrenia, such as hallucinations and delusions. I propose to examine the relationship between these two mechanisms and test if they lie on the same unified causal pathway towards impaired cognition in schizophrenia. Generating this knowledge will provide the in vivo markers of target engagement for many emerging pro-cognitive treatments. Recent work suggests neuromelanin sensitive MRI (NM-MRI) could provide a proxy measure of dopamine system function, based on the tendency of NM, a breakdown product of dopamine, to accumulate in the substantia nigra. NM-MRI is practical and non-invasive, providing a highly feasible and acceptable approach to study patients living with schizophrenia. This study aims to: (1) investigate if prior research results on excess neuromelanin in established schizophrenia extends to a first episode sample; and (2) determine the effect of dopaminergic turnover on the connectivity of the salience network. We hypothesize that: (1) first episode patients will have higher NM-MRI signal than healthy controls; and (2) patients with higher NM-MRI signal will have reduced connectivity between areas of the salience network.
Methods: N=40 first episode psychosis patients and N=40 healthy controls will be recruited. Patients will be recruited from the Prevention and Early Intervention Program for Psychosis in London, Ontario, as part of an ongoing CIHR-funded project (currently 27 psychosis patients and 32 controls completed baseline scans). The groups will be matched on sex, gender, age, education, and parental socioeconomic factors. Participants will undergo a resting state functional MRI scan and a NM-MRI scan. The effect of individual differences in neuromelanin on the connectivity within the salience network will be quantified using Dynamic Causal Modeling, a probabilistic statistical approach that allows inferences on the directionality and strength of network connectivity. We will also examine the effect of cannabis consumption on neuromelanin using spot salivary cannabis quantifications on the day of NM-MRI scanning.
Results: Not available yet. So far, the quantification of neuromelanin has been extremely successful based on quality measures and Contrast-to-Noise estimates.
Discussion: To date, no studies have addressed the modulatory effect(s) of neuromelanin on the salience network. This work is essential to understand how dopamine influences the salience network, thus clarifying a promising mechanism of cognitive deficits in schizophrenia. Current global efforts focused on neuromelanin in schizophrenia have highlighted the value of using this as a marker in upcoming clinical trials, which can significantly enhance therapeutic options for patients.

S101. REDUCED COUPLING BETWEEN OFFLINE NEURAL REPLAY EVENTS AND DEFAULT MODE NETWORK ACTIVATION IN SCHIZOPHRENIA

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Background: Schizophrenia is characterised by abnormal resting state and default mode network (DMN) brain activity. However, despite intense study, the mechanisms linking DMN dynamics to neural computation remain elusive. During rest, sequential hippocampal reactivations, known as 'replay', are played out within DMN activation windows, highlighting a potential role of replay-DMN coupling in memory consolidation and model-based mental simulation.
Methods: Here, we test an hypothesis of reduced replay-DMN coupling in schizophrenia, using magnetoencephalography (MEG) and a non-spatial sequence learning task designed to elicit off-task (i.e., resting state) neural replay. Participants with a diagnosis of schizophrenia (n = 28, mean age 28.2 years, range 20 – 40, 6 females, 13 not taking antipsychotic medication) and non-clinical control participants (n = 29, mean age 28.1 years, range 18 – 45, 6 females, matched at group level for age, IQ, gender, years in education and working memory) underwent an MEG scan both during task completion, and during a post-task resting state session. We used neural decoding to infer the time course of DMN activation (time-delay embedding hidden Markov model) and spontaneous neural replay (temporally delayed linear modelling) in resting-state MEG data. Using multiple regression, we then quantified the extent to which DMN activation was uniquely predicted by replay events that recapitulated the learned task sequences (i.e., 'task-relevant' replay-DMN coupling).
Results: In control participants, replay-DMN coupling was augmented following sequence learning, an augmentation that was specific for replay of task-relevant (i.e., learned) state transitions. This task-relevant replay-DMN coupling effect was significantly reduced in schizophrenia ($t(52) = 3.93$, $P = 0.018$). Task-relevant replay-DMN coupling predicted memory maintenance of learned sequences ($rho(52) = 0.31$, $P = 0.02$). Importantly, reduced task-relevant replay-DMN coupling in schizophrenia was not explained by differential replay or altered DMN dynamics between groups, nor by reference to antipsychotic exposure. Finally, task-relevant replay-DMN coupling during rest correlated with stimulus-evoked DMN modulation as measured in a separate task session.
Discussion: In the context of a proposed functional role of replay-DMN coupling, our findings shed light on the functional significance of DMN abnormalities in schizophrenia, and provide for a consilience between task-based and resting-state DMN findings in this disorder. Moreover, our findings provide a pointer towards how the computational function of offline RSN dynamics may be relevant for understanding the complex phenomenology of schizophrenia, opening up new avenues of investigation of resting state brain activity in psychiatry.

S102. POSTER WITHDRAWN

S103. EVALUATION OF THE GLYMPHATIC SYSTEM IN PATIENTS WITH SCHIZOPHRENIA

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Background: Although abundant metabolic reactions occur in the human brain every day, the central nervous system (CNS) lacks the conventional lymphatic system. Instead, it has been recently proposed that the human brain possesses a glial-dependent waste drainage pathway called the glymphatic system. The glymphatic system is mainly composed of a network of perivascular channels and astrocytes, whose endfeet expresses AQP-4 water channels to facilitate the convective exchange of interstitial fluid (ISF) with cerebrospinal fluid (CSF) and ultimately elimination of soluble proteins and metabolites from the CNS. The glymphatic system is thought to be disrupted in aging, neurovascular diseases, and neurodegeneration, including Alzheimer's disease and idiopathic normal pressure hydrocephalus, and is characterized by solute aggregation. Despite genetic, metabolic-vascular and neuroimaging evidence suggesting impaired brain clearance in schizophrenia (SCZ), no study has been conducted to explore the glymphatic system in patients with SCZ. Notably, glymphatic system impairment has been shown to be reflected in increased macromolecule (MM) levels quantified by proton magnetic resonance spectroscopy (1H-MRS). Accordingly, the present analysis aimed to quantify the aggregation of high molecular-weight MM as a measure of glymphatic system dysfunction in patients with SCZ.

Methods: This cross-sectional study was carried out at the Center for Addiction and Mental Health, Toronto, Canada. Participants included 1) healthy controls (HC), 2) first-line antipsychotics responders (non-treatment-resistant schizophrenia, nTRS), 3) clozapine responders (treatment-resistant schizophrenia, TRS), and 4) clozapine-resistant patients (ultra-treatment-resistant schizophrenia, UTRS, n=24). A 3-Tesla GE Discovery MR750 scanner equipped with an 8-channel head coil was used for scanning the participants. Individuals underwent a 3D IR-prepared T1-weighted magnetic resonance imaging (MRI) scan with the following parameters: TR = 6.74 ms, TE = 3.00 ms, TI = 650 ms, flip angle = 8 degrees, field of view = 230 mm, 256 by 256 matrix, slice thickness = 0.9 mm. Tissue-corrected 1H-MRS data (PRESS, TE = 35ms, TR = 2000ms, spectral width = 5000 Hz, 4096 datapoints, 128 water-suppressed and 16 water-unsuppressed averages, 8 number of excitations) were collected. Spectral data were obtained to quantify MM in the bilateral dorsal-anterior cingulate cortex (dACC), left dorsolateral prefrontal cortex (DLPFC), and left-dorsal caudate. The LCModel was utilized for spectral analysis. MM at 0.9 ppm (MM09+Lip09) and 2.0 ppm (MM20+Lip20) were included in the analysis (Cramer-Rao Lower Bound (CRLB) SD≤15%). Groupwise mean differences were analyzed using SPSS software.

Results: Our sample consisted of 117 participants, 75 patients with SCZ (UTRS = 24, TRS = 27, nTRS = 24) and 42 HCs. The mean age for the entire sample was 43.197 (±13.866), which was largely composed of male subjects (n = 89, 76.1%). Brain's MM levels did not differ between patients with SCZ and HC ($p > 0.05$). However, MM20+Lip20 in the left DLPFC was different between groups ($F_{3,105} = 2.872$, $p = .040$, $\eta p2 = .076$). A post-hoc test revealed that the UTRS group exhibited decreased levels of MM20+Lip20 in the DLPFC as compared to the nTRS group ($p = 0.049$). When controlling for age, gender, and smoking status, the results did not change ($F_{3,102} = 3.478$, $p = .019$, $\eta p2 = .093$; UTRS < nTRS, $p = 0.029$). No other group pairwise comparisons were significant.

Discussion: To our knowledge, this is the first study to report 1H-MRS measurement of high-molecular-weight MM for the evaluation of the glymphatic system in SCZ. Our study did not find a difference in brain MM accumulation in patients with SCZ relative to HC participants. However,

MM levels may vary in clinical subtypes of schizophrenia based on antipsychotic response, which suggests that distinct subgroups of schizophrenia patients may have differential glymphatic system clearance. These findings may help inform how differences in the waste drainage pathway are related to treatment response in SCZ. More direct assessment of the glymphatic system, such as the evaluation of the perivascular space, may provide useful understanding into biological differences between these groups.

S104. STRUCTURAL VARIABILITY OF THE BRAIN CORTEX IN SCHIZOPHRENIA AND ITS ASSOCIATION WITH CLINICAL SYMPTOMS

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Background: Despite substantial evidence on structural abnormalities of the brain cortex in schizophrenia (SZ), its clinical implication has been limited. A case-control design has been used to investigate group-level differences in morphometric features of the brain, which, however, barely accounts for the inter-individual difference. Recently, the heterogeneity of morphometric features of the brain cortex has drawn attention in its relation to clinical heterogeneity of SZ.
Methods: We used harmonized neuroimaging data of 420 healthy controls (HC) and 695 patients with SZ from seven different studies. Four structural measures of the brain cortex were obtained using the FreeSurfer automated pipeline, including surface area (SA), gray matter volume (GV), thickness (CT), and local gyrification index (LGI). We calculated the coefficient of variation (CV) and person-based similarity index (PBSI) within each group and performed group comparisons. Associations of the PBSI scores with cognitive functions were evaluated using Spearman's rho and normative modeling.
Results: Patients with SZ had a greater CV of SA, CT, and LGI compared with HCs. All PBSI scores across the cortical measures were decreased in patients with SZ than HCs, indicating a greater heterogeneity in the cortical structural profiles of the patients. In the patient group, the PBSI scores for GV and those from all cortical measures were positively correlated with the full-scale IQ score. In terms of the PBSI scores for GV and those from all cortical measures, deviant patients had a lower full-scale IQ score than other patients.
Discussion: We showed an increase in the regional and global structural variability of the brain cortex in patients with SZ compared with HCs. In terms of the similarity of cortical structural profiles, deviant patients exhibited lower general intelligence than other patients.

S105. FEASIBILITY OF ACQUIRING BRAIN IMAGING AND BIOSAMPLE COLLECTION IN THE TORONTO ADOLESCENT AND YOUTH (TAY) COHORT STUDY

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Background: One of the goals of the Toronto Adolescent and Youth Cohort (TAY) study is to characterize the neurobiological trajectories of psychosis spectrum symptoms (PSS), functioning, and self-injurious thoughts and behaviors (SITB) in a large sample (n > 1500) mental health help-seeking youth longitudinally, over 5 years. Here, we report feasibility and quality control (QC) metrics for the first 20% of the expected baseline imaging and biosample.
Methods: 'All-comers' to a large tertiary care centre child and youth mental health service (aged 11-24 years) were recruited. The most common diagnoses included: anxiety, depressive, and neurodevelopmental disorders. Each participant was offered the opportunity to provide a: (i)1-hour MRI or EEG scan, (ii)blood or saliva sample, and urine sample, and (iii) 5-minute resting heart rate recording for respiratory sinus arrhythmia (RSA). Visual QC and standardized preprocessing pipelines (MRIQC, FMRIPREP, QSIPREP and ASLPREP) were completed to produce quality control measures.
Results: Of the first 300 participants who consented to the overall study, 98% agreed to neuroimaging and 79% completed scanning (MRI, n=201; EEG, n=35). 98% agreed to biosample collection (n=126 blood, n=112 saliva, n=208 urine samples collected, n=239 completed RSA protocol). Following QC, data usability remained high (MRI: DWI 95%, ASL 89%, resting-fMRI 87%, task-fMRI 80%; EEG: 80%; RSA: 97%). Participants who completed biosample characterization were representative in age, demographic, and clinical characteristics of the overall sample.
Discussion: The high consent, completion rates and QC metrics, and lack of bias in the data indicate that collecting and characterizing a large clinical child and youth cohort is feasible.

S106. FMRI INVESTIGATION OF PERSONAL SPACE INTRUSION IN SCHIZOPHRENIA PATIENTS WITH PARANOIA

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Background: People often experience discomfort when other individuals infringe upon a self-established physical personal space during social interaction. Inter-personal space (IPS) identified paranoia with high sensitivity and specificity and is therefore clinically relevant to detect paranoia. Models of paranoia suggested limbic and prefrontal circuit pathology related to threat processing and emotion regulation. We hypothesize that patients with paranoia will respond with altered activation in IPS-relevant brain areas (i.e., amygdala, fronto-parietal cortex) toward personal space intrusion, especially in aversive contexts.

Methods: 50 patients diagnosed with schizophrenia - n=26 without paranoia: mean Age = 35.2(12.6), n=19 with paranoia: mean Age=41.5(13.2), and 30 controls mean Age=35.4(11.7) were included in this fMRI Approaching faces study. Participants passively viewed pictures of facial expressions from the Karolinska Directed Emotional Face in either approaching, still or retracting motions. Paranoia was assessed with the Green et al Paranoid Thoughts Scale (GPTS).
Results: We could observe a main effect of group (F-test, $p(FWE)<0.05$) within the superior frontal gyrus (left, $p(FWE)=0.019$) and the right anterior insula ($p(FWE)=0.02$) and inferior frontal gyrus (pars triangularis, $p(FWE)<0.001$). More precisely, post-hoc T-Tests revealed a hyperactivation of the SFG ($t=5.29$, $p(FWE)<0.001$) and hypoactivation of the inferior frontal gyrus / insula cluster ($t=5.65$, $p(FWE<0.001)$) in patients with paranoia when compared to healthy controls. Furthermore, the task overall activated bilaterally the amygdala: Importantly patients exhibited a trend of lower amygdala activation ($p=0.051$) than controls when controlling for age and gender. Further post hoc tests showed significant differences between patients with and without paranoia (patients with paranoia < patients without paranoia, $p=0.015$).
Discussion: In conclusion, patients with schizophrenia exhibited significant hyperactivation of a key emotional control area and could not adequately activate the amygdala during the approaching-faces task. Following previous neuroimaging results we could hypothesize that patients with paranoia present an overall high activity of the amygdala and cannot further increase amygdala's activity during the task. Thus, as a compensation mechanism, activity increases in key emotional control areas.

S107. A REVIEW ON RESTING-STATE FUNCTIONAL MRI IN TREATMENT-RESISTANT SCHIZOPHRENIA

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Background: Abnormalities in brain regions involved in the pathophysiology of schizophrenia may present insight into individual clinical symptoms and treatment response. Specifically, functional connectivity irregularities may provide potential biomarkers for treatment response or treatment resistance as such changes can occur before any structural changes are visible. The aim of the present review is to summarize resting-state functional magnetic resonance imaging (rs-fMRI) findings from the last decade to provide an overview of the current knowledge on brain functional connectivity abnormalities and their associations to symptoms in treatment-resistant schizophrenia (TRS) and ultra-treatment resistant schizophrenia (UTRS) and to look for support for the dysconnection hypothesis.
Methods: PubMed database search was performed for articles published in the last 10 years (i.e., December 2012-November 2022) on rs-fMRI in treatment-resistant schizophrenia. Articles were included if the cohort investigated included individuals with TRS, i.e. failure of at least two adequate treatment episodes with different antipsychotic drugs. Articles were excluded if: 1) there was either no rs-fMRI acquisition or no rs-fMRI measures as an outcome, 2) the rs-fMRI was not acquired with a 3.0 Tesla MR scanner, 3) the cohort did not include TRS or TRS was not clearly defined as “not responding to at least two different antipsychotics despite adequate dose and duration”, or 4) the article was a case report, a study protocol, or a review.
Results: 18 (out of 158) articles were selected for this review involving 648 participants (TRS and control groups). The studies reported functional connectivity before treatment initiation with clozapine (CLZ), riluzole, or electroconvulsive therapy (ECT); during treatment with clozapine

(and/or mixed medication), riluzole and ECT; and post-ECT treatment. The results showed frontal hypoconnectivity before initiation of treatment with CLZ or riluzole, increase in frontal connectivity after riluzole treatment, fronto-temporo-occipital hypoconnectivity that may be specific for non-responding individuals, widespread abnormal functional connectivity during mixed treatments, and ECT induced effects specifically on the limbic system.
Discussion: Probably due to the high heterogeneity in the patient cohorts concerning medications and other clinical variables (e.g., treatment response, exposure to medication, duration of illness, treatment adherence), widespread abnormalities in connectivity were noted. However, functional irregularities in the frontal brain regions, especially in the prefrontal cortex, were noted which are consistent with previous SCZ literature and the dysconnectivity hypothesis. There were major limitations though as most studies did not differentiate between TRS and UTRS (i.e., CLZ-resistant schizophrenia) and investigated heterogeneous patients groups treated with mixed treatments (with or without CLZ). This is critical as in different subtypes of the disorder an interplay between dopaminergic and glutamatergic pathways involving frontal, striatal, and hippocampal brain regions in separate ways is likely. Better definitions of treatment responders and non-responders are necessary in future longitudinal studies to correctly differentiate brain regions underlying pathophysiology of SCZ which could serve as potential functional biomarkers for treatment resistance.

S108. ASSOCIATIONS BETWEEN STRUCTURAL COVARIANCE NETWORK AND ANTIPSYCHOTIC TREATMENT RESPONSE IN SCHIZOPHRENIA

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Background: Approximately 30% of patients with schizophrenia do not respond to antipsychotics and are termed treatment-resistant schizophrenia (TRS). Several studies showed that patients with TRS have widespread strong reductions in cortical thickness compared to healthy controls (HC) as well as patients with TnRS. Recently, to evaluate these structural changes in terms of brain networks, structural covariance has been used to assess the associations of structural measures between two regions. Structural covariance increases when similar structural changes occur in two independent regions, suggesting that those regions share a common pathophysiology. A previous study reported that structural covariance between the two regions with strongly reduced cortical thickness increased in patients with schizophrenia. In this study, we examined the association between treatment resistance and structural covariance changes in this disorder.
Methods: We used international multi-site cross-sectional neuroimaging datasets comprising 102 patients with TRS, 77 patients with TnRS, and 79 HC. Eighty-nine, seventy, and ninety-nine participants were enrolled at Komagino Hospital (Tokyo, Japan), Shimofusa Hospital (Chiba, Japan), and the Centre for Addiction and Mental Health (Toronto, Canada). Antipsychotic

treatment resistance was defined by the modified Treatment Response and Resistance in Psychosis Working Group Consensus criteria.
T1-weighted structural images were preprocessed using the bpipe pipelines, then cortical thickness was calculated using CIVET for each of 68 regions of the Desikan-Killiany-Tourville atlas. We used a CovBat harmonization method to control for the site differences in the cortical parameters while considering disease status, age, and sex as biological variables. We calculated the residuals of cortical thickness controlling for age and sex. Analysis of variance and post-hoc pairwise t tests were used to examine group differences in residuals of cortical thickness for the 62 cortical regions. Structural connectivity was quantified with partial correlation coefficient between all pairs of regions, controling for age and sex. This approach yielded a separate connectivity matrix of dimension 62×62 for each group. Based on the Fisher method for comparing correlation coefficients, thickness correlations were r-to-z transformed. From the difference in the resulting r-to-z values between the 2 groups, we estimated a z-score that tested the null hypothesis of equality in thickness correlations between the 2 groups. Calculated z-score in each edge was normalized using the standardized deviation of z-scores in 1,000 bootstrap samples. The network-based statistic with 50,000 permutations was used to obtain the structural covariance network with significant difference, controlling the 1,891 multiple comparisons. A primary z-score threshold of 3 was used, with a family-wise error rate threshold of 5%. We estimated the degree centrality for each node of the obtained structural covariance network. This study was conducted after obtaining approval from the respective ethics review committees.

Results: Group differences in residuals of cortical thickness were found in 58 out of 62 cortical regions. A total of 59 and 31 regions were found to show cortical thickness reductions in TRS and TnRS compared with HC, respectively. Also, cortical thickness in 26 regions was reduced in the TRS group than in the TnRS group. Both In the TRS and TnRS groups, regions with cortical thinning were located mainly in the frontal and temporal lobes and the cingulate cortex. No significant difference was found in the variances in residuals of cortical thickness among the three groups. Structural covariances across 1,891 pairs of cortical regions were higher in the TnRS group compared with the HC and TRS groups. The null hypothesis of equality in structural covariance between the TnRS and HC groups was rejected using network-based statistics. We found a single network comprising connections with elevated structural covariance in patients with TnRS compared with HC. The inferior temporal gyrus and insula had high degree centrality in the structural covariance network. The null hypothesis could not be rejected for structural covariance between the TRS group and the TnRS or HC groups.
Discussion: While patients with TRS showed stronger cortical thinning in the frontal and temporal lobes compared to HC and patients with TnRS, there was no structural covariance network with significant difference between the TRS group and the HC or TnRS groups. On the other hand, the TnRS group had a brain network with increased structural covariance compared to the HC group. Our findings suggest that coordinated cortical thinning in the brain network is related to treatment response in schizophrenia while TRS may have greater heterogeneity in the pathophysiology of cortical thinning than TnRS, resulting in lower structural covariance. Another possibility is that cortical thinning was severe or had reached the plateau long ago in patients with TRS such that the elevation of structural covariance may not be detected. Further longitudinal study is warranted to confirm the link between pathophysiology of structural alteration and treatment resistance in schizophrenia.

S109. ABERRANT EFFECTIVE CONNECTIVITY DURING EYE GAZE PROCESSING IS LINKED TO SOCIAL FUNCTIONING IN SCHIZOPHRENIA

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Background: Abnormal gaze perception contributes to social dysfunction in schizophrenia (SZ). As we have previously shown (Tso et al., 2021), in SZ gaze perception induces aberrant effective connectivity among brain regions involved in visual processing, social cognition, and cognitive control. Here, in an independent sample, we used Dynamic Causal Modeling (DCM) to 1) determine whether gaze processing induces aberrant effective connectivity in SZ, and 2) in a novel extension of previous work, reveal how aberrant connectivity contributes to symptom severity and social dysfunction.

Methods: fMRI data from 72 participants (39 SZ, 33 HC) were analyzed. Participants completed a gaze perception task during which they viewed faces with varying gaze angles (using stimuli from six different actors). Two conditions were employed: a) explicit gaze processing (i.e., identifying stimuli as having self-directed vs. averted gaze) and b) gender discrimination (i.e., identifying stimuli as male vs. female). Effective connectivity was examined in an a priori network of four brain regions—secondary visual cortex (Vis), superior temporal sulcus (STS), inferior parietal lobule (IPL), and medial frontal cortex (MFC). Using DCM, effective connectivity was modeled in terms of 1) connections present during general face processing (i.e., across both task conditions) and 2) how these connections were modulated during explicit gaze processing. From the estimated DCM parameters, canonical correlation analysis was used to examine associations with external measures of social cognition/functioning.

Results: Generative model structures were similar across groups, but differences in magnitude were noted for some parameters; specifically, SZ showed stronger intraregional inhibition of the MFC (asz = -.09, aHC = -.23) and stronger inhibition of Vis by IPL (asz = -.46, aHC = -.14). Relative to general face processing, engaging in explicit gaze processing led to increased excitatory, bottom-up connections from Vis to STS (bsz = .21, bHC = .20) and IPL (bsz = .08, bHC = .22), and stronger inhibitory top-down connections from MFC to Vis (bsz = -.46, bHC = -.61) in both groups. SZ and HC differed in patterns of top-down modulation from MFC to STS (bsz = -.44, bHC = .33) and IPL (bsz = -.31, bHC = .08). Specifically, whereas inhibitory connections were attenuated during explicit gaze processing in HC, these connections were strengthened in SZ. In patients, stronger top-down inhibition was associated with fewer negative symptoms ($r = .33$, $p = .04$). Parameters that differentiated groups were also associated with social cognition/functioning, when examined in both groups combined ($r = .76$, $p = .01$).

Discussion: As we have previously shown (Tso et al., 2021), similar patterns of effective connectivity support general face processing in HC and SZ. During explicit gaze processing, SZ showed notably stronger top-down inhibition, which was counterintuitively associated with reduced symptoms, suggesting this pattern of aberrant connectivity may serve a compensatory or protective function in SZ. Despite some discrepancies in the specific group differences seen in the current study versus our previous work (Tso et al., 2021), we found consistent evidence for generally altered intraregional connections and abnormally strong top-down inhibition in SZ. Taken together, findings suggest that abnormal excitatory-inhibitory balance and top-down inhibition during social perception may be plausible mechanisms of social dysfunction in SZ.

S110. PREDICTION OF PSYCHOTIC DISORDERS BY MULTIPLE MODALITIES AND MACHINE-LEARNING

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Background: Among individuals with an at-risk mental state (ARMS) who exhibit prodromal symptoms of psychotic disorders such as schizophrenia, only about 25% would eventually develop frank psychosis. Therefore, objective biomarkers which could reliably predict future onset of psychosis among this population are warranted. Recently, some studies used multiple modalities and machine learning techniques such as support vector machine (SVM) to identify ARMS subjects who later develop overt psychosis.

Methods: Sixty subjects were recruited and evaluated using Comprehensive Assessment of ARMS (CAARMS) at the Toyama University hospital. Subjects were clinically followed at least for 2 years, and 15 of the subjects developed full-blown psychosis (ARMS-P) while other 45 did not (ARMS-NP).

We examined following items and used for the classification: 1) Clinical symptoms were evaluated by Positive and Negative Syndrome Scale (PANSS). 2) The Japanese version of the Brief Assessment of Cognition in Schizophrenia (BACS-J) was used for the evaluation of cognitive function. 3) T1-weighted three-dimensional magnetic resonance images (MRI) were obtained and preprocessed via FreeSurfer (version 6). We extracted six regions of interest based upon the group comparisons (i.e., ARMS-P versus ARMS-NP) and our previous literatures (Sasabayashi et al., 2017; Takayanagi et al., 2022). 4) We recorded two event-related potentials (ERP), namely P300 and mismatch negativity (MMN). 5) Erythrocyte membrane levels of six polyunsaturated fatty acids (PUFAs) (EPA, DHA, DPA, linoleicacid, DGLA, and arachidonicacid) were measured.

For the classification of ARMS-P and ARMS-NP groups, we performed linear SVMs with 10-fold cross validation by LibSVM implemented in the data-mining software WEKA. First, we performed SVMs using single modality. Then, we conducted SVMs with a variety of combinations of modalities. Classification accuracy was accessed by the area under curve (AUC) of the receiver operating characteristic (ROC) curve.

Results: Among classifications with single modality, AUCs ranged between 0.5 and 0.644, indicating poor to fair classifications. When multiple modalities were used, AUCs were increased, ranging 0.561 to 0.883. Particularly, classification performances were enhanced when clinical and structural MRI variables were combined (AUCs ranged between 0.762 and 0.883).

Discussion: Our data suggest that classification performances for predicting future onset of overt psychosis in ARMS subjects could be enhanced by combining several clinical and biological features. The limitations of this study are relatively small sample size and the risk of over-fitting in SVMs. The classifiers obtained in this study should be validated by independent cohorts.

S111. LONGER ILLNESS DURATION IS ASSOCIATED WITH GREATER INDIVIDUAL VARIABILITY IN FUNCTIONAL BRAIN ACTIVITY IN SCHIZOPHRENIA, BUT NOT BIPOLAR DISORDER

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Background: Individuals with schizophrenia exhibit greater inter-patient variability in functional brain activity during neurocognitive task performance. Some studies have shown associations of age and illness duration with brain function; however, the association of these variables with variability in brain function activity is not known. In order to better understand the progressive effects of age and illness duration across disorders, we examined the relationship with individual variability in brain activity.

Methods: Neuroimaging and behavioural data were extracted from harmonized datasets collectively including 212 control participants, 107 individuals with bipolar disorder, and 232 individuals with schizophrenia (total n=551). Functional activity in response to an N-back working memory task (2-back vs 1-back) was examined. Individual variability was quantified via the correlational distance of fMRI activity between participants; mean correlational distance of one participant in relation to all others was defined as a 'variability score'.

Results: Greater individual variability was found in the schizophrenia group compared to the bipolar disorder and control groups ($p=1.52e-09$). Individual variability was significantly associated with aging ($p=0.027$), however, this relationship was not different across diagnostic groups. In contrast, in the schizophrenia sample only, a longer illness duration was associated with increased variability ($p=0.027$).

Discussion: An increase in variability was observed in the schizophrenia group related to illness duration, beyond the effects of normal aging, implying illness-related deterioration of cognitive networks. This has clinical implications for considering longterm trajectories in schizophrenia and progressive neural and cognitive decline which may be amiable to novel treatments.

S112. PSYCHOMOTOR DISTURBANCE IN PATIENTS WITH PSYCHOTIC DEPRESSION IS PREDICTED BY FUNCTIONAL CONNECTIVITY WITHIN THE DEFAULT MODE NETWORK

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Background: Psychomotor disturbance (PMD) is related to clinical outcome for patients with major depressive disorder (MDD) with psychotic features (psychotic depression). Our group previously found that the total score of the psychiatrist-rated sign-based CORE measure for PMD was related to relapse in patients with psychotic depression. A subsequent factor analysis found that the CORE's non-interactiveness and retardation items can be combined in a single factor. There is also cross-sectional evidence that between-network default mode (DMN) functional connectivity is implicated in psychotic depression, however there is little research on the neurobiology of PMD in this patient population. We aimed to address this gap and examined cross-sectional DMN-related functional connectivity and its relationship with PMD. We hypothesized that between-network DMN functional connectivity is associated with CORE total and non-interactiveness/retardation factor scores.

Methods: All patients met criteria for MDD with psychotic features based on the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) Axis I Disorders (SCID-IV), participated in the Study of Pharmacotherapy of Psychotic Depression (STOP-PD II), and were treated with sertraline and olanzapine. Patients with cross-sectional resting state functional magnetic resonance imaging (R-fMRI) of sufficient quality (N = 58) were included in analyses and R-fMRI as well as CORE data were collected after all patients were stabilized. The DMN was defined based on the Cole-Anticevic Brain Network Parcellation, within-DMN and between-network DMN-related functional connectivity with the rest of the brain was examined, and mixed effects linear models were employed while controlling for age, sex, and site. The primary analysis examined the ability of DMN-related functional connectivity to predict CORE total scores and the secondary analysis examined the ability of DMN-related functional connectivity to predict the CORE non-interactiveness and retardation factor scores.

Results: Contrary to our hypothesis, CORE total scores were not significantly predicted by a model including DMN between-network functional connectivity with the rest of the brain (beta=-19.23, SE=15, t=-1.28, p=.206), however CORE total scores were significantly predicted by within-DMN functional connectivity (beta=16.45, SE=6.49, t=2.54, p=.014). Similarly, the combined CORE non-interactiveness and retardation scores were not significantly predicted by a model including between-network functional connectivity with the rest of the brain (beta=-16.21, SE=13.93, t=-1.16, p=.250), however CORE non-interactiveness and retardation scores were significantly predicted by within-DMN functional connectivity (beta=13.30, SE=6.11, t=2.18, p=.034).

Discussion: Our results suggest that cross-sectional within-DMN functional connectivity predicts PMD as measured by CORE total scores and the combined CORE non-interactiveness and retardation factor scores in patients with psychotic depression. Additional research is needed on the relationship between longitudinal changes in CORE scores and longitudinal changes in within-DMN functional connectivity, whether relapse can be predicted using within-DMN functional connectivity, and whether within-DMN functional connectivity predicts PMD in other psychotic disorders and non-psychotic depression.

S113. CLOZAPINE LEVELS AND THERAPEUTIC RESPONSE: A ROC CURVE ANALYSIS USING INDIVIDUAL PATIENT META-ANALYSIS DATA

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Background: Clozapine has been well established as the most efficacious medication for treatment refractory schizophrenia. Optimising the benefit during clozapine trial is an important clinical consideration. Therapeutic drug monitoring of clozapine plasma or serum levels has formed a critical part of this. Though there is no agreed standardised therapeutic range, advice traditionally recommends a clozapine level of >350ng/mL in order to effect best response. Most studies analysing the relationship between treatment response and clozapine level are older, have small sample sizes, and do not consider whether additional factors might assist in determining optimal clozapine level for response.
Methods: We conducted a systematic review of PubMed, PsycInfo and Embase for studies that provided individual participant level data on clozapine levels and response. This data was analysed using Receiver Operating Characteristic (ROC) curves to determine the prediction performance of serum clozapine levels for treatment response.
Results: We were able to include data on 294 individual participants. ROC analysis yielded an area under the curve (AUC) of 0.612. The clozapine level at the optimal Youden index was 372ng/mL, and at this level there was response sensitivity of 57.3%, and specificity of 65.7%. The interquartile range for treatment response was 223ng/mL – 558ng/mL. There was no improvement in ROC performance with mixed models including patient sex, age or length of trial.
Discussion: Clozapine dose should be optimised based on clozapine therapeutic levels. We found that a range between 250 – 550ng/mL could be recommended, while noting that a level of >350ng/mL is most optimal for response.

S114. TREATMENT-RESISTANT SCHIZOPHRENIA AND A SUCCESSFUL CLOZAPINE RE-CHALLENGE AFTER CLOZAPINE-INDUCED MYOCARDITIS

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Background: Approximately 30 % of patients with schizophrenia develop treatment resistance (treatment-resistant schizophrenia, TRS) with 70-80 % being evident during the first psychotic episode. Presently, TRS is diagnosed according to international consensus criteria that have been established in 2017. Importantly, despite progress in psychopharmacological treatment options, thus far, clozapine remains the first line and only effective drug of choice in TRS. This is underscored by the fact that clozapine not only mitigates positive symptoms but also reduces all-cause mortality. However, clozapine remains underutilized resulting from e.g., a widespread fear of side effects including clozapine-induced myocarditis (CIM). CIM rates are higher compared to agranulocytosis. The underlying pathophysiological mechanisms causing CIM remain elusive. A recent meta-analysis identified concurrent sodium valproate as a potential risk factor as well as rapid dose titration regimes. Importantly, CIM necessitates immediate termination of clozapine and in consequence leads to permanent clozapine discontinuation with potential detrimental effects on the patient's global psychopathology and long-term outcome. Hence, presently a clozapine re-challenge after CIM is discussed. To date, clinical data based on case reports imply a re-challenge

after CIM to be a reasonable approach after risk-benefit assessment and an appropriate hospital setting including specialists, i.e., cardiologists. The success rate is estimated at 60 %.
Methods: We present the case of a 26-year-old male patient with TRS. We initiated treatment with clozapine after discontinuing valproate while tapering off olanzapine and the patient responded well during the first weeks. The dose was increased by 25 mg per day. Three weeks after initiation (daily dose 200 mg, plasma clozapine level 265 mmol/L) laboratory monitoring indicated signs for myocarditis which was corroborated by further clinical and electrophysiological findings. Clozapine was discontinued and we initiated alternative treatment including electroconvulsive therapy and antipsychotic combination treatment – however without any significant success. After 11 weeks of non-response, we initiated a clozapine re-challenge, which was followed by a significant clinical improvement. This re-challenge was conducted with a slower dose titration regime in close exchange with our cardiologists. Moreover, we intensified laboratory, clinical and electrophysiological monitoring.
Results: The target dose of 200 mg/d was reached after four months without any signs for a recurrent CIM. He was discharged to an assisted living facility in a stable mental state which continued during follow-up visits at our outpatient department.
Discussion: In summary, although data regarding risk factors are inconclusive, in this case an association with the preceding treatment with valproate as well as a slow clozapine metabolization should be discussed. Overall, this case reflects the relevance of clozapine treatment and supports previous reports proposing a re-challenge to be a reasonable approach in specific cases. In addition, the case highlights the central role of slow dose titration regimes and the potential impact of concomitant medication as well as the benefits of adequate monitoring which facilitates safe use of clozapine.

S115. ACUTE MODULATION OF BRAIN GLUTAMATERGIC METABOLITES BY BENZODIAZEPINES IN INDIVIDUALS AT CLINICAL HIGH-RISK FOR PSYCHOSIS

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Background: Post-mortem and preclinical studies indicate that abnormal excitation-inhibition balance within a corticolimbic brain circuit plays a key role in the development of psychosis. In vivo imaging research has identified elevations of glutamatergic metabolite levels (i.e., Glx: glutamate + glutamine) in the medial frontal cortex including the anterior cingulate cortex (ACC) in individuals at clinical high-risk of psychosis (CHR). In later stages of psychosis progression, elevations in Glx were identified in the medial temporal lobe, including the hippocampus, in unmedicated schizophrenia patients. Evidence from an influential neurodevelopmental animal model (methylazoxymethanol acetate, MAM) suggests that psychosis pathophysiology originates from impaired prefrontal regulation of the amygdala's response to stress, leading to GABAergic dysfunction in the ventral hippocampus, driving increased glutamatergic output and ultimately increasing subcortical dopamine activity. Importantly, enhancing GABAergic neurotransmission

through premorbid administration of diazepam to this model prevented the schizophrenia-relevant phenotype from emerging at adulthood. However, whether the acute administration of diazepam can modulate glutamatergic metabolite levels in subjects at CHR for psychosis remains to be established.

Methods: We investigated the effects of a single oral dose of diazepam (5mg) compared to placebo (ascorbic acid) in 21 participants (age: 23.9(±4.9) years, 57% female) at CHR as defined by CAARMS criteria, using a double-blind, within-subject, randomised, cross-over design. Participants were scanned twice (minimum three-week washout period between scans) in a 3T GE scanner using proton magnetic resonance spectroscopy (1H-MRS) measuring Glx levels in the ACC and left hippocampus. Metabolite concentrations were quantified using FID-A pre-processing, and spectral fitting using LCModel. Absolute Glx concentrations were corrected for voxel tissue composition (grey matter, white matter, cerebrospinal fluid). Three participants were excluded from the hippocampal 1H-MRS analysis (two failed quality control measures, one outlier identified using Grubbs test). Diazepam vs. placebo effects were investigated using a two-tailed paired t-test, with significance set at $p<0.05$.

Results: There were no significant effects of a single-dose of diazepam on hippocampal Glx levels ($n=18$, $t(17)=1.145$, $p=0.27$; placebo: mean(±SD) = 11.0(±1.7) mM; diazepam: mean(±SD) = 11.5(±1.3) mM). Compared to placebo, diazepam significantly decreased Glx levels in the ACC ($n=21$, $t(20)=2.26$, $p=0.04$; placebo: mean(±SD) = 19.3(±2.2) mM; diazepam: mean(±SD) = 18.4(±1.7) mM).

Discussion: Our study demonstrates region-dependent effects of acute diazepam administration, reducing Glx levels in CHR individuals, which were known to be increased by previous literature. Given that preclinical research showed efficacy of chronic diazepam administration in preventing psychosis-relevant neurophysiology and behaviour, our findings suggest that the mechanisms underlying such modulatory effects may involve decreasing elevated glutamatergic concentrations in the ACC. These findings support the notion that targeting excitation-inhibition balance early may be a promising therapeutic strategy for psychosis.

S116. POSTER WITHDRAWN

S117. SAFETY OF BEN GUIDELINES IN CLOZAPINE TREATMENT: A CANADIAN PERSPECTIVE

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Background: Clozapine represents the only drug approved for treatment-resistant schizophrenia. It remains markedly underutilized, though in part related to hematologic concerns, the main concern is the risk of agranulocytosis which can be fatal. Agranulocytosis is defined as an absolute neutrophil count (ANC) of < 500/μL of blood. Unidentified benign ethnic neutropenia (BEN) has been recognized as a factor contributing to clozapine underutilization and discontinuation,

although these individuals are not at higher risk of adverse events. In 2018, Canada followed the footsteps of the United Kingdom and United States, permitting a modified ANC monitoring algorithm for patients with BEN that allows for initiation of clozapine treatment in those with ANC values ≥ 1000/μL. Our main objective was to evaluate if clozapine can be safely utilized in a sample of Canadian psychiatric patients with BEN.

Methods: A retrospective chart review was conducted at the Centre for Addiction and Mental Health. Through the clozapine clinic and registry, participants were identified who (i) received clozapine using the Health Canada approved BEN guidelines for hematological monitoring, and (ii) had at least one complete blood count pre- and post-clozapine initiation. Patients with illnesses associated with neutropenia or receiving concomitant lithium treatment were excluded due to potential elevation in white blood cell counts and ANC values.

Results: Our sample population was comprised of 41 BEN patients who were Black-Caribbean (49%), Black-African (34%), Black-North American (12%), Middle-Eastern (2%), and Indian-Caribbean (2%). There were 323 incidents of mild neutropenia (0.5 X 109/L ≤ ANC < 1.0 X 109/L) and 1017 incidents of moderate neutropenia (ANC < 1.0 X 109/L). However, after BEN identification only 15 incidents of mild neutropenia and 33 of moderate neutropenia were reported. The mean within-patient ANC value was not significantly different one year after clozapine initiation compared to baseline. 32 patients (78%) were successfully treated with clozapine and are still receiving treatment monitored under the BEN guidelines. Moreover, none were discontinued for hematologic reasons.

Discussion: Current evidence from this Canadian cohort suggests that pre-clozapine neutropenia did not predict an increased risk of agranulocytosis. Collectively, our findings indicate that patients monitored under the modified hematological guidelines for BEN can be safely treated with clozapine. Earlier identification of this hematological phenotype by clinicians, that is before clozapine initiation ideally, may prevent and reduce the frequency of unnecessary blood draws, treatment interruption and possible drug discontinuation. Moving forward, increased awareness and knowledge of BEN may translate to greater clozapine access.

S118. DOES SHORT-TERM ANTIPSYCHOTIC DISCONTINUATION WORSEN SYMPTOMS IN ACUTE SCHIZOPHRENIA? A POOLED ANALYSIS OF PLACEBO WASHOUT DATA

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Background: To address whether short-term discontinuation of antipsychotics can induce symptom exacerbation in acute schizophrenia, we examined changes in symptom severity after a short-term antipsychotic discontinuation by pooling and analyzing the data of double-blind randomized controlled trials (RCTs) involving patients with acute exacerbation of schizophrenia.

Methods: The data from three double-blind, randomized, controlled trials comparing lurasidone versus placebo in patients with acute exacerbation of schizophrenia were pooled and analyzed. Symptom severity was assessed using the Positive and Negative Syndrome Scale (PANSS) total and the Clinical Global Impression–Severity scale (CGI-S) scores. The scores before and after the antipsychotic discontinuation phase were compared. Factors associated with score changes were also explored.

Results: Among 2,154 patients participating in the trials, 600 who received antipsychotic monotherapy and completed the antipsychotic discontinuation phase were included in the analysis. No patients received clozapine. The mean ± standard deviation of the duration of the discontinuation phase was 5.9 ± 2.5 days. The PANSS total and CGI-S scores statistically significantly changed from 94.0 ± 9.5 to 95.4 ± 10.5 and from 4.9 ± 0.6 to 4.9 ± 0.7, respectively, during this phase; however, the absolute difference was minimal. The score changes were not associated with the type or dose of prior antipsychotics, or the duration or strategy (abrupt versus gradual) of antipsychotic discontinuation.
Discussion: Symptoms did not worsen to a clinically meaningful degree after a short-term discontinuation of non-clozapine antipsychotics in patients with acute exacerbation of schizophrenia, suggesting that the efficacy of antipsychotics persists at least several days after discontinuation.

S119. COCAINE ADDICTION-LIKE BEHAVIOUR IN A GENETIC MOUSE MODEL OF SCHIZOPHRENIA RISK: EVIDENCE OF GENETIC COMORBIDITY BETWEEN DRUG ABUSE AND SCHIZOPHRENIA

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Background: Patients with schizophrenia have high rates of comorbid drug addiction, and this worsens symptoms, complicates medication adherence, and increases hospitalisation risk. One potential explanation for this comorbidity is similar neuropathophysiology in both drug addiction and schizophrenia. To date there is only limited clinical data indicating that genetic risk for schizophrenia is associated with increased drug abuse, and clinical studies can be confounded by polydrug use and the polygenetic nature of schizophrenia. We sought to investigate this relationship without these confounds, by examining drug reward and reinforcement for cocaine in an established mouse model of genetic risk for schizophrenia, the Neuregulin 1 transmembrane domain heterozygous (Nrg1 TM HET) mouse.
Methods: We examined drug-induced locomotor sensitization and conditioned place preference for various cocaine doses (5, 10, 20, 30 mg/kg) in male adult Nrg1 TM HET and wild type-like (WT) littermates. We also investigated intravenous self-administration of and motivation for cocaine (doses: 0.1, 0.5, 1 mg/kg/infusion), as well as extinction and cue-induced reinstatement.
Results: Cocaine reward was similar between Nrg1 TM HET mice and WT littermates, at all doses tested. Locomotor sensitization to cocaine was not affected by Nrg1 genotype at any dose. Although self-administration of and motivation for cocaine was unaffected, extinction of cocaine self-administration was impaired in Nrg1 mutants compared to WT mice. Cue-induced reinstatement was similar between Nrg1 TM HET and WT controls.
Discussion: These results suggest an addiction-like phenotype for cocaine in Nrg1 TM HET mice and indicate that genetic susceptibility for schizophrenia can increase susceptibility to some addiction-like behaviour for cocaine. This supports the hypothesis that shared genetic vulnerability may underpin addiction risk in patients with schizophrenia.

S120. ASSESSING PREFERENCES FOR APP-BASED PSYCHOLOGICAL INTERVENTIONS TO DECREASE CANNABIS USE IN YOUNG ADULTS WITH

PSYCHOSIS: RESULTS FROM A SEQUENTIAL QUALITATIVE AND QUANTITATIVE STUDY

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Background: Face-to-face psychosocial interventions are the mainstay of cannabis use disorder (CUD) treatment in Early Intervention Services (EIS) for psychosis. Implementation in EIS is hampered by heterogeneity in staff training, availability to manage CUD, and limited access to treatment for rural populations. Mobile health interventions could circumvent existing barriers and are effective in decreasing cannabis use in the general population. To date no app-based psychosocial intervention for CUD in individuals with first episode psychosis (FEP) has been developed and formally tested. The aim of our research was to explore and assess treatment parameters and app components that could increase acceptability of app-based interventions in this population.

Methods: We used a sequential study design that included qualitative and quantitative methodologies to explore (study 1) and assess (study 2) preferences for an app-based intervention. In study 1 (June-September 2019), ten individuals aged 18 to 35 years with FEP and CUD participated to a focus group and 10 clinicians working in EIS for psychosis in Quebec participated to semi-structured interviews. We used a hybrid deductive-inductive analysis approach and synthesized and interpreted data by comparing the opinions of patients and clinicians. In study 2 (January 2020-July 2022), 104 patients from seven FEP intervention programs in Canada responded to an electronic survey. We used the Best Worst Scaling (BWS) and the item ranking methodologies to design questions. For BWS data we used conditional logistic regression and for ranking data we used Luce regression models to estimate preferences.

Results: In study 1 we provide a framework of factors that are relevant for an app-based psychological intervention for CUD: attitudes and beliefs (e.g., behavioral stage of change), strategies (e.g., motivational interviewing), incentives (e.g., contingency management), general interest (e.g., face-to-face vs. app-based interventions, feedback from clinicians, location for participating), and app tailoring recommendations (e.g., intervention intensity and format, widgets, communication methods). In study 2, BWS analyses showed lower preferences for in person versus technology-based interventions (OR=0.86; CI: 0.75; 0.98), higher preferences for receiving assistance for using the app from the clinician one time per week (vs. every session, OR=1.16; CI: 1.01; 1.33), for receiving feedback related to cannabis consumption from both the app and the clinician (vs. app only, OR=1.74; CI: 1.51; 2.00), and for participating in the intervention outside the clinic (vs. at the clinic, OR=1.24; CI: 1.08; 1.42). Participants favored intervention modules

with a length of fifteen minutes (vs. 5 minutes, OR=1.19; CI:1.03; 1.37), and for completing intervention modules once a week (vs. every day, OR=2.06; CI: 1.79; 2.37). Luce models revealed higher preferences (i.e., item worth, w) for using smartphones (vs. computer, w=1.65, CI: 1.14; 2.38), for communicating with clinicians via chat (vs. text, w=1.47, CI: 1.03; 2.10) and for having access to a reward point table (vs. the possibility to personalize the application, w=1.67; CI: 1.16; 2.40). We found lower preferences for written text (w=0.57; CI: 0.41; 0.81) or audio (w=0.61; CI: 0.43; 0.86) compared to videos with an animated character.
Discussion: Our methodological approach that accounts for patient preferences aligns with recommendations for developing highly acceptable mobile mental health interventions. Our results provide critical information to researchers and clinicians interested in integrating technology with existing face-to-face interventions for CUD in individuals with FEP.

S121. THE KEY COMPONENTS OF A VIRTUAL REALITY BASED COGNITIVE REMEDIATION PROGRAM FOR INDIVIDUALS WITH PSYCHOSIS: RESULTS FROM AN ITERATIVE USER-CENTERED APPROACH TO CO-DESIGN

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Background: Psychotic disorders are often associated with deficits in neurocognition and social cognition, leading to impairments in community functioning. Cognitive remediation (CR) therapy has been shown to be effective at improving outcomes in both of these domains. However, CR has shown limited transfer of learned skills into real-world situations. Virtual reality (VR) may help bridge this gap by delivering CR interventions within more realistic environments, thereby increasing ecological validity. The purpose of the current research is to develop and implement a novel VR-based CR program informed by individuals living with a psychotic disorder and healthcare professionals.
Methods: Twelve working groups will be completed between February 2020 and January 2023; nine groups comprising individuals living with a psychotic disorder ("content experts"; CEs) and three groups comprising psychiatrists, psychologists, and occupational therapists with relevant clinical experience ("healthcare professionals"; HPs). During each working group, participants discuss personal (CEs) and professional (HPs) opinions on the neurocognitive and social-cognitive challenges associated with psychotic disorders. Participants also provide feedback on the development and implementation of the VR-based CR program. Seven CE groups and one HP working group have been included in the preliminary inductive thematic analyses, which has been performed on the transcripts, separately for both groups.
Results: Four themes were identified: targeting cognition and motivation, promoting transfer, experience factors, and barriers and facilitators to implementation. First, both groups described a necessity to target motivation and neurocognition but identified different social cognition domains

(CEs emphasized the need to focus on attribution bias, while HPs generally identified social cognition as a key target). Second, both groups highlighted the importance of designing the training to target meaningful outcomes, including the promotion of transfer to real-world problems. Third, both groups identified the need to promote different design aspects of the program itself. For example, CEs highlighted that the program should have a high level of immersion, while HPs focused on the program providing a personalized approach. Finally, both groups identified several barriers and facilitators to implementation. For instance, HPs identified high attrition rates as a significant barrier. A supportive and integrative medical approach (CEs) and the integration of the program into a clinical setting (HPs) were identified as possible facilitators to implementation.
Discussion: Our preliminary results indicate that CEs and HPs have similar perspectives on the key components of a VR-based CR program. These perspectives have informed the design of a novel VR-based CR program which is currently in the final stages of development. To our knowledge, the present research is one of the first to use an iterative, user-centered approach to co-develop a VR-based CR program for individuals with psychotic disorders. In February 2023, the first clinical trial will start to examine the feasibility and effectiveness of the VR-based CR program.

S122. VISUAL REMEDIATION TARGETING LOW- AND MID-LEVEL PERCEPTUAL ABILITIES MAY IMPROVE CLINICAL AND NEUROPHYSIOLOGICAL FUNCTIONING IN SCHIZOPHRENIA: A PRELIMINARY CLINICAL TRIAL

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Background: Visual impairments in individuals with schizophrenia (SZ) are well documented and are related to deficits in higher-level cognition and functional outcome. The current study investigated a novel visual remediation intervention for SZ targeting low-level and mid-level visual deficits. We hypothesized that visual remediation would result in improvements on psychophysical and electrophysiological measures of visual function and clinical functioning.
Methods: SZ (N = 47) were recruited from the Nathan S. Kline Institute for Psychiatric Research and New York-Presbyterian Westchester Behavioral Health Center. The low-level intervention targeted visual contrast sensitivity (CS). The mid-level intervention targeted contour integration (CI). The control intervention was Happy Neuron (HN), a cognitive remediation training. Each type of remediation alone lasted approximately 30 minutes. Four groups were formed, each receiving a pair of interventions: CS+HN; CI+HN, CS+CI; HN+HN, so that each participant received ~1 hour of training per session. SZ received at least 20 sessions with some completing up to 40 sessions. At baseline (BL) and after every 10 sessions (Time Points 1-4), visual function, including visual evoked potentials (VEPs), were assessed. Symptoms were assessed at BL and after the last intervention session with the Positive and Negative Syndrome Scale (PANSS), which was scored using a five-factor model. VEPs examined early excitatory and inhibitory mechanisms in the visual system using a contrast-reversing 64x64 checkerboard stimulus (85% contrast, 16’

check width). Time-domain (peak-to-trough amplitude, latency) and frequency-domain measures were used to measure electrophysiological change over time. Linear mixed-effects models (LMM) were used to measure group differences in change over time on PANSS and electrophysiological measures, with participant as a random intercept and group and time point as fixed effects.
Results: For the PANSS positive symptom factor, there was a significant two-way interaction of Group x Time Point ($F(3, 30.4) = 3.18$, $p = .037$). Participants in the combined experimental group (CS+CI) demonstrated a significantly larger decrease in positive symptom severity from BL to post-intervention (last time point assessed) compared to the control (HN+HN) group ($B = -5.22$, 95% CI [-8.61, -1.77]). There were no other significant group differences from BL to post-intervention for the remaining PANSS factors. No significant differences were found among groups for signal power (frequency band 14-28 hz; $F(3,40) = 0.855$, $p = .472$) or N75-P100 amplitude ($F(3, 41) = 1.33$, $p = .277$) at BL. Main effect of group and Group x Time Point interaction did not reach significance. However, post hoc pairwise comparisons demonstrated greater signal power for the CS+CI group compared to the HN+HN group ($B = .366$, 95% CI [.001-.732]) across time points. Similar LMM models for VEP latency measures yielded no significant differences.
Discussion: A significantly greater decrease in positive symptom severity and greater VEP signal power were found in participants assigned to the combined CS+CI intervention relative to the control intervention. The change in signal power in the CS+CI group warrants further study with a larger sample to determine if visual remediation can improve neurophysiological function as assessed by VEPs. Finally, it is noteworthy to point out that of the three active remediation groups, the group receiving combined CS and CI training experienced the greatest positive symptom and electrophysiological changes. These findings support further study of the potential for computerized training targeting low- and mid-level visual processes to improve clinical and perceptual functioning in SZ.

S123. SAT-MC: EVALUATION OF AN ALTERNATIVE SCORING APPROACH IN A CLINICAL HIGH RISK SAMPLE

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Background: Social cognition is impaired in individuals with schizophrenia and accumulating evidence suggests that deficits are present in youth at clinical high risk for psychosis (CHR). One aspect of social cognition is the ability to identify social intention. However, ability to detect movement as animate and ability to attribute social intent to that movement can be difficult to separate. The Social Attribution Task-Multiple Choice (SAT-MC) was developed to assess ability to detect social interactions from animate motion portrayed by geometric shapes in a silent video created by Heider and Simmel (1944). Previous studies in schizophrenia patients (Bell et al., 2010) and children with autism (Burger-Caplan, et al., 2016) have consistently found impaired ability to correctly infer social meaning in these stimuli, which correlated with external measures of social cognition and social adaptive function, respectively. The SAT-MC includes 19 questions, each with four possible responses: one describes action with correct social intent, two describe action with incorrect social intent, and one describes object motion without intent. A single score is

computed based on the number of responses identifying the correct social intent; however, examination of incorrect responses could provide more nuanced information about the extent to which motion is perceived as animate and whether animate movement is attributed to social intent. Aim: The primary aim of this study was to evaluate an alternative scoring system to separate animacy perception from social attribution in a sample of CHR youth and their non-CHR biological siblings.
Methods: This study was completed at the PRIME prodromal clinic at Yale School of Medicine. All subjects were age 12 to 30 with no history of psychosis. All CHR probands met criteria for attenuated psychosis syndrome (APS) (SIPS/SOPS). Siblings did not meet psychosis-risk syndrome criteria, but psychosis-risk symptoms could be present. An alternate form of the SAT-MC (SAT-MC-II, Johannesen et al., 2013) was administered by computer in standard format. Under the revised scoring approach, the four possible answer choices were coded into the following categories: 1) correct social intention "Correct Social", 2) motion attributed to social intention, but incorrect interpretation "Other Social", 3) motion seen as animate, but not attributed to social intention "Action", and 4) no animacy identified (shapes perceived only as moving objects) "Object". Mean scores for each answer category were calculated, including the standard total correct score. Proband and sibling groups were compared using t-test.
Results: 17 APS probands and 26 APS-discordant siblings completed the SAT-MC-II. Age, sex, education, and ancestry did not differ between groups and were not associated with SAT-MC-II responses. Probands and siblings did not differ significantly when compared on total number of correct items [Correct Social mean score (sd): probands = 14.7 (2.7), siblings = 15.5 (2.7)]. However, using the proposed alternate scoring approach, probands were found to endorse significantly more responses identifying object movement without animate intent [Object mean score (sd): probands = 1.65 (1.6), siblings = 0.69 (1.2); p = .036].
Discussion: These results support utility of an alternate scoring approach on the SAT-MC to better separate perception of animacy from ability to identify social intention. Next steps include examining the association between SAT-MC response patterns and measures of social functioning in this sample.

S124. TRYPTOPHAN CHALLENGE IN INDIVIDUALS WITH SCHIZOPHRENIA AND HEALTHY CONTROLS: ACUTE EFFECTS ON CIRCULATING KYNURENINE AND KYNURENIC ACID, COGNITION AND CEREBRAL BLOOD FLOW

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Background: Cognitive impairments predict poor functional outcomes in people with schizophrenia. These impairments may be causally related to increased levels of kynurenic acid (KYNA), a major metabolic product of tryptophan (TRYP). KYNA acts as an antagonist of the of α7-nicotinic acetylcholine and glutamatergic NMDA receptors, both of which are critically involved in cognitive processes. To examine whether KYNA plays a role in the pathophysiology of schizophrenia, we compared the acute effects of a single oral dose of TRYP (6 g) in 32 healthy

controls (HC) and 37 people with either schizophrenia, schizoaffective or schizophreniform disorder (PSz).
Methods: Our design was a placebo-controlled, randomized crossover study. We examined plasma levels of KYNA and its precursor kynurenine; selected cognitive measures from the MATRICS Consensus Cognitive Battery; and the average resting cerebral blood flow (CBF) across whole brain gray matter using arterial spin labeling imaging. Linear mixed effect models were performed using R software to examine main effects of both TRYP (vs. placebo) and diagnosis (PSz vs. HC) on each of these outcome measures, as well as potential TRYP*diagnosis interaction effects.
Results: In both cohorts, the TRYP challenge produced significant, time-dependent elevations in plasma kynurenine and KYNA. Resting CBF was affected differentially in groups by TRYP, such that TRYP was associated with higher CBF in HC, but not in PSz. While TRYP did not significantly impair cognitive test performance, there was a trend for TRYP to worsen visuospatial memory task performance in HC.
Discussion: Our results demonstrate that oral TRYP challenge substantially increases plasma levels of kynurenine and KYNA in both groups, but exerts differential group effects on CBF. Future studies are required to investigate the mechanisms underlying these CBF findings, and to further evaluate the impact of KYNA fluctuations on brain function and behavior. (Clinicaltrials.gov: NCT02067975)

S125. THE GUT MICROBIOME IN SCHIZOPHRENIA AND CLOZAPINE TREATMENT: A PILOT STUDY

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Background: Through evolution, the human organism has maintained a symbiotic relationship with the gut microbiome. There is increasing evidence linking a 'dysfunctional' gut microbiome to onset of psychiatric conditions, including schizophrenia. Current evidence shows that chronically treated patients with schizophrenia have a less diverse gut microbiome composition than that of antipsychotic-naïve patients with first-episode schizophrenia, suggesting that antipsychotic medication may have some effect of the gut microbiome which might also be associated with antipsychotic-induced weight gain (AIWG). We are conducting a pilot study examining patients with schizophrenia (compared to healthy controls) and patients starting clozapine, prescribed exclusively to patients with more severe forms of schizophrenia and is frequently associated with AIWG. We aim to characterize the impact that clozapine has on the gut microbiome and to identify target organisms/pathways associated with positive and negative treatment outcomes.
Methods: We employed two different cohorts of patients. The first cohort is a cross-sectional study that includes 25 patients with schizophrenia who have been treated with clozapine for a minimum of 6 months and 25 healthy controls matched based on age, sex, BMI and smoking status. Participants were assessed on one visit, where they provided biosamples (blood, stool, saliva), anthropometric measures, and underwent various clinical assessments that capture symptom changes, comorbidities, eating habits, exercise, gastrointestinal symptoms, and smoking habits. A second (ongoing) cohort is a 6-week, single arm, open-label study of 40 treatment-resistant patients

with schizophrenia who are switching/starting to clozapine therapy. Participants in this cohort are coming in for 3 visits: before starting clozapine, 3 weeks after starting clozapine, and 6 weeks after starting clozapine. Similar to the first cohort, participants will provide biosamples and undergo clinical assessments at each visit. The gut microbiome composition was determined using 16S rRNA gene amplification of stool samples collected via the OMNIgene GUT collection kits.
Results: To date, 25 chronic clozapine patients, 25 controls, and 11 clozapine new starters have completed the study. Chronic clozapine patients present with a microbiome that is different from that of controls. The alpha diversity of chronic clozapine patients is lower than controls through the Shannon diversity index (P=0.013). Using the Bray Curtis dissimilarity matrix, the microbiome of chronic clozapine patients is more variable than controls. When we compared relative abundances of taxonomic compositions at various taxa, we found an increase of Eggerthella and a decrease of Pseudobutyrivibrio in patients with schizophrenia. However, the differences did not survive multiple comparisons.
Discussion: We have shown, employing two different cohorts of patients, that clozapine treatment likely impacts fecal microbiome composition significantly. Majority of studies on the gut microbiome did not take into consideration the type of antipsychotic medication and were conducted cross-sectionally. Clozapine treatment appeared to affect the diversity of the gut microbiome composition. Changes in various genus was also observed with the use of clozapine. However, these results did not survive multiple comparisons and should be confirmed with additional patients that are followed longitudinally. Once completed, our longitudinal study will enable us to closely monitor the effect of clozapine treatment on the gut microbiome and how the microbiome might affect AIWG.

S126. AN ALGORITHMIC PHARMACOLOGICAL APPROACH TO PREVENTION AND TREATMENT OF ANTIPSYCHOTIC-INDUCED WEIGHT GAIN

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Background: Patients with schizophrenia (SCZ) have a 15–20-year shorter life expectancy than the average population, a finding directly attributable to their increased rates of obesity, cardiovascular disease, and type 2 diabetes. Antipsychotics remain the cornerstone of treatment in schizophrenia but are associated with serious metabolic adverse effects that are often most pronounced in the first few months after their initiation. As such, there is an urgent need for safe and effective adjunctive pharmacological approaches such as metformin to be implemented at the earliest stages of illness to ameliorate antipsychotic-induced weight gain (AIWG). Simultaneously, it is important to remember that not all patients benefit from metformin, necessitating search for other efficacious agents. Semaglutide is a weekly injectable Glucagon-Like Peptide 1-Receptor Agonists (GLP1-RA) that has recently been approved for obesity management but the efficacy and tolerability of semaglutide in AIWG has not been explored to date. This talk will review the efficacy of an algorithmic pharmacological approach involving metformin and semaglutide for prevention and treatment of antipsychotic-induced weight gain, respectively, in two independent real-world clinical datasets.

Methods: We conducted a retrospective chart review of patients newly initiated on clozapine at Centre for Addiction and Mental Health (CAMH) in Toronto, Canada, from January 2014 to March 2021. We also conducted a separate chart review of all the patients enrolled in the Metabolic Clinic between 2019-2021 at CAMH, who were diagnosed with schizophrenia spectrum disorders, did not respond to metformin, and were started on semaglutide. A mixed model analysis with subjects as random effects, controlling for age, sex, T2D status, and smoking status, was used for our primary outcome measures of body weight and body mass index (BMI) at 6 and 12 months after initiation of intervention.

Results: In the first dataset, among 396 patients (males: 71.5%, mean age: 42.8 years) initiated on clozapine, 69 were on metformin or prescribed it ≤3 months after clozapine initiation. The clozapine+metformin group demonstrated significantly less weight gain compared with the clozapine-only group at 6 months (clozapine+metformin: 0.15 kg [SE = 1.08] vs. clozapine-only: 2.99 kg, SE = 0.54) and 12 months after clozapine initiation (clozapine+metformin: 0.67 kg, SE = 1.22 vs. clozapine-only: 4.72 kg, SE = 0.67). Adaptive changes were also observed for fasting glucose ($F = 3.10$, $p = 0.046$) and triglycerides ($F = 8.56$, $p < 0.001$) in the clozapine+metformin group compared with clozapine only. Patients in the clozapine+metformin group were also significantly more likely to continue taking clozapine at 12 months (clozapine+metformin: 65.2%; clozapine only: 51.1%; $p = 0.03$).

In the second dataset from the Metabolic Clinic, twelve patients who did not respond to metformin and were subsequently started on semaglutide weekly injections (mean dose: 0.71 ± 0.47 mg/week) were included in the analysis. A weight loss of 5.16 ± 6.27 kg (p=0.04) and 8.67 ± 9 kg (p=0.04) was seen at 6 and 12 months respectively after initiation of semaglutide with relatively well-tolerated side effects.

Discussion: Co-initiation of clozapine and metformin was associated with lesser weight gain at 6 and 12 months after initiation than being on clozapine alone, providing evidence for the effectiveness of metformin in preventing AIWG. Evidence from the Metabolic Clinic cohort suggests that semaglutide may be effective in reducing AIWG in patients not responding to metformin. Randomized control trials are needed to corroborate these findings.

S127. METABOLOMIC SIGNATURES ASSOCIATED WITH WEIGHT GAIN AND PSYCHOSIS SPECTRUM DIAGNOSES

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Background: Psychosis spectrum disorders (PSDs) are characterized by intrinsic metabolic dysfunction. Beyond the intrinsic metabolic risk, antipsychotics (APs), the cornerstone of treatment for PSDs, confer additional metabolic adversities including weight gain. Currently, major gaps exist in identifying psychosis illness biomarkers, as well as risk factors and mechanisms for AP-induced weight gain. Metabolomic profiles may help identify candidate biomarkers of PSDs and AP-induced weight gain.

Methods: In this 12-week prospective naturalistic study, we compared serum metabolomic profiles of AP-naïve cases to healthy controls at baseline to examine biomarkers of intrinsic metabolic dysfunction in PSDs. We then examined changes in serum metabolomic profiles over 12 weeks of AP treatment in AP-naïve cases to identify metabolites that may predict or associate with AP-induced weight gain. Statistical analyses of metabolomic data were conducted using Metaboanalyst 5.0. T-tests were used to compare mean metabolite concentrations at baseline between: 1) AP-naïve cases and controls, and 2) AP-naïve cases who do and do not experience clinically significant increases (≥5%) in body weight. Two-way repeated measures ANOVA was used to test changes from baseline to week 12 between AP-naïve cases who do and do not experience ≥5% body weight gain. Pearson correlations were calculated between change in weight gain and change in metabolite concentrations from baseline to week 12 for cases. To control for multiple comparisons, a false discovery rate (FDR) of the resulting post hoc P values was calculated.
Results: Twenty-five AP-naïve cases and six healthy controls were enrolled and completed baseline visits. Seventeen cases additionally completed 12-week follow up visits. Following 12 weeks of AP exposure, cases experienced increases in body weight ($p<0.001$), body mass index ($p<0.001$), waist circumference ($p=0.015$), LDL cholesterol ($p=0.009$), and total cholesterol ($p=0.027$). Additionally, a subgroup of cases (N=9) experienced clinically significant increases (≥5%) in body weight. Overall, 20 amino acids, 20 bile acids, 30 fatty acids, and 29 acylcarnitines were identified and quantified. At baseline, AP-naïve cases were distinguished from controls by six fatty acids (FDR<0.05), specifically reduced levels of palmitoleic acid, lauric acid, and heneicosylic acid, and elevated levels of behenic acid, arachidonic acid, and myristoleic acid. Baseline levels of the fatty acid adrenic acid was increased in individuals who gained ≥5% body weight following 12 weeks of AP exposure as compared to those who gained <5% body weight (FDR=0.0408). None of the quantified metabolites met threshold for significance when examining associations between changes in metabolite concentrations and body weight over 12 weeks of AP exposure.
Discussion: Certain fatty acids may represent psychosis illness biomarkers and early predictors of AP-induced weight gain. The findings hold important clinical implications for early identification of individuals who could benefit from prevention strategies to reduce future cardiometabolic risk. It may further lead to novel, targeted treatments for mitigating metabolic dysfunction in PSDs.

S128. EFFECT OF STAGE AT DIAGNOSIS AND TREATMENT OF CANCER ON MORTALITY AMONG PEOPLE WITH PSYCHOTIC DISORDERS: A CAUSAL MEDIATION ANALYSIS

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Background: People with psychotic disorders suffer from significantly higher mortality rates following cancer diagnoses compared to people without psychotic disorders (Kisely et al., 2008, 2013; Lawrence et al., 2000; Toender et al., 2018). Previous examinations of how stage at diagnosis and differences in treatment affect survival following cancer diagnosis among people with psychotic disorders have relied on traditional regression approaches (Cunningham et al., 2015; Ishikawa et al., 2016; Mahar et al., 2020; Manderbacka et al., 2017). Regression-based approaches to mediation analysis are prone to assumption violations resulting in biased estimates

of indirect and direct effects, particularly when there is a post-exposure confounding of the relationship between the mediator and outcome that is influenced by the exposure (Vanderweele et al., 2014).
As depicted in the directed acyclic graph (DAG) in figure 1, stage at diagnosis is affected by diagnosis with NAPD, which influences cancer treatment, and influences time to death following cancer diagnosis. Therefore, both mediators, stage at diagnosis and treatment, act as post-exposure confounders. Both failure to adjust for this confounding and adjustment with traditional regression analyses will produce biased effect estimates. We will use marginal structural modelling in a mediation analysis to examine the decomposition of effects of stage at diagnosis and cancer treatment in the relationship between diagnosis with NAPD and time to death following cancer diagnosis.

Methods: This study will use population-based health administrative data from Ontario, held by ICES. The creation of the cohort of people with non-affective psychotic disorders (NAPD) and a 4:1 matched comparison group from the general population has been described previously. Briefly, those who developed cancer over the course of the follow-up will be included in the analysis.
We aim to estimate the proportion of the effect of having NAPD on time to death from cancer diagnosis which is mediated through stage at diagnosis, time to treatment, and type of treatment received. We will use Cox proportional hazards models with inverse-probability weighting (IPW) to adjust for confounding estimate marginal effects.

IPWs are created by modelling the propensity of each person having different values of the exposure and mediating variables using baseline covariates, as well as post-exposure confounders. The inverse of these scores is then used to create weightings for each observation. The inclusion of these weights in a regression model creates a pseudo-population with those covariates balanced across each level of exposure and mediator; thereby, estimating the marginal effects of the exposure or mediator, rather than the conditional effects in traditional regression analyses. The estimation of marginal effects allows for the adjustment of confounders which are affected by the exposure without blocking the effect of the exposure through that confounder. We will create a series of IPWs to adjust for confounding of each relationship and include them in a proportional hazards regression model to estimate decomposition of effects of diagnosis with NAPD on time to death following cancer diagnosis through stage at diagnosis and treatment. Comorbidities will be adjusted for via inclusion of the John Hopkins aggregated diagnostic group (ADG) in the calculation of IPWs (Johns Hopkins ACG System | Population Health Analysis Tool, 2019).

The data used for the present analysis are expected to have a certain degree of missing data. The missing data mechanism will be explored using logistic regression models of missingness, dependent on all other variables included in the dataset. MICE will be used to impute missing values in the dataset.

Results: We anticipate that people with psychotic disorder will have higher cancer mortality rates and be less likely to receive adequate treatment. Furthermore, we hypothesize that both advanced stage at diagnosis and inadequate treatment will contribute to a substantial portion of the cancer mortality gap.
Discussion: This study will be the first to examine the indirect effects of having a non-affective psychotic disorders through stage at diagnosis and treatment using marginal structural models, which are equipped to manage post-exposure confounding, unlike traditional regression mediation

analyses. Providing an estimate of the indirect effects through stage at diagnosis and treatment will determine how much of the mortality gap among people with non-affective psychotic disorders can be accounted for by delays in diagnosis and treatment disparities. By identifying how these variables account for mortality, we can work to develop effective programs to target these disparities, in turn reducing the mortality gap.

S129. ACTIVATION OF NON-CLASSICAL M1 MONOCYTE SUBSET ASSOCIATED WITH ACCELERATION OF ATHEROSCLEROSIS IN SCHIZOPHRENIA: CAROTID ULTRASONOGRAPHY STUDY

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Background: Arterial atherosclerosis is the most common underlying pathology of cardiovascular diseases (CVDs), which are the main causes of premature mortality in patients with schizophrenic disorder (SCZ). SCZ and arterial atherosclerosis share the same pathogenesis- inflammatory activation. Higher carotid intima media thickness (CIMT) measured by carotid ultrasonography is sensitive for detecting early atherosclerosis, but CIMT study for SCZ remains limited. Monocytes and monocyte-derived macrophages are of paramount importance in atherosclerosis. We attempted to find out the association between atherosclerosis and monocyte/macrophage in SCZ.
Methods: The physically healthy participants aged 20-55, including clinically stable out-patients with SCZ (DSM-5) and healthy control volunteers, were recruited to measure the bilateral CIMT. Peripheral blood mononuclear cells were stained with conjugated monoclonal antibodies to define monocyte and macrophage subpopulations. Monocyte and macrophage phenotypes were assessed by flow cytometry. All clinical information and medication status were obtained by directly interviewing patients themselves and reviewing all medical records.
Results: Forty five SCZ patients (43.6 ± 11.9 years old) and 55 normal controls (42.1 ±12.0 years old) were recruited. SCZ group had significantly higher mean values of CIMT and proportions of CD16-positive monocyte subsets, including M1 and M2 ones, than those of control group. No medication variable was correlated to any proportion of monocyte/macrophage subset in SCZ group. After phenotyping monocyte subsets and adjustment for the effects of BMI and age, multiple regression analyses showed that only higher proportion of non-classical M1 monocyte CD14+CD16+CD86+ subset was significantly associated with higher CIMT, accounting for 14.5% of variance.
Discussion: To the best of our knowledge, this is the first report that activation of subset-specific monocyte may be associated with acceleration of arterial atherosclerosis in SCZ. The strengths of this study are directly identifying the subset-specific monocye/macrophage frequencies and CIMT measurement allowing the direct quantification of subclinical atherosclerosis. M1 is a pro-inflammatory subtype of monocyte. Immunomodulation of non-classical M1 monocytes, particularly CD14+CD16+CD86+ subset, could be a future therapeutic and research target for preventing premature CVDs in SCZ.

S130. ECHOCARDIOGRAPHIC STUDY OF CARDIAC HEALTH IN OLDER ADULTS DIAGNOSED WITH SCHIZOPHRENIA

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Background: Patients with schizophrenia are at an increased risk of cardiovascular disease during the aging process. Transthoracic echocardiography is a non-invasive and reliable tool to detect abnormalities of cardiac structure and function. However, few studies have evaluated cardiac health in aging patients with schizophrenia using the transthoracic echocardiography.

Methods: This study recruited older adults (age≧45 years) with schizophrenia (DSM-5) and mentally healthy controls to undergo M-mode and pulse wave Doppler echocardiography performed by a board-certified cardiologist blinded to the clinic information. The echocardiographic measurements of cardiac chamber dimension included interventricular septal thickness at end-diastole, left ventricular posterior wall thickness at end-diastole, left ventricular internal diameter at end-diastole, and left ventricular internal diameter at end-systole. The indices of cardiac systolic and diastolic function were left ventricular ejection fraction and mitral valve E/A ratio, respectively. Clinical data were obtained through interview and chart review.

Results: A total of 35 older adults diagnosed with schizophrenia (male: n = 12) and 31 mentally healthy controls (male: n = 10) were enrolled in this study. The mean ages were comparable between the two groups (schizophrenia: 55.6 ± 6.2 years old vs. healthy controls: 57.3 ± 6.4 years old, p = 0.251). With respect to the cardiac chamber dimension, patients with schizophrenia had significantly higher mean values of interventricular septal thickness at end-diastole than did the healthy controls (schizophrenia: 11.53 ± 3.09 mm vs. healthy controls: 9.60 ± 1.62 mm, p = 0.001). Regarding the cardiac function, patients with schizophrenia had significantly lower mean values of mitral valve E/A ratio as compared to the controls (schizophrenia: 0.88 ± 0.30, healthy controls: 1.08 ± 0.26, p = 0.012). The mean CPZ equivalent dose of antipsychotics was not significantly correlated with the interventricular septal thickness at end-diastole (r = 0.036, p = 0.863) and mitral valve E/A ratio (r = 0.133, p = 0.527).

Discussion: Aging patients with schizophrenia exhibited greater cardiac diastolic dysfunction and interventricular septal thickness than did the mentally healthy controls. Exposure to the antipsychotics was not correlated to unfavorable cardiac health in the present study sample. Future research is warranted to examine other mediators of the observed associations, including the lifestyle, cognitive function, and symptom severity of schizophrenia.

S131. LONG-TERM TREATMENT WITH TV-46000, A LONG-ACTING SUBCUTANEOUS ANTIPSYCHOTIC (LASCA) FORMULATION OF RISPERIDONE, DEMONSTRATED IMPROVED PATIENT-REPORTED OUTCOMES IN ADULT PATIENTS WITH SCHIZOPHRENIA (SHINE)

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Background: The Safety in Humans of TV-46000 subcutaneous INjection Evaluation (SHINE) study (NCT03893825) was a multicenter, double-blind, parallel-group study that evaluated the long-term safety, tolerability, and effectiveness of TV-46000 in adult and adolescent patients with schizophrenia. TV-46000 is a long-acting subcutaneous antipsychotic (LASCA) that combines risperidone and an innovative copolymer-based drug delivery technology.
Methods: Adults and adolescents with schizophrenia, including patients from the TV-46000 and placebo groups who completed the RIsperidone Subcutaneous Extended-release (RISE) study (NCT03503318) without relapse, were eligible to participate in the SHINE study. After stabilization on oral risperidone for 12 weeks (completed in RISE for patients who rolled over, or in SHINE for those newly enrolled), patients were randomized to TV-46000 once monthly (q1m) or once every 2 months (q2m) for up to 56 weeks. Patient-reported outcomes, assessed in adults only (reflecting the age ranges for which the measures have been validated), included the Schizophrenia Quality of Life Scale (SQLS), the 5-Level EuroQoL 5-Dimensions Questionnaire (EQ-5D-5L), the Personal and Social Performance Scale (PSP), and the Drug Attitudes Inventory 10-item version (DAI-10).
Results: 333 adult patients (106 new and 227 rolled over from RISE [172 from TV-46000, 55 from placebo]) were randomized to TV-46000 q1m (n=173) or q2m (n=160). Reductions in SQLS (indicating improvement) were observed for both treatment groups at the last assessment compared with baseline, with a numerically larger reduction for TV-46000 q2m (least-square [LS] mean change from baseline [SE], −0.43 [0.98]) than for q1m (−2.16 [0.98]). Reductions were also observed for patients in the de novo group (mean change from baseline [SE], −2.7 [1.45]) and placebo rollover (−5.6 [1.61]) group, but not for the TV-46000 rollover group (0.0 [0.81]); within these patient-source groups, no consistent trend was observed across dosing regimens. Changes in EQ-5D-5L descriptive items from baseline to last assessment were minimal (<1.5) for all dimensions in both treatment groups. PSP total scores showed minimal changes over time in the study, with no meaningful differences between treatment groups. At the last assessment, a numeric improvement from baseline was observed for both the TV-46000 q1m (LS mean [SE] change from baseline, 0.40 [0.78]) and q2m (0.69 [0.79]) treatment groups. The largest improvements in PSP total score were seen in patients in the placebo rollover group (mean change from baseline [SE], 2.0 [0.73]) compared with the TV-46000 rollover group (0.6 [0.43]) and the de novo group (0.2 [1.36]). Baseline mean (SE) DAI-10 total scores were positive (indicating a favorable view of treatment)—6.6 (0.24) in the TV-46000 q1m group and 6.6 [0.26] in the q2m group—and were minimally changed at the last assessment (6.2 [0.30] and 6.5 [0.23], respectively) and similar across patient sources (TV-46000 rollover, 6.3 [0.26]; placebo rollover, 6.3 [0.45]; de novo, 6.5 [0.35]). These results were consistent with patient-reported outcomes reported in the RISE study.
Discussion: The long-term quality of life and attitudes towards treatment in adult patients with schizophrenia either remained stable or improved with TV-46000. Improvements were observed across patient-source groups, with the largest improvements observed for patients who began TV-46000 during SHINE (ie, patients who were newly enrolled, or who received placebo in RISE), while gains made during RISE were minimally improved or maintained in patients in the TV-46000 rollover group.

S132. INTRODUCING S.C.O.P.E.™: SCHIZOPHRENIA CLINICAL OUTCOME SCENARIOS AND PATIENT-PROVIDER ENGAGEMENT—AN INTERACTIVE DIGITAL PLATFORM TO EDUCATE ON SCHIZOPHRENIA CARE

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Background: Healthcare professionals (HCPs) face unique challenges when managing patients with schizophrenia. Educational initiatives targeting the most common dilemmas encountered by clinicians, including the frequent problem of partial or nonadherence, may alleviate knowledge gaps and help clarify the role of long-acting injectable antipsychotic agents (LAIs) in treating this population.

Methods: A panel of 4 experts in schizophrenia management used empirical evidence to identify 11 key clinical dilemmas where LAIs may be useful. The panel then developed a heuristic, educational tool (S.C.O.P.E.™: Schizophrenia Clinical Outcome Scenarios and Patient-Provider Engagement) based on empirical evidence and expert opinion for clinicians to use when encountering similar scenarios, to help optimize schizophrenia care by prompting consideration of various factors. The scenarios or key clinical dilemmas were categorized according to clinical setting (emergency department, inpatient, or outpatient), current treatment (oral or LAI), patient status (stable, residual symptoms, first episode, and relapse), and clinical concerns (nonadherence and/or history of substance use, or substance use disorder).

Results: S.C.O.P.E.™ is a freely-available resource comprising an interactive digital platform providing educational materials for HCPs involved in the continuum of care for patients with schizophrenia. S.C.O.P.E.™ provides a framework to inform considerations in common clinical scenarios met in inpatient and outpatient settings, as well as questions to consider when patients present to the emergency department. In addition, methods to determine nonadherence and the potential usefulness of LAIs is explored in each scenario. S.C.O.P.E.™ does not replace clinical judgment, guidelines, or continuing medical education, and is not a platform for recording patient-level data, nor intended for payer negotiations or access-related questions by HCPs. Among the clinical dilemmas addressed is a patient experiencing relapse while taking an oral antipsychotic agent (OA) in the context of a variety of factors that can exacerbate symptoms of schizophrenia (such as drug-drug interactions, suboptimal dosing, and nonadherence). For this scenario, the S.C.O.P.E.™ framework provides the following items to consider based on published empirical evidence: evaluate antipsychotic plasma concentrations in addition to standard toxicology, rule out other possible causes of the exacerbation of psychotic symptoms, investigate the possibility of nonadherence, and identify additional sources of collateral information (ie, caregivers, family members).

Discussion: Despite data supporting the efficacy of LAIs in improving adherence and preventing relapse, myths, attitudes, and preconceived perceptions have limited their adoption in real-world clinical practice. S.C.O.P.E.™ is an educational tool for HCPs to use alongside standard psychiatric evaluations to improve understanding of how to manage common clinical dilemmas when treating patients with schizophrenia and the role of LAIs in schizophrenia management.

S133. DIFFERENCES BETWEEN ARCHETYPES OF HEALTHCARE PROFESSIONALS WHO USE LONG-ACTING INJECTABLE ANTIPSYCHOTIC AGENTS TO TREAT PATIENTS WITH SCHIZOPHRENIA: A SURVEY OF US-PRACTICING PSYCHIATRIC CLINICIANS

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Background: Understanding varying attitudes and perceptions of healthcare professionals (HCPs) toward the use of long-acting injectable antipsychotic agents (LAIs) for the treatment of patients with schizophrenia is important for overcoming barriers to LAI use.

Methods: An invitation to participate in an online survey was emailed to psychiatrists, psychiatric nurse practitioners, and psychiatric physician associates practicing in the United States. HCPs were placed into archetype groups (early-prescriber, severity-reserved, adherence-reserved, and LAI-hesitant) based on their response to "Which of the following best fits the current way you view your use of LAIs for your patients with schizophrenia?" Available responses included: "I actively use LAIs as early as possible," "LAIs are reserved for patients with more severe symptoms, or… when other treatments have failed," "LAIs are reserved for patients with identified adherence issues," "I'm hesitant to recommend LAIs… but would consider using them more," and "LAIs do not offer a significant advantage versus oral medication." Archetype groups were compared using analyses of variance and chi-squared tests.

Results: Of 380 total responders, 123 (32%) were in the early-prescriber archetype group, 88 (23%) in the severity-reserved group, 113 (30%) in the adherence-reserved group, and 56 (15%) in the LAI hesitant group. The estimated proportion of patients with schizophrenia receiving LAIs was greater in the early-prescriber archetype group (42%) than in the severity-reserved (22%, P<.01), adherence-reserved (19%, P<.01), and LAI-hesitant (8%, P<.01) groups. When asked about their LAI to oral antipsychotic agent (OA) usage ratio, a higher proportion (46%) of HCPs in the LAI-hesitant group responded, "I am dissatisfied with the ratio–my use of OAs is too high," than those in the early-prescriber (28%, P<.05), severity-reserved (27%, P<.05), and adherence-reserved (16%, P<.01) groups. HCP estimates of nonadherence to OAs nationwide were similar between archetypes (50%–56%) and higher than their estimates for patients in their own practices. In this regard, HCPs estimated greater mean proportions of their patients were nonadherent on OAs in the early-prescriber (32%) group compared with the adherence reserved (22%, P<.01) and LAI-hesitant (21%, P<.01) groups, whereas the severity reserved (26%) group was in the middle. Archetypes displayed characteristics congruent with the defining question; ie, on average, HCPs in the early prescriber group more strongly disagreed on a 5 point scale, from −2 (strongly disagree) to 2 (strongly agree), that "LAIs are reserved for patients with more severe symptoms" (−1.05), compared with severity-reserved (0.34, P<.01), adherence-reserved (−0.09, P<.01), and LAI-hesitant (0.05, P<.01) groups. The proportions of HCPs who responded that managing patients with schizophrenia "increases my level of stress" and makes me "feel burned out" were higher for HCPs in the LAI-hesitant archetype group (54% and 30%, respectively) compared with the early-prescriber (15% and 10%, both P<.01), severity-reserved (33% and 14%, both P<.05), and adherence-reserved (31% and 11%, both P<.01) groups.

Discussion: Overall, these key differences between HCPs with varying perspectives on LAI use should be considered when developing targeted educational materials that are focused on increasing HCP familiarity and comfort with prescribing LAIs and overcoming barriers to LAI use for patients with schizophrenia.

S134. AN AUTOMATED LINGUISTIC ANALYSIS OF FIRST-PERSON ACCOUNTS OF PSYCHOSIS

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Background: Language and thought disorder are defining features of schizophrenia but self-initiated personal narratives are rarely analyzed to extract clinically meaningful variables. Moreover, past studies of first-person accounts (FPAs) did not tend to compare the results from individuals with schizophrenia (SZ) with narratives from community controls (CO). We aimed to compare FPAs of SZ published in an academic journal with narratives by CO, using an automated linguistic analysis tool.

Methods: Two groups of independent raters evaluated and conducted a qualitative review of 269 narratives from Schizophrenia Bulletin, published between 1979 and 2022. They screened non-psychosis related narratives, categorized, and counted self-reported symptoms (e.g., disorganized thought) and behaviors (e.g., loneliness). There were 187 FPAs of SZ that met the inclusion criteria. The Open American National Corpus (OANC, https://anc.org) was used to obtain data from CO: 187 out of 5979 narratives were randomly selected with a bootstrapping approach. The Linguistic Inquiry and Word Count program (LIWC; Pennebaker et al, 2015) was used to quantify the narratives. We focused on the frequency of pronoun use and clinically relevant variables: formal and logical thinking patterns (Analytic); social confidence or leadership (Clout); degree of self-monitoring (Authenticity); and positive affect (Emotional Tone).

Results: First, we examined patterns of pronoun use. CO used fewer total ($p < .001$) and personal ($p < .001$) pronouns than SZ. SZ used "I" more often than CO ($p < .001$). Impersonal pronoun ('it') use was also increased in SZ compared with CO ($p < .001$). Then, we examined clinically relevant variables. SZ were more 'authentic' than CO ($p < .001$). CO scored higher than SZ on Clout ($p < .001$) and Analytic ($p < 0.001$) but there were no other group differences. Lastly, we examined the role of self-reported loneliness and disorganized symptoms on the language output. SZ reporting loneliness ($n = 52$) showed lower analytical ($p = .009$) and clout ($p = .011$) scores and greater authenticity ($p = .019$) than SZ without loneliness ($n = 135$). SZ reporting loneliness used personal pronouns more often ($p = .033$), especially "I" ($p = .005$) than SZ without loneliness. SZ with disorganized symptoms ($n = 59$) showed significantly less clout ($p < .001$) and greater authenticity ($p < .001$) than SZ without these symptoms ($n = 128$). SZ with disorganized symptoms produced personal pronouns more often than those without symptoms. ($p < .013$)

Discussion: Using an automated linguistic tool, we extracted clinically meaningful variables from published narratives. It is difficult to interpret the differences in pronoun use between SZ and CO due to the varied nature of these narratives, but within SZ group, loneliness and disorganized symptoms impacted pronoun use. Loneliness seemed to highlight "I" in SZ. Similarly, disorganized symptoms were associated with increased personal pronoun use. Lower 'clout' in SZ

reflects diminished social status and confidence, suggestive of social defeat; many FPAs describe ongoing social challenges. 'Authenticity' was increased in SZ, reflecting weakened self-censorship and filtering. Lower 'analytic' score in SZ may indicate cognitive deficits that impact formal or logical thinking abilities.
Importantly, loneliness and disorganized symptoms were associated with reduced 'clout' and greater 'authenticity', highlighting the tenuous social status of the lonelier and more symptomatic SZ who reveal their inner experiences without filters, but the direction of effect is unknown.

To summarize, this study showed the utility and feasibility of applying automated linguistic tools to extract clinically relevant information from a large corpus of written narratives. However, further research is needed to validate this approach with established assessments of language and thought disorder in schizophrenia spectrum conditions.

S135. 20 YEAR FOLLOW-UP OF THE TIPS (EARLY INTERVENTION IN PSYCHOSIS STUDY) - SYMPTOMS, FUNCTION AND RECOVERY

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Background: Severe psychotic disorders are associated with substantially increased risk of poor symptom, functional and somatic outcomes. Early detection and intervention can improve chances of better outcomes. TIPS (The early Detection and Intervention in Psychosis) have collected data on an epidemiological catchment area based sample of individuals with first episode psychosis at 1, 2, 5,10 and now 20 years after inclusion applying a quasi-experimental design. Rogaland applied extensive information campaigns to increase early intervention, and sectors in Denmark and Oslo, Norway served as control sectors. At ten-year follow-up, rates of full functional recovery were 31 vs 15% in an early compared to a usual detection health care region. The TIPS long-term follow-up study presents the one of few opportunities to assess long-term outcome in a large, representative cohort.
This study aimed to investigate the differences in symptoms, function, recovery and somatic health after 20 years between regional health care sectors with and without a comprehensive program for the early detection of psychosis.

Methods: The authors assessed 281 patients 18 to 65 years old with a first episode of nonaffective psychosis at baseline, included between 1997 and 2001. Of these, 47 patients in the early-detection area and 20 patients in the usual-detection area were followed up at 20 years, and the authors compared their symptoms and recovery.
Results: Preliminary findings on 20-year symptom, function and somatic health outcomes will be presented.
Discussion: Early detection of first-episode psychosis appears to increase the chances of reduced deficits and improved functioning across long time spans. Findings over 20 years indicate that improvements are sustained across decades.

S136. THE MODERATING EFFECT OF AGE ON THE RELATIONSHIP BETWEEN SELF-EFFICACY AND PA LEVEL AMONG COMMUNITY WOMEN WITH PSYCHOSIS IN HONG KONG

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Background: Adequate levels of physical activity could improve clinical symptoms and physical health and functional outcomes in patients with psychosis, but exercise compliance is consistently low in this population. Some studies have shown that self-efficacy is one of the crucial determinants of physical activity level while others have demonstrated that there are age differences in this empirical relationship, although the moderating role of age is rarely studied. This study aims to examine how age moderates the relationship between exercise self-efficacy and physical activity in women with psychosis in Hong Kong.
Methods: Thirty-eight women with psychosis were recruited from a community mental health project in Hong Kong. Baseline assessments of demographics, clinical profiles, exercise self-efficacy and physical activity levels were conducted. Moderation analyses were performed using the Hayes PROCESS macro model.
Results: The study suggested the moderating effect of age between the exercise self-efficacy of "must exercise alone", and both the moderate-intensity and total physical activity in women with psychosis. The moderating role of age between the exercise self-efficacy of "resistance from others" and total physical activity was also demonstrated.
Discussion: The findings represent an important step towards understanding age-related determinants of physical activity in women living with psychosis. It is suggested that age-specific strategies should be applied when designing interventions to increase physical activity in this population.

S137. VALUE OF GYM-BASED EXERCISE TRAINING VERSUS USUAL CARE FOR YOUNG ADULTS RECEIVING ANTIPSYCHOTIC MEDICATION: A PRAGMATIC, SINGLE-BLINDED, MULTI CENTRE RANDOMIZED CONTROLLED TRIAL - THE VEGA TRIAL

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Background: Patients with severe mental illness treated with antipsychotics have increased risk of developing obesity, metabolic syndrome, and type II diabetes. Exercise may be a cost-efficient adjunctive treatment in improving personal recovery, symptom burden, cognition, quality of life, functioning, and multiple cardiometabolic outcomes in patients treated with antipsychotics. Furthermore, exercise carried out in communities have the potential to reduce the sensation of isolation, loneliness, and stigma and may improve long-term change of physical activity behaviour. According to the challenges of managing the long-term health consequences of mental illness, evidence-based long-term exercise interventions, which may be transferred to and sustained in real-world settings, are needed.
The ongoing Vega trial aims to evaluate the effectiveness of gym-based group exercise (Vega Exercise Community) compared to usual care for young adults receiving antipsychotic medication. We hypothesise that Vega Exercise Community will be superior to usual care for personal recovery after four months.

Methods: The Vega trial is a pragmatic, single-blinded, multi-centre randomised controlled trial. The study is conducted at four sites across Denmark, where we aim to include 400 patients in total during a two-year inclusion period. Participants are included if they are: 1) between 18-35 years; 2) currently receiving a regular daily dose of antipsychotic medication for □1 month; 3) diagnosed within the F20- or F30-spectrum according to ICD-1. Participants are randomized (2:1) to the Vega Exercise Community and usual care. Vega Exercise Community offers three weekly supervised group-based functional training sessions hosted in commercial centers delivered by certified Vega instructors. Participants in Vega Exercise Community will be randomized (1:1) after four months to minimal versus extended support with regards to sustained physical activity. Participants allocated to the usual care group will be offered free access to three weekly exercise sessions for four months including subsidized gym membership after completing the 12 months end of study visit. Assessment of outcomes occurs at baseline, four, six and 12 months.
The primary outcome is personal recovery assessed by Questionnaire about the Process of Recovery at four months. Additional outcomes include behavioral and functional symptoms, health-related quality of life, metabolic health, and cardiorespiratory fitness, and cost-effectiveness of the Vega Exercise Community. Finally, the quality of life and physical and mental health of the participants' primary relative is evaluated.

Results: Recruitment of participants started in October 2022. 124 have been screened for eligibility, whereof 9 were excluded due to ineligibility of which 8 were excluded due to not being treated with antipsychotics and 1 was excluded due to not being able to read and understand Danish. 25 declined where the main reason was distance to the Vega Exercise Community. As of Dec 8th, 2022, 27 have completed the baseline visit and are randomised. 11 primary relatives have been identified by the participants, whereof 3 primary relatives have completed the baseline questionnaire. Two Vega Exercise Communities are ongoing and the remaining two will commence in the beginning of 2023.
Discussion: If the Vega Exercise Community program is superior to usual care, it has the potential not only to improve recovery and health of individuals with mental illness but also enable mental health care professionals to promote exercise as an integrated part of treatment of severe mental illness. Vega Exercise Community has the potential to link mental healthcare services and the civil society potentially promoting sustainable physical activity behaviour and social inclusion.

S138. MULTIDIMENSIONAL AND INTERGENERATIONAL IMPACT OF SEVERE MENTAL HEALTH CONDITIONS

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Background: Severe Mental Health Conditions (SMHCs) affect multiple generations although this is poorly studied. The aim of this study was to investigate the intergenerational and multidimensional impacts of SMD in rural Ethiopia.
Methods: This comparative study was nested within an existing population-based cohort study. We collected data from a total of 5762 family members of 532 households (266 households with at least one family member with SMHCs and 266 sex and age-matched mentally well controls from the neighborhood) in 2019. The main outcomes were multidimensional poverty, mortality, food insecurity, and family satisfaction.
Results: The multidimensional poverty Index was higher in the households of persons with SMHCs (74.44%) than in the comparison households (38.35%). School attendance was lower in children of people with SMHCs (63.28%) than in children of the comparisons (78.08%). The median years of schooling were also lower among children of people with SMHCs than the controls. This lower attendance was also true among siblings of people with SMD (35.52%) than the comparisons (49.33%). Over the course of 20 years, family members who have a person with SMHCs in their household had a 23% increased risk of death compared to family members who did not have a person with SMHCs in their household. Severe food insecurity was also higher in the SMHCs households (20.68%) than in the comparison (13.53%) while family satisfaction was lower.
Discussion: Families of people with SMHCs experience pervasive multidimensional and intergenerational impacts. Interventions should consider the broader family social and healthcare needs of the broader family

S139. DISCONTINUING CANNABIS USE: SYMPTOMATIC AND FUNCTIONAL OUTCOMES IN PEOPLE WITH AN ESTABLISHED PSYCHOTIC DISORDER

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Background: The negative outcomes associated with ongoing cannabis use for people with psychotic disorders suggests that this population would benefit from discontinuing their use of cannabis. However, the evidence that stopping cannabis is associated with better clinical outcomes is inconsistent. Since findings have come predominantly from studies in early episode psychosis populations, it remains unclear whether discontinuing cannabis use is associated with improvements in outcomes for people with an established psychotic disorder.
Methods: This 3–5-year longitudinal study examined baseline and follow-up symptomatic and functional profiles of 371 people with an established psychotic disorder. Changes in the presence of past-year hallucinations, severity of negative symptoms and level of functioning (Personal and Social Performance Scale) in continuing cannabis users were compared with those of users who

stopped cannabis use after baseline assessment. Sociodemographic, clinical and lifestyle factors known to be associated with differing outcomes were taken into account.
Results: At follow-up, one third (33.3%) of baseline cannabis users had stopped using. The odds of experiencing past-year hallucinations at follow-up, after adjusting for all covariates including baseline hallucinations, were reduced for people who stopped cannabis compared to those who continued to use (OR=0.26, 95% CI 0.08-0.87, p=0.03). On average, users who stopped cannabis showed an improvement in level of functioning of 0.50 (95% CI 0.04-0.97), while continuing users had a non-significant decline of -0.10 (95% CI -0.43-0.22). The difference in these changes was statistically significant even after adjustment for all covariates (p=0.04). No significant differences in severity of negative symptoms were observed.
Discussion: Only a few longitudinal studies have examined symptomatic and functional outcomes for people with established psychotic disorders who continue to use cannabis compared to those who stop. Our findings show that stopping cannabis is associated with significant clinical improvements and provides encouraging evidence that negative outcomes related to cannabis use can be reversed later in the course of illness.

S140. FAMILY COMMUNICATION AND INVOLVEMENT AMONG FAMILIES WITH A PERSON WITH PSYCHOSIS

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Background: Certain family communication patterns have been shown to affect outcomes in people with schizophrenia. The salient construct in Western, high-income countries is 'expressed emotion.' Aspects of expressed emotion found detrimental to people with schizophrenia include critical comments, hostility, and emotional overinvolvement. However, these expressed emotions represent cross-culturally variable features of a family response to an ill relative. Cultural influences have tended to be ignored in expressed emotion research. The 'expressed emotion' construct may not, therefore, capture meaningful family interaction in non-Western cultures. This study aimed to develop rich, socially contextualized understanding from Ethiopia of family communication patterns when one family member has psychosis.
Methods: A focused ethnography was conducted to develop an in-depth understanding of family communication and involvement (FCI). We recruited 14 households with a person with psychosis (PWP) from rural and urban districts in Ethiopia. In addition, 40 in-depth interviews were conducted with family caregivers, PWP, community leaders, and mental health care providers. Data were analysed thematically.
Results: Four main themes were identified. (1) FCI from the PWP perspective: This theme expounded the various needs of the PWP, fulfilled wishes, experiences, and consequences of those experiences. Multiple needs related to full citizenship and companionship were emphasized. In addition, PWP felt neglected and had to hide their distress and pain in efforts to reduce the perceived family burden. (2) FCI experienced by family members: this theme included the various reactions that family members expressed towards their relative with mental illness. Perceptions of the potential for recovery and the functioning and well-being of the PWP affected reactions. The family experience was described as a trajectory, with family unity and desire for a cure framing early care and shifting to a focus on maintaining homeostasis and coming to terms with chronic

caregiving. The role of certain reinforcers of caregiving was also identified. (3) The family unit: this theme emphasized the family as one unit. Family members worked together to achieve essential priorities and balanced caregiving and survival. They suffered as a family from the burdens of illness and rejoiced in their relative's illness recovery. Aspects of family resilience were elaborated. (4) Family society nexus: There was a visible influence of societal expectations and attitudes on the PWP, and the interaction between the PWP and their families. Continuous societal appraisal of the PWP's well-being shaped the degree of citizenship within the society.

Discussion: Only a handful of ethnographic studies focused on FCI exist, especially in LMICs. As observed in other studies, there is a similarity across countries regarding the huge burden families bear.

Our findings showed that cultural differences in the nature of family interactions and responses to the person with psychosis were apparent, suggesting that the 'expressed emotion' construct does not capture important aspects of experience in this setting. The framing of family responses as duty to care due to a shared family burden highlighted the importance of actions as well as emotions. Nonetheless, PWP and family caregivers differed in their perceptions of what was experienced as support or control. Important influences on FCI included the recency and severity of illness, but also situated interactions in the wider context of socioeconomic struggles and societal exclusion of the family.

S141. MISSING STORIES: EXPLORING THE PORTRAYAL OF MENTAL ILLNESS IN VIDEO TESTIMONIALS PRODUCED BY CANADIAN MENTAL HEALTH SOCIAL MARKETING/FUNDRAISING CAMPAIGNS

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Background: Mental health video testimonials have been used by social marketing and fundraising campaigns to promote personal stories of people living with mental illness, to normalize the conversation, raise awareness, and reduce stigma. With little known about the impact of video testimonials on either storytellers or viewers, this study aimed to unpack the various dimensions of video content (e.g., verbal, visual, modality, etc.) as a first step in the search for a better understanding of how mental health campaigns in Canada have used video testimonials to portray mental illnesses, including psychosis and schizophrenia. Our focus on visual and content representations provides a unique perspective on this topic.

Methods: A two-step search strategy was used: 1) a keyword search on Google (e.g., Canadian mental health associations, mental health hospitals/institutes, etc.), and 2) a search on the websites of mental health hospitals/institutes and Canadian mental health associations for video testimonials. Based on the eligibility criteria (first-person video testimonials, 1-5 minutes in duration, produced in English or French), a total of 105 testimonials were selected and retained for analysis. Several dimensions guided the extraction and coding of content for each testimonial: general and visual characteristics, modality, characteristics of actors and their emotional experiences. The analysis involved the creation of links between different categories of visual and verbal data, which were interpreted in terms of the study objectives.

Results: In total, 105 videos were published between 2010 and 2022, mainly in English (84). Most video characters self-identified as female (63), with only 8 representing the 2SLGBTQIA+ community and White (77). The actors' emotional experiences were expressed through speech related to keywords identified in the literature: fear, shame, doubt, hope, courage, stigma, warmth, compassion, empathy, resilience, and support. The need for support was most often expressed, followed by difficult emotions around the stigma of mental illness and the need for hope. The lived experience of mental illness was captured in videos that portrayed fifteen mental health diagnoses, notably anxiety/depression, whereas diagnosis was not mentioned in 20 of the 105 testimonials (19%). Eleven participants (10.5%) reported having schizophrenia (n=9) or schizoaffective disorder (n=2). Four study participants, three of whom were diagnosed with schizophrenia, mentioned doubt as an emotional experience. Individuals with schizophrenia also expressed difficulty accepting their diagnosis and believing in themselves. While support and hope were the emotional experiences most often mentioned by people living with schizophrenia, those living with schizoaffective disorder expressed the need for support as their sole emotional experience.
Discussion: The overall findings suggest that emotional experiences expressed in video testimonials may greatly enhance public awareness of the challenges associated with various mental disorders as people increasingly share their recovery journeys. One major gap in the identified videos concerned their lack of attention to sociocultural and racial diversity, calling into question the ability of social marketing/fundraising campaigns to model resilience, recovery and agency as values and achievements shared by minority individuals in the mental health population. This presentation will also consider how video testimonials are operationalized to promote social awareness, another area for calling attention to diversity and inclusion, and to secure funds for research and treatment.

S142. THE RELATIONSHIP BETWEEN CHILDHOOD/ADULTHOOD TRAUMA AND PSYCHOTIC EXPERIENCES AND MEDIATING ROLE OF INTERPERSONAL STRESS: A NETWORK ANALYTIC APPROACH

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Background: Psychosis is a transdiagnostic and heterogeneous clinical phenomenon. It has been proposed that psychosis exists as a continuum in the general population, encompassing a full range of experiences from subclinical manifestations to clinically significant psychotic symptoms. Trauma is consistently identified as a risk factor for psychosis, however, the underlying psychopathological pathways are not fully understood. One of the possible pathways is the heightened sensitivity to interpersonal stress. However, it is uncertain if specific types of trauma and the age of their exposure are unique to particular psychotic experiences. Besides, different trauma can share the same psychopathological pathway with psychotic experiences. Recruiting a regionally diverse sample of adults, our study used a network analytic approach to model the unique relationship of types of trauma (i.e. non-interpersonal, interpersonal and betrayal) and the age of their exposure (i.e. childhood and adulthood) with positive and negative psychotic experiences. We also explored if interpersonal stress would mediate the relationship between trauma and psychotic experiences.

Methods: A convenience sample of adults completed an online survey measuring psychotic experiences, exposure to trauma and interpersonal stress. Psychotic experiences were assessed with the Community Assessment of Psychic Experiences, from which positive (i.e. hallucinations, paranoia, grandiosity, delusions and paranormal beliefs) and negative (i.e. social withdrawal, affective flattening and avolition) dimensions of psychotic experiences were assessed. Non-interpersonal, interpersonal and betrayal trauma, occurring in childhood and adulthood respectively, were assessed with the corresponding subscales from the Brief Betrayal Trauma Survey. Interpersonal stress was assessed with the Bergen Social Relationships Scale. The Gaussian graphical model with psychotic experiences and trauma as nodes was first estimated without, and then with interpersonal stress as an additional node. Edges were estimated as unique associations between nodes.
Results: The sample consisted of 468 participants (92.6% female, age range= 18-65), of which 348 (74.4%) reported at least one psychiatric diagnosis (schizophrenia: n= 1, affective disorders: n= 344, dissociative disorders: n= 29). Participants were mainly from North America (35.5%) and Europe (30.6%). The network model with psychotic experiences and trauma as nodes revealed that paranoia was associated with childhood interpersonal (r= 0.07), childhood betrayal (r= 0.07), adulthood non-interpersonal (r= 0.02), adulthood interpersonal (r= 0.05), and adulthood betrayal trauma (r= 0.05). Hallucinations was associated with childhood interpersonal (r= 0.06) and childhood betrayal (r = 0.05) trauma, whereas delusions was associated with childhood non-interpersonal trauma (r= 0.04) only. Paranormal beliefs was associated with childhood interpersonal (r= 0.02) and childhood betrayal trauma (r= 0.03). When interpersonal stress was added to the model, only paranoia was found to be associated with childhood and adulthood betrayal trauma via interpersonal stress.
Discussion: Using a network analytic approach, the results indicate the specificity of relationship between trauma and psychotic experiences. Interpersonal stress could be a psychopathological mechanism from betrayal trauma (both in childhood and adulthood) to paranoia. The findings demonstrate a need to consider the types of trauma, as well as the age of their exposure, in the relationship between trauma and psychosis. Our findings also suggest that trauma may have differential psychopathological pathways depending on heterogeneous psychotic experiences.

S143. INVESTIGATING THE RELATIONSHIP BETWEEN THE KYNURENINE PATHWAY AND TREATMENT RESISTANCE IN SCHIZOPHRENIA

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Background: The neurobiology of schizophrenia is highly complex and multifaced, and the multitude of interactions between different biological systems contribute further to such complexity. Several attempts to disentangle the heterogeneity of the disease were made over the years and, gradually, a more detailed knowledge has been achieved, despite several issues still represent a challenge for research. Two cardinal elements in the pathophysiology of schizophrenia are with no doubts neuroinflammation and the dysregulation of neurotransmission, and interestingly, the kynurenine pathway of tryptophan is at the crossroad between them, constituting a potential causal link and a therapeutic target. However, the possible relationship between changes

in biomarkers of the kynurenine pathway and psychopharmacotherapy in schizophrenia is still to be examined. Given such premises, the current study aims at evaluating the link between circulating biomarkers of the kynurenine pathway and the condition of pharmaco-resistance to first-line treatments in schizophrenia.
Methods: We examined plasma biomarkers related to the metabolism of tryptophan via kynurenine (Kyn) pathway in 75 patients with schizophrenia, 43 treated with first generation antipsychotics (FGA) or second generation antipsychotics (SGA) except clozapine, and 32 treated with clozapine after failure of at least two trials of adequate length and dosage with at least one SGA, and thus considered treatment resistant. Psychopathology was assessed using Positive and Negative Syndrome Scale (PANSS) and, in addition to the standard sub-scores, PANSS MARDER factors were used in the analysis.
Results: ANOVA analysis (age and duration of illness as covariates) showed increased levels of Kyn in treatment resistant patients compared to first-line responders ($p=0.024$), highlighting a greater activation of the kynurenine pathway related to pharmaco-resistance. We then investigated possible differential effects of downstream metabolites of Kyn on psychopathology using multiple Separate Slope Models and found differential effects only in first-line responder patients. Specifically, quinolinic acid levels resulted inversely associated with PANSS general score ($\beta=0.603$; $p=0.005$), PANSS total score ($\beta=0.525$; $p=0.016$) and MARDER anx/depr factor ($\beta=0.442$; $p=0.045$). Moreover, the kynurenic acid/quinolinic acid ratio resulted positively correlated with PANSS general score ($\beta=0.451$; $p=0.0002$), PANSS total score ($\beta=0.299$; $p=0.019$), MARDER anx/depr factor ($\beta=0.373$; $p=0.003$) and MARDER positive factor ($\beta=0.304$; $p=0.016$).
Discussion: Our findings showed a significant relationship among circulating biomarkers of the Kyn pathway, psychopathology and response to pharmacotherapy in schizophrenia confirming the hypothesis that this metabolic pathway may be at the crossroad of pathophysiology and pharmacotherapy of the disorder, and that Kyn pathway biomarkers may be further investigated for a possible role in the personalized therapy of individuals with schizophrenia.

S144. THE EFFECTIVENESS OF PUBLIC HEALTH INTERVENTIONS, INITIATIVES, AND CAMPAIGNS DESIGNED TO IMPROVE PATHWAYS TO CARE FOR INDIVIDUALS WITH OR AT RISK OF PSYCHOTIC DISORDERS: A SYSTEMATIC REVIEW

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Background: Lengthy duration of untreated psychosis and duration of untreated illness in people with At-Risk Mental States (ARMS) is associated with poorer outcomes. Individuals with first episode psychosis (FEP) often experience negative pathways to care involving contacts with police, crisis services and requiring compulsory admissions, and evidence suggest that individuals with both FEP and ARMS often experience lengthy delays to treatments. Early detection interventions may be one way to reduce delays. This systematic review aimed to synthesis the available evidence on such interventions.
Methods: Searches of four databases were conducted. Studies were included if they compared an intervention designed to improve timely access to treatment for individuals with FEP or ARMS to a control group. Interventions may be targeted at potential patients, their families, the general

public, or non-healthcare professionals. Outcomes of interest were duration of untreated psychosis or duration of untreated illness, and/or characteristics of pathways to care.
Results: Nineteen studies met the inclusion criteria. All consisted of FEP populations, none of ARMS populations. There were mixed findings about the effectiveness of interventions at reducing duration of untreated psychosis and interventions appeared to differentially impact groups. Pathways to care information was limited and mixed.
Discussion: Finding on the effectiveness of interventions designed to improve timely access to treatment was inconclusive. More research is warranted to better understand where delays occur and factor which may influence this for both FEP and ARMS populations. This research may help to develop more targeted interventions to address delays.

S145. STG DIRECTED NEUROFEEDBACK REDUCES AUDITORY HALLUCINATIONS (AH) AND BRINGS NETWORK-WIDE CHANGES IN BRAIN REGIONS INVOLVED IN AH ACROSS SEVERAL MEASURES OF BRAIN FUNCTION.

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Background: Schizophrenia (SZ) is often associated with auditory hallucinations (AH) which may be resistant to medication. We have developed an fMRI-based neurofeedback intervention (NFB), aided by meditation, and aimed at AH reduction: we tested patients in either real (rNFB) or sham (sNFB) conditions. Our target area was superior temporal gyrus (STG), a region associated with AH. Based on our prior work and available evidence, we hypothesized that patients in rNFB but not in sNFB will show AH reduction, and that associated brain changes will be observed in a network of brain regions involved in AH including STG and default mode network (DMN): medial prefrontal cortex (MPFC) and posterior parietal cortex (PCC), using both activation and functional connectivity (FC) measures. In past research, increased STG activation was found in hallucinating patients and increased FC in the DMN was found in SZ, while increased STG-DMN connectivity was suggested by Northoff hypothesis.
Methods: 25 SZ patients with medication-resistant AH were randomly assigned to either rNFB (N=12) or to sNFB (N=13). RNFB subjects were shown NFB from their individually identified STG, and SNFB subjects saw the NFB from their motor cortex (MC). During both rNFB and sNFB patients listened to prerecorded sentences spoken in their own voice or in a stranger's voice delivered over headphones. Patients were taught to upregulate their brain activity by listening to their own voice recording and to downregulate it by ignoring a stranger's voice recording and engaging in noting practice meditation. All subjects were assessed for AHs pre and post intervention with the PSYRATS. Activation changes were examined pre-relative to post-NFB using whole brain analysis. Functional connectivity (FC) was conducted with MPFC as seed.
Results: Post-NFB targeting STG, AHs were reduced in rNFB but in sNFB group (p=0,05), and STG was reduced in rNFB (p=0.006, corrected) but not in sNFB (p=0.59) group. Further, FC was reduced between MPFC and PCC (p=0.001) and MPFC and STG (p=0.001) in the rNFB group only. MPFC-STG FC reduction was associated with reductions in AH (p=0.05)
Discussion: These results suggest that AH can be reduced by FMRI based NFB. Importantly, they support our hypothesis of network-wide effects where brain changes manifest in brain regions

involved in AH, as activation reduction in the target area (STG) but also as connectivity changes in the DMN. As mentioned above, both regions are associated with AH and support aspects of AH experience. These results are significant as they demonstrate that in spite of targeting one region (STG), changes are observed in a network of regions involved in AH and not directly targeted by NFB. Furthermore, these changes showed both in activation and connectivity measures. Together, they underscore a role of the STG and DMN in AH, and provide support for the Northoff hypothesis.

S146. EMOTION RECOGNITION IN INDIVIDUALS AT FAMILIAL HIGH RISK FOR SCHIZOPHRENIA

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Background: It has been consistently observed that people living with schizophrenia (SZ) have social cognitive impairments, specifically in recognizing and regulating emotions. Individuals who have a first-degree relative with SZ are considered at familial high risk (FHR) for developing the illness. Both lower emotion recognition performance and abnormal amygdala shape, a structure important in emotion processing, have been linked to the development of psychosis in individuals at FHR. Further studies need to be done to better understand whether abnormal amygdala activity could be linked with lower emotion performance in FHR. The current study aims to investigate emotion recognition performance in individuals at FHR as well as related amygdala activity.

Methods: To date 19 participants have been enrolled in the study, 15 healthy controls between the ages of 22 to 31 years (M = 25.50, SD = 4.04) and 6 individuals at FHR between the ages of 19 to 32 years (M = 25.57, SD = 4.50). All participants completed the PENN Emotion Recognition test to assess emotion recognition performance. Participants also underwent a functional magnetic imaging scan, with an emotion recognition task, following a block design to model the hemodynamic response. Participants were presented with randomized facial expressions and asked to identify the emotion as fearful, angry, or neutral. All fMRI data was analyzed in Freesurfer, with the amygdala as the region of interest, including fearful versus neutral and anger versus neutral contrasts.

Results: Individuals at FHR showed a trending higher response time required to identify emotions (M = 2590.42 ms, SD = 727.56) compared to healthy controls (M = 2303.86 ms, SD = 412.71) on the PENN. The size difference between the average amount of time required to identify emotions was small to moderate (d = 0.48). Individuals at FHR also had a trending lower accuracy in identifying emotion (M = 33, SD = 3.67) compared to healthy controls (M = 34.53, SD = 2.95) on the PENN with a medium size difference (d = 0.48). More specifically, individuals at FHR had a trending lower accuracy in identifying anger, fear, and neutral emotions compared to healthy controls. Our preliminary neuroimaging results do not show a significant difference in amygdala activity between healthy controls compared to individuals at FHR when identifying fearful versus neutral facial expressions or when identifying anger versus neutral facial expressions.

Discussion: The current study is ongoing. Our preliminary findings illustrate emotion recognition deficits in individuals at FHR when identifying emotions, especially fear and anger. The role of amygdala functioning as a neural mechanism underlying these deficits is not currently supported by our preliminary results however this could be explained by the very small sample of FHR we

currently have (n=6). Further evidence is required to determine if amygdala dysfunction precedes social cognition deficits as a result of genetic predisposition in individuals at FHR and more participants will be included in the analyses in the following weeks.

S147. PROPRIOCEPTION AND SOCIAL COGNITION: DO THEY GO HAND BY HAND?

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Background: People affected by schizophrenia often show deficit in self-recognition and self-attribution of thoughts and actions, respectively Body Ownership and Sense of Agency. Both plays an important role in patient's proprioception, which also is impaired in the disease. Evidence suggests a link between proprioceptive abilities and both clinical symptoms and cognitive deficits, however findings are still sparse, a standardized assessment of these abilities is lacking and the relationship with socio-cognitive domains is still unexplored. Thus, the aim of the present study is two-fold: 1) to identify a fine-grained profile of Body Ownership and Sense of Agency; 2) to analyze the relationship between proprioception and psychopathology, neurocognition and social cognition.

Methods: In this experimental observational study, 37 adults with diagnosis of schizophrenia according to DSM-5 criteria, were enrolled. All patients were assessed for psychopathology, neurocognitive abilities, theory of mind, Body Ownership and Sense of Agency. We use t-test to analyze differences in questionnaires scores between the four RHI conditions (synchronous, asynchronous, 90-degrees and wood), as well as between Body Ownership and Sense of agency in the synchronous one. We use cluster analyses to identify profiles of patients' proprioceptive abilities. We conducted preliminary correlations between socio-demographic, clinical and cognitive variables on one side and RHI scores to the other. Based on these, then we ran forward stepwise regression to analyze the predictive effect of RHI scores on positive symptoms and theory of mind.

Results: Concerning the experimental condition, patients experienced high RHI illusion in synchronous, asynchronous, and 90-degrees condition, without showing the significant decrease in illusion typically observed in healthy controls when comparing the synchronous to all the other conditions. A significant decrease emerged only between the synchronous and wood condition. As for the specific domains assessed by the questionnaire in the synchronous condition, Sense of Agency resulted overall more impaired than Body Ownership. At a more fine-grained levels, three specific profiles of proprioceptive abilities were identified, the first composed by subjects who were globally more susceptible to the illusion, while in the other two, globally less susceptible to the illusion, a dissociation emerged for Sense of Agency. In cluster 2 subjects were more prone to the illusion of losing control over their own hand but did not feel that they were gaining control over the rubber hand/piece of wood, while the opposite pattern was observed in cluster 3. Finally, regarding the relationship with other clinical and cognitive domains, significant correlations emerged with age at onset, symptoms, and Theory of Mind abilities. Specifically, Body Ownership

scores resulted significant predictors of psychotic symptoms severity as well as of affective Theory of Mind.
Discussion: This study highlights different profiles of proprioceptive abilities in people with schizophrenia through a fine-grained analysis. Results suggest that Sense of Agency is globally more compromised than Body Ownership, and that the former is more differentiated and shows a dissociation between the two components (agency over the rubber hand vs agency loss of one's own hand). Moreover, disturbances in Body Ownership are associated to psychotic symptoms and Theory of Mind abilities, especially in the affective component. The relationship found between proprioception and both clinical and socio-cognitive outcome highlights that a deeper knowledge of the first could significantly contribute to improve personalization of patient's rehabilitation treatment.

S148. THE CASCADE EFFECT OF AUTISTIC SYMPTOMS ON PRAGMATICS IN SCHIZOPHRENIA: THE ROLE OF EXECUTIVE FUNCTIONS AND THEORY OF MIND

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Background: Autism Spectrum Disorder (ASD) and schizophrenia show significant pragmatics impairment with negative implications for daily functioning. Both diseases share also cognitive and socio-cognitive deficits, particularly in executive functions (EF) and Theory of Mind (ToM), and the relationship between pragmatics and both ToM and EF in schizophrenia is still under debate. Interestingly, individuals with schizophrenia and co-occurring autistic symptoms (not reaching the diagnostic threshold for ASD), show greater impairment in cognitive and socio-cognitive abilities, suggesting that the co-occurrence of schizophrenia and autistic symptoms might be associated with a 'double dose' of deficit. The same could be hypothesized concerning pragmatic impairment, being a hallmark of both conditions. However, to date the effects of autistic symptoms on pragmatics is schizophrenia has not yet been investigated. Then, the aim of this study is to evaluate the interplay of autistic symptoms, ToM, EF with pragmatics, using a path analysis approach.
Methods: 125 patients with schizophrenia were assessed for autistic symptoms (PANSS Autism Severity Score, PAUSS), ToM (Picture Sequencing Task, PST), EF (Brief Assessment for Cognition in Schizophrenia, BACS), and pragmatics (Assessment of Pragmatic Abilities and Cognitive Substrates test). Two path analyses were run: the first path analysis evaluated the direct and indirect effects of predictors on global pragmatics, while the second on both pragmatic production and comprehension. A robust selection criterion of the predictors and the paths to include was applied, based on the correlation matrix ($p<.005$).
Results: The first path analysis on global pragmatics showed a good fit ($\chi2=1.36$, $\chi2$ p-value=.24, CFI=.99, SRMR=.02, RMSEA=.05) and explained 35% of variance on global pragmatics. Results showed direct negative effects of autistic symptoms ($\beta=-0.003$, SE=0.002, 95%CI=-.006 to -.0001), ToM ($\beta=0.003$, SE=0.001, 95%CI=.001 to .006), and EF ($\beta=0.005$, SE=0.002,

95%CI=.0001 to .009), and also indirect effects of autistic symptoms firstly via EF (β=-0.001, SE=0.001, 95%CI=-.003 to -.0001), then via EF and ToM (β=-0.001, SE=0.001, 95%CI=-.002 to -.0001).
The second path analysis on pragmatic production and comprehension showed a good fit ($\chi2$=1.36, $\chi2$ p-value=.25, CFI=.99, SRMR=.02, RMSEA=.05) and explained 17% of variance on pragmatic production and 34% of variance on pragmatic comprehension. As for pragmatic production, we found a direct negative effect of EF (β=0.005, SE=0.002, 95%CI=.0001 to .009) and an indirect effect of autistic symptoms through EF (β=-0.001, SE=0.001, 95%CI=-.002 to -.0001). Concerning pragmatic comprehension, results showed a direct negative effect of ToM (β=0.006, SE=0.002, 95%CI=.003 to .01) and an indirect effects of autistic symptoms through EF and ToM (β=-0.002, SE=0.001, 95%CI=-.004 to -.001).

Discussion: Our findings show that autistic symptoms affect global pragmatics directly, and indirectly, by eliciting detrimental effects on EF and ToM, which in turn affect pragmatics. Given that EF seems the main promoter of pragmatically appropriate speech, while ToM is more strictly related to the ability to infer the speaker's non-literal meaning, we found that autistic symptoms show a cascade effect on EF (which, in turn, impacts on production) and on EF and ToM (affecting comprehension). Overall, our findings may help to reconcile the contrasting data on the relationship between pragmatics, ToM and EF, highlighting the 'double dose' effect of autistic symptoms on pragmatic deficit, which, in turn, points out the need to target multiple and entangled domains in order to reduce pragmatic impairment and resize disability.

S149. LIFETIME SUBSTANCE ABUSE AND ADVERSE CHILDHOOD EXPERIENCES IN PSYCHOSIS: IMPACT ON CLINICAL OUTCOMES

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Background: Patients suffering form psychosis show a high incidence of substance use disorders (SUDs), with an estimated prevalence of 40-65%. Subjects are frequently poly-drug users and the most commonly misused drugs are tobacco, alcohol, cannabis, and cocaine. SUDs in patients with psychosis have been associated with more severe positive and negative symptoms, higher rates of suicide attempts, increased aggression and violence, poorer functional outcomes, higher risk of relapse, poorer treatment response and compliance, and higher incidence of antipsychotic drug-related extrapyramidal symptoms. Both SUDs and psychosis have been linked to adverse childhood experiences (ACEs). On the one hand, healthy subjects who report physical or sexual abuse in childhood are more likely to abuse substances in adulthood. On the other hand, childhood trauma increases the risk for psychosis and affects severity and type of psychotic symptoms. Based on these premises, we aimed to explore the relationship between substance abuse, ACEs and clinical, cognitive, and functional outcomes of psychosis.
Methods: Our sample included 74 patients with psychosis stratified according to lifetime substance use (37 users and 37 non-users). Clinical, therapeutic, and socio-demographic data were collected through direct interviews and clinical records. All patients were assessed for ACEs, clinical, cognitive and functional status, through the use of Risky Family Questionnaire, Positive

and Negative Syndrome Scale for Schizophrenia, Brief Assessment of Cognition in Schizophrenia and Quality of Life Scale (QLS). Finally, subjects were interviewed to quantify and describe their lifetime substance use (type of drug, age of onset, duration, frequency and amount of substance misused). First, we compared users vs non-users, as well as single-drug users vs poly-drug users on the above-mentioned measures through ANCOVA or Chi-Squared Test. Then, focusing on the subgroup of users, we analysed the effects of substance-related variables on psychopathology, cognition and daily functioning.

Results: As expected, the most commonly used substances were tobacco, alcohol, cannabis and cocaine. When comparing users and non-users, ANOVA showed a significantly higher prevalence of long-acting injectable (LAI) antipsychotic treatment among users. Significant differences emerged between single-drug and poly-drug users, with the latter showing higher levels of ACEs and poorer cognitive performance. We also observed a significant effect of onset of drug abuse on QLS, with earlier onset being related to poorer daily functioning, as well as a significant association between a longer duration of substance abuse and higher levels of ACEs. Finally, in alcohol users, we reported significant negative effects of both duration and earlier onset of abuse on two core cognitive domains, i.e. executive functions and processing speed.

Discussion: Our study confirms previous literature showing an association between substance abuse and LAI antipsychotic treatment. It also provides novel data through an in-depth analysis of substance-related factors. We found worse cognitive outcomes in poly-drugs compared to single-drug users. Moreover, we observed a detrimental impact of an earlier onset of drug abuse on daily functioning, as well as an association between a longer duration of drug abuse with higher levels of ACEs. Finally, similarly to the general population, we showed that an earlier onset and a longer duration of alcohol abuse significantly affect cognition also in patients with psychosis. Overall, our study highlights the importance of promptly recognizing substance abuse in patients with psychosis to better tailor interventions and prevent cognitive and functional decline.

S150. HIGH ACES IN INDIVIDUALS WITH EARLY PSYCHOSIS ASSOCIATED WITH HOUSING INSTABILITY AND SUICIDAL IDEATION: PRELIMINARY DATA FROM THE CALIFORNIA EPI-CAL PROJECT

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Background: California's EPI-CAL project (https://epical.ucdavis.edu) joined 5 university- and 13 county-based early psychosis (EP) programs to create a sustainable learning health care network as part of the NIMH EPINET project. Research shows individuals with psychosis often have a history of trauma that contributes to poor outcomes across multiple domains. Qualitative data

from California community partners highlighted how adverse childhood experiences (ACEs) impact the lives of individuals experiencing psychosis; however, few EP programs currently evaluate or treat trauma using empirically supported approaches. This analysis examines the self-reported prevalence and clinical correlates of ACEs in the EPI-CAL EP sample.
Methods: Individuals with first episode affective or nonaffective psychosis (FEP) or at clinical high risk for psychosis (CHR) completed self-report surveys at enrollment in EPI-CAL via Beehive. To capture both ACEs and social determinants of health, participants completed the Pediatric ACEs Screening and Related Life-events Screener (PEARLS; adolescent version). Adults are asked to rate experiences prior to age 18. ACEs scores of 4 or higher are considered high risk for poor outcomes. Descriptive analyses summarize the demographic, ACEs, and outcomes data collected to date; chi-square analyses examine relationships between low (3 or fewer) versus high (4+) ACEs and participants' experience of suicidal ideation on the Modified Colorado Symptom Index (MCSI), lifetime housing instability, and lifetime justice contact.
Results: At enrollment, 217 clients (Ages 12-32, M=19.04, SD=4.28; 71% FEP, 21% CHR, 8% Diagnosis unconfirmed), completed the PEARLS ACEs (M = 3.52, SD = 2.74). The respondent sample identified as 50.5% female sex at birth; 42% female gender; 25% non-heterosexual; 73% non-White; 41% Hispanic/Latinx; and 7% were not born in the US. 47% respondents had an ACEs score of 4 or higher and 24% had scores of 6 or higher, which is associated with 20-year reduction in life expectancy. More than half (51%) of individuals endorsed feeling "unsupported, unloved and/or unprotected" and 47% reported having "lived with a parent/caregiver who had mental health issues (e.g., depression, schizophrenia, bipolar disorder, PTSD, or an anxiety disorder)". 76 respondents (35%) endorsed lifetime justice contact, and 18% had experienced contact with the justice system within the past 6 months. 82 individuals (38%) experienced housing instability at some point in their life, with 13% of those (n=28) reporting living on the street at some point. Individuals with a low ACEs score were less likely to experience housing instability ($p<.001$) when compared to individuals with high ACEs, but no differences between groups was found for lifetime justice contact ($p>.05$). Individuals with high ACEs (score 4+) were more likely to report suicidal ideation in the past month ($p<.01$) compared to individuals with low ACEs (50% of high ACE scorers vs 25% of low ACE scorers).
Discussion: The experience of adverse childhood experiences is very common for individuals receiving care within early psychosis programs. These experiences are associated with higher rates of housing instability and suicidal ideation. As homelessness and death from suicide are two prevalent negative outcomes for individuals with psychosis, these data highlight the need for EP programs to identify and treat individuals who experience traumatic events with the goal of improving long-term outcomes.

S151. LONGITUDINAL EFFECTS OF ARIPIPRAZOLE ON HIPPOCAMPAL-CORTICAL CONNECTIVITY IN FIRST-EPISODE PSYCHOSIS

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Background: There is growing evidence that some antipsychotics (e.g., aripiprazole, brexpiprazole, lurasidone, cariprazine) exert pro-cognitive effects in first-episode psychosis (FEP).

A common target of these medications is the serotonin 1A receptor, which has been proposed as a potential mechanism underlying their pro-cognitive effects. Serotonin 1A agonism has been linked to increased serotonin in the hippocampus, a key cognitive region, as well as to increased dopamine in the mesocortical pathway, including the prefrontal cortex. We previously reported that aripiprazole is associated with increased volumes of the hippocampus and surrounding white matter regions, (e.g., fimbria) over 12 months following a FEP. Given the importance of brain connectivity on cognition, the current study sought to examine the role of aripiprazole on hippocampal-cortical connectivity over 18-months following a FEP.

Methods: 100 FEP patients and 60 controls underwent 3.0 Tesla structural magnetic resonance imaging and a comprehensive assessment at 4 timepoints (3, 6, 12, and 18 months following admission). Patients were grouped based on their antipsychotic medication use in the previous month: (1) aripiprazole (oral or injectable), other antipsychotic (e.g., olanzapine), and no/low antipsychotic (unmedicated or adherence < 75%). Choice of antipsychotic medication was determined by the treating psychiatrist. Structural covariance-based hippocampal-cortical connectivity was computed with the participation coefficient graph measure, with one hippocampal module (five hippocampal subfields [CA1, CA2/CA3, CA4/DG, subiculum, and stratum radiatum/lacunosum/moleculare] and 4 white matter regions [alveus, fimbria, fornix, and mammillary body]) and seven cortical modules (Yeo networks [visual, somatosensory, dorsal attention, ventral attention, limbic, frontoparietal, and default-mode]). Generalized estimating equations were then computed for each of the 18 regions of the hippocampal module (9 left hemisphere, 9 right hemisphere) with the covariates of sex, age, total brain volume, and baseline connectivity of the given region.

Results: Significant Group by Time interactions were observed for the left CA4/DG ($\chi2 = 16.83$, $df = 9$, $p = 0.05$), right fimbria ($\chi2 = 17.83$, $df = 9$, $p < 0.05$), right mammillary body ($\chi2 = 23.69$, $df = 9$, $p < 0.01$), and right fornix ($\chi2 = 17.41$, $df = 9$, $p < 0.05$). Pairwise comparisons revealed a similar pattern of increasing intramodular hippocampal connectivity in the aripiprazole group, which was not present in the other groups and was most prominent from 12 to 18 months.

Discussion: We demonstrated distinct patterns of hippocampal-cortical connectivity in FEP patients taking aripiprazole versus other or no antipsychotic medications as well as healthy controls. Hippocampal regions, including the left CA4/dentate gyrus and right hemisphere white matter regions, became more strongly connected to other regions within the hippocampal module relative to large-scale cortical networks. This increased intramodular connectivity could indicate strengthening connections between hippocampal and surrounding white matter regions in patients taking aripiprazole relative to the other groups. These changes were observed primarily between 12 and 18 months, subsequent to the volumetric changes observed in our previous work from 3 to 12 months in an overlapping sample. Future work incorporating other neuroimaging modalities (e.g., functional connectivity) and more selective cortical networks (e.g., cognitive networks) could shed light on the mechanisms underlying pro-cognitive effects of some medications.

S152. INVESTIGATING THE RELATIONSHIP BETWEEN CONTROL OVER AUDITORY HALLUCINATIONS AND SPEECH PROPERTIES USING NATURAL LANGUAGE PROCESSING

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Background: Auditory hallucinations and thought disorder are one of the most common and debilitating symptoms of psychosis. Recent work has shown that higher degree of control over voice-hearing experiences (VHE) is related to better clinical outcomes and less VHE-related distress, independent of diagnostic status. Previous work using Natural Language Processing (NLP) has shown that psychotic-spectrum and at-risk populations tend to have lower speech coherence and poverty of speech than non-clinical populations, thought to be reflective of underlying thought disorder. However, it is not known how control over VHE might be related to the properties of speech across voice-hearing populations.
Methods: In this study, we examined the content of freely-written descriptions about VHE from 150 participants, 39 with psychosis spectrum diagnosis and 111 without, in the Yale Control Over Perceptual Experiences (COPE) project. We used the Natural Language Toolkit's native sentiment analyzer to assess the affective content of the descriptions. Additionally, we used the Bidirectional Encoder Representations from Transformers (BERT) machine learning algorithm to estimate speech coherence and complexity.
Results: The resultsfrom two generalized linear models illustrated relationships between sentiment, coherence, and complexity of speech and degree of control over VHE as well as likelihood of having a diagnosis of a psychosis-spectrum disorder. Participants with low control and a diagnosis referred more negatively to their experiences, while those with high control used more positive words. We also found that participants with a higher degree of direct control over VHE wrote more and exhibited greater fluency and syntactic complexity.
Discussion: Our results indicate that the ability to exercise control over voices, independently of the diagnosis, is related to a potential positive redefinition of the experience and better thought articulation. Future work should investigate how these NLP-derived biomarkers vary with changes in disease state and changes in control capacity. Ultimately, this study demonstrates how we can use non-invasive techniques, such as NLP, to extract biomarkers for disease severity and cognitive dysfunction.

S153. PERCEIVED COMPETENCE TOWARD COGNITIVE TASKS IN SCHIZOPHRENIA: IMPLICATIONS FOR TREATMENT AND FUNCTIONING

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Background: Cognitive impairment has emerged as a strong predictor of poor functioning and disability in schizophrenia. Cognitive remediation is an evidence-based treatment that produces significant restoration of many cognitive skills. The excitement for this intervention is somewhat offset by a limited transfer of cognitive gains to improvement in functioning. This prompted the search for features that mediate the transfer of cognitive improvements to everyday functioning gains. However, we first need to increase our understanding of how individuals engage with cognitive tasks, including their own perceptions of their abilities. In the current study we examined how perceived competence may be associated with cognitive ability and cognitive performance, and the avoidance of challenging tasks in individuals with schizophrenia.
Methods: The sample included 70 individuals who were consecutive admissions from an early psychosis program as part of a routine psychological assessment. Symptom severity was rated with the Brief Psychiatric Rating Scale. Participants completed the Cognitive Failures Questionnaire (CFQ), the Sheehan Disability Scale (SDS), and the Behavioral Avoidance for Depression Scale

(BADS). Measures of cognition included estimated premorbid intelligence, verbal fluency, processing speed, planning, and verbal memory. Immediately before and after completing the cognitive battery, participants completed the Perceived Competence Questionnaire (PCS) – a 7-point Likert scale indicating how well they think they will do (pre-testing) and how well they think they did (post-testing) perform on tests of their "thinking skills such as attention and memory".
Results: Participants rated their perceived ability on the task as significantly higher before (M = 5.3, SD = 1.1) than after (M = 4.8, SD = 1.1) the cognitive assessment. Negative symptom severity (r = -.53), SDS (r = .33), and all scores on the BADS (r's = -.35 to -.52) were associated with lower pre-assessment scores on the PCS. Significant correlates of the decline in ratings of self-confidence included all BADS scores and, at a trend, the CFQ total. Actual cognitive performance was associated with functioning (SDS), but not associated self-perceptions of cognitive ability including pre-, post-, or change scores on the PCS or on the CFQ.
Discussion: Early psychosis participants show significant declines in their perception of their cognitive abilities after completing a battery of cognitive tests, yet the degree to which their perception changes, as well as their initial and final perception, is not significantly associated with actual cognitive abilities. Lower perceived cognitive abilities, and the tendency to reduce one's perception of their cognitive abilities after testing, is associated with behavioral avoidance.

S154. THALAMOCORTICAL STRUCTURAL CONNECTIVITY IN EARLY-COURSE PSYCHOSIS AND FIRST-DEGREE RELATIVES

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Background: Thalamocortical circuit abnormalities have been identified as a putative biomarker for psychotic disorders. Resting-state functional connectivity studies consistently reveal abnormally increased thalamic connectivity with primary sensory and motor regions and decreased connectivity with prefrontal cortex in schizophrenia and other psychotic disorders, and this connectivity pattern predicts conversion in clinical high risk. Here, we utilized diffusion-weighted imaging (DWI) and probabilistic tractography analyses to characterize thalamocortical structural connectivity in in early course, minimally treated patients with psychotic disorders (PSY), their young, first-degree relatives (familial high risk: FHR) and matched healthy comparison (HC) subjects. The goal of the present study was to determine if thalamocortical structural connectivity was abnormal in psychosis and FHR and to determine whether it predicts psychotic symptoms and cognitive functioning.
Methods: Sixty participants (PSY=14, FHR=21, HC=25), aged 13-35 years old, underwent MRI in a 3T Siemens Prisma scanner and completed clinical and neurocognitive assessments in a separate session. DWI were analyzed with FSL and thalamocortical structural connectivity was quantified with probabilistic tractography using the thalamus as the seed and six cortical regions as targets (prefrontal, motor, somatosensory, temporal, parietal and occipital). The primary measure, total connectivity was estimated between seed and target regions as a distance-adjusted proportion of connectivity to the region compared to total connections from the thalamus. Group difference analyses included additional factors for hemisphere, sex and age. Additional mixed-

effect models examined the relations of thalamic connectivity with symptoms in PSY and FHR (as measured with PANSS) and psychotic-like experiences (PLEs) in the entire sample as measured with the Chapman Scales, and cognitive function (as measured with the MATRICS Consensus Cognitive Battery) in the entire sample.
Results: Contrary to our hypothesis, we did not find any group differences in structural connectivity for primary sensory, primary motor or prefrontal cortex. We observed a significant group effect for the parietal cortex target reflecting increased thalamic connectivity in psychosis compared to HC ($p=0.05$) but not in FHR ($p=0.15$). Cognitive measures, symptom severity and PLEs were not related to thalamocortical connectivity.
Discussion: In young early-course patients with psychotic disorders and their first-degree relatives, we did not observe any differences in structural connectivity of sensory, motor or prefrontal thalamocortical circuitry. This is in contrast to our findings, and that of others, of abnormal resting-state functional connectivity in psychosis and first-degree relatives in these regions. Our primary finding was of increased structural connectivity of the thalamus with the parietal cortex only in the psychosis group. Further, we did not find any relations between thalamocortical connectivity and symptoms, cognition, or PLEs. These null effects could be due to the functional heterogeneity of the large cortical targets we have used. Future plans include implementation of functionally-distinct smaller cortical targets to increase spatial precision of our tractography analyses to better understand the relationship between thalamocortical circuity, cognition, and symptoms.

S155. LOW-FREQUENCY MONITORING FOR COMMUNITY CLOZAPINE INITIATIONS: A COMPARATIVE STUDY RELATIVE TO STANDARD FREQUENCY ASSESSMENTS

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Background: During the COVID-19 pandemic, the risk of patients and staff being exposed to SARS-CoV-2 required face-to-face contact to be minimised where feasible and appropriate. In this context, we developed a low-frequency physical monitoring (LFM) protocol which reduced in-person contact by approximately 40% during the first 3 weeks of community clozapine initiation. To evaluate the safety of this protocol, we carried out a retrospective cohort study comparing clinical outcomes to patients receiving standard-frequency monitoring (SFM) before the pandemic.
Methods: The study was part of a clinical audit of patients undergoing community clozapine initiations with the Treatment Review and Assessment Team (TREAT) service in South London and Maudsley NHS Foundation Trust. The LFM and SFM protocols differed in frequency of in-person physical monitoring during the first 3-weeks of clozapine initiation (LFM: three days per week during Weeks 1-2 and two days per week during Week 3; SFM: five days per week during Weeks 1-2 and three days per week during Week 3). We reviewed the medical notes of 16 patients who initiated clozapine in the community under the LFM protocol between March 2020 to August 2021. Controls (n=16) were selected blind to outcome and individually matched to cases based on

sex, age, and smoking status (SFM group). Our primary outcome was all-cause discontinuation of clozapine. Secondary outcomes were hospitalisation due to clozapine-related side effects, and the incidence of side effects requiring physical monitoring for detection. Clinical outcomes were compared descriptively due to the small sample size.
Results: Demographic and clinical characteristics were comparable between the LFM and SFM groups (Age: 41.2 ± 13.6 vs. 40.8 ± 11.8; Males/females: 6/10 vs. 6/10; Smoker/non-smoker: 8/8 vs. 7/9; PANSS total score: 78.0 ± 16.1 vs. 81.2 ± 9.4). During the first 3 weeks of monitoring, there were zero cases of discontinuation in both the LFM and SFM groups. Moreover, there were no cases of clozapine-related side effects that required hospitalization or resulted in fatalities in either group. Common side effects detected through physical monitoring in the LFM and SFM groups included postural drop (3 cases vs. 5 cases), asymptomatic tachycardia (3 cases vs. 0 cases), and hypotension (1 case vs. 3 cases). Ongoing hypertension, which was evident from the beginning of clozapine treatment, was detected in 4 cases vs. 1 case and were referred to primary care for management. There was no evidence that the LFM protocol missed symptomatic tachycardia, hypotension, syncope or other disorders.
Discussion: While the sample size is small, our preliminary findings suggest that the low-frequency physical monitoring protocol for community clozapine titrations is relatively safe compared to monitoring currently recommended by treatment guidelines. Although the LFM protocol was originally designed to minimise face-to-face contact during the pandemic, these finding indicate potential for the protocol to be applied to a wider range of community services to lessen the burden to patients/staff and improve access to clozapine treatment. Further work is warranted on the adherence, cost-effectiveness, and subjective experiences of patients undergoing clozapine titrations under the LFM protocol.

S156. THE TORONTO ADOLESCENT AND YOUTH COHORT STUDY: STUDY DESIGN AND EARLY DATA RELATED TO PSYCHOSIS SPECTRUM SYMPTOMS, FUNCTIONING, AND SUICIDALITY

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Background: Psychosis spectrum symptoms (PSS) occur throughout adolescence, and are linked to serious adverse outcomes. Identifying PSS and modifiable antecedents is a public health priority. The Toronto Adolescent and Youth (TAY) Cohort study aims to characterize developmental trajectories in mental health help-seeking youth and understand associations with PSS, functioning, and suicidality. This poster describes the longitudinal study design, and baseline characteristics of the first 300 participants.
Methods: The TAY study is a longitudinal cohort study of children and youth (11-24 yrs.) presenting to a large

tertiary care psychiatric hospital. Participants undergo extensive diagnostic and clinical characterization of psychopathology, substance use, functioning, suicidality, social/health equity evaluations, and health service utilization assessment, with follow up every 6 months over 5 years.

Results: Across the first 300 participants (recruited June 2021-May 2022), 70.3% were female, and 46.0%
identified as cis-gender girls/women. Participants met diagnostic criteria for an average of 3.5 mental disorders, most frequently anxiety disorders (80.1%) and depressive disorders (71.8%). 47.9% met criteria for PSS, and exhibited higher rates of functional impairment and current and lifetime suicidality compared to non-PSS participants.

Discussion: Initial findings from the TAY study demonstrate the feasibility of extensive clinical phenotyping in mental health help-seeking youth. Our results indicate a much higher PSS prevalence than that identified in community cohorts, with greater functional impairment and suicidality. These results underscore the critical need to better understand longitudinal trajectories of clinical child and youth cohorts to improve prediction of psychosis, functioning, and suicidality.

S157. BRAIN NETWORK LOAD ENGAGEMENT IN SCHIZOPHRENIA: ASSOCIATIONS WITH OUTCOMES

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Background: Cognitive deficits in patients diagnosed with schizophrenia are a core feature of the disorder. There are currently no treatments for these cognitive deficits. Our aim was to examine and compare patterns of increased versus decreased activity in the central executive network (CEN), salience network (SN), and default mode network (DMN) between healthy controls (HCs) and patients diagnosed with schizophrenia (SZs) as well as to explore the influence of task load on these networks between HCs and SZs.

Methods: Analyses focused on a secondary dataset comprising Blood Oxygen-Level Dependent (BOLD) data collected from 25 HCs and 27 SZs who completed a working memory (WM) task (N-back) with 5 load conditions while undergoing functional magnetic resonance imaging (fMRI). Region of interest (ROI) data were analyzed using linear mixed-effects models. Additionally, we examined neuronal activity at ideal task difficultly for patients diagnosed with schizophrenia as it relates to age, sex, education, duration of illness, antipsychotics, positive and negative symptoms, task performance, bias, WRAT-3 scores, effort, visual search, processing speed, verbal learning, working memory, category fluency, and functional outcomes.

Results: Group activation differences were found in the posterior salience network (pSN), default mode network (DMN), dorsal default mode network (dDMN), and ventral default mode network (vDMN) showing greater activity for SZs. Specifically, pSN, DMN, dDMN, and vDMN all showed increased activity in SZs compared to HCs. The curve of brain activity was consistent between HCs and SZs with the exception of the vDMN, where HCs show greater activation at modest mental workload (quadratic curve) and SZs showed greater brain activation at lower mental workload (linear). In the CEN, there were no group differences, and the response curve was the same for both groups. Increased default mode network activity was associated with decreased performance and increased illness indicators, while increased salience network activity was associated with greater performance and decreased illness indicators.

Discussion: Results indicate the default mode network and salience network relationship is not performing as expected in patients. That is, the default mode network is dysregulated, but more interestingly, the salience network simultaneously shows increased activity. These group differences demonstrate network difference between HCs and SZs and could show value in treatments targeting cognitive deficits in SZs from a large-scale brain network connectivity perspective. Future studies are needed to confirm these results with larger sample size in order to examine potential subtleties of interactions between these networks.

S158. PREDICTION ERROR NEUROCORRELATES DURING ASSOCIATIVE LEARNING TASK FAIL TO SHOW ASSOCIATIONS WITH DELUSIONS IN TRANSDIAGNOSTIC PSYCHOSIS SAMPLE

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Background: Recent neuroimaging studies have reported an association of the neural substrates of prediction error – brain signals that encode expectation violations - with not only pathological changes in psychosis but also delusion symptoms. However, due to small samples size of prior studies the generalizability and reproducibility of these findings is unclear. Using a transdiagnostic psychosis sample this study aims to investigate prediction error neural activity abnormality is associated with either self-reported or clinician rated delusion severity.

Methods: 54 psychotic patients and 20 healthy controls were recruited at the University of Chicago from within the Bipolar and Schizophrenia Network for Intermediate Phenotypes 2 (B-SNIP2) study. Patients were either diagnosed with schizophrenia, schizoaffective disorder, and bipolar disorder with psychosis. Prediction error was captured using associative learning paradigm published by (Corlett et al., 2012). Prediction error neurocorrelates were identified using differences in fMRI BOLD activation in expectation violation versus expectation confirmation trials. In three separate primary analyses the magnitude of prediction error BOLD response was correlated with the severity of delusions: clinical assessed current delusions (PANSS Delusion Severity – P1), clinician assessed lifetime delusion severity (LDPS Total Delusion) , and participant self-rated delusional belief burden (PDI Total Delusions). Age and sex were included as covariates in all analyses and significance results were defined at $p < .05$, familywise error corrected.

Results: Final neuroimaging analysis included 47 psychosis patients and 15 healthy controls as 7 patients and 5 healthy controls need to be excluded due poor-quality behavioral or fMRI data. In both patient and healthy controls, expectation violation events were associated with activation in several brain regions identified in previous prediction error studies including. Prediction error neural activation during the task was not found to be significantly associated with delusions using either clinician rated or patient self-report measures. Several supplemental analyses were conducted to help rule out whether the negative finding may be related to methodological differences from the prior studies including alternative measures of delusion severity, subgroup analysis excluding bipolar, and exploratory region of interest analysis restricted to regions

previously identified in the literature. No association with delusion measures was observed in these supplementary analyses.
Discussion: This results of this study contrast with prior neuroimaging showing delusion severity is associated with prediction error activation in the prefrontal cortex, midbrain and basal ganglia activation in associative learning fMRI paradigms. Supplemental analyses showed differences in delusion dimensions, patient heterogeneity, regions of interests did not account for lack of replication. A likely explanation for this discrepancy may be due to decreased probability of type 1 error in this study due to limited sample size and insufficient power of prior work. Limitations and challenges in accurately assessing prediction error may also explain discrepancies. This and prior work attempt to use experimenter controlled expectation violation during associative learning paradigms, however cognitive and attentional confounds may lead to highly varied processing of the task. Alternative measures may be more suited to more reliably and robustly study prediction error in task-based designs. These finding suggest that further investigation is necessary to confirm the role of abnormal prediction error activity in psychotic delusions.

S159. UNPACKING CULTURAL BARRIERS AND PROGRAMMATIC RESPONSES TO CULTURAL AND RACIAL DIVERSITY IN EARLY PSYCHOSIS SERVICES

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Background: A substantial proportion of service users in early psychosis services (EPS) are members of minoritized cultural groups. Culture-related variables, including migration in adversity, acculturation stress, historical segregation, and racial discrimination, exert significant influence over pathways to care, engagement in services and, ultimately, outcomes. The goal of the current study was to understand diverse providers' perspectives on how culture-related variables impact outcomes and engagement and to map variations in culture-related training and competency across sites.
Methods: We conducted a sequential mixed methods study of EPS providers across 5 countries (UK, US, AU, CAN and Chile; survey n = 164; interview n = 25). Survey data was analyzed quantitatively and open-text responses systematically coded. For the purposes of expansion and triangulation, in-depth interviews were conducted after initial analysis of survey data and coded using thematic analysis in order to extend and deepen survey findings.
Results: Across all countries surveyed, concrete culture-related trainings, assessments and interventions were implemented in only a minority of programs. Providers reported a range of substantive concerns regarding lack of capacity in these areas, and inadequate attention to the complex entanglements of culture, race and trauma, including racial and historical trauma. Interviews document pronounced challenges involved in adequately serving smaller newcomer immigrant and refugee communities, particularly in areas with limited access to translators and also foregrounded the often highly localized contexts of cultural mistrust.
Discussion: Findings underscore gaps in both practice and clinical expertise regarding minoritized clients and their families. Practices related to culture and trauma, as well as their intersections, arguably require significantly more attention and resource allocation in both implementation and research contexts. Exclusively adopting Anglo-American approaches to psychosis intervention carries risks unless substantive cultural adaptations are prioritized.

S160. BIOMARKERS OF COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA: USING TMS-EEG TO ASSESS PREFRONTAL OSCILLATORY DEFICITS IN EARLY-COURSE PATIENTS

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Background: Accumulating evidence suggests that patients with schizophrenia have a reduced ability to generate fast oscillatory activity in the dorsolateral prefrontal cortex (DLPFC). It is believed that this deficit underlies the cognitive dysfunction commonly observed in these subjects. Chronic patients with schizophrenia have a reduction in several oscillatory parameters evoked by transcranial magnetic stimulation (TMS) and simultaneously recorded with electroencephalography (TMS-EEG) in the DLPFC, with the main oscillatory frequency (or "natural frequency") showing the larger effect compared to healthy controls (HCs). However, it remains to be established whether a slowing of the DLPFC natural frequency is present since early in the course of schizophrenia and relates to cognitive dysfunction at the beginning of illness.
Methods: We used TMS-EEG to investigate local brain dynamics elicited by stimulation of the left DLPFC in 18 subjects with early-course schizophrenia (ECSCZ, i.e. within 2 years from the onset of psychosis) and 19 age and gender-matched HCs. Single-pulse TMS was delivered at 120% of the resting motor threshold and a neuronavigation system was used to precisely target the DLPFC. State-of-the-art real-time monitoring of the EEG response and noise masking procedures were employed to ensure data quality. In each subject, an automated algorithm was employed to identify the oscillatory frequency with the highest cumulate spectral power at the electrode closer to the stimulation site, i.e. the natural frequency. Local cortical synchronization following the TMS pulse was quantified by calculating the EEG spectral power in each frequency band relative to the broadband power (i.e. the relative spectral power, RSP). Goal-directed working memory performance was assessed using the "AX" Continuous Performance Task (AX-CPT).
Results: The natural frequency of the left DLPFC was significantly reduced in ECSCZ patients compared to HCs showing a large effect size (Cohen's $d > 2.0$). Patients also showed an abnormally higher frontal RSP in the beta band relative to HCs. The AX-CPT performance was significantly worse in ECSCZ patients. Furthermore, in the ECSCZ group, the beta-band RSP in frontal channels correlated inversely with the AX-CPT performance.
Discussion: Our results suggest that a reduction in the main oscillatory frequency of the prefrontal cortex may be an early neural signature associated with schizophrenia. Furthermore, abnormalities in the intrinsic oscillatory properties of the DLPFC appear to reflect worse goal-directed working memory performance since early in the course of the disorder. This evidence may provide background for the development of novel therapeutic strategies targeting this core clinical dimension of the disorder.

S161. ALEXITHYMIA AND EMOTION REPRESENTATION IN SCHIZOTYPY: EFFECTS ON SOCIAL FUNCTIONING

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Background: The ability to accurately construct and utilize conceptual knowledge about emotions may have a significant impact on an individual's social functioning abilities. Research has found that individuals on the psychosis-spectrum have difficulty identifying and describing their own emotions, which has been associated with worse social functioning outcomes. Study 1 explored whether the dimensions of schizotypy (positive, negative, disorganized) were related to the degree with which an individual differentiates between emotions, or emotion granularity. Study 2 examined the relationship between schizotypy, difficulty identifying and describing ones' emotions, emotion granularity, and social functioning.

Methods: Participants in Study 1 (N = 409) completed a measures schizotypy (Multidimensional Schizotypy Scale—Brief; MSSB), and an emotion granularity task where they rated the similarity between pairs of emotions. Participants in Study 2 (N = 238) also completed the MSSB and emotion granularity task, as well as measures of emotion understanding (Toronto Alexithymia Scale) and social functioning (UCLA Loneliness Scale; Multidimensional Scale of Perceived Social Support).

Results: Results from Study 1 revealed that higher positive symptoms were associated with lower emotion granularity ($r = -.20$, $p < .001$), while Study 2 revealed that positive ($r = -.29$, $p < .001$), negative ($r = -.28$, $p < .001$), and disorganized symptoms ($r = -.36$, $p < .001$) were all associated with lower emotion granularity.

Results from Study 2 also revealed that positive ($r = .46$, $p < .001$), negative ($r = .41$, $p < .001$), and disorganized symptoms ($r = .48$, $p < .001$) were all associated with difficulty identifying ones' emotions (DIF). Results from three separate mediation analyses indicated that difficulty identifying ones' emotions partially mediated the relationship between schizotypy symptoms and emotion granularity.

DIF partially mediated the relation between positive symptoms and emotion granularity (indirect: $b = -.03$, $p < .001$; direct: $b = -0.05$, $p = .002$), negative symptoms and emotion granularity (indirect: $b = -.03$, $p = .004$; direct: $b = -0.05$,$p = .01$), and disorganized symptoms and emotion granularity (indirect: $b = -.03$, $p = .01$; direct: $b = -.07$, $p = .002$), such that as symptoms increased, difficulty identifying ones' own emotions increased, which was associated with less differentiation between emotions.

Further, DIF partially mediated the relationship between negative symptoms and loneliness (indirect: $b = .39$, $p < .001$; direct: $b = .74$, $p < .001$), disorganized symptoms and loneliness (indirect: $b = .39$, $p < .001$; direct: $b = .77$, $p < .001$), and fully mediated the relationship between positive symptoms and loneliness (indirect: $b = .51$, $p < .001$; direct: $b = .15$, $p = .35$). DIF did not mediate the relationship between schizotypy symptoms and feelings of social support.

Discussion: Our findings replicate previous findings that individuals on the psychosis-spectrum have difficulty properly identifying and interpreting their emotions. Our findings also suggest that this population has disruptions in their emotion concept knowledge, which may be partially explained by these difficulties in understanding ones' emotional experiences.

Previous research provides evidence that people use emotion concept knowledge to create mental representations of others' emotions. Any disruption in this conceptual knowledge may thus lead to difficult with mental state inference, a known impairment across the psychosis-spectrum. Future work will investigate the roles of emotion understanding and emotion concept knowledge in disrupted mental state inference for individuals on the psychosis-spectrum.

S162. COMPARISON BETWEEN STANDARD AND HIGH-DOSE LONG-ACTING INJECTABLE ARIPIPRAZOLE INITIATION IN HOSPITALIZED PATIENTS

Santiago Ovejero*[1], Marina Llaguno[2], Raquel Alvarez[2], Laura Mata[1], Sergio Sanchez-Alonso[1]

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Background: The recommended starting dose of aripiprazole long-acting injectable (LAI) is 400 mg, which should be supplemented with oral presentation for 14 days. The present work aims to compare the results on efficacy and tolerability with lower and higher dose options of this drug during hospitalization.

Methods: Descriptive observational retrospective study by review of medical records between January 2015 and December 2022, of 48 patients over 18 years of age admitted to the short hospitalization unit of the Hospital Fundación Jiménez Díaz in Madrid. Demographic variables, therapeutic conditions prior to the administration of high doses of aripiprazole LAI, as well as post-administration variables (dose administered, length of hospital stay and side effects) were evaluated. Also, the correlation between the day of aripiprazole LAI administration and mean length of hospital stay was assessed.

Results: Forty-five patients aged 21-48 years (34.8% male), with a diagnosis of severe mental disorder (24.4% with schizophrenia, 28.9% unspecified psychosis, 31.1% bipolar disorder, 4.4% schizoaffective disorder and 11.1% delusional disorder) were included.

Seven patients received a dose of 300 mg, 14 of 400 mg, 10 of 600 mg and 14 of 800 mg. On average, it was administered 5.5+4.2 days after admission. The mean number of days of hospital stay was 13.6+9.8. Patients with early administration, in the first week, had a shorter mean length of stay (Mann-Whitney U, p=.004) than those administered after the first week of admission. No differences in hospital stay were found between the standard dose groups (300 and 400 mg) and the high dose group (600 and 800 mg) (Mann-Whitney U, p=.300). There were also no differences between these groups in the presence of side effects (Mann-Whitney U, p=.980) or in the use of biperidene (Mann-Whitney U, p=.350).

Discussion: It had been observed that earlier administration of induction doses of the drug is associated with a shorter hospital stay. In addition, no differences in hospital stay were observed between the standard dose groups and the high dose group. Comparative interventional studies would be necessary to evaluate the efficacy and safety of high-dose aripiprazole LAI administration.

S163. COMPARISON BETWEEN STANDARD AND HIGH-DOSE LONG-ACTING INJECTABLE ARIPIPRAZOLE INITIATION IN HOSPITALIZED PATIENTS

Santiago Ovejero*[1], Marina Llaguno[2], Raquel Alvarez[2], Laura Mata[3], Sergio Sanchez-Alonso[4]

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S164. THE ACOUSTICS OF PSYCHOSIS: ALTERATIONS IN VOCAL RESONANCE DURING AN UNTREATED FIRST EPISODE

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Background: Acoustic features in patients with schizophrenia are one of the less explored speech analyses and the results are still controversial. The fundamental frequency and second formant variability were associated with negative symptoms in patients with schizophrenia during a spontaneous speech sample while other authors failed to find these differences. In this work, we

analyzed the acoustic parameters in 65 first-episode psychosis (FEP) patients and in 36 matched controls (HC).

Methods: All participants underwent a clinical assessment and a picture description task (3 pictures/ one minute each) while they were recorded. For the acoustic features, we measure with VoiceSauce the fundamental frequency, formants, amplitude corrections, energy, Ceptral peak prominence, harmonic-to-noise ratio and strength of excitation. We compare the hypothesis with Bayes Factors (BF) and reported 95% credible intervals (CI) for each group.

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Discussion: Our results show a lower intensity and a higher frequency in patients with FEP compared to controls. These features are promising speech biomarkers of FEP. We call for crosslinguistic comparison for future clinical applications in diagnosis.

S165. NEUROLOGY-RELATED PROTEIN BIOMARKERS AND EARLY PSYCHOSIS: ASSOCIATIONS WITH CLINICAL DIAGNOSIS AND COGNITIVE PERFORMANCE

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Background: Stress biomarkers have been associated with the risk of developing a psychotic disorder. Proteomic analyses allow the study of multiple biomarkers, which can enhance the detection of biomarkers associated with the psychotic phenotype at early stages of the illness. We aimed to study peripheral biomarkers related to the clinical diagnosis and the cognitive phenotype in a sample of people with clinical-high-risk (CHR) for psychosis, first episode psychosis (FEP) and healthy controls.

Methods: The sample included 180 participants (95 FEP, 36 CHR and 49 healthy controls [HC]) between 18 and 35 years old. CHR and FEP participants were attending an Early Intervention Service for Psychosis. CHR diagnosis was obtained with the CAARMS. The MATRICS was administered for assessing cognitive functioning in all participants (baseline and at follow-up 1 year later for those with available information). A fasting blood sample was obtained for detecting proteomic biomarkers in plasma. Ninety-two neurology-related proteins (Olink® Proteomics) were assessed. In a first analysis, we explored the association between clinical diagnoses (CHR and FEP vs HCs) with an ANOVA. We used a p value cut-off <0.001 for selecting significant proteins (as we were conducting multiple comparisons). In a secondary

exploratory analysis, we explored the association between those selected proteins (associated with the diagnosis) and cognition in each of the 10 MATRICS cognitive tasks. Baseline associations were explored with multiple linear regression analyses (cognitive task as the dependent variable). Longitudinal associations were explored with mixed linear regression models.

Results: Of all 92 proteins, 89 surpassed the quality check control. Seven proteins were associated with the clinical diagnosis (CHR, FEP) taking into account the $p<0.001$ threshold: Carboxypeptidase A2, GDNF family receptor alpha-1, Scavenger receptor class A member, Serine/threonine-protein kinase receptor R3, Epithelial discoidin domain-containing receptor 1 (DDR-1), Neutral ceramidase, Kynureninase. Three of these proteins were associated with the cognitive phenotype (increased expression associated with poorer cognition): neutral ceramidase (speed of processing at baseline and follow-up); GDNF family receptor alpha-1 (speed of processing at baseline); DDR-1 (working memory at follow-up).

Discussion: Our study found an association between the psychotic phenotype and proteins that play a role in neurological processes involving neuronal development and apoptosis, central nervous system extracellular matrix, and development of blood vessels and coagulation. Some of these proteins were also associated with the cognitive phenotype at baseline and follow-up. Plasma levels of a number of neurology-related proteins seem to play a role in the pathogenesis and cognitive outcome of early psychosis.

S166. CO-CONSTRUCTING POOR PHYSICAL HEALTH AMONG PEOPLE WITH SCHIZOPHRENIA AS 'NORMAL'

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Background: People with severe mental illness have shortened life expectancy partly due to ill physical health. Management of coexisting mental and physical health issues as part of everyday life is complex, and knowledge about the field is lacking.

The aim of the study was to develop explanatory theory about factors influencing the interactional processes of managing physical health issues in everyday life by integrating findings from three separate analyses conducted in an ethnographic study.

Methods: This study was designed as an ethnographic study and drew on social constructionism. Nine participants with schizophrenia were recruited at two residential facilities (n=4) and an outpatient clinic providing for younger people with newly diagnosed schizophrenia (n=5). Additionally, 27 mental health care professionals contributed with their perspectives on

management of physical health in mental health services. Qualitative methods were employed, and three separate analyses were conducted using thematic and discourse analysis. A progressive focusing technique was used to integrate findings from the three analysis.

Results: An explanatory theory about the complex social processes that were enacted as part of managing physical health in everyday life was developed. Sustaining factors were identified as interacting in complex, multi-dimensional processes in the social context of everyday life, resulting in everyday life situations in which management of debilitating physical health issues with inexpedient strategies, was continuously sustained among the participants with schizophrenia.

Discussion: An explanatory theory about the complex social processes that were enacted as part of managing physical health in everyday life was developed. Sustaining factors were identified as interacting in complex, multi-dimensional processes in the social context of everyday life, resulting in everyday life situations in which management of debilitating physical health issues with inexpedient strategies, was continuously sustained among the participants with schizophrenia.