SIRS

Florence, Italy

2022 Annual Congress
Abstract Book

Wednesday, April 6, 2022

Concurrent Workshops

1:45 p.m. - 3:45 p.m.

1. SIRS EXPERT CLASSES: A BRIGHT FUTURE FOR ECRS IN SCHIZOPHRENIA RESEARCH

Gemma Modinos

King's College London

Overall Abstract: In the past year, the SIRS Membership Committee launched the SIRS EXPERT Classes, a series of exclusive virtual events for SIRS members who are early-career researchers (ECR). The overarching aim of the EXPERT Classes is to support the career development of ECRs in schizophrenia. The topics for each Class have covered some of the most important concerns at this career stage and were based on questions submitted to the Mentoring panel discussion at SIRS 2021. EXPERT Classes have provided a unique platform for ECRs to access and interact with eminent scientists in the SIRS community as role models. This series has represented an exceptional space for networking, mentoring and inspiration for SIRS ECRs, and has covered a series of topics critical for career development, delivered by leading figures in our field, including a clinical and a basic scientist. Topics have included "Finding your own path", where Robin Murray and Kim Do provided advice on research careers and the transition to independence. The second session covered "Academia and family life", where Raquel Gur and Tony Grace offered their views and guidance on work-life balance and combining a researcher's career with caring responsibilities. The third session focused on "Researcher Mobility", with Andreas Meyer-Lindenberg and Cynthia Shannon Weickert sharing their views and advice on advantages and challenges for working in different labs and locations. This fourth session will take a workshop format, as a summary session where the 6 experts are brought together in one room for a panel discussion and a direct, stimulating interaction with ECRs. This will be a unique opportunity for attendees to personally engage in an active conversation with the Experts, to ask questions and receive mentoring relevant to concerns and aspirations at this important career stage.

1.1 SIRS EXPERT CLASSES: A BRIGHT FUTURE FOR ECRS IN SCHIZOPHRENIA RESEARCH

Robin Murray

Institute of Psychiatry, King's College London

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Kim Do

Unit for Research in Schizophrenia, Center for Psychiatric Neuroscience, Lausanne University Hospital

Individual Abstract: In the past year, the SIRS Membership Committee launched the SIRS EXPERT Classes, a series of exclusive virtual events for SIRS members who are early-career researchers (ECR). The overarching aim of the EXPERT Classes is to support the career development of ECRs in schizophrenia. The topics for each Class have covered some of the most important concerns at this career stage, and were based on questions submitted to the Mentoring panel discussion at SIRS 2021. EXPERT Classes have provided a unique platform for ECRs to access and interact with eminent scientists in the SIRS community as role models. This series has represented a exceptional space for networking, mentoring and inspiration for SIRS ECRs, and has covered a series of topics critical for career development, delivered by leading figures in our field, including a clinical and a basic scientist. Topics have included "Finding your own path", where Robin Murray and Kim Do provided advice on research careers and the transition to independence. The second session covered "Academia and family life", where Raquel Gur and Tony Grace offered their views and guidance on work-life balance and combining a researcher's career with caring responsibilities. The third session focused on "Researcher Mobility", with Andreas Meyer-Lindenberg and Cynthia Shannon Weickert sharing their views and advice on advantages and challenges for working in different labs and locations. This fourth session will take a workshop format, as a summary session where the 6 experts are brought together in one room for a panel discussion and a direct, stimulating interaction with ECRs. This will be a unique opportunity for attendees to personally engage in an active conversation with the Experts, to ask questions and receive mentoring relevant to concerns and aspirations at this important career stage.

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Raquel Gur

University of Pennsylvania

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Anthony Grace

University of Pittsburgh

Individual Abstract: NA

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Cynthia Shannon Weickert

Neuroscience Research Australia: Schizophrenia Research Laboratory

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Andreas Meyer-Lindenberg

Central Institute of Mental Health, University of Heidelberg

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2. PSYCHOSIS AND INTERSECTIONALITY

Cecilia McGough

Students With Psychosis

Overall Abstract: There is no one size fits all experience, no one size fits all treatment/approach, and no one size fits all appearance for people living with psychosis. The three intersections highlighted in this workshop include LGBTQ+, BIPOC, and Comorbidity. Presenters will share their lived experience perspectives and unique needs, challenges, and barriers presented within these intersections. This workshop has the structure of lived experience testimony, facilitated discussion, and interactive activities, along with input and data collected from students and advocates living with psychosis worldwide. We want to clarify that these are not the only intersections that a person living with psychosis may have; furthermore, this workshop does not speak for the entire Psychosis or intersecting communities. Students With Psychosis is a 501(c)(3) nonprofit that empowers student leaders and advocates worldwide through community building and collaboration. We provide over 160+ hours monthly of virtual programming at no cost to our student leaders and advocates with at least five hours facilitated each day and opportunities to get more involved. Learning objectives for this workshop include: (1) resources and care for people living with psychosis must be inclusive towards intersectional community members, (2) leadership and decision-making

must center and reflect the community being served, (3) peer support/community-based care is integral to the overall wellness of people living with psychosis.

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Shira Agam

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Vera Muñiz-Saurré

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3. SIRS WORKSHOP ON WOMEN IN SCIENCE: HURDLES AND ACHIEVEMENTS

Elisabetta C. del Re

Harvard Medical School, Veterans Affairs Boston Healthcare System

Overall Abstract: One of the major goals of SIRS, since its inception, has been to strive for increasing diversity and for achieving sex equality in academia and neuroscience, with a focus on schizophrenia research and to that end has established a Diversity Task Force as a key committee. This workshop is run by the Diversity Task Force with input from the

Education Committee. There is concerning data from many academic institutions indicating a higher percentage of female researchers at early and mid-career levels but a sharp drop at senior career level. This is sometimes referred to as the "leaky pipeline". In this workshop we will examine this issue to see whether it applies to women in academic positions in neuroscience, psychiatry and psychology. We will present data from different countries and then hear from some countries who have introduced initiatives to tackle this problem. We will then host a wide-ranging discussion and end with suggestions on how we as SIRS members can help bring about change. The workshop is inspired by a paper recently published by several SIRS members in Psychiatry research [A snapshot of female representation in twelve academic psychiatry institutions around the world" Kenney J, Ochoa S,.....del Re EC, Psychiatry Research, (2022)] and follows on from a workshop held at the SIRS virtual conference in 2021. This workshop is recommended to all striving for diversity and equality.

3.1 AN UPDATE ON FEMALE REPRESENTATION IN PSYCHIATRY AND NEUROSIENCE INSTITUTIONS IN SPAIN

Susana Ochoa

Parc Sanitari Sant Joan de Deu

Individual Abstract: The representation of women in science is a lower that men. Several theories are related with this underrepresentation, one of them is the "Vicious cycle" (Clark and Horton, 2019). This framework suggest that women lead lower leadership positions in the publications, receive lower funding and have lower possibilities of access to relevant positions and this underrepresentation keeps the cycle from breaking. A research project lead by AQUAS in Catalonia suggest that only 25% of women have an important leadership in the publication. In order to understand the gender inequalities in mental health research we conduct a preliminary research. The aim was to explore the job positions of men and women belonging to the different mental health groups of our institution. The results show that higher number of men than women are coordinators of the research groups, although in several cases the co-PI was a woman. Regarding the distribution between women and men in early phases of the research career was equal considering both genders. However, the number of women with PhD were superior to the number of men. The results of the study will be discussed.

3.2 FEMALE REPRESENTATION IN ACADEMIC INSTITUTIONS IN PORTUGAL

Ana Pinheiro

University of Lisbon

Individual Abstract: The phenomenon of unequal representation of females in science will be discussed by offering empirical data from Portuguese academic institutions devoted to training and research in neuroscience and schizophrenia. The data presented suggests two pathways to career advancement that reflect sex/gender differences.

3.3 WOMEN IN SCIENCE IN TURKEY AND THE NETHERLANDS

Gamze Erzin

Dışkapı Training and Research Hospital

Individual Abstract: Efforts to increase the presence of women in science in recent years are promising. In the last ten years, in Turkey, the representation of women and men in science

become very similar in universities to which medical faculties are affiliated but it is still not enough. In the also Netherlands, there is an active effort to increase the representation of women in science. In this presentation, I will talk about the similarities and differences between these two countries and the changes over the years in terms of women in science.

3.4 FEMALE REPRESENTATION IN ACADEMIC INSTITUTIONS IN JAPAN

Jun Miyata

Kyoto University

Individual Abstract: Gender diversity is one of the most important values in the current society. To achieve this goal we need scientific evidence. In this talk, we will review the female representation in academic institutions in East Asia including Japan, and discuss the way to improve the situation.

3.5 FEMALE REPRESENTATION IN CLINICAL TRIAL RESEARCH

Kia Crittenden-Ward

Signant Health

Individual Abstract: An exploration of role and geographic trends as it relates to female representation as clinical trial researchers, both within schizophrenia trials and across other indications.

3.6 THE “WOMEN IN RESEARCH” AND "FEMALE PROFESSOR INITIATIVE" IN IRELAND

Joanne Kenney

School of Psychology, Dublin City University

Individual Abstract: There is a negative correlation between career stages and female presence in psychiatry/neuroscience research and academia in general in Ireland. The 2021 Higher Education Authority Higher Education Institutional Staff by Gender Report, published by the Higher Education Authority in Ireland, highlights that in 2019, 26% of professor posts were filled by women as compared to 74% held by men. 52% of academics on full-time temporary contracts were female, while 71% of those on part-time temporary contracts were female. In a recent paper published in Psychiatry Research (Kenney et al., 2021), this trend was found to also be reflected across three psychiatric departments in Irish institutions where there was a clear majority of females at lower career stages, replaced by a clear majority of males at higher career stages. Analysis carried out by the 2018 Gender Taskforce (Higher Education Authority) estimated that with the current recruitment and promotion practices, it could take 20 years to reach an average of 40% females at professor level in Irish institutions. There is an urgent need for improved career training and supports for female and other underrepresented groups in academia particularly those on precarious temporary contracts in early career stages (e.g. postdoctoral researchers, research fellows).

This presentation will discuss 2 recent initiatives to address this negative correlation between career stages and female presence in academia and the barriers women face in their academic careers in Ireland. The SALI (Senior Academic Leadership Initiative (SALI)) is a new initiative run by the Higher Education Authority (HEA) which aims to accelerate gender equality at the senior levels i.e. professor or senior lecturer level. It is aimed that up to 30 posts will be filled by 2022 as part of the scheme. Women and other underrepresented groups can encounter

significant barriers in their promotion to senior academic positions. Women in Research Ireland (WIRI), a volunteer-run charity, was established in 2017 to provide support and a platform for women and other underrepresented groups in academia. WIRI organises monthly events and workshops aimed at addressing a variety of issues faced by these groups in their careers.

3.7 ATHENA SWAN: ADVANCING GENDER EQUALITY IN HIGHER EDUCATION IN IRELAND

Avril Hutch

University College Cork

Individual Abstract: Athena SWAN, a gender equality charter for higher education institutions (HEIs), launched in Ireland in 2014. Athena SWAN requires the development of a gender equality action plan, informed by quantitative and qualitative data analysis. Successful applicants must undertake a comprehensive critical self-assessment, evidence-based reflection on the findings, and set out/implement SMART actions to address any issues highlighted. An important component to this success of Athena SWAN is that HEIs are required to attain this accreditation in order to retain research funding from the three main Irish research funding bodies. Awards are granted at institutional and departmental level across three categories of bronze, silver and gold and must be renewed/upgraded every four years.
Athena SWAN has resulted in significant cultural changes in the Irish HEI sector. The process has resulted in a marked increase in female representation in higher education institutions across the Ireland. When Athena SWAN commenced in 2014, there were no female Presidents of seven Irish universities, in 2022 there are four. Positive actions measures include a dedicated female professorship scheme, which was launched in 2019. This paper will assess the impact of Athena SWAN on the Irish HEI sector and map the opportunities and lessons learned from intersectional Athena SWAN gender equality action plans that might be applied in other disciplines.

4. SIRS EARLY CAREER AWARD WORKSHOP 2022: WHAT CAN WE LEARN FROM OUR RISING STARS?

Susan Rossell

Swinburne University

Overall Abstract: Since its inception SIRS has been dedicated to supporting the continued development of early career researchers and clinicians. The Awards program has supported 100s of applicants, many of which have gone on to have established and decorated careers.
The aim of this current workshop is to hear from three awardees. The awardees will speak about their careers, their goals and the benefit that the SIRS Early Career Award had on their career. We will hear about their journey to becoming a successful schizophrenia researcher. Our speakers have been selected across the last 10 years of awardees from 2014 Dr Yuliya Zaytseva (Czech Republic), 2018 Dr Eric Tan (Australia), to most recently, 2020 Dr Alessandro Pigoni (Italy).

This workshop is recommended for all, but especially for those at the inception of their careers who may want to get some useful tips to assist with their journey.

4.1 A GUIDE FOR BUILDING AND MAINTAINING INTERNATIONAL COLLABORATIONS

Yulia Zaytseva

National Institute of Mental Health

Individual Abstract: I have been extremely fortunate to receive SIRS award that has been real game-changer in terms of what it has allowed me to accomplish in my academic career. It helped to build international ties through research collaboration which is the key to build and maintain a successful research career in today's globalized world. Interdisciplinary and inter-organizational collaborations enabled me to: 1) expand my network (to meet my mentor and other important collaborators, and to become a member of the International Hallucinations Consortium); 2) learning new skills and expanding the expertise in phenomenology and neuroscience; 3) maximize the outputs by bringing together various resources that helped to initiate collaborative projects; 3) attract funding (both national and international); 4) increase the scientific impact by publishing collaborative papers.

4.2 BALANCE AND BLEND

Alessandro Pigoni

IMT School for Advanced Studies - Lucca

Individual Abstract: Since I have always found life’s intricacy so fascinating, the choice of becoming a medical doctor was the most logical and, in some ways, essential. Within medicine, the human brain interests me the most, as the source of emotions, art, and philosophy, but diseases too. I became a psychiatrist because I had the desire to understand mental processes and to identify the source of psychiatric problems, hence my interest in neuroscience.
I chose psychiatry also because it gives me the possibility to confront myself with the human being in every single moment of my profession.

Therefore, I do believe that research should always be patient-centered and needs always to come back to the patient's bed. I try to balance clinical and research work since both are essential and not separable for me.

My research journey brought me to Yale University, to study cells and animal models, and then to the Ludwig-Maximillian University in Munich, to learn machine learning techniques. I did my residency in Milan and then moved to the IMT School for Advanced Studie in Lucca for my Ph.D., in a very rich environment where I had the possibility to confront myself with professionals from other disciplines, such as engineering, economics, computer sciences, and also visual studies. I think this "contamination" or blend from different sources really brought me where I am and I hope this journey will continue in this way.

4.3 WHEN I CHOSE THE RIGHT FORK IN THE ROAD

Eric Tan

Swinburne University of Technology

Individual Abstract: The 7 years since I completed my PhD have been an enlightening experience into the workings of research and academia, as well as a greater appreciation of the complexities of my chosen topics of study. Moving from Singapore to Melbourne, Australia was a catalyst for change. Curious by nature, there is still a lot I want to know about. Ups and downs are part of the research ride, and in this talk I will discuss my career trajectory thus far,

what else I would love to do and how being part of organisations like SIRS has been a major positive for me personally and professionally.

Keynote Lecture: Students with Psychosis by Cecilia McGough

4:45 p.m. - 5:45 p.m.

5. KEYNOTE: STUDENTS WITH PSYCHOSIS

Til Wykes

Institute of Psychiatry, Psychology and Neuroscience

Overall Abstract: People with a diagnosis of psychosis are often left out of the mental health/brain health conversations on college campuses. Cecilia McGough, the founder of the non-profit organisation "Students With Psychosis", with colleagues will tell us about their student-led lived experience work and what SIRS members can contribute to help overcome the challenges of social and educational inclusion.

5.1 STUDENTS WITH PSYCHOSIS

Cecilia McGough

Students With Psychosis

Individual Abstract: Students are fed up with the current public perception of psychosis. In this keynote, Founder and Executive Director Cecilia McGough of the nonprofit Students With Psychosis is joined by their colleagues to voice the student-led lived experience perspective and the nonprofit's origins, current activity, and future goals. Students With Psychosis is a 501(c)(3) nonprofit that empowers student leaders and advocates worldwide through community building and collaboration. Students With Psychosis provides over 160+ hours monthly of virtual programming at no cost to their student leaders and advocates with at least five hours facilitated each day and opportunities to get more involved. Students With Psychosis envisions a world where no student or advocate living with psychosis worldwide goes without community and access to education. Students With Psychosis values (1) the lived experience perspective in leadership positions, (2) both the accurate and respectful representation of people living with psychosis, (3) community, workplace, and educational environments to not only be supportive but also empowering to people living with psychosis, (4) a person's worth is not determined by grades or degree level, and (5) shared decision making in treatment options. Students With Psychosis does not promote any particular treatment option. Students With Psychosis aims to expand mental health/brain health advocacy at the college level to ensure psychosis representation, including a global perspective. Too often is psychosis left out of the mental health/brain health conversation on college campuses, and our narrative is also often limited, excluding intersectional community members. The nonprofit's primary objectives include (1) growing and connecting their virtual and in-person programs, (2) organizing outreach initiatives, and (3) founding in-person college clubs/affiliates/hubs.

Thursday, April 7, 2022

Plenary Session I: Oye Gureje

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

6. NEW WAYS OF SEEING THE WORLD - LESSONS FROM THE STUDY OF PSYCHOSIS IN UNDERSTUDIED POPULATIONS

Robin Emsley

University of Stellenbosch

Overall Abstract: While schizophrenia and related psychotic disorders occur across the world, most of the research is conducted in relatively few well-resourced countries. Understudied populations provide novel and unique research opportunities for better understanding psychotic disorders. In this plenary lecture, Professor Oye Gureje considers these opportunities.

6.1 NEW WAYS OF SEEING THE WORLD - LESSONS FROM THE STUDY OF PSYCHOSIS IN UNDERSTUDIED POPULATIONS

Oye Gureje

College of Medicine, University of Ibadan

Individual Abstract: Psychotic disorders are a major cause of disease burden globally, with impact on individual sufferers, their families, and societies. Despite their huge public health importance, there is still so much we do not know about these disorders. Variations in rate of occurrence and what social and other contextual factors may be undergirding them, lay understanding of the disorders and its possible influence on how affected persons and their families make sense of their situation, help-seeking behavior and how differences in the pattern of care may affect outcomes, are a few of currently existing gaps in knowledge. On the other hand, what we currently know these disorders has been provided mainly by researchers working in the global North. Understudied populations in different parts of the work, particularly those in the global South, may provide opportunities for filling current gaps in knowledge and, perhaps, provide leads that may raise new vistas of enquiry. In this lecture, an insight is provided to some of the possibilities for such expansion in knowledge. Drawing on studies examining lay views of psychosis, especially of schizophrenia, the prototypical psychotic disorder, onset and course of psychosis, treatment approaches and how they affect outcomes, the lecture will seek to highlight how the findings from such studies may help provide new ways to address the burden of psychotic disorders in different populations.

Concurrent Symposia

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

7. COGNITIVE DECLINE IN SCHIZOPHRENIA: ORIGINS, LIFE COURSE, AND MECHANISMS

Abraham Reichenberg

Icahn School of Medicine at Mount Sinai

Overall Symposia Abstract: This symposium will look at new research on the origins and course of the neurocognitive impairment in schizophrenia across the lifespan by going beyond cross-sectional description of group averages. Specifically, the four speakers will focus on core questions around (1) course, (2) familial vs. disease specific, and (3) potential biological mechanisms and biomarkers of cognitive decline.

Dr. Katherine Jonas will present new data charting the trajectory of IQ from age 5 to 76 in schizophrenia and other psychotic disorders. Data are from the Suffolk County Mental Health Project, in which premorbid IQ scores were extracted from school and medical records, and post-onset IQ scores were based on testing at 6-month, 24-month, 20-year, and 25-year follow-ups. The study identified three phases of cognitive change, with evidence for premorbid decline in schizophrenia, and accelerated cognitive decline in late adulthood in all psychotic disorders.

Dr. Avi Reichenberg will focus on the origins of the cognitive impairment in schizophrenia, examining the hypothesis that the early cognitive impairment in schizophrenia reflects a decrement from the expected familial level of cognitive functioning. Building on unique multi-generation information from the Israeli Conscripts Cohort and linking cognitive test scores to psychiatric hospitalization data on father-offspring pairs showed progressively increasing cognitive impairment across generations: Fathers of future schizophrenia patients had a cognitive impairment when they were teenagers. The cognitive impairment in the offspring was greater than that in their respective fathers when the fathers were at the same age. Low paternal IQ was associated with increasing risk for schizophrenia in the offspring.

Dr. Heather Whalley will present work investigating the impact of parent-offspring deviation in cognitive ability on psychopathology in a general population sample. Prior studies have defined deviation in intelligence in reference to population norms. However, given the high heritability of intelligence, the degree of parent-offspring deviation in intelligence may provide a more personalized, possibly more sensitive, measure of the association between cognition and psychopathology. Using cognitive data from the Generation Scotland (N=23,000) study, a large community-based sample of parents and offspring, we show that that parent-offspring cognitive deviation was significantly associated with schizotypal symptoms, but not measures of mood-related symptoms. Comparisons with general cognition will also be discussed.

Finally, Dr. Oliver Howes will focus on the mechanism underlying cognitive impairments in schizophrenia. He will present new multi-modal imaging PET and fMRI data of synaptic terminal density and neural activity during cognitive tasks in patients with schizophrenia across the course of the disorder from first episode to chronic schizophrenia. These data provide in vivo evidence for lower synaptic terminal density in schizophrenia, and that the normal relationship between synaptic terminal density and neural activity during cognitive processing is disrupted in schizophrenia, and that this is potentially linked to glutamate synaptic loss. This provides a potential mechanism to explain cognitive impairments in schizophrenia.

The four presentations of this symposium will offer new insights into the neurocognitive impairment in schizophrenia, and an up-to-date summary of what we know and need to know. Discussant Dr. David Glahn will summarize the findings for the audience and highlight future directions.

7.1 THE COURSE OF COGNITIVE DECLINE IN PSYCHOTIC DISORDERS

Katherine Jonas*[1], Wenxuan Lian[1], Jennifer Callahan[2], Camilo Ruggero[2], Sean Clouston[1], Abraham Reichenberg[3], Gabrielle Carlson[1], Evelyn J. Bromet[1], Roman Kotov[1]

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Background: Schizophrenia is associated with major cognitive deficits, and has been conceptualized as both a neurodevelopmental and a neurodegenerative disorder. The neurodevelopmental model posits cognitive deficits emerge due to disruptions in brain development, marking the beginning of a disease process that ends in psychosis. The neurodegenerative model conceptualizes the illness as the result of progressive deterioration. The former predicts cognitive deficits stabilize after illness onset, while the latter implies cognitive declines continue. Despite these well-established theories, a great deal remains unknown about when cognitive deficits emerge and how they change over the illness course. To our knowledge, no study has charted the cognitive trajectories of individuals with schizophrenia and other psychotic disorders across the lifespan. Following individuals across long periods of time is necessary to identify when cognitive decline begins, and how it progresses across the illness course. This study's purpose was to trace cognition from elementary school to old age, in order to test neurodevelopmental and neurodegenerative theories of psychotic disorders.

Methods: Data are drawn from the Suffolk County Project, a longitudinal study of first-admission psychosis. During the baseline assessment period (1989-1995), individuals in their first admission for psychotic symptoms were recruited from all 12 inpatient facilities in Suffolk County, New York. The response rate during this wave was 72%. Eligibility criteria included residence in Suffolk County, age between 15 and 60, ability to speak English, no diagnosis of intellectual disability, first admission within the past 6 months, current psychosis, no apparent medical etiology for psychotic symptoms, and capacity to provide informed consent. The Stony Brook University Committee on Research Involving Human Subjects and the hospital institutional review boards approved the protocol annually. Written consent was obtained from all study participants, or from their parents for those who were minors. Six-hundred and twenty-eight individuals were ascertained at baseline. These analyses are based on the 428 individuals within the cohort for whom at least 2 IQ scores were available, from either premorbid or follow-up assessments, and therefore a cognitive trajectory could be estimated. Premorbid cognitive function was assessed by collecting data from participants' school records. Post-onset cognitive function was assessed through neuropsychological batteries at the 6 month, 24 month, 20 year, and 25 year follow up interviews. Altogether, 1619 IQ scores were available across the lifespan.

Results: The best-fitting model for the full cohort included three phases. The first phase spanned childhood to 10 years before symptom onset, during which IQ was stable. Ten years before symptom onset--when the average participant was 17 years old--the trajectory changed to one of decline, which continued until 23 years after symptom onset. On average participants lost 1 point every 4 years during this phase. In the final phase, IQ decline accelerated to a rate of more than 1 point every 2 years. Diagnosis moderated this trajectory, such that those with schizophrenia experienced a more rapid decline (1 point every 3 years) in the second, declining phase, than those with other psychotic disorders (1 point every 7 years).

Conclusions: Schizophrenia has been described as both a neurodevelopmental and a neurodegenerative disorder. Our findings provide support for both theories. We observe cognitive decline beginning in adolescence, implying abnormal neural development. However, continued cognitive decline after psychosis onset and accelerated decline in the third decade of illness is consistent with the neurodegenerative theory. The pace of decline in schizophrenia, while gradual, resulted in over 16 IQ points lost over the lifespan. In other psychotic disorders, the rate of decline is initially slower but accelerates, resulting in a loss of 9 IQ points. Interventions to prevent this cognitive cascade are urgently needed, as cognitive deficits leave millions unable to function in society.

7.2 PREMORBID INTELLECTUAL DECLINE IN SCHIZOPHRENIA: EVIDENCE FROM A POPULATION BASED TRANSGENERATIONAL STUDY

Abraham Reichenberg*[1], Mark Weiser[2], Michael Davidson[3]

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Background: Evidence suggests that some future schizophrenia patients experience intellectual deterioration from childhood through adolescence. It has been proposed that in some patients the early cognitive impairment may reflect failure to reach the expected level of cognitive functioning based on familial potential.
Methods: The study used a nested case-control design. The cohort comprised of all 17-years-old adolescents who, over the course of 5-years, received a mandatory assessment by the Israeli Draft-Board for intellectual performance and educational attainment. Cases were 159 cohort-members with a diagnosis of adult-onset schizophrenia ascertained through linkage to the National Psychiatric-Hospitalization Registry. Data on intellectual performance and educational attainment of the fathers of cases were also obtained from the Draft-Board. Each case-father pair was individually matched to 5 control- father pairs by gender, birth year of the case, school attended at time of testing and father's year-of-assessment by the Draft-Board.
Results: Fathers of future patients had significantly lower IQ scores compared of fathers of controls ($p<0.001$; Effect Size: 0.31). As expected, future cases also had significantly ($p<0.001$) lower IQ scores compared to controls. However, the magnitude of effect was 30% larger than that of their fathers (Effect size: 0.42). The magnitude of this effect increased after accounting for changes over generations in education. More than one third of future patients had premorbid IQ scores that were lower-than-predicted based on father's IQ. Furthermore, lower IQ in fathers was significantly associated with increased risk for schizophrenia in the children. Lower child IQ was also associated with increased risk for schizophrenia, including after adjusting for the father's IQ.
Conclusions: A large proportion of future patients show intellectual function decrement before the onset of schizophrenia as defined by a failure to reach expected level of functioning based on father's intellectual levels.

7.3 PARENT-OFFSPRING COGNITIVE DEVIATION IN A GENERAL POPULATION FAMILY-BASED SAMPLE

Heather Whalley[1], Miruna Barbu[1], Shalaila Haas[2], Rene Kahn[2], Avi Reichenberg[2], Sophia Frangou[2], Miruna Barbu*[1]

[1]*University of Edinburgh,* [2]*Icahn School of Medicine at Mount Sinai*

Background: General intelligence has been shown to be a predictor of multiple functional outcomes, including mental health. Prior studies linking cognition and psychopathology have typically defined deviation in intelligence in reference to population norms. However, given the heritability of intelligence and the close resemblance in parent-offspring cognitive ability, it has been argued that the degree of parent-offspring deviation may provide a more personalized and potentially more sensitive measure of cognitive deviation in relation to psychopathology. Here, we used a large family-based cohort to compare the offspring's own measure of intellectual ability with a parent-offspring cognitive deviation measure, in relation to psychopathology measures.
Methods: In the Generation Scotland cohort (N=23,000; N=3,506 parent-offspring pairs), we applied principal component analysis to four cognitive tests to obtain a general intelligence component score (g) for all participants. The parent-offspring cognitive deviation was

computed by subtracting parent g from offspring g. We then associated both measures with three psychopathology measures: the General Health Questionnaire (GHQ), the Mood Disorder Questionnaire (MDQ), and the Schizotypal Personality Questionnaire-Brief (SPQ-B). Additional analyses were run separately in offspring of parents with (N=542) and without (N=2,942) a family history of psychopathology, and further we tested whether excluding offspring with a lower IQ had an effect on this association (N=2,974).

Results: Offspring g was significantly associated with all three psychopathology measures (SPQ: beta=-0.135, p<10-8, GHQ: beta=-0.060, p=0.003, MDQ: beta=-0.075, p=0.007). Parent-offspring cognitive deviation measure was only associated with SPQ (beta=-0.069, p=0.009). Sensitivity analyses indicated significant associations between all psychopathology measures and offspring g for those whose with parents who had a history of psychiatric disorders (SPQ: beta=-0.238, p=0.0008; GHQ: beta=-0.139, p=0.013; MDQ: beta=-0.161, p=0.035), as well as those with no family history (SPQ: beta=-0.121, p<10-6; GHQ: beta=-0.044, p=0.042; MDQ: beta=-0.064, p=0.028). SPQ was significantly associated with the parent-offspring cognitive deviation measure when stratifying by history of psychiatric disorders, only in those with no family history (history present: SPQ: beta=-0.071, p=0.323, GHQ: beta=-0.001, p=0.979, MDQ: beta=-0.098, p=0.199; history absent: SPQ: beta=-0.081, p=0.004; GHQ: beta=-0.022, p=0.336; MDQ: beta=-0.047, p=0.135). Finally, offspring g was significantly associated with SPQ (beta=-0.098, p=0.0002) and MDQ (beta=-0.081, p=0.006), but not with GHQ (beta=-0.017, p=0.423) when stratifying by IQ. The parent-offspring cognitive deviation measure was not associated with any psychopathy measures in this subset (SPQ: beta=-0.05, p=0.087, GHQ: beta=0.013, p=0.579, MDQ: beta=-0.057, p=0.077).

Conclusions: These findings support previous reported associations between cognition and mental health , particularly for measures of schizotypy. This was reported here for both general intellectual ability and, extending this work, to the parent-offspring cognitive deviation scores. This pattern remained similar for all stratified samples for general intellectual ability, but was only consistent for the parent-offspring cognitive deviation in those with no family history, potentially related to sample size. Notably however, effect sizes for associations with psychopathology were consistently higher for measures of general intellectual ability than for the parent-offspring cognitive deviation measure in this community sample. Exploration of the parent-offspring cognitive deviation measure in a case-based sample may be required to further test the additional utility of this more personalised measure of cognitive deviation in relation to clinical outcomes.

7.4 THE RELATIONSHIP BETWEEN COGNITIVE FUNCTION AND SYNAPTIC TERMINAL DENSITY IN SCHIZOPHRENIA

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Background: It is hypothesized that aberrant synaptic pruning underlies cognitive impairments in schizophrenia. Supporting this, post-mortem studies show lower synaptic density in schizophrenia, and functional imaging studies show that schizophrenia is associated

with impaired functional connectivity and altered responses during cognitive tasks. However, whether there is loss of synapses in vivo in patients, and whether this underlies altered functional connectivity and cognitive impairments in schizophrenia remains unclear. Finally, it has been hypothesized that antipsychotics reduce whilst lithium increases synaptic density. However, it is not clear if psychotropic drugs alter synaptic marker levels measured in vivo in patients. It is now possible to measure levels of a protein, synaptic vesicle glycoprotein 2A (SV2A), in vivo in people and animals using PET imaging. SV2A is ubiquitously expressed in synaptic terminals, providing an in vivo measure of synaptic density. We used this novel technology to address these questions using complementary clinical and preclinical studies.
Methods: Study 1: Seventy subjects (n=35 subjects with chronic or first episode schizophrenia; n=35 controls) received PET imaging using [11C]UCB-J with arterial sampling to index SV2A distribution volume ratios (DVR). Subjects also received fMRI to measure resting state functional connectivity during resting state and the trail making task.
Study 2:

Sprague-Dawley rats were randomised to receive either lithium, antipsychotic treatment or vehicle for 28 days (n=10-12/group). Synaptic Vesicle glycoprotein 2A (SV2A) markers and Neuroligin (NLGN) clusters were measured in frontal cortex by western blot, quantitative autoradiography using [3H]-UCB-J, or immunostaining and confocal microscopy.

Results: Study 1: [11C]UCB-J DVR was significantly lower in patients relative to controls in cortical regions (anterior cingulate cortex, ACC, $p = 0.001$, Cohen's $d = 1.1$). There was a negative relationship between performance on the trail making task and frontal UCB-J DVR in the patients with schizophrenia ($r=-0.63$, $p<0.05$). In healthy volunteers, [11C]UCB-J DVR in the default mode network was significantly positively correlated with the fractional amplitude of low frequency fluctuations in the default mode (HV, $r=0.56$, $p=0.002$), but this relationship was not seen in patients with SCZ ($p>0.30$). There was no significant relationship between prior antipsychotic exposure and DVR ($p>0.3$).
Study 2: There was no effect of antipsychotic or lithium treatment on SV2A markers or total synaptic clusters (p values all>0.4). There was a significant group effect on the neurolignin cluster density ($F(1,28)=8.478$; $p<0.01$) driven by an increase in neurolignin in the lithium group.

Conclusions: As SV2A is ubiquitously expressed in synaptic terminals, these data indicate lower synaptic density in schizophrenia and indicate that lower synaptic density is associated with poorer cognitive performance. Moreover, they also indicate that there is a loss of the normal relationship between functional connectivity in the default mode network and synaptic density in schizophrenia. Together these findings are consistent with synaptic loss leading to dysconnectivity and cognitive impairments in schizophrenia. Antipsychotic or lithium did not affect synaptic terminal markers, despite lithium increasing post-synaptic marker levels, indicating that findings of lower synaptic density in schizophrenia are unlikely to be due to treatment effects. These findings add to other data indicating that synaptic loss could lead to cognitive impairments in schizophrenia.

8. VULNERABILITY TO EARLY-LIFE INSULTS AS A RISK FACTOR FOR PSYCHIATRIC DISORDERS: DEVELOPMENTAL TRAJECTORIES AND LONG-TERM CONSEQUENCES

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Overall Symposia Abstract: Exposure to early-life insults is an important environmental risk factor for psychiatric and neurological disorders with neurodevelopmental components, such as schizophrenia and autism. When occurring during sensitive periods of brain development, environmental stressors have the potential to change the offspring's neurodevelopmental trajectories and increase the risk to develop psychiatric and neurological disorders later in life. Despite the increasing evidence from both clinical and preclinical research for significant health consequences of early-life insults, it is important to note that the long-term outcomes are variable and heterogenous. The underlying developmental factors that are determining vulnerability or resilience, however, remain largely unknown. Yet, a further understanding of the developmental trajectories and molecular underpinnings that determine vulnerability and resilience is of critical importance for the development of alternative, more targeted treatment and preventive approaches, as demanded for personalized medicine. Against this background, our multidisciplinary symposium will bring together the expertise of key opinion leaders working on distinct aspects in this area of research and comprise novel findings from animal models and clinical cohorts across different early-life insults: Prof. Anthony Grace (University of Pittsburgh) will discuss how early life stress affects susceptibility to major psychiatric disorders in rat models, that is dependent on the timing of stress. Specifically, lesions of the prelimbic PFC, which regulates stress responses, makes rats more vulnerable for schizophrenia, depression and anxiety as adults. Stress administered prepubertally causes a precocious maturation of the amygdala-prelimbic PFC projection. He discusses how preadolescent stress-induced precocious maturation of amygdala-PFC plasticity is enabling early adaptation to stress with the consequence of increased vulnerability to pathology in adults. Dr. Ulrike Weber-Stadlbauer (University of Zurich) will present data on vulnerability towards maternal immune activation in isogenic mice and show how adult offspring can be stratified into resilient and susceptible subgroups based on behavioral, molecular or neuroanatomical signatures. She will also discuss that an early-onset of behavioral deficits can predict the dissociation into resilience and susceptibility in adulthood, with potential implications for preventive treatment approaches. Prof. Marco A. Riva (University of Milan) will show how exposure to prenatal stress in rodents produces short and long-lasting changes on brain function. He will specifically focus on adolescence as a critical time window for the manifestation of a fully blown phenotype, but also for developing new approaches aimed at minimizing the pathologic consequences of early in life stress exposure. Dr. Annamaria Cattaneo (IRCCS Fatebenefratelli Institute, University of Milan) will show biological blood transcriptomic signatures mapping patients with schizophrenia and with a childhood trauma history and the role of miRNAs in mediating the effect of early stress on the underlying biology.
Together with the discussant (Tertia Purves-Tyson, Neuroscience Research Australia), the expert panel of speakers will discuss how these findings can advance the understanding of mechanisms involved in vulnerability towards early-life insults and the potential towards the identification of novel, more targeted strategies for preventive and therapeutic interventions.

8.1 PREPUBERTAL STRESS CAUSES PRECOCIOUS MATURATION OF THE AMYGDALA-PREFRONTAL PATHWAY AND INCREASES VULNERABILITY TO DYSFUNCTION IN ADULT RODENTS

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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 stressors or disruption of stress regulation increases vulnerability to disorders in adulthood. We have found that the pathological consequences depend strongly on the timing and intensity of the stressors.
Methods: Male and female rats were subjected to either daily handling or daily footshock + 3 restraint sessions over 10 days from PD21-30 (prepubertal), 31-40 (peripubertal) or from PD41-50 (postpubertal) and tested at PD 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. Stimulating electrodes were implanted in the BLA or plPFC, and evoked responses recorded in the plPFC or BLA, respectively. Behavioral tests include elevated plus maze (EPM) and novel object recognition (NOR).
Results: Male rats that received combined stressors prepubertally exhibited hyperdopaminergic state (increased number of DA neurons firing) as well as anxiety and deficits in NOR in the adult; however female rats were resilient to the stressors. In contrast, exposure to stress postpubertally caused female rats to exhibit increased DA population activity, primarily in the affect-related medial VTA; in this case the males were resilient. In the vHip and BLA prepubertal stress caused elevated firing rate in the male and postpubertal stress caused elevated vHip firing rate in females, without affecting the other sex. In normal rats high frequency stimulation (HFS) of the BLA elicited LTD in the PFC only in adult rats; however, after peripubertal stress HFS showed precocious development of LTD. Sex differences in P21-30 prepubertal stress-induced PFC-BLA plasticity deficits were observed, again indicating male-specific precocious development.
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 similar to that observed in MAM models of schizophrenia, whereas females are resilient. In contrast, female rats were susceptible only to stress administered postpubertally and demonstrated alterations only in the affect-related medial VTA, consistent with anxiety and susceptibility to depression. We propose that prepubertal stress causes precocious maturation of the reciprocal BLA-PFC and PFC-BLA pathway as a means of dealing with trauma; however, the consequence is that the abnormal development of stress responsivity renders the subject vulnerable to affective disturbances as adults.

8.2 SUSCEPTIBILITY AND RESILIENCE IN A MOUSE MODEL OF MATERNAL IMMUNE ACTIVATION

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Background: Epidemiological studies over the past decades have repeatedly implicated maternal immune activation (MIA) in the etiology of psychiatric illnesses, including schizophrenia and related psychotic disorders. Not all offspring exposed to MIA, however, develop overt pathologies, suggesting that some are susceptible while others are resilient to MIA. To elucidate susceptibility and resilience in MIA, we used a mouse model that is based on prenatal exposure to the viral mimic poly(I:C).

Methods: Poly(I:C)-based MIA was induced in C57BL6/N mice on gestation day 12. Control dams received vehicle solution only. Offspring of poly(I:C)- or vehicle-exposed dams were subjected to a comprehensive behavioral testing battery in adolescence and/or when they reached adulthood (12 weeks of age onwards). Peripheral cytokine levels were measured to assess the inflammatory cytokine status of adult MIA and control offspring. Moreover, next-generation mRNA sequencing and gene pathway analyses were conducted after behavioral testing to explore the molecular correlates of resilience and susceptibility to MIA.
Results: Behavioral characterization coupled with unbiased TwoStep cluster analysis of a large number offspring (N >150) revealed that offspring exposed to MIA could be stratified into susceptible and resilient subgroups. While the former was characterized by deficits in social interaction, sensorimotor gating, and working memory, the behavioral profile of the latter was indistinguishable from control offspring. Susceptible and resilient MIA offspring were also dissociable by the presence of distinct molecular profiles in cortical and subcortical brain areas. In the medial prefrontal cortex, susceptible MIA offspring displayed a more profound deregulation of genes relevant for oxidative phosphorylation and mitochondrial functions than resilient MIA offspring. In the amygdala, the susceptible and resilient offspring differed in gene transcription pertinent to DARPP-32 signaling, and G protein-coupled receptor signaling. In a second, independent cohort containing 50 MIA and control offspring, we identified a subgroup of MIA offspring that displayed elevated peripheral production of innate inflammatory cytokines, including IL-1β, IL-6, and TNF-α, in adulthood. This subgroup also showed significant impairments in social approach behavior and sensorimotor gating, whereas MIA offspring with a low inflammatory cytokine status did not. Behavioral characterization in adolescence and adulthood revealed an early-onset and a predictive potential of MIA-induced behavioral deficits.
Conclusions: Our data show that MIA can result in substantial phenotypic and transcriptomic variability even in the context of genetic homogeneity and under identical experimental conditions. If extended further, our model system may help to explain why only a subgroup of offspring exposed to MIA develops overt neurodevelopmental sequelae. These data have relevance for advancing our understanding of the variable neurodevelopmental effects induced by MIA and for biomarker-guided approaches in preclinical psychiatric research.

8.3 ADOLESCENCE: THE CROSSROADS BETWEEN EARLY LIFE STRESS AND PSYCHOPATHOLOGY

Marco Andrea Riva*[1]

[1]*University of Milan*

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.
Methods: We performed genome-wide and targeted analyses across postnatal development in different brain regions of rats exposed to stress during gestation (PNS), a model that is associated with persistent behavioral and functional alterations relevant for psychiatric disorders.
Results: We found that PNS exposure produces an array of behavioral alterations, including anhedonia and reduced sociability, which become manifest around adolescence. Such

abnormalities are associated with transcriptional and epigenetic changes of many genes throughout postnatal development. While long.-term changes affect several biological systems, including neuronal plasticity and glucocorticoid signaling, we also observed profound alterations in inflammatory and immune mechanisms that peak around adolescence. Interestingly some of these changes can be corrected or prevented by sub-chronic treatment with the antipsychotic drug lurasidone during adolescence.
Conclusions: Our data provide support to the notion that early life stress leads to permanent functional and molecular changes in the offspring. Most of these alterations become fully manifest around adolescence, which is a critical time for the onset of different psychiatric disorders. However, adolescence may also represent an important time window for therapeutic intervention aimed at preventing or reducing the disease risk associated with early life stress exposure.

8.4 CLUSTERS OF MIRNAS TARGETING NEURODEVELOPMENTAL AND INFLAMMATORY RELATED PROCESSES ASSOCIATED WITH CHILDHOOD TRAUMA EXPOSURE AND SCHIZOPHRENIA DEVELOPMENT

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Background: MicroRNAs (miRNAs), one of the major small non-coding RNA classes, have been proposed as regulatory molecules in neurodevelopment and stress response. Although alterations in miRNAs profiles have been implicated in several psychiatric and neurodevelopmental disorders, the contribution of specific miRNAs in brain development and function is still unknown. Moreover, no findings are available on how vulnerability factors for these disorders, such as early life stress (ELS), can modulate the expression of specific clusters of miRNAs and their target genes and related pathways.
Methods: To cover this, here we have investigated the entire miRNOme profile from blood samples of patients with schizophrenia as well as from a group of control individuals, all characterized for childhood trauma events. We then run a targeting gene-based approach analyses by using miRWalk Software and pathway analyses by using Ingenuity Pathway Analyses.
Results: We have identified a panel of 27 miRNAs which are altered in the group of controls exposed to childhood trauma as compared to non-exposed subjects; moreover, 12 miRNAs out of these 27 have been also found affected also in the group of patients with schizophrenia. Interestingly, a pathway analyses revealed an enrichment in biological processes related to neurodevelopment and inflammation. As an example, we found that miRNA-19, which is a key regulator of brain trajectories, since it drives the differentiation of neural stem cells into mature neurons, is significantly downregulated both in controls exposed to childhood trauma (FC = −1.29, p-value = 0.024 for miR-19a; FC = −1.29, p-value = 0.016 for miR-19b in CTRL exposed to CT vs CTRL not exposed to CT) and also in patients with schizophrenia (FC = −1.21, p-value = 0.045 for miR-19a; FC = −1.19, p-value = 0.047 for miR-19b). When we tested the levels of some of the miRNA-19 target genes, we observed a significant increase of NRCAM (FC = 1.20, p-value = 0.027), IL4R (FC = 1.16, p-value = 0.046), and RAPGEF2 (FC = 1.21, p-value = 0.023) in patients with schizophrenia.
Conclusions: We suggest that ELS can cause a long-term downregulation of specific miRNAs which may be responsible of alterations in neurodevelopmental pathways and in immune/inflammatory processes, leading to an enhanced risk for schizophrenia later in life.

Intervention strategies targeting specific clusters of miRNAs may prevent alterations in these pathways, reducing also the impact of the ELS-related consequences.

9. BRIDGING THE GAP BETWEEN STANDARDS AND PRACTICES FOR IMPROVING OUTCOMES IN EARLY INTERVENTION FOR PSYCHOSIS: LEARNING FROM FIDELITY MONITORING AND LEARNING HEALTH SYSTEM APPROACHES IN FOUR COUNTRIES

Srividya Iyer

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Overall Symposia Abstract: While the early intervention service (EIS) model for psychosis has proven superior to usual care and has been widely implemented, evidence-practice gaps and adherence to standards/guidelines remain challenging. Furthermore, measurement and performance monitoring have not been consistently deployed in practice. These are critical gaps because such monitoring is essential to ensuring fidelity to the essential components of early intervention, a necessary condition to realize its promise of better outcomes. There has thus been growing attention globally to measuring adherence to the EIS model as enshrined in guidelines/standards. More recently, performance monitoring is being combined with implementation guidance and training to support programs in optimising interventions and adhering to best practices/standards. A range of strategies from fidelity measures to learning health systems are being used and this symposium (chaired by Iyer and Ferrari, Canada) brings together four nations, all leaders in EIS, to share their experiences with fidelity assessment and continuous quality improvement: Australia, Denmark, the USA, and Canada. The first two presentations showcase fidelity measures and the last two illustrate learning health system approaches.

First, Killackey (Australia) will present the development and utilization of a fidelity scale to improve and maintain adherence to a national EIS model in Australia. Although the world-renowned Early Psychosis Prevention and Intervention Centre was implemented in 1992, it is only in the last decade, that the country has shaped a national strategy for EIS implementation, which was adopted in 2013. The development of a fidelity scale and results from five waves of its deployment will be discussed, along with the need to provide programs with targeted support to improve areas in which there was low adherence.

Melau (Denmark) will then present a nationwide assessment of the quality and program fidelity of specialized early intervention for psychosis teams in Denmark. A Danish fidelity scale was used, which was found to be feasible and valued for its focus on how teams interact and organize themselves. The assessment revealed areas of high (e.g., referral practices) and low (e.g., ongoing supervision) adherence. Results will be discussed, along with efforts to enhance implementation outcomes (e.g., manuals, training) and assess fidelity as a key outcome in an ongoing RCT of an EIS for adolescents aged 12-17 years.

Bello (USA) will showcase OnTrackNY, New York State's learning healthcare system (LHS) for early psychosis treatment. She will present the essential components of this ambitious endeavour: the collection of data at the point of care, continuous monitoring of patient outcomes, synthesis of collected data, stakeholder engagement, integration of evidence-based care, and standardization and improvement of care processes.

This will be followed by Abdel-Baki (Canada) describing Quebec's rapid LHS of 11 early intervention services for psychosis. This research project involves iterative cycles of data collection on indicators that were chosen based on evidence, guidelines and stakeholder preferences; and personalized feedback and training. Using RE-AIM, an implementation science framework, this LHS was evaluated and found to be feasible to implement across programs with diverse levels of readiness and beneficial in improving adherence to standards.

Finally, Heinssen (NIMH/USA) will synthesize the four presentations' content and lead a discussion on how these four efforts from diverse jurisdictions serve as exemplars of ways to integrate performance monitoring and implementation support to improve care and outcomes in early psychosis.

9.1 THE UTILITY OF A MEASURE OF FIDELITY IN THE ESTABLISHMENT OF AN AUSTRALIAN NATIONAL EARLY PSYCHOSIS PROGRAM

Eoin Killackey*[1], Heather Stavely[1], Andrew Thompson[1], Georgia Leslie[1], Kristi van der EL[1], Patrick D McGorry[1]

[1]*Orygen*

Background: While Australia was a pioneer in the development of the concept of early intervention in psychosis in the early 1990s, it was not until the 2010s that a national program of early psychosis intervention was funded. This program was based upon a well-defined model initially called the EPPIC model and more recently the Australian Early Psychosis Model. This presentation will describe the development and use of a measure of fidelity to this model in the establishment of this national model

Methods: A fidelity scale (called the EPPIC Model Integrity Tool - EMIT) was developed based on the Australian Early Psychosis Model. Development involved consultation with clinicians, researchers, people with lived experience, and families. Predefined thresholds for levels of fidelity were also established. The tool was used to assess adherence to the model in six clusters of service sites across Australia. Ratings on the EMIT were informed by interviews with site staff and young people receiving the service, routinely collected data and review of documents such as policies and procedures.

Results: Over the 2.5 years period of establishment of the early psychosis services, all participated in five waves of fidelity assessment. Across that time average fidelity scores across the network improved from 'low' fidelity (i.e., <75%) to 92.35%, reflecting 'superior' fidelity. Feedback from site managers indicated that the fidelity process was helpful in the establishment of the services.

Conclusions: Utilisation of ongoing fidelity assessments has proved an effective method to improve and maintain adherence to the model. Establishment of services based on pre-defined models of care is aided by a mixture of fidelity assessment supported by targeted support to improve areas identified as having lower adherence to the model. This presentation will review this process and present ideas about future developments.

9.2 PROGRAM FIDELITY OF SPECIALIZED EARLY INTERVENTION IN DENMARK.

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Background: The evidence-based Specialized Early Intervention (SEI) has in Denmark grown to be a nationwide service for young adults 'experience a first episode psychosis. The implementation of the program was carried out without the use of fidelity measures.
Methods: To rectify this, we developed and tested out a Danish fidelity scale for SEI teams, and for the first time we did a nationwide assessment of the quality and program fidelity of the SEI teams in Denmark. We found the fidelity scale to be a feasible and easy manageable tool for collecting fidelity data, and by using a multimodal approach we got a good understanding of how multidisciplinary teams interact and manage various aspects of a patient's treatment.
Results: Totally 96% (n = 22) of the SEI teams participated and all in all 59 % (n = 13) fulfilled the criteria for program fidelity in a satisfactory level. We found that there was high variability between SEI teams according to the structural domain of the fidelity scale. By contrast, we found great homogeneity between the teams in terms of item referring to treatment.
Conclusions: This mapping of SEI teams' program fidelity in Denmark makes it obvious that at a national level, there is an urgent need for a more systematic approach to training and supervision, with a centralized development of educational material, provision of training and organization of supervision. The study revealed a fragile organization of the educational activities.
The program fidelity of a SEI for children and adolescents age 12 – 17 years (OPUS YOUNG) will in a new RCT be assessed using a modified version of The Danish Fidelity Scale to guide and maintain adherence to the intervention throughout the trial period. Models for implementation of continuous fidelity measurements will be discussed.

9.3 ONTRACKNY: NEW YORK STATE'S LEARNING HEALTHCARE SYSTEM FOR EARLY PSYCHOSIS TREATMENT

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Background: New York State's (NYS) Coordinated Specialty Care program, OnTrackNY, is a nationally recognized model for delivering early intervention services to individuals experiencing early psychosis. The OnTrackNY Network is a learning healthcare system (LHS) focused on the collection of data at the point of care, continuous monitoring of patient outcomes, synthesis of collected data, stakeholder engagement, integration of evidence-based care, and standardization and improvement of care processes. The network is comprised of 1) the NYS Office Mental Health who provides state-level oversight and financial support; 2) OnTrackCentral responsible for oversight of implementation focused on quality improvement; 3) three councils- youth, family, and provider; and 4) 23 OnTrackNY teams across the state. In 2019, OnTrackNY was funded as a regional hub within the Early Psychosis Intervention Network, the National Institute of Mental Health initiative focused on developing a LHS for young adults with early psychosis.
Methods: The OnTrackNY LHS is based on the principles of the Institute of Medicine's (IOM) model for a continuously learning healthcare system that brings together stakeholders to review data and technologies to develop and apply strategies to improve quality and increase efficiency. This model has six stages: scanning and surveillance, design, implement, evaluate, adjust, and disseminate. We will map the activities and processes of the OnTrackNY LHS,

specifically as they relate to fidelity, to each of the phases of the IOM model, to demonstrate how to integrate measurement to improve implementation and service quality.
Results: In the Scanning and Surveillance phase, the OnTrackNY network measures performance and identifies gaps through several mechanisms. When delivering technical assistance, OnTrackCentral learns from providers about facilitators and barriers to CSC implementation as well as regular program-level, patient-level, and patient self-report data collection about team processes and patient outcomes. The data get visualized in various reports and shared with OnTrackNY teams. Annual fidelity visits are conducted with each team to assess performance on model specific fidelity indicators, and the three stakeholder councils provide regular feedback about gaps and challenges. This information is discussed within OnTrackCentral and informs priorities. In the Design phase, a fidelity report is shared with the team and a remediation plan is developed collaboratively. Guided by the findings of the team's fidelity report combined with knowledge acquired from other stakeholders, OnTrackCentral develops a training plan that follows-up on issues identified. The Implement and Evaluate phases, consist of an iterative process of monitoring the data reports, providing consultation to teams based on data received, and collaboratively identifying ways to improve fidelity indicators and patient outcomes. Patterns that arise across teams are shared with OMH and other stakeholder groups to obtain feedback. During the Adjust phase, implications for the larger LHS are considered and adjustments to fidelity thresholds or standards are made as needed. In the Disseminate phase lessons learned and changes to the model are shared widely with the LHS using available mechanisms or instance, through webinars and development of guidance materials and tools to enhance implementation.
Conclusions: The OnTrackNY LHS is an example of how a stakeholder-driven LHS can work to promote measurement-based care within a structure supporting continuous quality improvement to improve care and outcomes for individuals with early psychosis.

9.4 A RAPID LEARNING HEALTHCARE SYSTEM FOR EARLY INTERVENTION FOR PSYCHOSIS SERVICES– RESULTS OF A 2 YEARS PILOT PROJECT ACROSS 11 SITES IN THE QUEBEC PROVINCE, CANADA.

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Background: Although there is strong consensus around essential components of early intervention services (EIS) for psychosis, there is considerable heterogeneity across programs and over time within the same program in the extent to which they are implemented. Learning health systems, premised on iterative cycles of data collection and translation of data into knowledge and decision-making, are increasingly emerging in various areas of medicine as means to improving service quality and the uptake of evidence into practice. Accordingly, we implemented a rapid learning health system (RLHS) involving 11 EIS for psychosis in Quebec, Canada.
Methods: Grounded in Integrated Knowledge Translation, we involved knowledge users (service users, families, clinicians and decision-makers) throughout the research process. The RLHS was deployed in six phases: 1) Identification of indicators 2) Development of a platform to allow collection of real-time data (indicators) on service performance, service experience and outcomes from clinicians, service users and relatives. 3) Data collection at all sites 4)

Feedback to each program of their performance at each time point compared to the mean of all participating programs and their own performance over time 5) Data-informed capacity-building activities to support programs in improving performance 6) Measurement of the same indicators to determine change over time and additionally support programs if needed.
Using the RE-AIM framework, this pilot research project aimed to determine the feasibility of implementing a RLHS in EIS and its early impacts in terms of fidelity to essential components and service user outcomes.

Results: Preliminary results indicate that our learning health system was feasible to implement within two years and resulted in changes in program and provider performance so as to align with standards/best practices. Specifically, we found: 1) Reach and adoption: 100% of the 11 invited EIS agreed to participate to the RLHS, and are represented at each meeting. 100% are using our electronic platforms for collecting program-level data and user satisfaction. 100% participated in at least 3/4 training sessions. 10/11 clinics responded to questionnaires at each of the six timepoints and time required to collect data has decreased by half. 2) Effectiveness : There was rapid integration of knowledge into clinical practice: a reduction in time from referral to psychiatric evaluation (16 days to 13 days), a decrease in programs with exclusion criteria (3 to only 1 program), an increase in proportion of professionals participating in continuing education (30% to 80%), the optimization of outreach interventions to avoid disengagement (60% to 82%) and increased referrals from sources other than emergency services: self-referral (2.3X),by relatives (1.9X) and by a school (2.9X). 3)Implementation: Facilitators included the creation of a community of practice, knowledge sharing sessions and one-on-one coaching and feedback. 4)Maintenance: Participating programs have expressed an interest in continuing to use the platform over the long term. Other programs in Quebec have reached out to join the learning health system.
Conclusions: Our results show that a rapid learning health system holds much promise for increasing performance monitoring across and improving the service quality of EIS. Our research has also yielded insights on the value of implementation science approaches to understanding facilitators of and barriers to implementing learning health systems. These results will be presented along with impacts on patient and family experiences/outcomes and plans to sustain and scale up this learning health system across all programs in our region.

10. COMPLEMENT PATHWAY DYSREGULATION IN SCHIZOPHRENIA; FROM MECHANISMS TO A POTENTIAL TARGET FOR NOVEL THERAPIES

David Cotter

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Overall Symposia Abstract: The complement pathway is implicated in schizophrenia by a strong genetic association involving the complement component 4 (C4) gene, postmortem evidence of dysregulated C4 RNA expression in schizophrenia, and blood studies. These latter studies have demonstrated dysregulated complement proteins preceding first reports of psychotic experiences, in association with transition from the clinical high risk (CHR) to psychotic disorder (PD), and in association with first episode psychosis and antipsychotic drug response. Several studies analyzing complement pathway-specific activity have indicated increased complement activation in schizophrenia patients, although not all studies have yielded consistent findings. In animal models, overexpression of C4A revealed reduced cortical synapse density, increased microglial engulfment of synapses, as well as behavior. These findings are consistent with evidence for altered synaptic regulation in schizophrenia

and may provide a mechanism whereby complement pathway dysregulation impacts on synaptic and brain function leading to schizophrenia. Modulation of the complement pathway may offer novel therapeutic opportunities both in schizophrenia and among those in the CHR. Recent evidence suggests that omega-3 (n-3) polyunsaturated fatty acids (PUFAs) contribute to the regulation of complement pathway.

In the current symposium we bring together speakers for the first time who will address the potential roles of the complement pathway in schizophrenia from these different perspectives. Cynthia Shannon Weickert studied cortical complement RNA and protein in the developing human prefrontal cortex from 2 months to 25 years and showed that activation of the complement cascade occurs between 1 and 5 years but that in the adolescent brain complement activators are low, and inhibitors are high. Based on this she hypothesizes that an upregulation of C4 associated with the C4 CNV could lead to increased complement activity in the adolescent brain when reduced activity is the normal. Sophie Laye focusses on synaptic function and plasticity and how omega-3 polyunsaturated fatty acids (PUFAs) impacts on this through complement function. Using an animal model she shows that early life n-3 PUFA deficiency leads to enhanced microglial mediated phagocytosis of synapses and demonstrates that this effect is mediated by the complement system. David Mongan presents data which demonstrates dysregulated plasma complement pathway proteins at age 11 preceding later psychotic experiences and among those in the CHR who transition to PD. He also presents showing that raised n-3 PUFAs in childhood reduces risk of later PD and proposes that modulation of synaptic pruning by n-3 PUFAs may underpin this relationship. Emily Severance discusses how many known risk factors for schizophrenia, including inflammatory conditions, act as triggers for complement activation. In studies of an animal model of inflammatory bowel disease she demonstrates increases in many complement components in the blood, and in schizophrenia demonstrates that C4 levels are increased among subjects exposed to pathogens. She concludes that the complement system unites multiple risk factors for schizophrenia and that screening tools involving the complement pathway should be considered among those at risk of psychotic illness. Oliver Schubert, discussant, will bring these strands together. Overall our symposium explores the relationship of complement pathway to psychosis risk and the mechanisms, involving synaptic pruning, by which the pathway may mediate its effects. Potential therapeutic and preventative effects of the modulation of the complement pathway in schizophrenia will be discussed.

10.1 SURPRISINGLY, CORTICAL COMPLEMENT LEVELS PEAK IN TODDLERHOOD, NOT IN ADOLESCENCE

Cynthia Shannon Weickert[1], Rachel Sager*[2], Kate Robinson[3], Adam Walker[3], Frank Middleton[4], Maree Webster[5]

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Background: Increased C4 gene copy number variants and increased C4 gene expression are associated with increased risk for developing schizophrenia. Classical complement factor induction is critical for synapse elimination in postnatal neurodevelopment of the lateral

geniculate nucleus. It is generally believed that neocortical synaptic pruning occurs during adolescence and over exuberance of this normal process underpins schizophrenia onset.
Methods: We studied RNA (ST-PCR) and protein (Western Blotting) from the developing human prefrontal cortex (2 months to 25 years of age), and hypothesised that cortical complement mRNA or protein levels should increase during adolescence to coincide with synaptic pruning.
Results: In contrast to our prediction, we found that complement activator (i.e., C1QB and C3) mRNA levels increased early in life, were highest in toddlers, and declined in teenagers (all ANCOVAs between F = 2.408 -3.325, p = 0.05-0.012). The microglial complement receptor mRNA encoding the subunit CD11b also increased early in life and peaked in the toddlers (ANCOVA: pH, F = 4.186, p = .003). We found that C4 protein was highest during the first 5 years of life with the lowest levels found in adolescence (F=2.161, p=0.003), whereas C3 protein levels were unchanged with age. Neuronal complement inhibitor or "don't eat me signals" (CD46 and CD55 mRNAs) increased by school age and remained elevated during adolescence and young adulthood (both ANCOVAs, F > 4.4, p < 0.01).
Conclusions: These data suggest the activation of complement cascade occurs normally between 2 and 5 years in the human prefrontal cortex. We did not find evidence of induction of complement factors during adolescence. Instead, we found that complement activators are low and complement inhibitors are high in the normal adolescent brain. Thus, elevated levels of C4, as would be predicted to occur in those with increased CNVs for the C4 gene, could lead to abnormal increases in complement activity during adolescence, a late maturational stage that may normally require reduced complement activity.

10.2 DIETARY POLYUNSATURATED FATTY ACIDS TUNE NEURODEVELOPMENT THROUGH MICROGLIA-NEURON INTERACTIONS

Sophie Laye*[1]

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Background: Polyunsaturated fatty acids (PUFAs) are essential fatty acids belonging to 2 distinct families n-3 (or omega 3) and n-6 (or omega6). As our organism cannot produce them, they have to be provided through the diet. Once digested, PUFAs reach organs through the blood circulation and incorporate into cell membrane or are metabolized into other lipid signaling molecules. The brain is one of the richest organs in PUFAs. In humans, poor levels of blood and brain n-3 PUFAs are associated to a higher prevalence of psychiatric disorders, including schizophrenia. However, the mechanisms underlying the effect of n-3 PUFA deficiency on brain functions are poorly understood.
Methods: To study the impact of n-3 PUFA deficiency on brain development, we used a mice model of nutritional n-3 PUFA deficiency from the first day of gestation until weaning. At weaning, working memory and neuronal structure and functioning were assessed in the hippocampus using a combination of molecular, imaging and behavioral approaches. Then microglia profile and phagocytic activity were assessed using FACS, RNAseq and lipidomic approaches. To further link phagocytic activity, complement system, PUFA derivatives and behavior, in vitro and in vivo pharmacological approaches were used.
Results: Using a mice model of early-life n-3 PUFAs dietary deficiency, we revealed that the development of the hippocampus is altered, leading to altered neuronal morphology and affecting cognitive performance. We further revealed that dietary n-3 PUFA deficiency increases microglia (the main innate immune system cell in the brain)-mediated phagocytosis of synaptic elements. In addition, we revealed that microglia specific molecular pathways

involving the complement system and 12/15-lipoxygenase (LOX)/12-HETE signaling are responsible of altered synaptic pruning.
Conclusions: Altogether, our work brings a better comprehension of how early-life dietary n-3 PUFAs contribute to brain development and risk of disorders such as schizophrenia.

10.3 THE COMPLEMENT SYSTEM AND EARLY PSYCHOSIS: EVIDENCE AND IMPLICATIONS FROM PROTEOMIC STUDIES

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

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Background: There is converging evidence that the complement system is relevant to the pathophysiology of psychotic disorders such as schizophrenia. This presentation will focus on recent evidence derived from several plasma proteomic studies of early psychosis phenotypes.
Methods: The presentation will focus on results of three studies using mass spectrometry-based proteomics to assess differential expression of blood-based proteins with the aim of discovering novel prognostic biomarkers in people presenting with early psychosis phenotypes (such as psychotic experiences or the clinical high-risk state).
Results: Firstly, proteomic analyses of plasma from healthy 12 year old participants in the Avon Longitudinal Study of Parents and Children (ALSPAC) showed differential expression of proteins of the complement and coagulation cascades in those who did versus did not experience psychotic disorder or subthreshold psychotic experiences 6 years later when aged 18. This suggests that complement dysfunction occurs early, potentially years in advance of the onset of even subthreshold symptoms (PMID: 29036721).

Secondly, proteomic analyses of plasma from mice who were or were not exposed to social defeat stress showed dysregulation of several complement proteins with overlapping findings for proteins upregulated in the samples from ALSPAC participants who developed psychotic experiences (including C1r, complement factor H and complement component 5). This suggests that psychological stress may be associated with complement dysregulation, which is important in considering existing strong evidence for associations between trauma and psychosis (PMID: 30635638).

Thirdly, we performed proteomic analyses of plasma samples in a nested case-control study from the European Network of National Schizophrenia Networks Studying Gene-Environment Interactions, an international clinical high-risk for psychosis cohort. In a subsample of 133 clinical high-risk (CHR) participants (of whom 49 developed psychosis during follow-up of over 2 years), baseline proteomic data showed differential expression of multiple proteins with particular evidence for dysregulation of the complement and coagulation cascade. Machine learning techniques facilitated development of a predictive model for transition risk based on the 10 most predictive proteins (including several complement and coagulation markers) with area under the receiver-operating characteristic curve of 0.92 in withheld data (PMID: 32857162). Plasma proteomic changes in this CHR study that were consistent with results from previous proteomic studies of individuals who do versus do not go on to have psychotic experiences include increases in plasminogen, C1r, clusterin and complement factor H and decreases in alpha-2-macroglobulin, a key coagulation inhibitor.

Conclusions: The findings of these studies suggest that complement dysfunction is present and detectable in early psychosis and potentially even before the development of early psychotic symptoms. This is in contrast to studies of patients with chronic schizophrenia which have found inconsistent results regarding peripheral complement protein levels in comparison to controls. It is possible that this reflects underlying biological heterogeneity, or that complement dysfunction varies with time and stage of illness (potentially being maximal in early adulthood around the time of onset of psychosis). Interestingly, plasma levels of the omega-3 fatty acid DHA in adolescence have been found to be associated with reduced odds of developing future psychotic disorder in a general population sample (PMID: 34059620). Omega-3 fatty acids may module complement activity and hence excessive synaptic pruning thought to underlie schizophrenia, but this requires further elucidation in humans.
In this presentation the results of these studies will be reviewed and integrated with existing evidence to discuss the implications of complement system dysfunction in relation to the pathophysiology, prediction and prevention of psychotic disorders.

10.4 COMPLEMENT DYNAMICS IN SCHIZOPHRENIA REFLECT SUSCEPTIBILITIES TO ENVIRONMENTAL EXPOSURES AND GASTROINTESTINAL PHENOTYPES

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[1]*Johns Hopkins University School of Medicine,* [2]*Johns Hopkins University School of Medicine, University of Buffalo,* [3]*Sheppard Pratt*

Background: Complement pathway dysregulation in schizophrenia is consistent with immune system-related gene by environment etiologies. Peripherally, complement pathways are triggered by infectious, dietary and autoimmune antigens, exposures that are known risk factors for schizophrenia. In the brain, complement components act at synapses during pre- and post-natal neurodevelopment and in not fully understood non-developmental capacities. The dynamics between peripheral versus brain complement activities are not well-characterized, but may be presumably linkable via genetics. Complement C4 is a recurrently identified genetic susceptibility locus for schizophrenia.
An etiological role for the complement system in a disease state may be more reliably interrogated in the presence of infection or other antigenic stimuli such as gut dysbioses. In a series of translational experiments in mouse models of immune challenge and in individuals with schizophrenia, we evaluate external (pathogen) and internal (microbiome) triggers of complement activity and present evidence for gene-related complement dysregulation.

Methods: In mice, inflammatory bowel conditions were generated following exposure to Toxoplasma gondii. Complement activities were measured in serum using ELISAs and examined in tissues of the gastrointestinal (GI) tract and prefrontal cortex using immunohistochemistry and mRNA expression.
In human studies, we examined serological biomarkers of microbial translocation and GI inflammation (sCD14, LPS-binding protein (LBP), Candida albicans, Saccharomyces cerevisiae, dietary antigens), pathogen exposure (T. gondii, cytomegalovirus) and complement activation (C4) in individuals with schizophrenia and in individuals without a history of psychiatric disorders.

Results: In mice, T. gondii infection caused significant elevations of complement activity peripherally in the GI tract and serum, as well as increases of multiple complement components (C1q, C1r, C3, C4, C6) in the prefrontal cortex.

Baseline pathogen and GI biomarkers were increased in blood samples from individuals with schizophrenia compared with controls. C4 levels were not demonstrably altered until the schizophrenia group was stratified into pathogen exposure and clinical comorbidity subtypes. Peripheral C4 dysregulation in schizophrenia was then associated with exposure to T. gondii and C. albicans, as well as other GI, endocrine and cardiovascular disturbances.

In schizophrenia but not controls, there were extensive associations of all C4 haplogroups with plasma biomarkers of pathogen exposures and gut dysbioses including C. albicans, cytomegalovirus, LBP, and T. gondii. Most of the common C4 haplogroups studied were also associated with altered severity of psychiatric symptoms and cognitive functioning, especially C4 haplogroups in a homozygous state.

Conclusions: These data support a unique role of complement as a system that unites multiple risk factors for schizophrenia (inflammation, infection, dietary sensitivity, autoimmunity), participates in each venue of a gut-immune-brain pathway and is consistent with a gene by environment etiology of schizophrenia. Complement genotyping and serum monitoring of related biomarkers during and after pregnancy and in prodromal individuals, might be a useful screening tool to identify those who are susceptible to potentially deleterious immune activation from multiple infectious and antigenic sources. The current data also show that improving gut health and stabilizing endothelial barriers may have important consequences for the brain. Adjunctive treatments designed to keep the microbiome in check may help provide relief from symptoms of these complex disorders.

11. RETURNING TO THE LINGUISTIC ROOTS OF PSYCHOSIS: ADVANCING KNOWLEDGE THROUGH INTERNATIONAL COLLABORATION

Natália Mota

Federal University of Pernambuco

Overall Symposia Abstract: Psychotic disorders have a chronic intermittent course, with frequent and disabling relapses. Therapeutic interventions are often provided too late to change the course of this illness. Clinical symptom rating-scales have poor objectivity; their repeated use poses a high resource burden, they are often intrusive for patients and impractical for predicting therapeutic needs. We urgently need reproducible markers to track the illness course and enable wider implementation of early intervention at every stage of psychosis.

The form and content of speech provide the primary diagnostic and prognostic information for psychosis. Our speech tracks our mental state; it remains the most accessible, remotely generated, inexpensively acquired, objectively recorded, and automatically analyzed digital health marker. Recently, several groups have reported clinically relevant predictive signals using computational linguistics in psychosis. There is an acute need for clinically validated, multilingual, repeated, patient-generated speech data in psychosis for large-scale sustainable deployment of speech in digital healthcare. Harmonizing acquisition is a critical step towards assembling such corpora.

Recently we convened DISCOURSE in psychosis (https://discourseinpsychosis.org), a global network of interdisciplinary researchers focused on developing collaborative solutions to study the mechanisms underlying thought, language, and communication disturbances in psychosis. Our group currently includes 103 members from 28 sites and anticipates creating the first Psychosis Speechbank. We will build a shared corpus with linguistic, cultural, and socioeconomic diversity for communal usage from patients worldwide. We will provide an

open data source for measurement comparisons, psycholinguistic applications, human/computer training, and sociological applications.

This symposium proposal brings together four presenters from DISCOURSE, from 4 different continents, presenting recent data advancing basic and applied clinical research of psychosis. The four presentations will provide the opportunity to discuss results in the light of sociocultural diversity. The speakers will present cutting-edge progress that brings psycholinguistics, neurolinguistics, and computational linguistics together. The discussant, Lena Palaniyappan, will synthesize the presentations and highlight how the efforts towards data harmonization can tackle the challenges identified by the speakers. We will discuss translational opportunities for clinical benefit based on comparative research strategies (trans-diagnostic and interdisciplinary).

The first presentation from Maria Francisca Alonso (Chile and Canadá) will discuss longitudinal clinical and linguistic follow-up since first-episode psychosis and how semantic similarities from one-minute picture description protocol correlate with symptomatic progression of psychosis in early stages. Following, Sunny Tang (USA) will provide data on the mechanistic investigation on the linguistics association of theory of mind and emotion recognition mixing several computational approaches since structural analysis based on graph theory, parts-of-speech, lexical characteristics, and coherence. Eric Tan (Australia) will present quantitative speech variable data in schizophrenia and discuss the diagnostic and clinical utility of speech assessment. To conclude, Alberto Parola (Denmark and Italy) will discuss vocal and prosodic atypicalities in schizophrenia, with a focus on generalizability, specifically addressing the question of whether previous findings and machine learning models generalize to new samples and languages.

11.1 QUANTITATIVE SPEECH ASSESSMENT IN SCHIZOPHRENIA SPECTRUM DISORDERS: EXPLORING DIAGNOSTIC AND CLINICAL UTILITY

Eric Tan*[1], Erica Neill[1], Denny Meyer[1], Susan Rossell[1]

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Background: Aberrant patterns of speech and word use are a recognised feature of schizophrenia. Traditionally assessed via clinical interviews and speech ratings, newer methods of quantitative speech assessment are increasingly being used. Externally assessable, speech is a potential candidate for the still-elusive objective psychiatric marker. This study presents two analyses of quantitative speech data in examining both its diagnostic utility for schizophrenia spectrum disorders and symptoms, and its clinical utility in terms of its relationship to more traditional clinical (i.e. formal thought disorder) ratings.

Methods: Speech recordings from 43 schizophrenia/schizoaffective disorder (SZ; mean age=41.67) patients and 46 healthy controls (HC; mean age=38.89) were obtained and transcribed using the Systematic Analysis of Language Transcripts software to extract 6 types of quantitative speech variables: utterances, single words, speaking rate, turns, pauses and formulation errors. Schizophrenia symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS), while formal thought disorder was assessed using the Scale for the Assessment of Thought, Language and Communication (TLC). Gradient boosting and random forest machine learning algorithms were used to explore the diagnostic utility of quantitative speech variables, while Spearman's correlations were used to examine the relationship with

PANSS symptom domains and Global TLC scores. In the clinical utility analyses, Spearman's correlations and stepwise linear regressions were used in the patient group only to examine the relationship of quantitative speech variables to 6 individual TLC items: poverty of speech, tangentiality, derailment, circumstantiality, loss of goal and perseveration.
Results: Based on two machine learning algorithms, 21 speech variables across the same five speech variable types (again not including pauses) were identified as significant classifiers for a SZ diagnosis with 90-100% specificity and 80-90% sensitivity for both models. Selective relationships were also observed between these speech variables and only positive, disorganization, excitement symptoms and the Global TLC rating. Stepwise linear regressions revealed specific combinations of quantitative speech variables associated with individual TLC items.
Conclusions: The findings collectively indicate the potential diagnostic and clinical utility of these speech disturbances in SZ. Continued work is needed to build the evidence base for quantitative speech assessment as a future objective assessment tool for schizophrenia and its symptoms. It holds the promise of improved measurement accuracy leading to increased treatment efficacy and better patient outcomes.

11.2 SPEECH AND LANGUAGE DISTURBANCES IN SCHIZOPHRENIA ARE RELATED TO SOCIAL PROCESSING

Sunny Tang*[1], Amir Nikzad[2], Yan Cong[2], Aamina Dhar[2], Katrin Hänsel[3], Sunghye Cho[4], Sameer Pradhan[4], Mark Liberman[4]

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Background: Disturbances in speech and social processing are major consequences of schizophrenia spectrum disorders (SSD). In fact, we can conceptualize language as an inherently social phenomenon that requires real-time understanding of the listener's perspective. In this study, we attempted to address the following: 1) Is social processing impairment related to clinical ratings of disorganized speech (ambiguous, inefficient or incoherent expression of ideas), impaired expressivity (impoverishment), both, or neither? 2) Are theory of mind and emotion recognition ability reflected in quantitative measures of speech?
Methods: We prospectively evaluated 83 participants (34 SSD, 11 other psychiatric disorders, 38 healthy control). Social processing was assessed with the ER40 for emotion recognition and the Hinting Task for theory of mind. Speech was elicited with open-ended prompts and structured tasks (picture description, Hinting Task). Language disturbance was rated with the Scale for the Assessment of Thought Language and Communication (TLC) and two items from the Scale for the Assessment of Negative Symptoms (SANS; decreased vocal inflection and increased latency). Factor scores for disorganized speech and impaired expressivity were calculated. Overall psychosis symptoms were rated with the Brief Psychotic Rating Scale (BPRS), and premorbid verbal ability was assessed with the Wide Range Achievement Test (WRAT3). Adjusting for total words spoken, we quantified the use of discourse connectives (temporal, comparison, contingency, expansion types) and the modal verb "should". We also used graph analysis to evaluate relationships between words. Simple and multiple linear regressions were used to compare speech measures with social processing, with standardized coefficients reported for effect size.
Results: Theory of mind significantly predicted disorganized speech (Beta = -0.33, p = 0.005) and impaired expressivity (Beta = -0.29, p = 0.02) even when covarying for premorbid verbal ability and overall psychosis symptoms. When accounting for the same potential confounders,

we found that emotion recognition significantly predicted disorganized speech (Beta = -0.45, $p < 0.001$) but not impaired expressivity (Beta = -0.20, $p = 0.11$). Graph metrics reflecting more interconnected speech was associated with both theory of mind (average degree – Beta = 0.32, $p = 0.02$; size of the largest clique – Beta = 0.38, $p = 0.008$) and emotion recognition (average degree – Beta = 0.36, $p = 0.02$; size of the largest clique – Beta = 0.33, $p = 0.01$). Additionally, theory of mind performance was associated with more frequent use of the modal verb "should" during the Hinting Task (Beta = 0.20, p=0.05), and more frequent use of temporal discourse connectives (e.g., "when," "before," "while") in the overall interview (Beta = 0.24, p=0.04).
Conclusions: We found strong relationships between clinical ratings of disorganized speech and both theory of mind and emotion recognition. However, impaired expressivity of speech was only related to theory of mind and not emotion recognition. Both domains of social processing were also predicted by quantitative measures reflecting more interconnected speech. Theory of mind was related to the expression of obligation ("should") during the Hinting Task, as well as greater overall use of words providing orientation for temporal connections. Thus, we provide evidence that social processing is connected to both clinical ratings and quantitative measures of language disturbance in psychosis.

11.3 PROGRESSIVE CHANGES IN DESCRIPTIVE DISCOURSE IN FIRST EPISODE OF SCHIZOPHRENIA: A LONGITUDINAL NATURAL LANGUAGE PROCESSING STUDY

Maria Francisca Alonso*[1], Sabrina Ford[2], Michael MacKinley[3], Angelica Silva[4], Roberto Limongi[2], Lena Palaniyappan[4]

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Background: Language disorganization is a prominent feature in psychosis, and it is commonly encountered as a disorder in engaging in discourse. In particular, the restricted repertoire of word selection, characterized by smaller loops of word-to-word connectivity that occurs with more proximal repeats in selected words, becomes apparent even before overt psychosis, predicts later onset of psychosis, and becomes more pronounced during the first episode, and relates to reduces social and occupational functioning. Computational linguistic measures that rely on how words occur together in natural language offer a promising tool to study schizophrenia. At present, we do not know if these word-level choices in speech are sensitive to illness stage (i.e. acute untreated vs. stable established state), track cognitive deficits in major domains (e.g. cognitive control, processing speed) and relate to established dimensions of formal thought disorder.
Methods: We study samples of descriptive discourse in patients with untreated first episode of schizophrenia (mean 2.8 days of lifetime daily dose exposure) and healthy subjects (246 samples of 1-minute speech; n=82, FES=46, HC=36) using a co-occurrence based vector embedding of words. We obtained six-month follow-up data in a subsample (99 speech samples, n=33, FES=20, HC=13). Participants were cognitively assessed using modified digit symbol substitution task, semantic verbal fluency and colour-word Stroop test.
Results: At baseline, the evidence for higher semantic similarity during descriptive discourse in FES was substantial, compared to null hypothesis (Bayes Factor for alternative hypothesis= 6 for full description; 32 for 10-words window). Moreover, there was a linear increase in semantic similarity with time in FES compared to HC (Bayes Factor for alternative hypothesis = 6). Higher semantic similarity related to lower Stroop performance (accuracy and interference, response time), and was correlated with baseline PANSS-8 positive (r: 0.39, BF10: 9.24) but not with PANSS-8 negative (r: 0.08, BF10: 0.18), impoverished (r: 0.21, BF10:

0.49), disorganized (r: 0.14, BF10: 0.28) or dysregulated thinking (r: -0.06 BF10: 0.20) scores (Figure 3). Baseline semantic similarity was also higher in patients with reduced role functioning at the time of illness onset, based on SOFAS scores (r: -0.41, BF 10: 128).
Conclusions: Automated analysis of non-intrusive 1-minute speech samples provides a window on cognitive control deficits, role functioning and tracks latent progression in schizophrenia.

11.4 VOCAL ACOUSTICS AS A MARKER OF DIAGNOSIS, SYMPTOMS AND SOCIAL FEATURES OF SCHIZOPHRENIA: POTENTIALITY, LIMITS AND FUTURE PERSPECTIVES

Alberto Parola*[1], Arndis Simonsen[2], Katja Koelkebeck[3], Jessica Mary Lin[4], Shiho Ubukata[5], Yuan Zhou[6], Vibeke Bliksted[7], Riccardo Fusaroli[8]

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Background: Voice atypicalities have been a characteristic feature of schizophrenia (SCZ) since its earliest definitions. They range from poverty of speech, increased pauses, distinctive tone and intensity of voice, are often associated with core negative symptoms such as flat affect and alogia, and with the social impairments seen in the disorder.
Quantitative and automated acoustic analysis of vocal behaviour can therefore not only support the current assessment of negative symptoms, but also be considered a biobehavioral marker of the disorder and a window into its clinical and socio-cognitive aspects. However, while state-of-the-art speech signal processing technology has been used to identify vocal markers of other neuropsychiatric and neurological disorders and to develop systems that can monitor patients' symptoms, these efforts are still limited in schizophrenia. One of the reasons for this lag is the limited attempts to assess the replicability and generalizability of previous findings and to explicitly account for the heterogeneity of the disorder. In particular, we have yet to understand how vocal behaviour is influenced by linguistic and cultural factors, under what conditions they vary, and what variations in clinical and socio-cognitive characteristics might underlie vocal atypicalities.

In this presentation, we will explore how to address the problem of heterogeneity and generalizability of previous findings.

Methods: First, we present a systematic review and meta-analysis of the current state of the evidence on acoustic atypicalities in SCZ, and on their relationship with specific clinical features. The goal of the meta-analysis was, beyond providing an accurate assessment of vocal atypicalities in SCZ, to assess the basis for more effective future studies by identifying current practises, problems, and promising venues.
Results: We then present an attempt to develop a critical, cumulative scientific approach to the understanding of vocal and prosodic atypicalities in schizophrenia by drawing on the recommendations developed in the meta-analysis. We investigated acoustic patterns in SCZ in a large dataset of audio recordings from patients with schizophrenia and control subjects in four different languages (Danish, Chinese, Japanese, German) and three language families. This multilingual corpus allows us to explicitly compare the results between the different

languages, and thus assess whether the acoustic patterns are characteristic of SCZ or rather reflect linguistic/cultural variations. We also explicitly tested the robustness and variability of the vocal atypicalities between subjects and samples.
Then, in a third work we systematically evaluate the generalizability of machine learning (ML) results across language and context. Assessing the generalizability of the performance of ML classifiers is crucial: a) for the development of clinical applications, where it is necessary to define precisely not only how well ML algorithms generalize to new individuals, but also to new conditions (e.g subpopulations, tasks) b) for identifying potential sources of bias (e.g., sociodemographic) that may limit the generalizability of ML algorithms to underrepresented groups and thus raise important ethical concerns.

Conclusions: Finally, we will discuss the implications of these findings and the current literature on vocal markers in schizophrenia and attempt to answer the following questions: What is still missing to develop a concrete application of this technology? What reasons may be responsible for this delay? What concrete solution can be found in the near future?

Plenary Session II: Nina Schooler

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

12. TREATMENT FOR FIRST EPISODE PSYCHOSIS: LOOKING BACK TO LOOK FORWARD

Robert Buchanan

University of Maryland School of Medicine

Overall Abstract: The session will provide an overview of the history of the treatment of people with a first episode of a mental illness with psychosis. The presentation will focus on the use of antipsychotic medications to treat people with a first-episode of psychosis, but will also emphasize the emerging recognition of the importance of integrating psychosocial treatments with pharmacotherapy to optimize treatment outcomes. The presentation will conclude with a discussion of what should be the nature of future clinical trials in this population.

12.1 TREATMENT FOR FIRST EPISODE PSYCHOSIS: LOOKING BACK TO LOOK FORWARD

Nina Schooler

Suny Downstate Health Sciences Center

Individual Abstract: Treatment for first episode psychosis (FEP) has been of interest and a challenge since the earliest studies of neuroleptic antipsychotics. The general guiding hypothesis animating these studies is that initial or early treatment is more effective than treatment later in the illness course. Such studies can also assess biomarkers and other characteristics that are freer of the confounding effects of exposure to medications and the influences of life course and environmental factors. And finally, the idea of a degenerative course in psychosis, particularly non-affective psychosis provides impetus for such research.
This presentation will follow my personal history to illuminate the course of treatment research in FEP. The studies span 60 years; most were conducted in the United States and reflects its health care environment. The NIMH nine-hospital study of phenothiazines in schizophrenia

(1964) compared three phenothiazines to a placebo. It began as a first-episode study; recruitment challenges expanded inclusion criteria to acute symptom exacerbation. The next, the Pittsburgh first episode study (1998) was a biomarker study of FEP with embedded psychosocial and antipsychotic treatments. An international relapse prevention study compared the second-generation antipsychotic (SGA) risperidone to first generation haloperidol (2006). A study of initial treatment compared SGAs; olanzapine and risperidone (2006). Long-acting risperidone was compared to any oral antipsychotic in adherence and relapse prevention (2012). Long-acting aripiprazole was compared to any anti-psychotic in a prevention of hospitalization study (2020). These studies generally focused on medications and were randomized clinical trials (RCTs).

Some of these medication RCTs included psychosocial intervention platforms for all trial participants. Given an increasing recognition that successful outcomes require more than medication, an important focus in 21st century FEP studies has been comparison of interventions that include psychosocial and medication components to treatment as usual. In the US these are currently called Coordinated Specialty Care (CSC); across the world the term used is Early Intervention Services (EIS). The RAISE-ETP study represents that focus (2015) for me.

Study designs, implementation strategies and statistical methods have changed over time. Some studies have been double blind; others open treatment with blinded/masked assessors. Dose ranges of medications studied varied. Study length range was six weeks to over two years. Outcomes varied; they include symptoms, relapse, adherence, hospitalization and community functioning.

Based on these experiences and the work of many others, three questions for future FEP RCTs will be considered. What treatments should be evaluated? How should trials be designed? What outcomes should be assessed and how?

Concurrent Symposia

4:30 p.m. - 6:30 p.m.

13. DIGITAL TECHNOLOGIES IN THE TREATMENT OF PSYCHOSIS: NEW FINDINGS AND LESSONS FROM CLINICAL RESEARCH

Franscini Maurizia

University Hospital of Psychiatry/University of Zurich

Overall Symposia Abstract: Digital technologies have the potential for radical changes in service delivery and the development of new treatments. Healthcare providers around the world are adopting and adapting digital solutions to current challenges such as long waiting times for access to interventions and improving outcomes of existing therapies. Digital technologies offer new opportunities to improve psychological interventions in engaging and tailored ways, and offer new therapeutic contexts in which core psychological processes can be targeted in real time with instant feedback. Nevertheless, research on digital health interventions in psychosis is still in its infancy. Preliminary findings suggest great potential. However, collaboration between the research and clinical communities is needed to develop and adapt digital technologies that can improve access to psychological support, service user engagement and treatment outcomes. In this symposium, recent findings of clinical importance from four

current comprehensive research projects on the implementation, acceptance and effectiveness of digital technologies in the treatment of psychosis will be presented.

First, Dr. Laura M. Tully will present results from the multi-year California Early Psychosis Intervention (EPI-CAL) project about the implementation of stakeholder-centered ethical data use practices to promote data-driven care. Results indicate that individuals experiencing psychosis are willing to share their data for research purposes if it could be beneficial to their care or others but unwilling to share with commercial entities and expressed clear desire for total control over their own data, including the right to be deleted.

Next, Dr. Maurizia Franscini will present data from the prospective follow-up study ETRo (Evaluation of the treatment approach Robin). This is one of the first controlled trial to test the efficacy of a specific early psychosis treatment in combination with a smartphone application for adolescents at clinical high risk for psychosis. She will discuss the first results and their implications for the clinical practice.

Prof. Daniel Fulford will share findings of the development and testing of an Ecological Momentary Intervention for social functioning in people with schizophrenia. He will discuss the development and testing of the Motivation and Skills Support (MASS) smartphone app, a digital intervention designed to support social motivation and functioning in psychosis. The MASS app was developed using key theoretical frameworks and empirical findings rooted in motivation and affective science, targeting the complex, multifaceted nature of impaired social functioning in psychotic disorders.

In the last contribution, Dr. Javier-David Lopez-Morinigo will present novel findings from an unselected sample of outpatiens with schizophrenia concerning the low acceptability levels of a passive smartphone-based Ecological Momentary Assessment (EMA) app and what determined EMA acceptability. Based on these results, Dr Lopez-Morinigo will discuss the extent to which e-Mental-Health may neglect such a vulnerable group of patients.

Prof. Dr. Frauke Schultze-Lutter will lead the discussion. She is a leading expert in the field of early detection and intervention of psychosis, main author of the Schizophrenia Proneness Instruments (Adult Version SPIA, Child and youth version SPI-CY) and senior contributor to the European Association of Psychiatry (EPA) guidance papers on the early detection and intervention in clinical high-risk states of psychosis.

13.1 IMPLEMENTATION OF STAKEHOLDER-CENTERED ETHICAL DATA USE PRACTICES IN BEEHIVE: AN EHEALTH TECHNOLOGY THAT PROMOTES DATA-DRIVEN CARE IN THE CALIFORNIA EARLY PSYCHOSIS INTERVENTION NETWORK (EPI-CAL)

Laura M. Tully*[1], Kathleen Nye[2], Sabrina Ereshefsky[2], Mark Savill[2], Valerie Tryon[2], Rachel Loewy[3], Lindsay Banks[3], Viviana Padilla[2], Christopher Hakasui[2], Heather Garman[3], Christopher Blay[3], Edith Wilson[4], Amanda McNamara[4], Merissa Kado[4], Zhun Xu[4], Todd Gilmer[4], Andrew Padovani[5], Daniel I. Shapiro[2], Khalima A. Bolden[2], Karina Muro[2], Renata Botello[2], Rebecca Grattan[2], Leigh Smith[2], Adam Wilcox[6], Joy Melnikow[5], Daniel Tancredi[7], Bonnie Hotz[2], Donald Addington[8], Sonya Gabrielian[9], Steven Lopez[10], Lisa Dixon[11], Cameron S. Carter[2], Tara A. Niendam[2]

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Background: The California Early Psychosis Intervention (EPI-CAL) project links multiple early psychosis (EP) programs in a learning health care network using a core assessment battery of valid, low burden measures administered via a stakeholder designed eHealth technology platform (Beehive). Beehive facilitates collection of client-level information as part of standard care, visualizes the data on a clinician dashboard for treatment planning, and integrates data across clinics to support statewide EP outcomes evaluation. A successful learning health care network relies on EP clients choosing to share their data with EPI-CAL and NIH researchers. Typical eHealth software has long end user license agreements (EULAs) detailing the myriad ways user data are utilized and shared, with minimal transparency or user-level control. This limits willingness to share data and diminishes users' agency over their data. To promote ethical data use practices, we sought to develop an accessible, transparent, and flexible EULA shaped by stakeholder input as part of the Beehive implementation phase of EPI-CAL.

Methods: Two phases of semi-structured qualitative focus groups assessed stakeholder preferences of data-sharing and privacy of mental health data. Participants included 3 stakeholder groups active in EPI-CAL: 14 clinic staff and providers, 6 clients, and 4 family members/support persons. Phase 1 ascertained stakeholder data sharing preferences; phase 2 ascertained stakeholder reactions to data sharing options implemented in the Beehive EULA based on themes identified in phase 1. Beehive EULA materials included an informational animated whiteboard video presenting key points of the Beehive EULA and a page presenting options for data sharing for research purposes. We used conventional content analysis to describe stakeholder data-sharing preferences. The stakeholder-designed EULA was then implemented in Beehive in 3 pilot EP programs to evaluate impact on data sharing choices. Descriptive summaries of stakeholder data sharing are reported.

Results: In phase 1 participants reported willingness to share data for research purposes if it could benefit their care or improve care for others. Participants expressed a clear preference for sharing de-identified data and that they are not willing to share data with commercial entities, citing themes of trust, familiarity, and rapport as influencing data sharing. Factors that increased willingness to share data: transparency around data sharing options, clarity around data protections, and user control over data including the ability to revoke data permissions and delete data. In phase 2 participants responded positively to EULA materials, expressing increased willingness to share data given the transparency, clarity, and level of control over data sharing preferences. Additional suggestions for increased clarity of opt-in/opt-out options were incorporated. Implementation of the Beehive EULA materials in 3 EP programs resulted in 80% of individuals (range: 67%-94%) agreeing to share de-identified data with NIH.

Conclusions: Learning health care networks could identify treatment components that are most effective in promoting recovery and transforming EP care. eHealth technologies are integral to successful implementation of learning health care networks and require open data sharing from participants. Transparent ethical data use practices are desired by stakeholders and result in high rates of data sharing. Those choosing to implement eHealth software should carefully investigate the EULAs of any candidate product; any eHealth tool that shares user data outside of research or health care purposes should not be used.

13.2 UNMET NEEDS IN E-MENTAL HEALTH: LOW ACCEPTABILITY LEVELS OF A SMARTPHONE-BASED ECOLOGICAL MOMENTARY ASSESSMENT APPLICATION AMONG PATIENTS WITH SCHIZOPHRENIA

Javier-David Lopez-Morinigo*[1], Adela Sánchez Escribano-Martínez[2], Sergio Sanchez-Alonso[3], Paula Escobedo[4], Verónica González Ruiz-Ruano[5], Laura Mata-Iturralde[4], Laura Muñoz-Lorenzo[4], Enrique Baca-García[4]

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Background: Ecological momentary assessment (EMA) methods allow recording patients' behaviour and functioning in real-time. However, concerns have been raised about acceptability of EMA among patients with schizophrenia. The aims of this study were twofold, namely to investigate: i) the acceptability levels of a passive smartphone-based EMA app, the Evidence-Based Behavior (eB2), among an unselected sample of outpatients with schizophrenia; and ii) determinants of eB2 acceptability.

Methods: Sample: outpatients with schizophrenia spectrum disorders (SSD) (F20-29-ICD10), age 18-64, from the Hospital Universitario Fundación Jiménez Díaz (Madrid, Spain), receiving no financial incentives, recruited over 17/06/2019-11/03/2020 to enroll a randomised controlled trial of metacognitive training.

Assessment: We measured acceptability levels at the study inception (recruitment) and time of eB2 use (retention). Multivariable binary logistic regression model compared those who accepted eB2 -users- and those who did not -non-users- in sociodemographic, clinical, premorbid adjustment, neurocognitive, psychopathological, insight and metacognitive variables.

Results: Out of N=77 participants, n=24 were users (31.2%). Of these, n=14 (70%) had not uninstalled eB2 at follow-up (median=14.50 weeks). Users were younger, had higher education level, better early adolescence premorbid adjustment and executive function and greater cognitive insight than non-users, although only age (OR=0.93, 95%CI 0.86-0.99, p=0.048) and early adolescence premorbid adjustment (OR=0.75, 95%CI 0.61-0.93, p=0.010) survived the multivariable regression model.

Conclusions: Acceptability of a passive smartphone-based EMA app in this sample of outpatients with SSD was low, particularly among older individuals and those with poorer premorbid functioning.

Of concern, these results, which have been replicated, suggest that e-Mental-health within the COVID-19 context may neglect such a vulnerable group of patients.

13.3 ETRO: EVALUATION OF THE TREATMENT APPROACH "ROBIN" (STANDARDISED MANUAL AND SMARTPHONE APP) FOR ADOLESCENTS AT CLINICALLY HIGH RISK FOR DEVELOPING A PSYCHOTIC DISORDER

Franscini Maurizia[1], Traber-Walker Nina[1], Gerstenberg Miriam[1], Probst Fabian[1], Jenny Schimansky[1], Walitza Susanne[1], Nina Traber-Walker*[2]

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

Background: The construct of clinical high-risk (CHR) psychosis was established to describe potentially prodromal symptoms typically occurring during adolescence and young adulthood. This is a very sensitive developmental period and CHR is associated with increased functional impairment. Age-appropriate treatment approaches that address the complex symptomatology, associated distress and impaired functioning are needed. However, there is a lack of research on age-specific treatment strategies for this vulnerable age group. To fill this gap, the experts at the Specialist Outpatient Clinic for Early Intervention in Psychoses at the Department of Child and Adolescent Psychiatry and Psychotherapy, Psychiatric University Hospital of the University of Zurich (CAPS) have developed the combined treatment programme "Robin" (Standardised manual and smartphone app). The therapy programme focuses on risk symptoms and aims to improve quality of life as well as daily functioning. The smartphone application "Robin Z" is an additional treatment tool to support patients between sessions. While a number of studies using smartphone applications in therapy have shown promising effects in adult patients with psychosis, little is known on its use in therapy with young patients. "Robin Z" is one of the first smartphone apps to target adolescent patients with at-risk or full-blown psychotic symptoms. Since September 2017, the effectiveness of this combined treatment approach has been evaluated with the systematic clinical intervention study ETRo (Evaluation of the Treatment approach "Robin").
Methods: The ETRo study is a prospective, naturalistic follow-up study with matched control design. For the control condition (treatment as usual), participants from a previous screening study will be included. By the end of September 2021, a total of 30 help-seeking CHR adolescents (18 female, mean age 16.1) were recruited for the intervention group (16 weekly individual sessions + at least 4 family sessions). CHR-symptoms, comorbid symptoms, functioning, self-efficacy and quality of life will be monitored at six time points (baseline, during the treatment period, immediately after intervention, and 6, 12 and 24 months later) and compared with the respective measures of the active control group.
Results: The first results on treatment effects will be presented in Florence. In addition to data on treatment satisfaction, this includes baseline data on the intervention group, their intraindividual changes in symptomatology, well-being as well as functional level during and immediately after treatment. Furthermore, the results of the first follow-up investigation 6 months after treatment are presented.
Conclusions: "Robin" is a newly developed treatment approach for adolescents at clinical high risk (CHR) for developing a psychotic disorder that combines a standardised treatment manual with a smartphone application. To the best of the author's knowledge, this is the first controlled study to examine the effectiveness of a specific early psychosis treatment in combination with a smartphone app for CHR adolescents. The results of the study are of clinical importance and should provide essential information in the fields of eMental Health and in prevention and early intervention in psychosis.

13.4 DIGITAL SUPPORT FOR SOCIAL FUNCTIONING IN SCHIZOPHRENIA: TARGETING SOCIAL MOTIVATION AND APPRAISALS IN DAILY LIFE

Daniel Fulford*[1]

[1]*Boston University*

Background: Although there has been keen interest in recent years in the development and testing of digital interventions for reducing distressing symptoms of psychosis, few interventions provide direct support for meaningful outcomes such as social functioning using theoretical models of psychosocial impairment. Targeted and evidence-based digital

interventions have the potential to impact important recovery outcomes in daily life as supplements to standard care.
Methods: We developed the Motivation and Skills Support (MASS) smartphone app, an ecological momentary intervention, to provide targeted social goal support for people with schizophrenia receiving outpatient services in the community. 31 participants used the app for 8 weeks. We measured our primary outcome, social functioning, as well as positive and negative symptoms, from pre- to post-intervention and at three-month follow-up. We also measured key intervention targets—social motivation and appraisals—twice daily throughout the intervention using ecological momentary assessment.
Results: Self-reported social functioning improved significantly from baseline to treatment termination, particularly in female participants. Gains were not maintained at the three-month follow-up. Positive, but not negative, symptoms of psychosis improved over the course of the intervention and follow-up. Furthermore, higher momentary reports of social appraisals (e.g., perceived social competence) during the intervention predicted increased social functioning from baseline to treatment termination.
Conclusions: The MASS app shows promise as an ecological momentary intervention for improving recovery outcomes in people with schizophrenia. Positive appraisals of daily social interactions are one potential mechanism through which the intervention impacted social functioning.

14. PSYCHOSIS PREDICTION 2.0: INCREASING CAPACITY FOR PSYCHOSIS PREVENTION USING A "HIGH RISK SYSTEMS" APPROACH

Ian Kelleher
University College Dublin

Overall Symposia Abstract: There has been extensive research over the past two decades on psychosis prediction. This is important because successful prediction of psychosis opens up the possibility of psychosis prevention. Prediction research to date has largely focused on symptomatic risk for psychosis, based on the presence of subclinical psychotic symptoms or full-threshold but brief psychotic symptoms. Structured interviews, including the Comprehensive Assessment of At Risk Mental States (CAARMS) and Structured Interview for Psychosis Risk Syndromes (SIPS) have been developed to help identify individuals with an increased psychosis risk, termed an At Risk Mental State (also called Clinical/Ultra High Risk).

A major challenge for the field is that recent research has suggested that the At Risk Mental State approach identifies only a small proportion of the total number of individuals at risk of psychosis in the population. Additional approaches to identifying individuals at risk of psychosis are needed to complement the At Risk Mental State approach if we are to realise the potential of psychosis prediction and, ultimately, psychosis prevention.

This symposium will explore new approaches to identifying psychosis risk. As opposed to the Clinical/Ultra High Risk focus on identifying symptoms that indicate elevated psychosis risk, this symposium will focus on identifying systems that indicate elevated psychosis risk. This symposium will explore four different "systems" associated with psychosis risk and look at how we can leverage the risk that is naturally concentrated in these systems to help identify more young people at risk of psychosis.

Dr Kelleher will discuss inpatient admissions to Child and Adolescent Mental Health (CAMHS) units as a high risk system for psychosis. Looking at a total birth cohort born in

1987, they found that, of all individuals who had been admitted to a CAMHS inpatient unit during childhood, 20% were diagnosed with a psychotic disorder by age 28 years. The median time to diagnosis of psychosis in this cohort from the time of initial inpatient admission was more than 6 years, highlighting a large window of opportunity for preventive interventions.

Dr Kääriälä will discuss "out of home care" (being placed in the care of the State) as a risk system for early onset (<18 years old) psychosis and bipolar disorder. Looking at 3,254 young people placed in out of home care, they found that more than 5% of this group were diagnosed with an early onset psychotic or bipolar disorder by age 18 years (RR for diagnosis: 12.8, 95%CI 10.5–15.5). What is more, children in out of home care accounted for >40% of all psychosis and bipolar disorder diagnoses up to age 18 years.

Ms Lång will discuss non-normative school progress (failing to progress to upper secondary school with same age peers) as a risk system for psychosis. They found that this group had more than double the risk of psychosis and bipolar disorder of peers who had typical school progression over a 10-year follow up.

Dr Bolhuis will discuss hospital Emergency Departments as a risk system for psychosis, bipolar, and depressive disorders – specifically, Emergency Department presentations for self-harm. In a large Swedish population sample, they found that 50% of individuals who had presented to the Emergency Department with self-harm went on to ultimately receive a diagnosis of psychosis, bipolar disorder or major depressive disorder in secondary/specialist mental health services.

Dr Jalbrzikowski will summarise the key findings and discuss how a "High Risk Systems" approach might play an important role in the early detection and prediction of psychosis and other serious mental illness in the future.

14.1 INPATIENT CHILD AND ADOLESCENT MENTAL HEALTH SERVICES (CAMHS) AS A HIGH RISK SYSTEM FOR LATER PSYCHOSIS: A BIRTH COHORT STUDY

Ian Kelleher*[1]

[1]*University College Dublin*

Background: Prediction of psychotic disorder is a clinical research priority for psychiatry and a key step for illness prevention. The focus of psychosis prediction research to date has been largely based on identifying subclinical symptoms of psychosis or brief full threshold psychotic symptoms in order to identify individuals at risk for psychotic disorder. We wished, on the other hand, to take a systems approach to psychosis risk. Specifically, we wished to test whether contact with a particular healthcare system – inpatient Child and Adolescent Mental Health Services admissions – identified a high risk group for psychosis. While psychosis is an uncommon diagnosis in children and adolescents age <18 years, we hypothesised that this group would be at high risk for psychosis when followed into adulthood.

Methods: For all individuals born in Finland in 1987 (N=59,476), we identified all inpatient CAMHS admissions using the national inpatient register. In order to calculate the absolute risk of psychosis among individuals who have had a CAMHS inpatient admission, we followed these individuals' healthcare contacts over time (to age 28 years) in both the inpatient and outpatient healthcare registers and identified all psychosis diagnoses. We also calculated the

median time to psychosis diagnosis from first CAMHS inpatient admission as an indication of the potential window of opportunity for (preventive) intervention in this cohort.
Results: In total, 2,261 individuals had an inpatient CAMHS admission. In total, 1,370 individuals were diagnosed with a psychotic disorder by age 28 years. Twenty percent (n=452) of all individuals who had a history of CAMHS inpatient admission were diagnosed with a psychotic disorder by age 28 years (OR 14.2, 95%CI 12.6-16.1). Four percent of these diagnoses occurred in outpatient CAMHS (prior to first inpatient admission) and 33% occurred during the first inpatient admission. However, nearly two thirds of the psychosis diagnoses (63%) occurred after the initial inpatient admission – the median time to diagnosis of psychosis in this cohort from the time of initial inpatient admission was more than 6 years.
Conclusions: Although psychosis diagnoses are uncommon in Child and Adolescent Mental Health Services, young people with inpatient CAMHS admissions are a high risk group for psychosis when followed into adulthood. Only a minority of these individuals were diagnosed with a psychotic disorder on their initial inpatient admission. Nearly two thirds of psychosis diagnoses occurred subsequent to first inpatient admission and there was a long latency to diagnosis of psychosis – median time from initial inpatient admission to a diagnosis of psychosis was > 6 years. This indicates a large window of opportunity for intervention in terms of the time from initial inpatient CAMHS admission to ultimate diagnosis of psychosis, highlighting the opportunity for prevention. These findings demonstrate the important potential of inpatient CAMHS units for prevention of psychosis.

14.2 THE RISK OF CHILDHOOD ONSET PSYCHOTIC AND BIPOLAR DISORDERS AMONG CHILDREN PLACED IN OUT-OF-HOME CARE: A COHORT STUDY OF FINNISH CHILDREN BORN IN 1997

Antti Kääriälä[1], David Gyllenberg*[1], Reijo Sund[2], Elina Pekkarinen[3], Markus Keski-Säntti[4], Tiina Ristikari[5], Tarja Heino[4], Andre Sourander[1]

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Background: Child welfare can be considered as a potential "risk system" when developing strategies for identification of individuals who are at high risk of psychotic and bipolar disorders. Yet, research on the risk of psychotic and bipolar disorders among children who have experienced placement in out-of-home care by child welfare authorities remains scarce. To fill this knowledge gap, we examine the incidence of specialized service use due to psychotic and bipolar disorders in a total population involving children who were placed in out-of-home care.
Methods: We used the longitudinal administrative data of a complete Finnish birth cohort 1997 (N = 57,174) followed up to age 18 years. We combined national patient and child welfare registers to estimate the bidirectional risk ratios (RRs) for the association between psychotic and bipolar disorders and out-of-home care placements. We estimated the risk of childhood onset (i.e., onset before age 18 years) psychotic and bipolar disorders among children who were placed in out-of-home care, as well as the risk of placement among children who were diagnosed with such disorders. We used descriptive methods to explore the timing of first placement relative to the first diagnosis.
Results: Of all children placed in out-of-home care (n = 3254), 5.4% were diagnosed with a psychotic or bipolar disorder (RR for diagnosis: 12.8, 95% confidence interval [CI] 10.5–15.5). Conversely, of all children diagnosed with psychotic and bipolar disorders (n = 402), 43.5% were placed in out-of-home care (RR for placement: 8.0, 95% CI 7.1–9.0). There were 175 children who were both placed in out-of-home care and diagnosed with a psychotic or bipolar

disorder; these children were placed into out-of-home care for a mean of 3.3 years before their first diagnosis, with 69% of them being diagnosed after their first placement.
Conclusions: Children in out-of-home care had high risks of psychotic and bipolar disorders compared to their non-care peers. They comprised almost half of the child population diagnosed with psychotic and bipolar disorders, thus representing an important group for the prevention of severe mental illness.

14.3 NON-NORMATIVE SCHOOL PROGRESS IN ADOLESCENCE AS A MARKER OF RISK FOR PSYCHOTIC AND BIPOLAR DISORDERS

Ulla Lång*[1]

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Background: The identification of individuals at risk of severe mental illness, such as psychosis and bipolar affective disorder (BPAD), is a clinical and research priority. Current high risk approaches, however, detect only a limited number of all cases. Additional high risk strategies are needed. Given that population research has shown that adolescent educational attainment is associated with risk for psychosis and BPAD, we wished to investigate non-normative school progress as a risk marker for later psychosis and BPAD in the general population.
Methods: We identified a cohort of all individuals turning 16 years old in 2003, the age at which individuals apply to upper secondary school in Finland. We identified all individuals who did (n = 51,615) and did not (n = 4,260) apply to upper secondary school at age 16. We then compared their risk of psychosis and bipolar disorder over a 12 year follow up period.
Results: In total, 7.6% of young people had non-normative school progress at age 16. This group, however, accounted for 14% of all psychosis and BPAD diagnoses over the 12 year follow up (OR 2.1 95% CI 1.8-2.4).
Conclusions: Individuals with non-normative school progress in their teenage years are at substantially elevated risk of psychosis and BPAD when followed into early adulthood. Further research will look at characteristics of this group that help to identify those at greatest risk of psychosis and BPAD.

14.4 A SWEDISH NATIONAL REGISTER STUDY OF 34,796 INDIVIDUALS PRESENTING TO HOSPITAL WITH SELF-HARM AND LATER RISK OF PSYCHOTIC OR BIPOLAR DISORDER

Koen Bolhuis*[1]

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Background: Identification of young people at risk of psychotic and bipolar disorders, is an important focus of psychiatric research. Existing “high risk” research has focused on individuals at symptomatic risk for psychosis, based on the presence of attenuated psychotic symptoms. We wished to investigate whether individuals who made contact with a particular healthcare system, specifically hospital presentation with self-harm, were at high risk for going on to develop a psychotic or bipolar disorder.
Methods: All individuals born in Sweden from 1981 onwards alive and living in Sweden at their 12th birthday were included through the Total Population Register (N=2,878,812), and were followed until the event of interest, death, or migration outside Sweden or 31 December 2013, whichever came first. We used healthcare registers to identify all presentations with self-

harm as well as all inpatient and outpatient (available from 2001 onwards) healthcare registrations of first diagnoses of psychotic, bipolar, and depressive disorders, using the International Statistical Classification of Diseases and Related Health Problems. First, proportions and Cox proportional hazards models were used to assess the prospective associations of self-harm hospital presentations with subsequent diagnosis of psychotic, bipolar and depressive disorders in secondary (specialist) care. All analyses were calculated separately for males and females.

Results: In total, 34,796 (1.6%) individuals were recorded to have presented to hospital with self-harm throughout the follow-up. Of these individuals, 50.4% were subsequently diagnosed with a psychotic, bipolar or depressive disorder in secondary care. Among males who had presented to hospital with self-harm, 8% were diagnosed with a psychotic disorder and 6% were diagnosed with bipolar disorder over the course of follow up (HR=12.56, 95% CI 11.46-13.76 and HR=15.18, 95% CI 13.72-16.82). Among females who had presented to hospital with self-harm, 5% were diagnosed with a psychotic disorder and 11% were diagnosed with bipolar disorder over the course of the follow up (HR=14.22, 95% CI 13.09-15.45 and HR=14.63, 95% CI13.85-15.45).

Conclusions: Individuals who present to hospital with self-harm are at substantially elevated risk of psychotic bipolar and depressive disorders. Our findings suggest that individuals who present to hospital with self-harm may represent an important cohort for early detection and prevention of serious mental illness.

15. INTEGRATING PHYSICAL HEALTH INTERVENTIONS INTO THE CARE OF PSYCHOTIC DISORDERS

Brian O'Donoghue

Orygen, the National Centre of Excellence in Youth Mental Health

Overall Symposia Abstract: The integration of physical health intervention and services into the routine care for people affected by schizophrenia and other psychotic disorders has been identified as an urgent priority. Due to the high prevalence of physical comorbidities in this population and the associated early mortality, there is a need to identify effective interventions that can be provided within the mental health services. This symposium will bring together the evidence evaluating these interventions and findings from novel interventions.

Prof Dan Siskind will present the outcomes of embedding an endocrinologist into a mental health service, as previously there was high levels of non-attendance. The presentation will highlight that taking an innovative approach led to higher levels of engagement and improved outcomes in relation to metabolic markers for people with a diagnosis of schizophrenia.

Dr Karen O'Connor, the National Lead for Early Intervention for psychosis services in Ireland will present the findings from a review on physical health interventions for first episode psychosis. This review, which included fifteen studies, demonstrates that positive effects were observed in physical health markers and that interventions were more effective when they were introduced early, consistent with the early intervention paradigm. Importantly, the review has highlighted the deficits of the current research and identifies where further research should be focused.

Dr Helene Speyer will present the findings from a systematic review and meta-analysis on the reversibility of antipsychotic-induced weight gain. The study included 55 trials, with a total of 12,279 participants. This review provides clinicians with the effectiveness of strategies, such as dose reduction, discontinuation or switching to a partial agonist.

A/Prof Brian O'Donoghue will present findings from a randomized controlled trial on whether the weight gain and metabolic complications that occurs early in the course of a psychotic disorder can be prevented by the addition of a physical health nurse into the care of young people with a first episode of psychosis.

Prof Fiona Gaughran, who has led clinical trials on physical health interventions for psychotic disorders, will act as a discussant for the symposium.

15.1 AN INTEGRATED METABOLIC CLINIC EMBEDDED IN AN OUTPATIENT MENTAL HEALTH CLINIC

Dan Siskind*[1], Balaji Motamarri[1], Moe Thuzar[2], Wesley Yen[3], Anthony Russell[4]

[1]*Metro South Addiction and Mental Health Service,* [2]*Princess Alexandra Hospital,* [3]*Logan Hospital,* [4]*University of Queensland*

Background: People with schizophrenia die 18 years earlier than the general population, mostly due to avertable cardiometabolic diseases. Engagement with primary and tertiary health services can be challenging for this population. By embedding the endocrinologist in an environment familiar and acceptable to people with schizophrenia, the community mental health clinic, failure to attend rates were reduced and metabolic health markers were improved.
Methods: Metabolic data were collected retrospectively through electronic records from 48 consecutive patients with schizophrenia, reviewed in the integrated metabolic clinic over a 12-month period. Data from baseline, first follow up and last follow up within 12 months from the initial visit were analysed. Attendance rates at the integrated clinic and those at the general endocrine clinics by a similar mental health patient population were also compared.
Results: Compared with baseline, there was significant improvement in mean ±SEM total cholesterol (5.5±0.3 vs 4.9±0.3 mmol/L, p=0.003) and triglyceride (3.0±0.3 vs 2.2±0.2 mmol/L, p=0.001). Attendance rate was significantly better in the integrated clinic compared to the that in general endocrine clinics for both initial consult (80.0% versus 51.2%, p<0.001) and review appointment (64.3% vs 47.6%, p<0.001).
Conclusions: Embedding physical health services within a mental health outpatient clinic improves the efficiency of resource usage and leads to improved patient metabolic health outcomes.

15.2 PHYSICAL HEALTH INTERVENTIONS FOR PATIENTS WHO HAVE EXPERIENCED A FIRST EPISODE OF PSYCHOSIS: A NARRATIVE REVIEW

Fergal Fouhy[1], Walter Cullen[2], Karen O'Connor*[1]

[1]*University College Cork,* [2]*University College Dublin*

Background: Service users with severe psychiatric illnesses, such as schizophrenia, major depressive disorder and bipolar disorder, are more likely to suffer from ill-health. There is evidence that lifestyle interventions, for example, exercise, dietary advice, and smoking cessation programmes for service users with severe mental illness can be of health benefit. This review was carried out to identify the literature pertaining to physical health interventions for service users who have experienced a first-episode psychosis (FEP), to examine the nature of the interventions which were carried out, and to assess these interventions in terms of feasibility and efficacy.

Methods: A narrative review was conducted in August 2019 by searching 'Pubmed' and 'Embase' electronic databases. Studies investigating the effect a physical health intervention had on service users who had experienced a First Episode of Psychosis were included in the review.
Results: Fifteen studies met inclusion criteria: 12 quantitative studies and 3 qualitative. Exercise, dietary advice, smoking cessation and motivational coaching were some of the physical health interventions utilised in the identified studies. Positive effects were seen in terms of physical health markers wherever they were investigated, particularly when the intervention was delivered early. The impact on psychiatric symptoms and longer-term impacts on health were less frequently assessed.
Conclusions: Physical health interventions have a positive impact on service users who have experienced a FEP. More research is warranted in this area in Ireland. These studies should include controls, have longer follow-up periods and should assess the impact on psychiatric health.

15.3 REVERSIBILITY OF ANTIPSYCHOTIC-INDUCED WEIGHT GAIN: A SYSTEMATIC REVIEW AND META-ANALYSIS

Helene Speyer*[1], Casper Westergaard[2], Nikolai Albert[2], Anne Emilie Stürup[2], Mette Karlsen[2], Merete Nordentoft[3], Jesper Krogh[4]

[1]*Mental Health Centre Copenhagen,* [2]*Copenhagen Research Center for Mental Health – CORE,* [3]*Mental Health Center Copenhagen, University of Copenhagen,* [4]*Mental Health Centre Copenhagen, Copenhagen University Hospital*

Background: Weight gain is a major adverse effect of antipsychotic medication, negatively affecting physical and mental well-being. The objective of this study was to explore if dose reduction, discontinuation, switch to a partial agonist, or switch from polypharmacy to monotherapy will lead to weight loss
Methods: Controlled and uncontrolled studies reporting the effects of discontinuation, dose reduction, switch to a partial agonist, or switch from polypharmacy to monotherapy on weight were included. Primary outcome was difference in weight compared to maintenance groups based on controlled studies. Secondary outcome was change in weight from initiation of one of the included interventions until follow-up in a pre-post analysis
Results: We identified 40 randomized controlled trials and 15 uncontrolled studies including 12,279 individuals. The effect of the interventions, i.e. dose reduction, drug discontinuation, or switch to a partial agonist, reduced the weight with 1.5 kg (95% CI −2.03 to −0.98; $P < 0.001$) compared to maintenance treatment. The weight change from pre to post was a reduction of 1.13 kg (95% CI −1.36 to −0.90; $P < 0.001$).
Conclusions: We found a significant but small reduction in weight, suggesting that antipsychotic-induced weight gain can be reversed to some degree. Only a few studies were designed to address the question as primary outcome, which limits the generalizability of our findings

15.4 PREVENTION OF WEIGHT GAIN AND METABOLIC COMPLICATIONS IN FIRST EPISODE PSYCHOSIS. A RANDOMIZED CONTROLLED TRIAL OF A PHYSICAL HEALTH NURSE INTERVENTION

Brian O'Donoghue*[1], Nathan Mifsud[1], Emily Castagnini[1], Alison Langstone[1], Andrew Thompson[1], Eoin Killackey[1], Patrick D McGorry[1]

[1]*Orygen, the National Centre of Excellence in Youth Mental Health*

Background: Individuals affected by psychotic disorders have a reduced life expectancy and the factors that contribute to this early mortality, such as obesity, smoking and sedentary behaviour occur early in the disorder. This randomized trial aimed to determine whether the integration of a physical health nurse in the care of young people with FEP could reduce the development of clinically significant weight gain (≥7% body weight). Secondary outcomes included whether the intervention led to lower rates of smoking, metabolic syndrome and sedentary behaviour.
Methods: This was a single-blinded randomized controlled trial. Participants were randomly allocated to have a physical health nurse added to their treating team for a period of 12 weeks or to treatment as usual (TAU), which consisted of a psychiatrist and case manager. Participants were attending the Early Psychosis Prevention and Intervention Centre (EEPIC) in Melbourne, were aged between 15 and 24, were diagnosed with a first episode of psychosis and had less than four weeks exposure to antipsychotic medication. The physical health nurse met with participants in the intervention group at least weekly and provided psychoeducation, facilitated attendance and engagement in physical health interventions, and referral to any indicated specialist.
Results: Of the 77 participants, 49.4% (n=38) were randomized to the intervention group and 50.6% (n=39) to TAU. 27.3% in the intervention group experienced clinically significant weight gain compared to 34.4% in the TAU group (OR=0.72,95% C.I. 0.25–2.06,p=.54). After six months, 40.7% of the intervention group gained clinically significant weight compared to 44.1% in the TAU group (p=.79). There was no difference in mean change in weight between groups after 12 weeks (2.6kg vs 2.9kg, p=.87) and after six months (3.6kg vs 4.3kg, p=.64). There was no difference in the rates of tobacco smoking cessation, the prevalence of metabolic syndrome, or physical activity levels between the two groups at either follow-up.
Conclusions: This intervention failed to prevent the metabolic complications that are highly prevalent in psychotic disorders and highlights that even more intensive interventions are required.

16. TRANSLATING MOLECULAR INFLAMMATION FINDINGS IN BRAIN TO CLINICAL BIOMARKERS WITH RELEVANCE TO NOVEL TREATMENTS IN SCHIZOPHRENIA AND RELATED PSYCHOSES

Thomas Weickert

State University of New York Upstate Medical University

Overall Symposia Abstract: There is mounting evidence from large scale genetic studies, first episode and clinical high risk studies, postmortem studies and chronically ill patient studies suggesting that inflammatory processes contribute to the expression of schizophrenia and related psychoses. However, the specific role of inflammation in expression of the illness and identification of inflammation markers of psychosis that are directly relevant to novel anti-inflammatory treatment are poorly understood. The present symposium will report the latest findings addressing inflammatory processes in postmortem brain tissue and clinical studies relating the inflammation markers to symptoms, cognition and brain structure in schizophrenia and related psychoses in addition to reporting on the results of a clinical trial of an adjunctive anti-inflammatory treatment aimed at reducing peripheral inflammation markers and psychotic symptom severity.

16.1 INCREASED COMPLEMENT ALONGSIDE REDUCTION IN DOPAMINE NEURON HEALTH IN SCHIZOPHRENIA

Tertia Purves-Tyson*[1], Jessica Chandra[2], Debora Rothmond[3], Cyndi Shannon Weickert[4]

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Background: Midbrain dopaminergic dysregulation is core to psychosis and cognitive deficits in schizophrenia. Elevated proinflammatory molecules exist in ~50% people with schizophrenia. The complement system is linked with the pathogenesis of schizophrenia. Here we predict that increased inflammation in the midbrain will be linked with poor dopamine neuron health. Nuclear receptor related-1 (Nurr1), is a transcription factor that both inhibits neuroinflammation and activates transcription of tyrosine hydroxylase (TH) and dopamine transporter (DAT), important for viability of dopamine neurons. We hypothesized that Nurr1 would be decreased in the midbrain in schizophrenia cases with neuroinflammation compared to both schizophrenia cases and controls that do not exhibit neuroinflammation.
Methods: Gene expression of C1qA, C3, C4, TH, DAT and Nurr1 were measured with qRT-PCR in the midbrain from 28 schizophrenia cases (13 high inflammation, 15 low inflammation) and 28 controls (low inflammation). ANCOVAs (with demographic variables, age, PMI and RIN as covariates when correlations were detected) were used to detect differences between diagnostic/inflammatory groups. For schizophrenia cases, antipsychotic doses were converted to chlorpromazine (CPZ) equivalents. Spearman's correlations were used to determine relationships between illness duration, antipsychotics, and gene expression.
Results: C1qA, C3 and C4 mRNAs were increased >98%, >54.9% and >37.3% respectively, in high inflammation schizophrenia cases compared to low inflammation schizophrenia cases and controls (all $F>5.51$, $p<0.001$). Nurr1 mRNA was decreased in the midbrain in schizophrenia cases compared to controls (21.4%) and this decrease was exacerbated in the high inflammation/schizophrenia subgroup ($F=4.58$, $p=0.015$). TH and DAT mRNA were also reduced in high inflammation schizophrenia compared to controls ($p<0.05$ and $p<0.01$ respectively). Nurr1 is strongly positively correlated with TH and DAT mRNAs in control and schizophrenia cases (Rho>0.8, $p< 0.001$). Complement factor mRNAs were positively correlated with some CPZ measures (Rho>0.4, $p<0.05$). Nurr1 mRNA did not correlate with antipsychotics and no transcripts correlated with illness duration (all $p<0.05$).
Conclusions: Increased complement in the midbrain, along with increased inflammatory cytokines and a reduction in the protective factor, Nurr1, may converge to contribute to dopamine neuron damage and subsequent dopamine dysregulation in schizophrenia. Although the effects of antipsychotics cannot be ruled out, these data suggest they are not directly related to the reduction of dopamine neuron markers, although are related to increased complement gene expression. Preclinical studies are needed to determine the direction of the relationship between neuroinflammatory pathways and dopamine neuron health. A better understanding of the processes of dopamine neuron damage in the midbrain could help pave the way for discovery of novel targets for drug development.

16.2 METABOLOMIC PROFILE OF AUTOIMMUNE PSYCHOSIS

Belinda Lennox*[1], Wenzheng Xiong[1], Ksenija Yeeles[1], Paddy Waters[1], Jeanne Tan May May[1], Tianrong Yeo[1], Daniel Anthony[1], Fay Probert[1]

[1]*University of Oxford*

Background: We have shown that a proportion of people with psychosis have serum antibodies against neuronal cell surface targets. However, the clinical relevance of these antibodies is unclear.
To try and address this question we undertook a metabolomic study comparing patients with and without antibodies, to see whether those with antibodies had a more inflammatory profile, and whether this was associated with particular clinical characteristics.

Methods: We measured the serum NMR metabolite profiles of 75 Antibody positive (NMDAR, LGI1, CASPR2, VGKC, GlyR) patients and 70 Antibody negative patients matched for age, gender, illness course and ethnicity. Multivariate analysis was carried out using an principal component analysis (PCA), an unsupervised analysis and orthogonal partial least squares discriminant analysis (OPLS-DA), a supervised method. Accuracy, sensitivity, and specificity were determined by Kolmogorov–Smirnov. Partial PANSS ratings on 8 items were undertaken by clinicians.
Results: An almost completely distinct metabolomic profile was found in unsupervised analysis in those with VGKCC or GlyR antibodies, compared with either antibody negative patients or NMDAR, LGI1, CASPR2 positive patients ($p<0.0001$). This profile was of a decrease in serum lipoproteins and increase in amino acid concentrations, The VGKCC and GlyR antibody patients also had more severe illness with higher PANSS scores, and in particular higher levels of negative symptoms than the other patient groups (22 (11-36) versus 13 (8-35) $p<0.001$).
Conclusions: Antibodies against VGKCC and GlyR are associated with an inflammatory profile and more severe illness in those with psychosis, and suggest that these serum antibodies are a marker of an autoimmune subtype of psychosis.

16.3 TOLL-LIKE RECEPTOR MRNA LEVELS AND CINGULATE GYRUS CORTICAL THICKNESS IN SCHIZOPHRENIA

Jochen Kindler*[1], Thomas Weickert[2], Danny Boerrigter[3], Jason Bruggemann[4], Maryanne O'Donnell[5], Cherrie Galletly[6], Ryan Balzan[7], Dennis Liu[8], Rhoshel Lenroot[9], Cynthia Shannon Weickert[10]

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Background: Increased cytokines of the innate immune system are found in schizophrenia and may be caused by alterations in endogenous pathogen recognition receptors upstream of cytokines. Toll like receptors (TLR) expressed on sentinel immune cells are cell surface receptors activated by bacteria (activating TLR1, TLR4), viruses (activating TLR3) or both (activating TLR8). We tested whether peripheral TLR1, TLR3, TLR4 and TLR8 mRNA levels differed between schizophrenia and healthy controls and if TLR mRNA levels were related to proinflammatory cytokines and cingulate gyrus cortical thickness.
Methods: Peripheral TLR mRNA levels and proinflammatory cytokine mRNAs were extracted from white blood cells of 86 people with schizophrenia and 77 controls by RT-PCR

and structural 3-T Magnetic Resonance Imaging scans were acquired in 51/86 people with schizophrenia and 57/77 controls.
Results: TLR4 and TLR8 mRNA levels were significantly increased and TLR3 mRNA levels were significantly decreased in schizophrenia versus controls. Proinflammatory cytokine subgroups had a significant influence on mRNA levels of all TLRs. Cingulate gyrus cortical thickness was inversely associated with TLR8 mRNA levels in schizophrenia and with TLR4 and TLR8 levels in controls.
Conclusions: Our results suggest more bacterial (based on TLR4 levels) relative to viral influence in the inflammatory response characteristic of schizophrenia. TLR4 and TLR8 expression was inversely related to cingulate gyrus thickness in schizophrenia and controls. Thus, the cingulate cortex may be particularly vulnerable to inflammation.

16.4 C-REACTIVE PROTEIN IS A RELIABLE, VALID AND USEFUL PERIPHERAL BIOMARKER OF INFLAMMATION IN SCHIZOPHRENIA AND RELATED PSYCHOSES

Thomas Weickert*[1], Rhoshel Lenroot[2], Julia Lappin[3], Andrew Lloyd[4], Cherrie Galletly[5], Dennis Liu[6], Cynthia Shannon Weickert[7]

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Background: While it is well accepted that schizophrenia and related psychoses most likely have multiple etiologies with generally ineffective or at best limited treatments, the most probable etiologies and effective treatments have been generally elusive. More recently, a relatively large body of research findings from genetic, first episode, ultra-high risk, human post-mortem, animal model and chronically ill patient studies supports a role for inflammatory processes in the expression of schizophrenia. Work from our labs have also provided evidence for inflammation (either in brain or in peripheral blood) in 40 to 60 percent of patients with schizophrenia. However, the specific peripheral markers that will best characterize the patients with schizophrenia who have active inflammation and will act as reliable and sensitive indicators of anti-inflammatory treatment response in these patients are uncertain. To provide a complete framework, the present report will briefly outline our previous work demonstrating the relationship of C-Reactive Protein (CRP) to acute psychosis, cognitive impairment, and brain structural abnormalities in schizophrenia. In addition, we will also describe our recent unpublished findings using CRP and other peripheral blood biomarkers to prospectively select patients with inflammation for a specific adjunctive monoclonal antibody treatment designed to reduce peripheral inflammation markers (such as CRP) and potentially reduce symptom severity in patients with schizophrenia.
Methods: In two independent, previously published, studies (one study of 499 patients/644 controls and another study of 97 patients and 87 controls) we collected peripheral blood (measuring CRP), cognitive abilities (assessing prefrontal cortex function such as working memory and attention), symptom severity and structural brain measures (cortical thickness) in patients with schizophrenia and healthy controls. In a more recent, currently unpublished study, we recruited 27 patients with schizophrenia or schizoaffective disorder who displayed elevated peripheral markers of inflammation (IL-6, IL-1β and CRP) to receive a single adjunctive treatment of the highly selective IL-β blocker (canakinumab) as part of a randomized, double-

blind, placebo-controlled trial with symptom severity and CRP measured at baseline and after 4 and 8 weeks of treatment.
Results: In our published studies we showed that elevated CRP (> 3) was present in 60 percent of patients admitted for an acute psychotic episode and in over 40 percent of chronically ill patients with schizophrenia who showed significantly worse working memory and attention and elevated CRP was inversely related to cortical thickness in frontal and temporal regions. Results from our unpublished clinical trial showed that adjunctive canakinumab treatment significantly decreased CRP relative to baseline in the treatment group only and significantly reduced positive symptom severity scores after 8 weeks of treatment. There was a relatively strong inverse correlation between peripheral CRP levels and positive symptom severity scores only after 8 weeks of treatment in the canakinumab group.
Conclusions: CRP is an easily measured peripheral marker of inflammation obtained in a substantial proportion of patients with schizophrenia and related psychoses across multiple samples. Peripheral CRP levels are also related to cognitive impairment and structural brain abnormalities and can be used as a measure of treatment efficacy in studies of anti-inflammatory agents in schizophrenia and related psychoses.

17. HERV AS A MISSING LINK BETWEEN INFLAMMATION AND SCHIZOPHRENIA IN THE CONTEXT OF COVID

Marion Leboyer
AP-HP, Université Paris-Est-Créteil

Overall Symposia Abstract: The presence of the pro-inflammatory and neurotoxic protein ENV, encoded by Human Endogenous Retroviruses type "W" (HERV-W), reactivated by perinatal infections, and related to chronic inflammatory and neurotoxic background is now clearly demonstrated both in psychotic disorders both in clinical and in pre-clinical settings. Data strongly suggest that neutralising antibody targeting the ENV protein could be used in subgroups of schizophrenic patients and developed as innovative treatments. Now HERV-W emerges as a link between inflammation and schizophrenia. This is particularly true in the context of the Covid pandemic, as new data have revealed that Coronavirus-Sars2 could reactivate HERV-W. With expert in the fields, immunologist, neurobiologist and psychiatrists, we will describe the state of the art on the major field of human Endogenous Retroviruses
In this symposium, we will describe the first psychotic outbreaks and psychiatric manifestations in post-acute COVID patients and its underlying neuroinflammatory rationale induced by the activation of Human Endogenous Retrovirus type W by SARS-CoV-2 (Hervé Perron, Grenoble, France). We will then discuss unpublished preclinical data from a novel mouse model that mimics transgenic expression of the HERV-W envelope protein, showing that mice with HERV-W envelope protein expression display a number of schizophrenia-related behavioural and cognitive deficits, and demonstrate that the severity of behavioural abnormalities induced by HERV-W envelope protein expression is exacerbated by prenatal exposure to maternal immune activation, known to be an environmental risk factor of schizophrenia and related disorders (Urs Meyer, Zurich, Switzerland). A review on the existing evidence implicating increased expression of HERV type W envelope in subsets of psychotic patients defined by distinct clinical and biological characteristics will be presented. Identifying a subset of patients show that we can develop biomarker-guided personalized medicine to develop novel therapeutic strategies based on neutralizing HERV-W ENV under inflammatory conditions (Marion Leboyer, Paris, France). In the context of Covid, we will present novel

epidemiological data showing that psychotic patients, before vaccination, hospitalised in French and Belgium settings have elevated markers of inflammation, of coronavirus and HERV activation in comparison to controls (Livia de Picker, Antwerp, Belgium).

17.1 FIRST PSYCHOTIC OUTBREAKS AND PSYCHIATRIC MANIFESTATIONS IN POST-ACUTE COVID PATIENTS: UNDERLYING NEUROINFLAMMATION LINKED TO THE ACTIVATION OF HUMAN ENDOGENOUS RETROVIRUS-W BY SARS-COV-2 LEADING TO NEW A THERAPEUTIC RATIONALE.

Hervé Perron*[1]

[1]*Geneuro*

Background: Psychotic disorders are now understood as genetically- and environmentally-mediated illnesses. Although the pathogenic mechanisms underpinning these disorders are still unclear, it recently emerged that immune-related genes and mobile genetic elements constitute major actors in the aetiopathological chain. Mobile genetic elements, including human endogenous retroviruses (HERV), are remnants of infections that took place several million years ago and embody around 8% of the human genome. Endogenous retroviruses have the capacity to control gene regulatory networks during human brain evolution and development and their growing association to major neurological and psychiatric disorders provides a new conceptual framework to decrypt the interplay between immunological, genetic, and brain systems. HERV are normally silenced by cell machineries, but they can be activated following infection with certain pathogens. HERV activation has consistently been associated with psychosis, in particular in schizophrenia with elevated RNA transcription of the HERV-W family and expression of its envelope (ENV) protein. In sera from schizophrenic patients, HERV-W ENV antigenemia correlated with increased levels of CRP and was recently found to cluster in a sub-group with elevated IL-6 levels representing a small half of the studied patients. As a TLR4 agonist, HERV-W ENV triggers innate immunity and inflammation. In the brain, it was shown to induce microglia-mediated neuroinflammation and to alter the NMDA receptor (NMDAR)-mediated synaptic organization and plasticity. Its expression in the rat hippocampus induced psychotic-like behavioral abnormalities that were significantly reduced in amimals treated with a neutralizing antibody targeting HERV-W ENV.
Most recent studies showed that SARS-CoV-2 activated HERV-W ENV expression in cultured lymphoid cells from a sub-group of healthy donors. In COVID-19 patients, it was found strongly expressed in white blood cells from patients with severe disease.

Patients with post-acute COVID syndromes (PACS) have frequent neuropsychiatric manifestations, including first schizophrenic episodes. We therefore addressed the question of a potential pathophysiological continuum between HERV-W activation in susceptible individuals and psychotic symptoms in PACS.

Methods: HERV-W ENV antigenemia and IgG reactivity to SARS-CoV-2 antigens were detected using immunocapillary Wes platfrom (Proteinsimple, USA). Cytokine we quantified using ELLA platform and kits (Biotechne, USA). Flow cytometry and Immunohistology were performed with dedicated protocols using HERV-W ENV specific monoclonals (GeNeuro, Switzerland).
Results: New results from studies on PACS neuropsychiatric disorders with a focus on schizophrenic first episodes will be presented, with data on HERV-W ENV, SARS-CoV-2 and cytokines in serum. The underlying pathophysiological continuum associating HERV-W ENV with neuroreceptor synaptic plasticity, microglia and innate immune cytokines in such

psychotic episodes of patients with classical or post-COVID occurrence will be argued following immunohistochemistry results from COVID-19 post-mortem brain samples.
Conclusions: Converging data from previous studies in patients with schizophrenia, on HERV-W activation by certain infectious agents and on HERV-W ENV immuno- and neuro-pathogenicity, strongly suggest the involvement of this endogenous retroviral protein in the pathogenesis of this psychotic disease in a sub-group of patients with elevated pro-inflammatory cytokine levels in blood.
As will be presented, the same HERV-W ENV activation in severe COVID-19 and in symptomatic post-COVID patients also suggest an role underlying neuropsychiatric symptoms. Based on existing science in the domain and in the light of ongoing clinical trials with a therapeutic antibody neutralizing HERV-W ENV in progressive multiple sclerosis, a rationale for HERV-W ENV targeted therapeutic intervention in schizophrenia and PACS psychiatric syndromes will be discussed.

17.2 HERV AND SCHIZOPHRENIA IN COVID-19 TIMES

Livia De Picker*[1], Kawtar El Abdellati[2], Alexandre Lucas[3], Hervé Perron[4], Steven Fried[3], Jean-Romain Richard[3], Ryad Tamouza[2], Violette Coppens[2], Manuel Morrens[2], Marion Leboyer[2]

[1]*University of Antwerp,* [2]*Collaborative Antwerp Psychiatric Research Institute, University of Antwerp and University Psychiatric Hospital Duffel,* [3]*INSERM,* [4]*GeNeuro*

Background: COVID-19 has been shown to activate the pro-inflammatory and neurotoxic Human Endogenous Retrovirus-W-envelope protein (HERV-W ENV), which sheds new light on the link between SARS-CoV2 infection and post COVID neuropsychiatric syndromes. HERV-W-ENV was found to be highly expressed in the lymphocytes of COVID-19 patients and correlated with inflammatory markers (Balestrieri et al, 2021). As previous evidence has indicated that HERV-W-ENV is elevated in up to 50% of patients with schizophrenia and bipolar disorder (Perron et al, 2008, 2012), we investigated the presence of HERV-W-ENV and SARS-CoV-2 seroprevalence among acute presentations of schizophrenia spectrum disorders.
Methods: HERV-W expression was measured in plasma samples of 262 recently hospitalized and acutely ill psychiatric patients, who were admitted to two large psychiatric hospitals (UPC Duffel in Belgium and AP-HP Paris in France) between January and June 2021. 62 patients were diagnosed with schizophrenia spectrum disorders. COVID-19 seroprevalence was determined by quantitative analysis of nucleocapsid, S1, S2 and spike protein IgG. Pro-inflammatory immune response was measured by IL-1b, IL-6, IL-8 and TNF-a. All analyses were performed at INSERM, France.
Results: COVID-19 seroprevalence among patients with schizophrenia spectrum disorders was 68.8% (Belgium) and 82.6% (France), allowing us to compare COVID-19-exposed and non-exposed individuals in terms of peripheral immune response and HERV-W expression. Peripheral blood HERV-W expression was significantly predicted by the presence of COVID-19 antibodies ($F=14.1$; $p=0.0004$) among schizophrenia patients. All patients were unvaccinated against SARS-CoV-2 at the time of inclusion.
Conclusions: Acutely ill schizophrenia patients hospitalized between January and June 2021 demonstrated a very high COVID-19 seroprevalence, and the presence of COVID-19 antibodies significantly predicted peripheral blood HERV-W expression in these patients, thus providing a mechanistic link between exposure to infections, HERV-W expression and

neuropsychiatric presentations. Results from a currently ongoing SARS-CoV-2 vaccination follow-up study in patients with severe mental illness will also be presented.

17.3 HERV-W ENVELOPE PROTEIN AND INFLAMMATORY MARKERS IN PSYCHOTIC DISORDERS

Marion Leboyer*[1], Ryad Tamouza[2], Jean-Romain Richard[3], Marianne Foiselle[4], Caroline Barrau[5], Alexandre Lucas[6], Urs Meyer[7], Hervé Perron[8]

[1]*AP-HP, Université Paris-Est-Créteil,* [2]*AP-HP/INSERM,* [3]*INSERM, U955, team 15, Créteil, 94000,* [4]*Mondor Institute of Biological Research - Translational Psychiatry Laboratory - INSERM - UPEC,* [5]*Plateforme de Ressources Biologiques, HU Henri Mondor, F94010,* [6]*Institut des Maladies Métaboliques et Cardiovasculaires (I2MC), plateau We-Met, Inserm UMR1048 and Université Paul Sabatier, Toulouse,* [7]*Institute of Pharmacology and Toxicology, University of Zurich-Vetsuisse,* [8]*GeNeuro*

Background: Human endogenous retroviruses (HERVs) are remnants of infections that took place several million years ago and represent approximately 8% of the human genome. Accumulating evidence implicates increased expression of HERV type W envelope (HERV-W ENV) in the spectrum of psychotic disorders, including schizophrenia and bipolar disorder. Despite of the existing evidence implicating increased expression of HERV type W envelope (HERV-W ENV) in schizophrenia and bipolar disorder, it remains unknown whether the expression of HERV-W is altered in only a subset of patients with distinct clinical or biological characteristics and symptoms.
Methods: To address this question, we performed unsupervised two-step clustering of a multivariate data set that included HERV-W ENV protein antigenemia, serum cytokines, childhood trauma scores, and clinical data of a cohort of patients with schizophrenia (n = 29), bipolar disorder (n = 43) and healthy controls (n = 32).
Results: We found that only a subset of patients with schizophrenia (~ 41%) and bipolar disorder (~ 28%) show positive antigenemia for HERV-W ENV protein, whereas the large majority (96%) of control subjects was found to be HERV-W ENV negative. Unsupervised cluster analysis identified the presence of two main clusters of patients, which were best predicted by the presence or absence of HERV-W ENV protein. HERV-W expression was associated with increased serum levels of inflammatory cytokines and higher childhood maltreatment scores.
Conclusions: Our study suggests that HERV-W ENV protein antigenemia and cytokines can be used to stratify patients with psychotic disorders into subgroups with differing inflammatory and clinical profiles. Our findings may be relevant for biomarker-guided personalized medicine and for novel therapeutic strategies based on neutralizing HERV-W ENV under inflammatory conditions

17.4 BEHAVIORAL AND MOLECULAR CONSEQUENCES OF HERV-W ENVELOPE PROTEIN EXPRESSION IN MOUSE MODELS

Felisa Herrero[1], Joel Gruchot[2], Hervé Perron[3], Patrick Küry[2], Ulrike Weber-Stadlbauer[1], Urs Meyer*[1]

[1]*University of Zurich,* [2]*Heinrich-Heine-University Düsseldorf,* [3]*GeNeuro*

Background: Human endogenous retroviruses (HERVs) are remnants of infections that took place several million years ago and represent approximately 8% of the human genome. Accumulating evidence implicates increased expression of HERV type W envelope (HERV-

W ENV) in the spectrum of psychotic disorders, including schizophrenia and bipolar disorder. Thus far, however, the link between increased HERV-W ENV expression and psychotic disorders largely remains circumstantial. To gain more mechanistic insights into the neurobiological disease pathways affected by HERV-W ENV expression, we generated and characterized a novel mouse model that mimics transgenic expression of this retroviral element in mice.

Methods: Mice with transgenic HERV-W ENV expression were generated by inserting the multiple sclerosis derived retrovirus (MSRV)-pv14env sequence, which features the HERV-W ENV open reading frame (ORF) and the 3' long terminal repeat (3'LTR) under the CAG promoter, into the hypoxanthine-guanine phosphoribosyltransferase (HPRT) locus. In a first series of experiments, adult transgenic (TG) mice and wild-type (WT) littermates were subjected to behavioral and cognitive phenotyping using a battery of tests assessing basal locomotor activity in novel environment, innate anxiety-like behavior, social approach behavior and social recognition memory, spatial working memory, and sensorimotor gating. Next-generation RNA sequencing of hippocampal tissue was then used to identify genome-wide transcriptional changes in TG mice relative to WT controls. Ingenuity pathway analysis (IPA) was applied to explore molecular signaling pathways affected by HERV-W ENV expression. In a second series of experiments, TG and WT mice were prenatally exposed to maternal immune activation (MIA) or prenatal control treatment in order to identify possible interactions between an immune-related environmental risk factor of schizophrenia and expression of HERV-W ENV protein. MIA was induced by maternal treatment with the viral mimetic, poly(I:C) (2.5 mg/kg, i.v.), given on gestation day 12.

Results: Ubiquitous expression of HERV-W ENV protein was verified in transgenic (TG) mice relative to wild-type (WT) littermates in multiple organs, including brain tissue. Compared to WT controls, TG mice with HERV-W ENV expression displayed a number of behavioral and cognitive anomalies, including increased locomotor activity in novel environments, impairments in social recognition memory 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 68 and 131 genes to be upregulated and downregulated, respectively, in the hippocampus of TG mice relative to WT controls. Functional network prediction using IPA further demonstrated that the differentially expressed genes annotated with the functional nodes "neurodevelopmental disorders", "schizophrenia", "quantity of dendritic spines" and "synapse formation". Prenatal exposure to poly(I:C)-induced MIA exacerbated some of the behavioral phenotypes (e.g. social behavior) in TG mice and led to the presence of novel deficits (e.g. impairments in ultrasonic vocalization) when combined with HERV-W ENV protein expression.

Conclusions: Our preclinical data provide causal evidence for a role of HERV-W ENV expression in disrupting brain functions relevant to schizophrenia and related disorders. Moreover, our findings demonstrate that expression of this retroviral element has the capacity to change the brain transcriptome and to interact with an immune-related environmental risk factor implicated in schizophrenia and other psychiatric disorders with neurodevelopmental components.

18. WORLDWIDE LONG-TERM OUTCOMES AFTER A FIRST EPISODE PSYCHOSIS - TAKING A LOOK AT THE LATER STAGES OF ILLNESS AMONG PATIENTS TREATED IN MODERN MENTAL HEALTH SERVICES FROM DIFFERENT SITES ALL OVER THE WORLD.

Merete Nordentoft

Mental Health Centre Copenhagen

Overall Symposia Abstract: Historically, a diagnosis of schizophrenia was perceived as a severe chronic disease with progressive worsening. Fortunately, the WHO multicentre studies initiated in the late 1960's has made it clear that people with schizophrenia can experience symptomatic improvements and regain a degree of social and occupational functioning. Because of this, it is now widely recognized that psychotic disorders are heterogenous with diverse clinical presentation and prognosis. However, the WHO lead studies included individuals from the pre-neuroleptic era with various stages of illness and large differences in health care systems. It is therefore questionable to what degree these investigations can be used to draw conclusion regarding the treatment outcomes of patients today.

Over the past two decades early specialised interventions have been proven effective on short-term outcomes in patients after a first episode psychosis. Still, there is a lack of knowledge on the long- term outcomes among patients treated in modern mental health services. In addition, few studies from large representative cohorts have been able to conduct longitudinal analyses of outcomes.

This symposium will give a unique opportunity to gain new knowledge on the longitudinal treatment outcomes in the later stages of illness when patients are entering mid- to late-adulthood. We will present data on illness outcomes including physical health and mortality among patients treated in modern mental health services from different parts of the world. We will reflect on treatment standards twenty years ago and examine the clinical symptoms as well as functional outcomes into the second and third decades of illness. Furthermore, due to the diverse cultural setting of the symposium panelists we have the opportunity to discuss transcultural differences and sociocultural influences on the treatment outcomes of schizophrenia on a global scale.

Prof. Merete Nordentoft is the cofounder of the OPUS trial and has supervised the reassessment of the OPUS cohort through 20 years and she will be chairing this symposium together with Co-chair Dr. Marie Starzer.

Dr Thara Rangaswamy will present interesting findings from her 35 year follow-up of 90 FEP patients in Chennai, India. This will include cultural factors such as marriage, employment etc.

New data from a Danish 20-year follow-up of a large FEP cohort of 578 persons, a part of the OPUS Trial, will be presented and discussed by Dr. Helene Gjervig Hansen

The EPICC study has longitudinal data on 723 FEP persons in Australia over 20 years and Prof. Sue Cotton will among others discuss findings on physical health and mortality.

Dr Eric Chen who has been leading the development of the Early Detection and Intervention Services (EASY) in Hong Kong since 2001 will present data from their work on long-term outcomes in a modern Chinese setting.

Dr. Katherine Jonas who has been working on the Suffolk County Mental Health Project from USA has conducted assessments of a cohort with psychotic disorders for over 20 years will lead the discussion on changing patterns in the course and outcome of schizophrenia.

18.1 20 YEARS FOLLOW-UP OF THE OPUS I TRIAL - A LONG-TERM FOLLOW-UP OF A COHORT OF 578 PATIENTS WITH FIRST EPISODE PSYCHOSIS

Helene Gjervig Hansen*[1], Marie Starzer[2], Carsten Hjorthøj[2], Nikolai Albert[2], Merete Nordentoft[2]

[1]*Copenhagen Research Centre for Mental Health, University of Copenhagen,* [2]*Copenhagen Research Centre for Mental Health*

Background: In the original OPUS I trial 578 participants were recruited between January 1998 and December 2020 and randomized to early specialized intervention treatment or treatment as usual. Participants were between 18 and 45 years of age (mean age 26) and the study lasted two years. The early specialised intervention treatment combined modified assertive treatment, family involvement and social skill training. This treatment approach was proven effective and consequently over the last 20 years treatment facilities targeting patients with a first episode psychosis and using specialized interventions have been implemented in many parts of the world.
The reassessment of the OPUS I cohort represent a unique opportunity to gain new knowledge about the long-term outcome of schizophrenia spectrum disorders treated within modern mental health services.

Methods: This study is a large prospective cohort study reassessing participants from the OPUS I trial. Participants have been reassessed at 1-, 2-, 5-, 10- and 20-year follow-up. Independent investigators blinded to the original treatment allocation of the participants conducted the 20-year follow-up. We used standardized assessment tools to collect all data. Data was collected on a broad range of topics, including psychopathology, functioning, cognition, quality of life, use of medication, suicidal ideation, somatic comorbidities, and drug and alcohol use.
Using the unique Danish registers, it is possible to have complete follow-up on all participants on a range of relevant outcomes.

When looking at long-term outcomes we analyze all participants as one cohort. Depending on the nature of the baseline variables we are using binary logistic regression models or linear regression models to see if any baseline characteristics can be associated to a better or poorer outcome.

Results: We will finish inclusion in October 2021, so far, we have included 176 participants which is roughly a third of the original study population. 106 declined participating and 165 never answered back. Sixty eight had died and 22 where lost to follow-up. For those who participated we will be able to present new results on outcomes of psychotic and negative symptoms, level of functioning, level of cognitive functioning, remission rates and recovery. Using the Danish registers we will also be able to present outcomes on independent living, substance abuse, vocational status, medication, and service use on all 576 former participants of the OPUS.
Conclusions: The 20-year follow-up study will provide valuable new evidence on the course of illness of patients diagnosed and treated within modern treatment facilities. The OPUS trial is the largest RCT testing early intervention services among individuals with a first-episode psychosis. Furthermore, the OPUS cohort consists of multiple follow-up points and an extensive assessment at baseline and all follow-up points allowing us to assess cognition, functioning and psychopathology over time. Knowing if the course of a schizophrenia diagnosis changes over time both regarding symptom severity and its impact on everyday life is crucial in evaluating treatment efforts and the development of targeted interventions.

18.2 THE MADRAS LONGITUDINAL STUDY- 35 YEAR FOLLOW UP OF FEP

Rangaswamy Thara[1], Olesya Ajnakina*[2]

[1]*Schizophrenia Research Foundation,* [2]*University College London*

Background: The Madras Longitudinal Study of 90 persons with first-episode schizophrenia was initiated in 1981 in India.
Methods: As a longitudinal cohort study this is one of the longest follow-up studies of FEP from this part of the world. In the first 10 years, follow up was done at regular intervals. Symptoms and functioning were assessed using standardised tools.
Results: I now present the 35-year follow-up of the 30 persons remaining in the cohort. Principal findings include high rates of mortality, over 60% had a course of illness punctuated by relapses but relapses were not always associated with rehospitalization, the burden of caregiving shifted over time from parents to spouses, siblings and children. Marital status appears to be associated with many of the outcomes, although further research is needed to confirm this. The challenges in conducting studies of this nature will also be discussed.
Conclusions: Long term follow up studies have many challenges in this part of the world, but also provide very useful information of the curse of illness, mortality, family support etc.

18.3 THE FIRST EPISODE PSYCHOSIS OUTCOME STUDY: PRELIMINARY DATA ON LONG-TERM PHYSICAL HEALTH AND MORTALITY OUTCOMES OF FIRST EPISODE PSYCHOSIS PATIENTS TREATED AT THE EARLY PSYCHOSIS PREVENTION AND INTERVENTION CENTRE FROM 1998 TO 2000

Susan Cotton*[1], Andrew Mackinnon[2], John Gleeson[3], Leanne Hides[4], Debra Foley[1], Helen Herrman[5], Kate Filia[5], Victoria Rayner[6], Paula Rodger[7], Aswin Ratheesh[8], Amity Watson[5], Sarah Herniman[9], Philippe Conus[10], Martin Lambert[11], Benno G. Schimmelmann[12], Patrick McGorry[13]

[1]*University of Melbourne,* [2]*Centre for Mental Health, Melbourne School of Population and Global Health, The University of Melbourne,* [3]*Australian Catholic University,* [4]*University of Queensland,* [5]*Orygen, the National Centre of Excellence in Youth Mental Health,* [6]*Centre for Youth Mental Health, The University of Melbourne, P2Orygen, The National Centre of Excellence in Youth Mental Health* [7]*Centre for Youth Mental Health, The University of Melbourne, 2Orygen, The National Centre of Excellence in Youth Mental Health,* [8]*Orygen, the National Centre of Excellence in Youth Mental Health 3Orygen Youth Health,* [9]*1Centre for Youth Mental Health, The University of Melbourne, 2Orygen, The National Centre of Excellence in Youth Mental Health,* [10]*Service of General Psychiatry, Lausanne University Hospital,* [11]*University Hospital Hamburg-Eppendorf,* [12]*University of Bern, University Hospital of Child and Adolescent Psychiatry and Psychotherapy,* [13]*Orygen Research Centre, University of Melbourne*

Background: Specialist early intervention (SEI) service models are designed to treat symptoms, promote social and vocational recovery, prevent relapse, and resource and up skill patients and their families. While the immediate benefits of SEI are clear, and have been demonstrated, the long-term impact of SEI on illness course is less clear.
Methods: The First Episode Outcome Study (FEPOS) involved a representative sample of 661 first episode psychosis patients who were treated at the Early Psychosis Prevention and Intervention Centre (EPPIC) between 1998 and 2000. The long-term outcomes of this cohort are now being examined in a new study (known as FEPOS15+).
Results: In this presentation, the preliminary data on physical health outcomes are reported. The rates of self-report physical health problems in 100 participants 15+ years after being

treated for a first episode psychosis were significant for high cholesterol (41%), asthma (33.7%), chronic pain (25.3%), allergies (19.3%), respiratory problems (16.9%) anaemia (12.2%), arthritis (12.0%), hepatitis C (10.8%) and diabetes (6.3%). Cardiovascular problems were also noted including heart attack (2.4%), other heart problems (8.4%), and stroke (3.6%). Sexual health problems are explored. A total of 68 of the cohort have been found to be deceased. Physical health characteristics pertaining to Coroners' findings on those who had died will be also used to describe the long-term impacts of psychotic disorder

Conclusions: The physical health outcomes of individuals 15+ years after the first episode psychosis are poor. The importance of monitoring and managing physical health problems in those with psychotic disorder is highlighted.

18.4 LONG-TERM OUTCOME FOLLOWING FIRST EPISODE PSYCHOSIS IN HONG KONG: THE IMPACT OF EARLY INTERVENTION

Eric YH Chen*[1], Christy LM Hui[1], Sherry Chan[1], WC Chang[1], Simon Lui[1]

[1]*The University of Hong Kong*

Background: Improving Long-term outcomes is the ultimate intervention goal for early psychosis programs. While clinical outcomes are often improved with the additional input of resources in the first few years following onset. It is not clear to what extent these improvements continued over the longer term.

Methods: We review and integrate outcomes from two different longitudinal cohorts of first-episode psychosis patients in Hong Kong. They involved (1) a historical control study looking at the functional outcome, hospitalization, and suicide; and (2) an RCT for discontinuation of maintenance medication in year 2, and look at the outcome in around 10-year follow-up

Results: DUP did not change in the study period. The benefits can be assumed to be related to the phase-specific critical period intervention. Despite some catch-up in the control group, the early intervention group showed lasting benefits in functioning and suicide prevention. Medication discontinuation is only considered for the best outcome group after the first year. It is followed by relapse in most patients. Early relapses neutralized some of the early gains in better outcomes following first-episode psychosis.

Conclusions: Early intervention in Hong Kong produced improved outcomes through phase-specific intervention rather than DUP reduction. The outcome showed improvement in functioning and reduction in suicide. Early relapses may neutralize the effect of better outcomes following the first episode.

Friday, April 8, 2022

Plenary III: Iris Sommer

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

19. OPTIMAL PSYCHOSIS CARE FOR WOMEN

Sohee Park

Vanderbilt University

Overall Abstract: Sex and gender differences in the onset, course of illness, outcome and experience of schizophrenia-spectrum conditions are well documented but currently, early intervention and clinical care are almost all tailored to the needs of men. In this lecture, Prof. Sommer will provide a comprehensive overview of psychosis from the perspective of women's health and propose a more personalized female-specific care to improve the quality of life and outcome for all persons diagnosed with psychosis.

19.1 OPTIMAL PSYCHOSIS CARE FOR WOMEN

Iris Sommer

UMC Groningen

Individual Abstract: When first diagnosed, women with a schizophrenia-spectrum disorder (SSD) have a better clinical profile than men. Several factors account for this benefit, amongst these is the higher level of estrogens, which ameliorate negative and cognitive deficits. Unfortunately, women with SSD
progress to the same state as men within the first years of living with SSD. They need just as many rehospitalisations and their chance for full recovery is only 12.9% (against 12.1% for men).

There are benefits to be gained across different areas in the care offered to women with psychosis. An important point for improvement is the early detection of female-specific signs of a first episode of psychosis, to shorten the duration of untreated psychosis, with prompt access to early intervention services. Early intervention programs are mostly tailored to the specific needs of men and could provide more attention to women's sexual health, any history of trauma and need fo relation management and child care.

Antipsychotics require dosing and prescription tailored to the female physiology that consider hormonal life phases such as menopause. Given the inhibiting effects of estrogens on the CYP1A2 enzyme and the lower renal clearance in women, serum levels of many antipsychotics easily become high in women. Side-effects are indeed much more common in women than in men. Special attention should be paid to prolactin, as high levels will reduce estrogen production, which negatively impacts mental, somatic and sexual health. Switching to prolactin-sparing medications or adding aripiprazole can be beneficial.

Menopause has many consequences and often deteriorates the clinical course. Hormonal replacement therapy should be considered for postmenopausal women. We recently replicated the beneficial effects of raloxifene, a selective estrogen receptor modulator, which improved negative symptoms and cognitive functioning in women but not in men.

In sum, women need different psychosis care than men. By providing female-specific care, women with schizophrenia-spectrum disorders can live up to their full potential.

Concurrent Symposia

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

20. POTENTIAL TARGETS AND APPROACHES TO DEVELOPING INTERVENTIONS FOR PSYCHOTIC EXPERIENCES IN YOUNG PEOPLE

Mary Cannon

Royal College of Surgeons in Ireland

Overall Symposia Abstract: Our understanding of subclinical psychotic experiences in young people from the general population has increased vastly over the past two decades. Psychotic experiences contribute to predictive models of later psychopathology over and above common mental health problems and disorders and are an important clinical marker of poorer functioning later in life, as well as both psychotic and non-psychotic mental disorders. This knowledge points to psychotic experiences as a promising target for early intervention and prevention of later severe mental health problems and disorders, yet studies of interventions directed at psychotic experiences in children and adolescents are lacking.
This symposium which is chaired by Mary Cannon (RCSI University of Medicine and Health Sciences, Ireland) and Martin Rimvall (Child and Adolescent Mental Health Centre, Roskilde, Denmark) aims to explore potential avenues and target populations for early intervention efforts directed at psychotic experiences.

Peter Jones (University of Cambridge, UK) will present data from a scoping review of published studies on interventions for psychotic experiences in young people showing that the evidence is sparse and further work needs to be done in this area.

Colm Healy (RCSI University of Medicine and Health Sciences, Dublin) will present secondary data analyses on Irish data from the Saving and Empowering Young Lives in Europe study. He examined whether three community-based primary preventative measure for suicidality could reduce psychotic experiences in youth. He presents evidence that the selective intervention (ProfScreen) - which comprised questionnaire screening by a mental health professional with referral of at-risk youths - reduced the prevalence of psychotic experiences at 12 months, whereas the gatekeeper intervention and universal intervention did not.

Maja Gregersen (Mental Health Center, Copenhagen, Denmark) will present results from the Danish High Risk and Resilience Study of children of parents with schizophrenia spectrum disorder, bipolar disorders and control children who were assessed both at age 7 and age 11. Psychotic experiences already at age 7, particularly if recurrent, increased the risk of developing mental disorders over follow-up, indicating that interventions can be targeted in early childhood. PE at age 7 predicted mental disorders non-differentially across the three groups of children.

Pia Jeppesen (University of Copenhagen, Denmark) will present data from Mind My Mind; a randomized controlled trial of a transdiagnostic cognitive-behavior therapy (Mind My Mind [MMM]) compared to management as usual (MAU) directed at youths aged 6-16 years with emotional and behavioral problems. The MMM was significantly superior to MAU in a wide range of clinically relevant measures of distress and functional impairments, and the findings add to the growing evidence for transdiagnostic need-based cognitive-behavior therapy for indicated prevention of common mental health problems and disorders.

Consideration of these studies led by our Discussant, Jim van Os (Utrecht University Medical Centre, The Netherlands), will advance our understanding of the need for interventions for psychotic experiences, which young people to target and what type of interventions are likely to be effective.

20.1 A TRANSDIAGNOSTIC APPROACH TO INDICATED PREVENTION OF MENTAL HEALTH DISORDERS IN YOUTHS – PERSPECTIVES FROM THE RANDOMIZED CONTROLLED MIND MY MIND TRIAL

Pia Jeppesen*[1], Ditte Vassard[2], Rasmus Trap Wolf[3], Sabrina Mai Nielsen[4], Robin Christensen[4], Kerstin Plessen[5], Niels Bilenberg[6], Per Hove Thomsen[7], Mikael Thastum[8], Simon-Peter Neumer[9], Mette Maria Agner Pedersen[10], Anne Katrine Pagsberg[11], Wendy K. Silverman[12], Christoph U. Correll[13]

[1]*University Hospital, Region Zealand,* [2]*Child and Adolescent Mental Health Centre, Mental Health Services – Capital Region of Denmark, University of Copenhagen,* [3]*Child and Adolescent Mental Health Centre, Mental Health Services – Capital Region of Denmark,; Danish Centre for Health Economics, University of Southern Denmark,* [4]*The Parker Institute, Bispebjerg and Frederiksberg Hospital, University of Copenhagen, Research Unit of Rheumatology, University of Southern Denmark, Odense University Hospital,* [5]*Child and Adolescent Mental Health Centre, Mental Health Services – Capital Region of Denmark, Lausanne University Hospital CHUV,* [6]*Child and Adolescent Psychiatry, Odense, University of Southern Denmark,* [7]*Child- and Adolescent Psychiatry, Aarhus University Hospital,Institute of Clinical Medicine, Aarhus University,* [8]*Centre for the Psychological Treatment of Children and Adolescents, Aarhus BSS, Aarhus University,* [9]*Centre for Child and Adolescent Mental Health, The Arctic University of Norway, Centre for Child and Youth Mental Health and Child Welfare, North Norway (RKBU North),* [10]*Child and Adolescent Mental Health Centre, Mental Health Services – Capital Region of Denmark,* [11]*Child and Adolescent Mental Health Centre, Mental Health Services – Capital Region of Denmark, University of Copenhagen, Copenhagen,* [12]*Anxiety and Mood Disorders Program, Yale Child Study Center, Yale University School of Medicine,* [13]*The Zucker Hillside Hospital, Hofstra North Shore LIJ School of Medicine, Charité Universitätsmedizin***Background:** About half of all mental disorders begin before age 14 years, and symptoms of anxiety, depression, or behavioral disturbances are common in childhood and are well-documented forerunners of mental disorders in young adulthood. Likewise, psychotic experiences are common in the youth population and associated with a broad range of neurodevelopmental, emotional, and behavioral problems and adverse adult outcomes. We tested the effectiveness of a transdiagnostic modular cognitive behavior therapy (Mind My Mind [MMM]) compared to management as usual (MAU) for indicated prevention and treatment of common emotional and behavioral problems in school-aged children. Secondary analyses will be conducted to explore the lifetime history of psychotic experiences as a potential moderator of long-term treatment effects.

Methods: This pragmatic, multi-site, randomized clinical trial (RCT) compared the MMM to MAU for youths aged 6-16 years with symptoms of anxiety, depression, or behavioral disturbances. The trial was conducted from September 7, 2017, to August 28, 2019 in Denmark. Consecutive help-seeking youth were randomized (1:1) to either MMM offering 9-13 sessions of cognitive behavior therapy (CBT); or MAU offering community care enhanced by two care coordination visits. The primary outcome was the child's distress and impact of mental health problems reported by the parents using the Strengths and Difficulties Questionnaire (SDQ)-impact score (range=0–10 points). All outcomes were assessed in the intention-to-treat population at week 18, and maintenance effects were explored at week 26. The long-term treatment effect, and the putative modification by psychotic experiences, will be explored for the time to/number of psychiatric diagnoses.

Results: A total of 396 children (age=10.3 ±2.4 years, 48% females) were randomized to MMM (n=197) or MAU (n=199). A lifetime history of psychotic experienced was present in 19% of the children at baseline according to the interview and assessment by the community psychologist. The primary outcome measure was collected for 89.8% in MMM, and 83.9% in MAU. The SDQ-impact score decreased significantly more (between-group difference =1.10; 95% confidence interval (95%CI) =0.75-1.45, $p<0.001$), and the number of responders (≥1-point reduction in SDQ-impact score) was greater with MMM than with MAU (73% versus

47%, number-needed-to-treat = 4; 95%CI =3-6). Secondary outcomes indicated significant benefits in a wide range of clinically meaningful measures of emotional and behavioral symptoms, daily and social functioning, and school attendance, and effects were maintained at week 26, except for school attendance. Harms were low, and significantly fewer children reported suicidal thoughts and hopelessness at week 26 with MMM compared to MAU (7 out of 150 (5%) versus 20 out of 120 (17%), risk ratio =0.28; 95%CI =0.12-0.64, P=0.003). The time to/number of psychiatric diagnoses after 2-3 years will be analyzed and presented at the conference.

Conclusions: The need-based transdiagnostic CBT-program (MMM) outperformed usual care (MAU) in a community setting. The findings support the transdiagnostic approach to delivery of psychotherapy for prevention and treatment of common mental health problems and might be a potential avenue for prevention of psychosis spectrum pathology later in life.

Clinical Trials Identifier: NCT03535805

20.2 DEVELOPMENTAL COURSE AND CLINICAL OUTCOMES OF EARLY CHILDHOOD PSYCHOTIC EXPERIENCES IN PREADOLESCENT CHILDREN AT FAMILIAL HIGH-RISK OF SCHIZOPHRENIA OR BIPOLAR DISORDER – THE DANISH HIGH RISK AND RESILIENCE STUDY, VIA 11

Maja Gregersen*[1], Jens Richardt Møllegaard Jepsen[2], Sinnika Birkehøj Rohd[3], Anne Søndergaard[1], Julie Marie Brandt[4], Ditte Ellersgaard[5], Carsten Hjorthøj[6], Jessica Ohland[1], Mette Falkenberg Krantz[4], Martin Wilms[3], Anna Krogh Andreassen[7], Lotte Veddum[7], Christina Bruun Knudsen[7], Aja Greve[8], Vibeke Bliksted[9], Ole Mors[10], Lars Clemmensen[11], Merete Nordentoft[12], Nicoline Hemager[1], Anne Amalie Elgaard Thorup[13]

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Background: Psychotic experiences (PE) are common in children and adolescents and are associated with both concurrent and subsequent mental disorders. Most knowledge on PE stems from general population studies whereas there is a sparsity of studies examining clinical outcomes of PE in familial high-risk (FHR) populations. The predictive value of PE measured in early childhood is largely unknown. Understanding the significance of PE in children at FHR provides important potential for characterizing vulnerable subgroups within this population.
Methods: The VIA 11 Study is the first follow-up in the Danish High Risk and Resilience Study. The original cohort consists of 522 children where one or both parents have been diagnosed with a schizophrenia spectrum disorder (N=202), or one or both parents have been diagnosed with bipolar disorder (N=120), or neither parent has been diagnosed with these disorders (N=200). PE were assessed with the psychosis supplement from K-SADS-PL at baseline (age 7) and follow-up (age 11). Axis I disorders were assessed with K-SADS-PL at both assessments. Retention from baseline to follow-up was 87.1%.
Results: Occurrence of more than one type of early childhood PE (measured at age 7) predicted persistence of PE into middle childhood. Occurrence of early childhood PE predicted a 2-fold increased risk of Axis I mental disorders in middle childhood (measured at age 11) after taking familial risk status and early childhood disorders into account. Children with 3 or more early childhood PE had a 2.5-fold increased risk of mental disorders in middle childhood. Persistent pathways of PE were associated with a 4-fold increased risk of mental disorders in middle childhood. PE in middle childhood were associated with concurrent mental disorders. Associations between PE and concurrent and subsequent mental disorders were non-differential across the three groups of children.
Conclusions: Early childhood PE are markers of vulnerability to mental disorders later in childhood. PE mark vulnerability to concurrent and subsequent mental disorders non-differentially in children at FHR and population-based controls. This study extends previous knowledge on PE to include early childhood PE in children at FHR. PE should be part of mental health screenings and this may begin in early childhood and extend to children at FHR. Occurrence of early childhood PE, especially when there are more than one type and when persistent, characterizes a vulnerable subgroup and should alert clinicians to assess individual needs for prevention and intervention.

20.3 SYNTHESISING THE LITERATURE ON THE CLINICAL AND COST-EFFECTIVENESS OF PSYCHOLOGICAL INTERVENTIONS FOR PSYCHOTIC EXPERIENCES IN PEOPLE WITHOUT A PSYCHOTIC DISORDER

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Background: Most people with psychotic experiences do not develop psychotic disorders. Those who seek help have complex clinical presentations with prominent depression and anxiety, and achieve poor outcomes. Identification of effective interventions for psychotic experiences is important.
Methods: In preparation for developing a new intervention, we systematically searched 13 databases for studies of psychological interventions for adults with psychotic experiences, but not psychotic disorders. Our primary outcomes were the proportion of participants remitting from psychotic experiences; secondary outcomes were reductions in positive and negative psychotic symptoms, depression, anxiety, functioning, distress; improvements in quality of life and reports of economic outcomes. We analysed results using multilevel random-effects meta-analysis and narrative synthesis.

Results: The search yielded 5506 reports; 27 (from 21 studies) met inclusion criteria. These provided no strong evidence for the superiority of any one intervention. Five studies reported on our primary outcome but only two reports were randomised controlled trials that provided evidence that psychological intervention (specifically, cognitive behavioural therapy; CBT) promoted remission from psychotic experiences. For secondary outcomes, we could only meta-analyse trials of cognitive behavioural therapy. CBT was more effective than treatment-as-usual for reducing distress (pooled standardised mean difference: -0.24; 95% confidence interval = [-0.37, -0.10]), but no more effective than the control treatment for improving any other outcome. Individual reports indicated that cognitive behavioural therapy, mindfulness-based cognitive therapy, sleep cognitive behavioural therapy, systemic therapy, cognitive remediation therapy, and supportive treatments improved at least one clinical or functional outcome. Four reports included economic evaluations, which suggested cognitive behavioural therapy may be cost-effective compared with treatment as usual.
Conclusions: Our meta-analytic findings were primarily null, with the exception that cognitive behavioural therapy may reduce the distress associated with psychotic experiences. Several intervention frameworks showed preliminary evidence of positive outcomes. However, the scarcity of studies, small samples, variable quality and the paucity of consistent evidence for clinical and functional improvement highlights that we need more high-quality research.

20.4 EVIDENCE THAT A SCHOOL-BASED INTERVENTION CAN BE EFFECTIVE IN PREVENTING PSYCHOTIC EXPERIENCES IN ADOLESCENTS: DATA FROM A CLUSTER-RANDOMISED CONTROLLED TRIAL.

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Background: Psychotic experiences (PEs) are prevalent in adolescence and are an early pluripotent marker of mental illness. No study has examined the efficacy of preventative community-based interventions for PEs in adolescence. We examined the preventive effects of three school-based interventions on PEs, specifically subsequent auditory hallucinations (AH). We also investigated post-intervention changes in depression and anxiety scores in those who reported AH at baseline.
Methods: We conducted secondary data analyses on the Irish site of the Saving and Empowering Young Lives in Europe study, a cluster randomised control trial designed to examine the effect of school-based interventions on suicidal thoughts and behaviour. Seventeen schools (n=1096) were randomly assigned to one of three intervention arms (gatekeeper arm, a universal intervention arm or a selective intervention arm) or a minimal intervention control arm. The interventions were: 1)Question, Persuade, and Refer (gatekeeper), 2)Youth Aware of Mental health programme (YAM, universal), and 3)Professional questionnaire Screening with

referral of at-risk (ProfScreen, selective). All outcomes were measured at baseline, 3-month and 12-month follow-up. AH were measured using a clinical validated item from the Adolescent Psychotic Symptoms Screener. Statistical analyses were conducted using mixed-effects modelling and stratified logistic regression in those without AH at baseline.
Results: Overall, 11% (n=120) of the sample reported AH at some point in time. At 12-months, the ProfScreen intervention arm had significant effect on AH when compared to the control arm (AdjOR:0.14,CI:0.03-0.68). This effect was also observed when those with AH at baseline were excluded from the analysis (OR:0.30, CI:0.09-0.97). No other intervention had a significant preventative effect on AH. Participants in the Profscreen arm with baseline AH had significant improvements in depression (3-months:IRR:0.67,CI:0.57-0.79; and 12-months:IRR:0.63,CI:0.39-1.01) and anxiety scores (3-months:β:-4.76,CI:-5.61- -3.92; and 12-months:β:-4.20,CI:-5.59- -2.81) relative to those without AH. Improvements in depression scores were also seen in the YAM arm (12-months:IRR:0.59,CI:0.40-0.85).
Conclusions: This study provides the first evidence that a school-based screening and referral intervention may have a preventative effect on PEs in adolescents. Although further research is needed, our findings point to the effectiveness of school-based programmes for prevention of psychotic phenomena.

21. TELEHEALTH DELIVERY BEYOND TALK THERAPIES

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Overall Symposia Abstract:

Telehealth has become increasingly popular across medical disciplines, and for a growing number of services and treatment populations, and telemedicine applied to behavioral health disorders is one of the most common applications of telehealth in the United States. The COVID-19 crisis led many nations to develop rapid and flexible plans to allow the expansion of, and reimbursement for, visits for telemental health. In the U.S., telemedicine use doubled between 2016 and 2019, from 14 to 28 percent. However, between March 11 and April 27, 2020, the use and implementation of telepsychiatry increased over 550%. The changes to regulations and lifting of many restrictions on telehealth during the pandemic made it even more possible for rates of video and telephone visits increase dramatically across the globe. Many psychiatric providers report that when the pandemic ends, they plan to continue use of telepsychiatry making it their primary or solo method of practice. The preponderance of published evidence suggests that most pharmacotherapy and evidence-based talk and training therapies for adults with serious behavioral health diagnoses are feasible to deliver via telehealth, can be delivered with fidelity to their respective models, and yield similar levels of satisfaction and outcomes to in-person treatments. However, less evidence is available on therapies that rely more on physical presence and hands-on work. This symposium examines the feasibility of providing Cognitive Adaptation Training (CAT), Cognitive Behavior Therapy for Psychosis, Individual Placement and Support and Assertive Community Treatment via telehealth platforms and examines available evidence on fidelity and efficacy of these evidence-based treatments delivered remotely. A remote version of Cognitive Adaptation Training which is typically a home-delivered treatment using environmental supports to bypass cognitive and motivational problems and to cue and sequence adaptive behavior in the home or work environment has been found to be feasible and acceptable to individuals with serious mental illness. Moreover, preliminary efficacy for remote CAT has been demonstrated. CBT

for psychosis (CBTp) often involves in vivo experiments and drawing and diagraming to understand emotions and test delusional thoughts. CBTp has been found to be acceptable, feasible and efficacious when delivered remotely for individuals and groups. Individual placement and Support (IPS) focuses on helping individuals to select, obtain and maintain employment and focuses on participant choice, rapid job search and unlimited individualized support which is often provided in the work environment. During the pandemic most programs provided those services through phone calls, teleconferences and text messages with both clients and prospective employers demonstrating feasibility and leaving practitioners wondering whether this form of treatment delivery will continue. Assertive Community Treatment is an evidence-based in community treatment program focused on out-reach in the home and community. This modality represented a unique challenge during Covid pandemic, but adaptation and innovation for telemedicine is ongoing and related to advocacy for telemedicine access, prioritizing essential services, optimizing team communication and client psychoeducation, novel group programs, and maintaining medical-legal assessments.

21.1 IPS SUPPORTED EMPLOYMENT: VIRTUAL SERVICES DURING THE PANDEMIC

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Background: IPS (Individual Placement and Support) is an evidence-based approach designed to help individuals with serious mental illnesses with employment. IPS is typically integrated in mental health agencies, and provided by IPS specialists whose sole focus is employment and careers. IPS specialists connect with local employers weekly to help job seekers find jobs related to their preferences.

The IPS Employment Center organizes a large learning community of 22 states, the District of Columbia, Alameda County (California), Broward County (Florida), and six countries/regions outside the U.S.: Italy, the Netherlands, Spain, New Zealand, England, and Montreal, Canada. More than 350 IPS programs from those areas share their employment outcomes quarterly, while government implementation teams share their experiences with the IPS Employment Center on a regular basis.

Methods: IPS specialists spend at least 65% of their working hours in community locations including businesses, workforce centers, state Vocational Rehabilitation offices, high schools, post-secondary educational settings, and so forth. They often engage clients by meeting them where they are most comfortable, for example at their homes, library meeting rooms, malls, coffee shops, and other locations.

Results: During the pandemic, most IPS specialists began working from their homes and met with clients by phone or through virtual platforms. They also attempted to develop relationships with employers through phone calls, emails, and on occasion, virtual meeting platforms. IPS teams continued to report that at least 40% of people are employed.

Conclusions: Although employment rates remained high during the pandemic, the job market also changed which means that it is difficult to determine whether virtual services were as effective as in-person services. Some businesses (warehouses, delivery drivers, and grocery stores) had difficulty hiring during the pandemic and so employer relationships with IPS specialists may not have been as important as usual.

Some states reported that diversity of job types declined. That may indicate that although people obtained employment, the jobs they found may not have been related to their preferences. Individual preferences for employment are positively related to job tenure.

Finally, some IPS supervisors reported that referrals to their programs were lower than normal--perhaps due to concerns about safety, though it could also be related to the difficulty of developing relationships with potential clients virtually.

21.2 ACCELERATING THE EVOLUTION OF COGNITIVE BEHAVIORAL THERAPY FOR PSYCHOSIS DURING THE PANDEMIC

Sarah Kopelovich*[1]

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Background: Cognitive behavioral therapy (CBT) has become the dominant psychological approach to treating psychotic disorders. Due to its adaptive nature, CBT for psychosis (CBTp) has been augmented in three key ways during the COVID-19 pandemic: First, CBTp has been adapted to tele-administration by making strategic adjustments in the scope and techniques employed. Second, high-yield cognitive behavioral techniques for psychosis (HY-CBtp) can be delivered by a range of providers using a task sharing or task shifting model, making better use of an over-taxed workforce. Leveraging this same approach, natural supports can be trained in high-yield strategies to enable in-home skill rehearsal. Finally, CBTp can be enhanced by clinician-assisted or self-guided digital interventions. Indeed, mobile health (mHealth) interventions can facilitate more consistent engagement in clinician-delivered care as well as in vivo rehearsal of cognitive and behavioral skills for those who are at the highest risk of disengagement and poor clinical outcomes.
Methods: In response to the pressing need to flexibly sustain high-quality, multi-modal care to individuals with psychosis during the COVID-19 pandemic, interventionists must consider common perpetuating factors of psychosis (e.g., sleep disruption, untreated anxiety) and employ HY-CBtp to maintain a recovery trajectory for clients in the community.
Results: Research supports delivering high yield interventions using technology alongside both professional and non-professional supports. This presentation will feature cognitive, behavioral, and problem-solving skills that can be learned and delivered by a range of practitioners, non-professional caregivers, and mHealth.
Conclusions: Cognitive behavioral interventions are highly adaptable to our current state of remote and hybrid care. In fact, emerging evidence suggests that mHealth focusing on common perpetuating factors are not only palatable to clients with psychosis but may be preferable to co-located service delivery. Similarly, research supports HY-CBtp delivery by allied and non-professionals. Because these approaches to delivering CBTp show promise in increasing access to the intervention, HY-CBtp may well constitute our new normal in CBT service delivery well after the public health crisis has passed.

21.3 REMOTELY DELIVERED COGNITIVE ADAPTATION TRAINING (CAT) IN THE TIME OF COVID-19 AND BEYOND

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Background: Therapies using primarily verbal interaction have been found to be feasible and effective when delivered via telehealth. Cognitive Adaptation Training (CAT) is a home-delivered psychosocial treatment using environment supports such as signs, checklists, pill containers, and the organization of belongings to bypass cognitive and motivational challenges and improve outcomes. CAT providers assess the home and work environments, examine the presence of distractions and of needed supplies, observe how the individual performs goal-directed activities and establish and maintain individualized supports during weekly home visits. These aspects of CAT may make adaptation to telehealth more challenging.

Methods: We report on our experience shifting to remotely delivered CAT from March 2020 January March 2021 during the pandemic. 35 individuals were receiving in-person CAT at four sites across the country as part of an NIMH-funded effectiveness trial and 30 individuals were participating in a value-based clinical CAT program for Medicaid recipients who are high utilizers of hospital and emergency department services. The program's primary aim is to decrease inpatient admission and improve outcomes. Reimbursement is paid at a per diem rather than on a fee-for-service basis for every day an individual is not hospitalized. Flexible funding allows for the purchase of CAT environmental supports and supplies.

At the start of the pandemic, all CAT shifted to remote delivery. CAT assessment was conducted as the individual displayed specific areas of their home to the CAT provider. Pillboxes were filled by the individual with remote assistance. CAT supplies were delivered through the mail or dropped off at the individual's home, and set up with the CAT provider offering direction on placement and use via telehealth.

Results: Remote assessments produced good information for treatment planning. Participants were successfully able to set up the supports as providers watched and provided appropriate assistance. Participants increasingly dealt with isolation, fear and boredom so visits were restructured to be shorter and more frequent. This flexibility in delivery is one reason CAT fits well with value-based versus fee for service reimbursement models. Treatment goals were adjusted. CAT therapists discussed symptoms of the COVID-19 virus, how to obtain vaccinations, potential side effects, making mindful decisions about social distancing, mask-wearing, and handwashing using CAT strategies to help individuals make new habits. Providers delivered pulse oximeters, cleaning supplies, and groceries to those who were unable to get out. Providers helped individuals stay engaged by taking virtual trips, cooking, using meditation or exercise videos, and taking virtual tours. Many started online school with CAT assistance to break down and organize tasks. CAT providers helped participants structure their children's time to reduce the stress of parenting. There was a focus on obtaining employment where precautions were used to keep workers reasonably safe. In multiple sites, additional services surrounding the community mental health centers were stopped, leaving a greater burden on CAT providers.

Supervision during the pandemic indicated that using Remote CAT helped individuals reach goals, maintain stability in a very difficult time, and follow-through with medication and treatment appointments. The greatest barriers were the lack of availability of appropriate technology and unfamiliarity with its use for both the participants and therapists and maintaining the high level of energy and creativity needed to keep individuals engaged without in-person visits. Staff could handle additional cases due to reduced driving time.

30 of the original 35 CAT research recruits remained in the NIMH study. All clinical participants were retained. 30 new referrals were made and half of those were successfully engaged. This percentage is not a different than pre-pandemic. Additionally, hospitalization rates in the clinical program remained at the same level as for in-person CAT treatment.

Conclusions: Cognitive Adaptation Training delivered via telehealth is feasible and appears effective. Plans for the future include reporting on an ongoing clinical trial comparing remote and in-person CAT for acceptability, feasibility, and preliminary efficacy and examining the possibility of a full-scale efficacy trial for remotely delivered CAT.

21.4 TELEHEALTH DELIVERY BEYOND TALK THERAPIES': ADAPTATIONS AND INNOVATIONS TO MINIMIZE OUTREACH COMMUNITY SERVICE DISRUPTION FOR PATIENTS WITH SEVERE MENTAL ILLNESS DURING COVID-19

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Background: Changes to community psychiatry during COVID-19 are unprecedented, affecting disproportionally the already vulnerable people with serious mental illness (SMI). Adaptations and innovations are challenging, especially given that the best-practice model is based on an in-person, at-home or in-community milieu engagement and treatment.
Methods: A descriptive study of front-line disruptions, observations, implementations, and reflections on changes towards expanding telehealth deliveries of mental health care. The focus is on Assertive Community Treatment and Intensive Case Management which were delivered in the community prior to the pandemic.
Results: We have responded to community service disruptions by actively formulating and prioritizing essential services, and adapted to the loss of community resources. Our pivoting to maintain essential services are aided by telehealth equipment that we have obtained and secured through charity donations and advocacy, and we have implemented on-line and phone based group programs, health promoting activities, psychoeducation, monitoring of functioning, engagement with allied professionals, team communications, and medical-legal assessments.
Conclusions: Incorporation of telehealth services is one of the main innovations gained from this pandemic. Our concerns touch on a more fundamental issue of access, in addition to difficulty operating and navigating the technologies. We highlight the advantages such as ease of access, time saved from travels, potential to increase frequency of services, improved connection with allied professionals, and maintaining key medical legal assessment. We are also mindful that the inevitable incorporation and expansion towards telemedicine also requires a foundation of person-to-person connection that builds towards a trusting therapeutic relationship.

22. IMPLEMENTATION OF COGNITIVE REMEDIATION INTO SERVICES: FACILITATORS AND BARRIERS

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Overall Symposia Abstract: Cognitive remediation is effective with several large meta-analyses demonstrating reasonable effect sizes for cognition and, more importantly, for functioning. It is now being mentioned in influential treatment guidelines for schizophrenia (e.g. APA, NICE. Despite this there is a dearth of evidence on the way in which this treatment should be implemented into real-world settings. Large scale roll-out also has to overcome barriers such as costs, staff scepticism and decisions about how and what to deliver. Not all of these can be considered in a single study, but some understanding of the performance of the therapy when rolled into health or recovery services is required for a decision. We will present

a series of studies that develop the process of implementation, highlighting the barriers, facilitators, and outcomes when cognitive remediation is provided as part of the real-word health services. We start with a meta-analysis on the effects of four CR characteristics that are thought essential for good CR practice and their individual and joint effects on outcomes. We then have two studies of real-world implementation in early intervention services. This will be the first time these studies will be presented. These speakers will explain how outcomes are reduced or boosted by specific aspects of the implementation. The final speaker will introduce a further important issue for large scale roll-out of any psychological treatment – training therapists. This is always a limiting factor for future patient benefit. There is evidence that active trained therapists boost CR outcomes, and any psychological treatment effects. Training is usually face-to-face, but these models are time consuming, so more are online. The development, implementation, adaptation, and clinical supervision needs to enhance benefits of this therapy.

22.1 EFFECTIVENESS OF COGNITIVE REMEDIATION IN SCHIZOPHRENIA

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

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

22.2 IMPLEMENTATION OF ACTION-BASED COGNITIVE REMEDIATION IN AN EARLY PSYCHOSIS NETWORK

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Background: Action-Based Cognitive Remediation (ABCR) is a behavioural treatment that addresses neurocognitive impairments associated with psychosis, using a series of computer exercises paired with elements of cognitive and behavioural therapies including goal setting,

practice of cognitive strategies in simulated real world environments, and behavioural activation. ABCR has been widely and internationally disseminated across a number of clinical sites, yet some sites have struggled with uptake or have had to modify the standard of treatment. In the present study, we aimed to understand the barriers that clinics face in the implementation of ABCR, how modifying procedures was related to outcomes, and perceived helpfulness of aspects of training.

Methods: 51 therapists from an early psychosis network throughout the province of Ontario, Canada who were trained in ABCR completed a survey on their experiences with delivering the treatment. Domains included perceived usefulness of the elements of training, modifications to the manualized procedures within the clinical setting, perception of the most useful treatment techniques, engagement with ongoing fidelity opportunities, perception of patient-related outcomes, and ranking of barriers they faced in its implementation.

Results: Therapists reported that protecting staff time was the greatest clinic-related barrier in administering ABCR, followed by manager support, patient geographics, equipment, and space. Therapists who modified the administration of ABCR (n=29) so that it was reduced in either or both the total number of sessions (35% of therapists) or by shortening the duration of sessions (31% of therapists) reported facing significantly greater barriers of manager support compared to those who administered regular ABCR dosage (n=22), $t(1, 49) = -3.13$, $p < .01$. However, there was not a significant difference between these two groups with regard to perception of positive patient outcomes (p=.79). A greater proportion of patients who completed their ABCR sessions was associated with a stronger patient rapport ($r = -.68$, $p < .001$), but not other factors. With regard to ongoing fidelity, 100% of therapists indicated that they continued to use the treatment manual. Engagement in community of practice fidelity procedures varied considerably, with the percent of therapists making use of training videos (90%) and engagement with an online help forum (94%) greater than those participating in fidelity phone calls (47%).

Conclusions: Addressing barriers of staff time, manager support, and patient rapport may help increase the successful implementation of cognitive remediation programs. Modifications to the treatment schedule did not result in significant changes in perceived patient outcomes. Anticipating and confronting the variable engagement with ongoing fidelity to treatment procedures might be important future steps.

22.3 THE FEASIBILITY AND EFFECT OF DELIVERING COGNITIVE REMEDIATION THERAPY IN FIRST EPISODE PSYCHOSIS HEALTH CARE SERVICES: AN ADAPTIVE RANDOMISED TRIAL

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Background: Cognitive remediation therapy for psychosis (CRT) can benefit cognition and everyday function. However the optimum, cost-effective method of service delivery in mental health care settings is yet to be determined. In a pragmatic, multi-arm multicentre adaptive trial we investigated the feasibility and effect of different CRT delivery methods in UK National Health Service (NHS) early intervention services for psychosis (EIS) compared to treatment as usual (TAU).

Methods: 377 participants with non-affective psychosis were recruited from the EIS of 11 mental health trusts serving diverse communities in rural and urban areas. Each participant was randomly allocated to receive TAU or 12 weeks of CRT which differed in allocated therapist input: Intensive (1:1 with a therapist), Group (4:1 with a therapist), Independent (limited telephone contact with a therapist). CRT was delivered with the CIRCuiTS computerised programme. The primary outcome was the degree to which participants achieved personalised goals during CRT using the Goal Attainment Scale (GAS). Secondary measures included change in global cognition and other services used. Measures were taken at baseline, 15 and 39 weeks post-randomisation.
Results: Group v Intensive CRT and Independent CRT v TAU comparisons were not significant for any measure at any time. At 15 weeks, pooled Group + Intensive CRT GAS scores were significantly improved compared to TAU with a medium effect size. Global cognition also improved in the Group + Intensive v TAU comparison with a small-to medium effect size. There were no significant effects at 39 weeks. There was no difference in costs between CRT methods.
Conclusions: CRT is feasible and cost effective when delivered in generic mental health care services for people with first episode psychosis, for example in the UK NHS. In this setting, CRT can improve the individual's self-determined social function and general cognition. However, such improvement is contingent on personal contact with a trained therapist but this can be provided in a group as well as individually. Why such improvements tail off over time is not clear but suggests that 'maintenance' CRT would be of benefit.

22.4 DEVELOPMENT AND EVALUATION OF AN ONLINE COGNITIVE REMEDIATION THERAPY TRAINING PROGRAMME FOR MENTAL HEALTH PROFESSIONALS

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Background: Increasing evidence suggests that therapist support is an important component of Cognitive Remediation (CR). It promotes therapy engagement and positively contributes to therapy related cognitive and functional outcomes. However, therapists' availability can be scarce, training challenging and resource intensive to achieve. This may limit CR therapist inclusion. This study evaluates the feasibility, acceptability and potential benefit of a new online training for CR therapists.
Methods: We developed a 11-module online CR training with the support of clinicians and research experts. We invited UK based qualified Mental Health (MH) professionals working with people with psychosis to undertake the training. Feasibility was assessed with parameters including training completion within 6 weeks, module completion, time to complete. Potential benefits were estimated using a knowledge test with pass rate set at 80%. Acceptability was assessed with a questionnaire and a follow-up feedback interview with a CR trainer.
Results: One-Hundred and thirty-five participants took part in the study with approximately one third describing their professional background as MH nursing, one third psychology and the remaining third as other MH professionals (e.g., occupational therapist, medical doctor).

Participants' average age was 36.8 years with 67% having achieved a university degree and 53% working in outpatient settings.
Fifty-four percent of the participants completed training in 6 weeks. Of those completing it, 90% passed the end of training knowledge test. The median completion time for the training was 35 days. Acceptability evaluation showed good to moderate satisfaction levels for ability to make progress, ease of understanding and use. The opportunity to consult a trainer at the end of the course was considered positively although trainees said all their learning needs were adequately met by the online training.

Conclusions: Online training has the potential to expand the provision of CR training for mental health professionals and this can improve the implementation capacity for CR. The results of our study suggest that online training is feasible and acceptable for a proportion of MH staff, but it may be challenging for others due to competing clinical demands, the availability of professional development opportunities and access to appropriate computer and internet connection. With further adaptations this and other online training programmes will develop the implementation potential for CR in psychosis services.

23. THE ACCELERATING MEDICINES PARTNERSHIP®– SCHIZOPHRENIA (AMP SCZ): NEW OPPORTUNITIES FOR EARLY INTERVENTION

René Kahn

Icahn School of Medicine at Mount Sinai

Overall Symposia Abstract: The National Institutes of Health (NIH) has launched a new public-private partnership to meet the need for early therapeutic interventions for people at risk of developing schizophrenia and other psychoses. As part of the Accelerating Medicines Partnership (AMP) □, AMP Schizophrenia (AMP SCZ) brings together NIH, the U.S. Food and Drug Administration (FDA), and multiple non-profit and private organizations. These partners will work towards the shared mission of discovering promising biological markers to help identify individuals at risk of developing schizophrenia and other psychoses as early as possible, track symptom progression and other outcomes, and define targets for treatment development. The overall aim is to generate tools that will improve success in developing early-stage interventions for at risk patients. A core component of AMP SCZ is to establish research networks focused on clinical high risk for psychosis (CHR) individuals, to identify biomarkers, clinical endpoints, and other measures that predict disease trajectory and outcomes in this group. The research networks will recruit and follow the largest CHR cohort to date with comprehensive multimodal and longitudinal data collection. A Data Processing, Analysis, and Coordinating Center (DPACC) will integrate and analyze data from this new CHR cohort, with all data and analyses made publicly available through the NIMH Data Archive. AMP SCZ findings will enable researchers to develop algorithms that predict illness course in CHR individuals, as well as further facilitating early intervention and development of targeted treatments that may improve CHR clinical outcomes, including delay or prevention of psychotic disorder. The symposium will present an overview of the AMP SCZ rationale, design, and progress to date, with speakers from the NIMH, research networks and DPACC. The discussant will be from one of the AMP SCZ industry partners.

23.1 THE ACCELERATING MEDICINES PARTNERSHIP® (AMP®) PROGRAM IN SCHIZOPHRENIA (AMP SCZ): OVERVIEW AND VISION

Laura Rowland*[1]

[1]*National Institutes of Health, NIMH*

Background: The Accelerating Medicines Partnership (AMP) program is a public-private partnership between the National Institutes of Health, the U.S. Food and Drug Administration, the European Medicines Agency, and multiple public and private organizations. The overall aim of the new AMP Schizophrenia (AMP SCZ) initiative is to generate tools that will improve success in developing early-stage interventions for patients who are at risk of developing schizophrenia.
Methods: Participants will complete an extensive battery of neuroimaging, EEG, cognitive, clinical, speech, genomic, blood-based, and functional assessments over a period of two years in order to detect diverse trajectories of risk and identify biomarkers predictive of the development of psychosis and other outcomes.
Results: Core components of AMP SCZ are a 42-site research network and a Data Processing, Analysis, and Coordinating Center to facilitate rapid availability of data to the scientific community via the NIMH Data Archive.
Conclusions: This presentation will provide an overview of the specific goals of the project, the organizational structure, and methods to be used to achieve these goals.

23.2 PRONET: PSYCHOSIS RISK OUTCOMES NETWORK

Scott Woods*[1]

[1]*Yale University*

Background: ProNET will work with its sister research network PRESCIENT, PREDICT-DPACC, and NIMH/FNIH and other Accelerating Medicines Partnership (AMP) □ and AMP Schizophrenia (AMP SCZ) private/public partners to collect a large and well-curated archival longitudinal dataset of biomarker predictors and clinical outcomes in patients at clinical high risk (CHR) for psychosis and to develop CHR stratification tools to predict individual outcome trajectories that can promote efficiency in future clinical trials.
Methods: ProNET will recruit 1040 CHR patients and 390 healthy comparison subjects at 26 international sites, including 17 in the US, two in Canada, two in the UK, and one each in Spain, Italy, Germany, South Korea, and China.
Results: ProNET investigators include many of the world's leading CHR researchers, enabling the network to deliver high quality data on the large sample and to collaborate with PREDICT-DPACC, PRESCIENT, and AMP SCZ public and private partners to develop robust CHR stratification/analytic data analysis tools that will predict individual outcome trajectories from multimodal clinical and biomarker early assessments.
Conclusions: This presentation will also focus on AMP SCZ innovations in MRI, EEG, cognition, and fluid biomarker assessment and potential clinical trial refinements offered by the AMP SCZ design: 1) adaptive static/dynamic patient ascertainment and 2) reducing site variance by inclusion of healthy comparison subjects. ProNET investigator capabilities and AMP SCZ methodologic innovations promise to contribute to the broad goals of relieving distress and life difficulties experienced by CHR patients, preventing schizophrenia and other psychoses, and ultimately benefiting patients and their families and communities.

23.3 TRAJECTORIES AND PREDICTORS IN THE CLINICAL HIGH RISK FOR PSYCHOSIS POPULATION: PREDICTION SCIENTIFIC GLOBAL CONSORTIUM (PRESCIENT)

Patrick McGorry*[1]

[1]*Orygen Youth Health Research Centre*

Background: The Prediction Scientific Global Consortium (PRESCIENT) is one of the research networks involved in AMP Schizophrenia®. PRESCIENT will collaborate with ProNET, PREDICT-DPACC, NIMH/FNIH and AMP-SCZ® public/private partners to realise the goals of AMP-SCZ® to discover biomarkers for early identification of young people at risk of schizophrenia and other psychotic disorders, track symptom progression and other outcomes, and define targets for novel treatment development.
Methods: PRESCIENT will use the Australian Early Psychosis Collaborative Consortium (AEPCC) national platform to consolidate a network of clinical high risk (CHR) recruitment centres, with Orygen in Melbourne functioning as the central hub with 2 Australian and 8 international clinics across Europe and Asia as spokes. The network will: recruit a large sample of CHR patients (n=937) and a healthy control (n=250) sample; implement repeated multimodal assessments; map trajectories and outcomes over a 2-year period (conversion to psychotic disorder, persistent/incident non-psychotic disorders, non-remission of CHR status, persistent negative symptoms, psychosocial functioning, full recovery).
Results: This research network of CHR recruitment centres will provide the clinical research infrastructure for future clinical trials in this clinical population informed by findings from the current program of work. The PRESCIENT assessment protocol and procedures have been full harmonized with ProNET, allowing for pooling data across the two research networks and conducting prediction model validation analyses.
Conclusions: This presentation will provide an overview of the structure of the PRESCIENT research network, progress to date, and focus on the rationale for selected aspects of the assessment battery (clinical measures, digital phenotyping, and speech/facial expression data).

23.4 PREDICT-DPACC – PSYCHOSIS RISK EVALUATION, DATA INTEGRATION AND COMPUTATIONAL TECHNOLOGIES (PREDICT): DATA PROCESSING, ANALYSIS, AND COORDINATION CENTER (DPACC)

René Kahn*[1]

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

Background: The PREDICT-DPACC will work with the two research networks, along with NIMH/FNIH and private/public partners, to provide data processing, analysis, and coordination and to develop and apply clinical high risk (CHR) stratification tools to identify and validate biomarkers for future clinical trials to predict individual outcome trajectories.
Methods: The PREDICT-DPACC team includes computer scientists and clinical CHR researchers with the requisite expertise to meet the goals set forth by the Accelerated Medicine Partnership in Schizophrenia (AMP SCZ).
Results: These goals include: 1) providing infrastructure to capture data in a uniform manner, 2) building flexibility to accommodate multiple data types, 3) developing and refining established pipelines for data flow that provide rapid processing, and quality assurance (QA) and quality control (QC), in close to real time, 4) providing QA/QC of the multiple data types, 5) uploading data to the National Data Archive (NDA), 6) developing and applying powerful and robust CHR stratification/analytic data analysis tools to identify and validate biomarkers to predict individual outcome trajectories, 7) disseminating information, including the tools developed, to the general research community, and 8) providing outreach to the community via a website that includes information about the AMP SCZ consortium and CHR to both the research community and to individuals seeking more information about CHR.

Conclusions: The ultimate goal will be identification of novel biomarkers for predicting individual CHR outcomes trajectories that will enhance clinical trials and lead to drug development and treatment targeting early interventions that halt and/or prevent progression to psychosis and other adverse outcomes in CHR.

24. PHENOMENOLOGICAL PSYCHIATRY TODAY, AND TOMORROW: METHODS, APPLICATIONS AND CONTEXT

Rosa Ritunnano

Institute for Mental Health, University of Birmingham

Overall Symposia Abstract: The importance of philosophy for the future of psychiatry is unquestionable. Today, more than ever before, conceptual, philosophical and ethical questions are at the forefront of schizophrenia and psychosis research: What is psychosis? What is it like to be in the midst of a delusion? Do delusions have and give meaning? How does the social and environment context shape the experience of schizophrenia? A phenomenological approach that returns to the lived experience of the person with psychosis may suggest new ways to approach these fundamental questions, while also redressing power imbalances through the integration of different and equally valuable perspectives. As phenomenology leads psychiatry off the beaten track, this symposium engages with novel interdisciplinary work that emphasises rich and in-depth understandings of individual patients with psychosis and their worlds.

The first presentation introduces a recent development in the field of phenomenological psychiatry: the integration of phenomenology and qualitative methods. The primary aim of this presentation is to introduce this methodological trend to provide the audience with helpful background for the following three presentations. The second presentation offers an example of a successful application of phenomenological approaches to the study of the lived experience of delusions in patients with a schizophrenia-spectrum diagnosis (Feyaerts et al., 2021). Implications of these phenomenological findings for psychosis research are far-reaching: they may shed light on current diagnostic discussions on the categorical or dimensional character of psychotic disorders, enliven current explanatory models of delusions, and inform the development of new person-centred therapeutic approaches. The third presentation draws on the results of the first systematic review of qualitative studies concerning the experience and meaning of delusions in psychosis (Ritunnano et al., in-progress). Rich and nuanced phenomenological data are discussed with a focus on three novel and yet unexplored dimensions of delusional experience: agency and selfhood, lived world and intersubjectivity, and meaning-making processes. These findings may not only assist with nosological and patho-aetiological issues but may also help redress power imbalances through the integration of different and equally valuable perspectives. In the fourth and final presentation, arguments for a contextual approach to the phenomenological and epidemiological investigation of schizophrenia are put forward, opening up new avenues for cross-disciplinary engagement. Several suggestions for modifying popular qualitative methods are discussed, which allow to expand the scope of phenomenological and epidemiological research and integrate extra-disciplinary findings. As schizophrenia is repositioned in the world, rather than within the narrow boundaries of the self, the contribution of social stigma and systemic discrimination to symptom development become clearer, with important implications for explanatory models of mental disorders.

24.1 QUALITATIVE METHODS IN PHENOMENOLOGICAL PSYCHOPATHOLOGY

Anthony Fernandez*[1]

[1]*University of Southern Denmark*

Background: In this presentation, I introduce a recent development in the field of phenomenological psychiatry: the integration of phenomenology and qualitative methods. The primary aim of this presentation is to introduce this methodological trend to provide the audience with helpful background for the following three presentations.
To begin, I briefly review the history of phenomenological psychiatry, with an emphasis on its unique methodological challenges and approaches. Like other fields of applied phenomenology, phenomenological psychopathology has had to contend with a key challenge: The philosophical tradition of phenomenology—which we can call "pure" phenomenology—was originally conceived as a study of essential or universally shared features of experience. Philosophically trained phenomenologists study, for instance, the general structure of temporal experience, the difference between moods and emotions, and the nature of selfhood. Insofar as their investigations aim to help us understand experience in general, they don't provide obvious resources for understanding particular ways of experiencing (e.g., the experience of depression, delusions, and so on).

Methods: Of the many fields that phenomenology has been applied to, psychiatry was the first to develop phenomenological approaches that could be applied to the study of particular cases or populations of human subjects. Historically, phenomenological psychopathologists have analysed case studies by drawing on theoretical and conceptual frameworks from philosophical phenomenology—examining, for instance, how temporal experience alters in depression or how the sense of self alters in schizophrenia. However, because their case studies have typically been drawn from a small selection of their own patients, their analyses have not been as systematic as one would like from a rigorous approach to scientific research.
Results: In the hopes of providing a more systematic approach, researchers across psychiatry, clinical psychology, and philosophy have recently begun integrating philosophical phenomenology with various approaches to qualitative research. I provide a brief overview of some of these new integrations, including the combination of philosophical phenomenology with qualitative methodologies such as Consensual Qualitative Research (CQR) and Amedeo Giorgi's Phenomenological Psychology.
Conclusions: By drawing on these examples, I demonstrate how philosophical phenomenology can be integrated at various stages of a qualitative study, including study design, interview, and data analysis. In some cases, philosophical phenomenology permeates the entire study. In other cases, it is integrated at only one stage, such as data analysis. Finally, I consider the possibilities for the future of qualitative approaches in phenomenological psychiatry and argue for a tighter integration between philosophical concepts and qualitative methods.

24.2 UNCOVERING THE REALITIES OF DELUSIONAL EXPERIENCE: RESULTS OF A QUALITATIVE PHENOMENOLOGICAL STUDY

Jasper Feyaerts*[1], Wouter Kusters[2], Zeno Van Duppen[3], Stijn Vanheule[4], Inez Myin-Germeys[5], Louis Sass[6]

[1]*Ghent University,* [2]*Stichting Psychiatrie and Filosofie,* [3]*UPC KU Leuven,* [4]*Ghent University,* [5]*KU Leuven, Center for Contextual Psychiatry,* [6]*Rutgers University*

Background: Delusions in schizophrenia are commonly approached as empirical false beliefs about everyday reality. Phenomenological accounts, by contrast, have suggested that delusions are more adequately understood as pertaining to a different kind of reality experience. How this alteration of reality experience should be characterised, which dimensions of experiential life are involved, and whether delusional reality might differ from standard reality in various ways is unclear and little is known about how patients with delusions value and relate to these experiential alterations. This study aimed to investigate the nature of delusional reality experience, and its subjective apprehension,
in individuals with lived experience of delusions and a schizophrenia-spectrum diagnosis.

Methods: In this qualitative phenomenological study, we recruited individuals with lived experience of delusions and a schizophrenia-spectrum diagnosis from two psychiatric-hospital services in Belgium using homogenous sampling. Criteria for participation were having undergone at least one psychotic episode with occurring delusional symptoms, present at least 1 year before participation, on the basis of clinical notes assessed by the attending psychiatrist; a schizophrenia-spectrum diagnosis, ascertained through clinical interview by the attending psychiatrist upon admission; being aged between 18 years and 65 years; and having the capacity to give informed consent. Exclusion
criteria included worries concerning capacity to consent and risk of distress caused by participation. We did phenomenologically driven semi-structured interviews with the participants to explore the nature of delusional reality experience and their subjective valuation of these experiences. We used interpretative phenomenological analysis, a qualitative method tailored to the in-depth exploration of participants' first-person perspective, to analyse their accounts.

Results: Between March 2, 2020, and Sept 30, 2020, 18 adults (13 men and five women, aged 19–62 years) participated in the interview study. The findings suggest that delusions are often embedded in wide-ranging alterations of basic reality experience, involving quasi-ineffable atmospheric and ontological qualities that undermine participants' sense of the world as unambiguously real, fully present, and shared with others. We also found that delusional reality experience can differ from standard reality in various ways (ie, in a hypo-real and hyper-real form), across multiple dimensions (eg, meaningfulness, necessity and contingency, and detachment and engagement), and that participants are often implicitly or explicitly aware of the distinction between delusional and standard reality. Delusional experience can have an enduring value and meaning that is not fully captured by a strictly medical perspective.

Conclusions: In my talk, I will discuss the implications of these phenomenological findings for (i) diagnostic discussions regarding the categorical or dimensional character of psychotic disorders, (ii) current and future explanatory models of delusions, and discuss (iii) how they could inform the development of new therapeutic approaches of delusions.

24.3 UNDERSTANDING THE EXPERIENCE AND MEANING OF DELUSIONS IN PSYCHOSIS: SYSTEMATIC REVIEW, META-SYNTHESIS AND SUGGESTIONS FOR FUTURE EMPIRICAL RESEARCH

Rosa Ritunnano*[1], Danniella Whyte-Oshodi[2], Joshua Kleinman[3], Maria Michail[1], Barnaby Nelson[4], Clara Humpston[1], Matthew Broome[1]

[1]*Institute for Mental Health, University of Birmingham,* [2]*Warwick Medical School, University of Warwick,* [3]*The Ohio State University College of Medicine,* [4]*Centre for Youth Mental Health, The University of Melbourne*

Background: In mainstream psychiatry research, delusions are often mapped using standardised measures for the assessment of psychotic symptoms, aimed at reliably quantifying clinical severity through the rating of a single item merging different aspects such as theme, conviction, frequency, systematisation, and bizarreness. However, while these dimensions can change independently of one another during the course of a psychotic episode, they also crucially fail to grasp and get closer to the lived experience of the person with delusion. This can lead to a significant epistemic loss, epistemic oppression, and to a widening conceptual mismatch between the operational constructs used to study delusions and the phenomenology of delusional experience. In addition, by statically evaluating predetermined categories, quantitative methods may also neglect important dimensions of experience that can be revealed via in-depth phenomenological and qualitative analysis. Despite an extensive body of psychological, philosophical, and psychiatric literature on delusions, so far there has been no attempt to systematically review and synthesise the accumulated qualitative knowledge-base. Therefore, this study aims to systematically investigate relevant qualitative research that has explored the lived experience of people with delusions. This can offer important insights into 1) what the experience of "becoming or being deluded" entails for the subject of experience (i.e., how dimensions of self, world and meaning may be transformed during delusional experiences) and 2) how individuals interpret and make meaning out of these experiences in the larger context of their life narratives.
Methods: The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P) statement guidelines. A protocol was developed to guide the review and was registered with PROSPERO (registration number CRD42020222104). A comprehensive literature search was conducted in January 2021, including five major bibliographic databases, grey-literature, relevant journals and contact with experts. Studies were included only if they provide an analysis of the phenomenon of interest (lived experience of delusions or delusion-like ideas) obtained through recognised qualitative methods such as interviews, focus groups, thematic analysis, grounded theory, phenomenological or narrative approaches. Two Qualitative Appraisal Tools were used to assess the overall quality of the qualitative studies: the Critical Appraisal Skills Programme (CASP, 2018) and the National Institute for Health and Care Excellence (NICE) methodology checklist for qualitative studies (2012). Twenty-four studies were included in the final synthesis. Thematic analysis was used to identify key themes and develop a novel theoretical framework with implications for clinical practice and future research.
Results: We expect the results of the review and meta-synthesis to be submitted for publication by January 2022. In my presentation, I will focus on three novel and yet unexplored dimensions of delusional experience as reported from the first-person and second-person perspectives: experiences of agency and selfhood, lived world and intersubjectivity, and meaning-making processes. By drawing on these findings, I will suggest novel phenomenological paths for future empirical and interdisciplinary research on delusions in psychosis.
Conclusions: The results of this novel meta-synthesis will be discussed with a cross-disciplinary and integrative focus. This may not only assist with nosological and patho-aetiological issues in psychosis research but may also redress power imbalances through the integration of different and equally valuable perspectives.

24.4 SCHIZOPHRENIA IN THE WORLD: ARGUMENTS FOR A CONTEXTUAL PHENOMENOLOGY OF PSYCHOPATHOLOGY

Elizabeth Pienkos*[1]

[1]*Clarkson University*

Background: Traditionally, phenomenological theories of schizophrenia have emphasized disturbances in self-experience, with relatively little acknowledgement of the surrounding world. However, epidemiological research consistently demonstrates a strong relationship between traumatic and stressful life events and the development of schizophrenia, suggesting that encounters in the world are highly relevant for many people diagnosed with this disorder.
Methods: This presentation draws on foundational texts in phenomenology to advocate for including world events and their subjective meaning as essential aspects of this disorder.
Results: This contextual approach to phenomenology emphasizes the relationship between self and world, one that is especially unstable, unclear, and untrustworthy in schizophrenia. Qualitative research methods are uniquely positioned to explore and delineate the nature of this relationship as it is lived by individuals with schizophrenia. The paper will make several suggestions for modifying popular qualitative methods and expanding the scope of phenomenological and epidemiological research to integrate extra-disciplinary findings. Such studies may, for example, clarify the subjective impact of social stigma, systemic discrimination, and coercive treatment methods and their role in symptom development.
Conclusions: Both epidemiological and phenomenological research can benefit from this approach: in epidemiology, researchers might consider the ways that various risk factors are experienced by persons vulnerable to schizophrenia, while phenomenologists are encouraged to inquire about the environmental and social context in which altered experiences occur and incorporate these considerations into their explanatory models.

25. PROTEIN MISFOLDING AND AGGREGATION: BIOLOGICAL CONSEQUENCES FOR SCHIZOPHRENIA AND RELATED DISORDERS

Frederick Nucifora

Johns Hopkins School of Medicine

Overall Symposia Abstract: Schizophrenia is a devastating and often chronic condition with a heterogeneous clinical presentation. The biological mechanisms remain poorly understood, in part because of their highly complex genetic basis and the likelihood of diverse mechanisms leading to schizophrenia. However, there may be common pathophysiological pathways that exist for subsets of the disease. As a complementary approach to the current genetic studies in the field, we have begun to investigate the possibility of studying some forms of schizophrenia and other major mental illnesses as proteinopathies: conditions in which specific insoluble aggregated proteins accumulate in the brain causing cellular and circuit disfunction. Dr. Bradshaw (Croatia) will provide background and updates on existing candidate aggregating proteins and their biochemistry. Dr. L. Nucifora (USA) will describe studies using human biospecimens to identify protein aggregation in a subpopulation of patients with schizophrenia, as well as describing the clinical correlations and novel proteins identified from this subpopulation of schizophrenia patients. Dr. Korth (Germany) will describe progress in identifying novel aggregating proteins and their possible role as biomarkers for these conditions and Dr. Hayashi (Brazil) will present neurodevelopmental and biochemical consequences of schizophrenia-related protein aggregation in a rodent model. This symposium will therefore, for the first time, bring together pioneers in this nascent field to explore what we know so far about protein aggregation in the pathology of schizophrenia, and how these discoveries can be translated into clinically relevant information.

25.1 PROTEIN INSOLUBILITY IN A SUBSET OF PATIENTS WITH SCHIZOPHRENIA

Leslie Nucifora*[1], Matthew MacDonald[2], Koko Ishizuka[3], Russell Margolis[3], Carol Tamminga[4], Robert Sweet[2], Christopher Ross[3], Akira Sawa[5], Frederick Nucifora[3]

[1]*Johns Hopkins University School of Medicine,* [2]*University of Pittsburgh,* [3]*Johns Hopkins School of Medicine,* [4]*University of Texas Southwestern Medical Center Department of Psychiatry,* [5]*John Hopkins University School of Medicine and Bloomberg School of Public Health*

Background: Despite significant efforts to understand the genetics of schizophrenia, the underlying mechanisms contributing to the disorder are not well understood and likely to be diverse. Protein aggregation as a pathological process has been implicated in many brain disorders, but its relationship to schizophrenia and other mental disorders is less known. In the present study, we hypothesize that protein aggregation occurs in a subset of patients with schizophrenia and that this pathological process can be identified in human biospecimens.
Methods: Prefrontal cortex or superior temporal gyrus from autopsy brains obtained from the University of Pittsburgh, University of Texas, and Harvard Brain Banks, and olfactory neurons obtained from living subjects from the Johns Hopkins Schizophrenia Center were processed using a fractionation protocol designed to extract the proteins into insoluble and soluble protein fractions. Levels of protein insolubility and ubiquitin reactivity, markers for protein aggregation, were quantified after SDS-PAGE separation followed by Coomassie staining and Western blot analysis and normalized to total homogenate protein. Mass spectrometry was performed in order to identify the protein composition in the insoluble fraction. Gene Ontology Enrichment Analysis and Ingenuity Pathway Analysis were used to assess the potential biological relevance of the detected proteins in the insoluble fraction. Clinical and cognitive testing was performed at the same time that the olfactory neurons were obtained from living patients providing the potential for clinical/cognitive correlations.
Results: A subset of patients with schizophrenia showed an increase in markers for protein aggregation, specifically protein insolubility and ubiquitination. Mass spectrometry of the insoluble fraction revealed that cases with increased insolubility and ubiquitination showed similar pattern of peptide clustering by principal component analysis. The proteins that were significantly altered in the insoluble pellet were enriched for processes relating to axon target recognition as well as nervous system development and function. Furthermore, protein insolubility was demonstrated in a subset of patient's olfactory neurons, with specific clinical/cognitive correlations.
Conclusions: This study demonstrates the pathological process of protein aggregation in a subset of patient with schizophrenia. Understanding the mechanisms related to protein aggregation in schizophrenia could lead to a better understanding of the disease process and novel therapeutic targets.

25.2 AGGREGATION OF "CANDIDATE PROTEINS" FOR PROTEINOPATHY IN MENTAL ILLNESS

Nicholas Bradshaw*[1], Bobana Samardžija[1], Beti Zaharija[1], Aristea Pavešić Radonja[2], Maja Juković[1], Maja Odorčić[1], Anja Hart[1], Éva Renner[3], Miklós Palkovtis[3], Gordana Rubeša[2]

[1]*University of Rijeka,* [2]*Clinical Hospital Center Rijeka,* [3]*Semmelweis University*

Background: Genetic analysis of schizophrenia has made great progress in the last 15 years, identifying many loci that may influence its pathology. However, the existence of many risk variants of small individual effect, combined with rare variants, makes it difficult to identify individual protein targets for downstream study of this devastating psychiatric condition.
To complement the genetic approach, we and others have been investigating potential disturbances of proteostasis in schizophrenia. Specifically, we hypothesize that there exist specific proteins that form insoluble protein aggregates in the brains of patients. These would be partially analogous to similar protein accumulations in the neurodegenerative disorders. This symposium will therefore open with a review and update of progress made to date in identifying proteins that aggregate in mental illness.

Methods: To date, most candidate aggregating proteins have been determined through the purification of the insoluble protein fraction of postmortem brain tissue (from patients with schizophrenia, bipolar disorder or major depressive disorder, plus controls). These have either been probed for the protein products of classic schizophrenia risk genes, or else subjected to proteomic analysis. Follow up work has largely consisted of expression of these proteins, in wild type, truncated or mutant forms, and examining their expression and effect in cultured cells or primary neurons, through a combination of immunofluorescent microscopy and biochemical techniques.
Data will also be shown from human blood serum samples collected at the Clinical Hospital Centre Rijeka (Croatia) and human brain samples collected at the Semmelweis University (Budapest, Hungary). Full ethical approval and informed patient consent (or legal permission) were obtained for all samples collected and all studies conducted on them.

Results: To date, five proteins have been identified that may form insoluble aggregates in the brains of patients with schizophrenia, and in some instances also in the affective disorders. Of these, DISC1, dysbindin-1 and NPAS3 represent the protein products of classical, pre-GWAS, candidate genes, while CRMP1 and TRIOBP-1 were identified by proteomic approaches, and had not previously been associated with schizophrenia. All are expressed in the brain, and are variously implicated in neurodevelopment and/or synaptic function. Each protein has also been confirmed to be capable of forming aggregates in various experimental systems.
We are studying the aggregation of these proteins. Notably, in the case of at least DISC1, TRIOBP-1 and NPAS3, their aggregation propensity is seen to be dependent on specific structural regions of the proteins. Such data allows further analysis of the mechanisms underlying their aggregation, and suggests routes ahead for their study. It is also notable that most of the proteins aggregate independently of each other, with only DISC1 showing a clear propensity to “co-aggregate” with other mental illness proteins in vivo and in vitro.

Conclusions: While still in its infancy as a field, the existence of several insoluble or aggregated proteins in the brains of schizophrenia patients has now been confirmed. Further replication in a wider number of patients is now needed to determine whether this indeed represents a general biological feature of the condition. In parallel, cell and animal studies will help us to understand the pathophysiological consequences of such protein aggregates.
Research was supported by the Croatian Science Foundation (Hrvatska zakalada za znanost, IP-2018-01-9424).

25.3 FROM PROTEIN MISASSEMBLY TO BIOLOGICAL DIAGNOSTICS IN SCHIZOPHRENIA

Carsten Korth*[1], Svenja Trossbach[1], Rita Marreiros[1], Andreas Müller-Schiffmann[1], Ovidiu Popa[1]

[1]*University of Düsseldorf*

Background: A significant amount of schizophrenia cases is likely non-genetic, i.e. triggered by trauma, social stressors or other environmental causes etc. Posttranslational protein modifications have been established as a convergence pathway inducing aberrant signaling of relevant signaling proteins. We investigated the possibility that misassembled r aggregated proteins could be a convergence point of non-genetic causes of schizophrenia or recurrent affective disorders and whether such a molecular circuitry could lead to novel diagnostic markers

Methods: The translational value of misassembled proteins was modeled in a transgenic rat by modest overexpression of full length human DISC1 (tgDISC1 rat), followed by behavioral assays, neuroanatomical, imaging and neurochemical characterization. Peripheral blood was analyzed in two independent cohorts of patients with schizophrenia and controls (n = 16/50, n = 5 /50, respectively) and subjected to advanced statistical analysis. Brain homogenates from independent postmortem collections of patients with schizophrenia was fractionated, and the insoluble fraction analyzed by mass spectrometry.

Results: To investigate potential environmental causes of protein insolubility in candidate proteins, we demonstrate that viral infection such as with influenza virus or oxidative stress promote insoluble, endogenous DISC1 protein. To demonstrate biological consequences of insoluble protein for brain functionality and behavior, deficits compatible with aberrant dopamine homeostasis were demonstrated in the tgDISC1 rat. In a reverse-translational approach we identified unique neuroimmunological signatures in peripheral blood of tgDISC1 rats. We also report on attempts of immunological detection of aggregated proteins in CSF of human schizophrenia patients and on attempts to identify novel insoluble protein markers in brains from schiizophrenia patients.

Conclusions: Identification and characterization of aggregated or misassembled proteins is a valuable approach to identify novel pathogenetic mechanisms and biomarkers for schiophrenia and, likely, other chronic psychiatric disorders. Furthermore, reverse translational identification and validation for blood biomarkers offers the exciting prospect of pairing a patient subset, a biomarker and an animal for developing tailored pharmacotherapies.

25.4 OLIGOPEPTIDASES IN A MODEL OF PROTEINOPATHY AND SCHIZOPHRENIA

Mirian Hayashi*[1]

[1]*UNIFESP/EPM*

Background: Neurodegenerative disorders characterized pathologically by cytoplasmic malformed proteins and consequent complex formation have recently attracted the attention of several scientists. The roles of Ndel1 (Nuclear distribution element-like 1) and ACE (angiotensin I converting enzyme) on neurodevelopment and brain function have been previously described, and ACE inhibitors showed to delay dementia progression in humans. Ndel1 enzyme activity was shown to be important for neuritogenesis and neuron migration, with potential contribution for brain formation, which mechanism was associated to its ability to bind to the protein product of a gene previously associated to schizophrenia (SCZ) susceptibility, namely DISC1 (Disrupted-in-Schizophrenia 1). Transgenic rat model overexpressing the full-length DISC1 (tgDISC1), showed phenotypes consistent mental illness with DISC1 misassembly. The tgDISC1 rat displayed perinuclear DISC1 aggregates in neurons, and also showed a robust signature of behavioral phenotypes pointing to changes in dopamine (DA) neurotransmission, including amphetamine supersensitivity, hyperexploratory

behavior and rotarod deficits. The importance of neuropeptides has been recognized in SCZ and other CNS disorders, in the last years, mainly due to their ability to modulate the signaling of classical monoaminergic neurotransmitters as DA. Interestingly, a class of enzymes coined as oligopeptidases are able to cleave several of these neuropeptides, and their potential implication in SCZ was demonstrated in both animal models and clinical studies.
Methods: aiming to investigate in the adult animals the relation of the ACE and Ndel1 oligopeptidase activity with the neurodevelopment and DA-related phenotypes, amphetamine-stimulated locomotion (evaluated in a open field) and blood and brain enzyme activity (by fluorimetry) of the tgDISC1 rat vs. wild-type (WT) littermate controls were evaluated. In addition, 3D assessment of neuronal cell body number and spatial organization of cell distribution was measured in striatum and cortex of tgDISC1 rat by histology and microtomography. The effect of antipsychotics on oligopeptidase activity was also evaluated here.
Results: Basal Ndel1 activity was lower in the blood and several brain regions of tgDISC1 compared to littermate WT. Locomotion and Ndel1 activity were both significantly increased by amphetamine in tgDISC1, but not in littermate WT. Decreased Ndel1 activity reflects both a trait (neurodevelopmental phenotype) and a state (amphetamine-induced dopamine release), and decreased baseline Ndel1 activity in the adult might be indicative of the presence of a subtle neurodevelopmental disturbance also described in treatment-resistant SCZ (TRS). However, chronic treatment with clozapine changed ACE but not Ndel1 activity in tgDISC1 and WT littermate rats.
Conclusions: Ndel1 activity is reduced in TRS compared to treatment non-resistant SCZ or healthy controls, and in tgDISC1 and WT littermate rats, which correlates with the increased sensitivity to amphetamine and neurodevelopmental disturbances in spatial neuronal distribution. This animal model could be useful to further elucidate and study serious conditions as the TRS, and the chronic treatment with clozapine changed only ACE but not Ndel1 activity, in addition to increasing the sensitivity to amphetamine. The correlation of this data with the TRS is not clear yet, but this study may contribute for further clarifying the molecular pathways underlying the etiology and pathophysiology of SCZ.

Plenary IV: Rodgrio Bressan

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

26. SCHIZOPHRENIA RESEARCH IN BRAZIL — FROM LEMONS TO CAIPIRINHA

Paola Dazzan

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

Overall Abstract: Adolescence is a crucial developmental period, when most adult mental health problems emerge. This age thus provide a key time in the life of an individual in which effective interventions can promote better psychiatric outcomes.
This presentation will provide an excellent example of how dynamics of psychopathology, environment and brain maturation can be studied to inform interventions synchronized with standard and deviant trajectories of development.

26.1 PSYCHOTIC EXPERIENCES SYMPTOMS OVER NEURODEVELOPMENT AND THE OPPORTUNITY FOR TIME DRIVEN INTERVENTIONS AND THE OBERTH EFFECT

Rodrigo Bressan

Universidade Federal de Sao Paulo - UNIFESP

Individual Abstract: Psychosis can be examined through the evolution of psychotic experiences in time, and unraveling these dynamics may provide insights for innovative interventions. Data about the trajectory of psychosis experiences during neurodevelopment from the Brazilian High-Risk Cohort Study for Psychiatric Disorders, in which 2,241 individuals aged 6–14 years were followed for the last 12 years will be presented. Subjects provided self-ratings of 20 psychotic experiences using the Community Assessment of Psychic Experiences (CAPE). A trained psychologist conducted an interview to validate reported experiences and to rate the presence of attenuated psychosis symptoms and affective flattening. In parallel, parents provided information about child mental health to an independent interviewer. General Psyhopatology, such as P-factor and structural and functional brain maturation during the adolescence will be presented as well as the emotional and social environment.

When searching for optimal moments to intervene, valuable insights may come from examining analogous phenomena. Increasing familiarity with dimensional psychopathology dynamics, brain maturation and environmental aspects is expected to fine-tune treatment. We illustrate how time-driven interventions can be used for controlled interference in clinical settings.

In orbital mechanics, the Oberth effect poses that an aircraft gains more kinetic energy when accelerating at the nearest point to a central body, where potential is lowest and speed is highest. These properties are used to spiral out of Earth's orbit for satellites. An intuitive example can be observed in the playground swing. In order to optimize efforts, adults push the seat synchronizing it with the natural motion of the pendulum when going down-and-forward. This manoeuvre uses gravitational forces to maximize kinetic energy and make transitions to orbits of larger amplitudes.

Using a similar timewise rationale to fine-tune psychosocial and drug interventions may be crucial to prevention and treatment efficacy. Examining the dynamics of psychotic states, general psychopathology, social emotional environment and brain maturation markers during neurodevelopment can give us insightful new ways to help people with mental disorders. Specifically, one may synchronize interventions with standard and deviant trajectories.

Saturday, April 9, 2022

Plenary V: Nev Jones

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

27. AGENCY IN CULTURAL CONTEXT: MAKING 'SENSE' OF PSYCHOSIS

Diane Gooding

University of Wisconsin-Madison

Overall Abstract: Dr. Diane C. Gooding will be introducing the Plenary speaker, Dr. Nev Jones, and chairing the session.

27.1 AGENCY IN CULTURAL CONTEXT: MAKING 'SENSE' OF PSYCHOSIS

Nev Jones

University of Pittsburgh

Individual Abstract: As anthropologists and qualitative researchers have long argued, the phenomenology of psychosis varies in many ways across distinct historical and cultural contexts. Nevertheless, the full ramifications of these diverse forms and experiences, and the systems of understanding in which they are embedded, arguably remain deeply under-theorized in the context of clinical and services research, perhaps particularly when it comes to investigations of the many and complex reasons why clients ultimately disengage from (or never truly engage with) psychosis services. Zooming out from these narrower clinical contexts, the presentation will also take up the question of the relationship between meaning-making, available cultural scripts and identities, and long-term healing and community integration. Throughout, the presenter will draw on sustained research, clinical and activist engagement with service users/experiencers in diverse cultural contexts; work, in turn, inspired and animated by long-term personal and family experiences of psychosis.

Concurrent Symposia

9:45 a.m. - 11:45 a.m.

28. THE IMPACT OF CANNABIS USE ON THE CHARACTERISTICS AND INCIDENCE OF PSYCHOSIS

Joni Lee Pow

The University of West Indies

Overall Symposia Abstract: The legal status of cannabis is changing in many countries with resultant increase in the use and potency of cannabis. Although most users enjoy their use and come to no harm, a minority develop dependence or psychiatric disorders. The evidence that cannabis use is a contributory cause of psychosis is now incontrovertible. However, it is not clear just how important cannabis use is in contributing to psychosis, and whether it is sufficient to have an impact on the incidence and nature of psychosis. This symposium will address these questions.

Dr Joni Lee Pow will present results from the INTREPID II study. Variation in the incidence of psychosis, and the extent of cannabis exposure, was examined across India, Trinidad and Nigeria. The incidence was higher in Trinidad, as was cannabis use. One hypothesis is that more frequent use of cannabis may be contributing to a) higher rates of psychotic disorder in the Trinidad sample, b) higher rates amongst males compared to females in Trinidad and c) higher rates amongst Afro-Trinidadians compared to Indo-Trinidadians. Higher cannabis exposure may also explain variation in the presence of affective symptomatology and age of onset of psychosis between and within sites.

Dr Diego Quattrone will present results from a unique study in which the incidence of schizophrenia, was tracked from the 1964 to 2012 in South-East London. Findings show a threefold rise in the incidence of schizophrenia with the increase particularly marked in latter

years. Over the same time, the proportion of patients reported to be smoking cannabis rose from 5% to over 50% with use of high potency cannabis especially common in the latter years.

Dr Carsten Hjorthøj will synthesize a range of studies, utilizing the unselected nationwide Danish registers to show how the incidence of cannabis-induced psychosis has increased over time, and so contemporaneously has the incidence of schizophrenia with comorbid cannabis use disorder. This presentation will demonstrate that cannabis-induced psychosis has important implications for the understanding of the association between cannabis and schizophrenia, possibly reflecting a cannabis-related subtype of schizophrenia.

Sir Robin Murray will present data from a Canadian-based study with Dr Russ Callaghan examining the associations between recreational cannabis legalization (October 17, 2018) and weekly emergency department (ED) presentation counts of cannabis-induced psychosis and schizophrenia and related conditions where presentations for cannabis-induced psychosis doubled between April 2015 and December 2019.

Evidence from the above-mentioned countries show the relationship between cannabis use and the frequency of various psychotic disorders. Cannabis is an important modifiable risk factor for schizophrenia. Reduction in use and potency would have population-level benefits in terms of greatly reduced incidence of schizophrenia. Current trends towards increased use suggest a likely further increase in incidence.

28.1 CANNABIS USE AND VARIATIONS IN PSYCHOSES IN 3 COUNTRIES IN THE GLOBAL SOUTH: INITIAL FINDINGS FROM INTREPID II

Joni Lee Pow*[1], Casswina Donald[2], Marta Di Forti[3], Tessa Roberts[4], Oye Gureje[5], Rangaswamy Thara[6], Alex Cohen[7], Helen Weiss[8], Sujit John[9], Bola Olley[10], Georgina Miguel Esponda[11], Robin Murray[12], Craig Morgan[13], Gerard Hutchinson[14]

[1]*The University of West Indies,* [2]*University of the West Indies,* [3]*SGDP, Institute of Psychiatry, KCL,* [4]*Institute of Psychiatry, Psychology and Neuroscience, King's College London,* [5]*College of Medicine, University of Ibadan,* [6]*Schizophrenia Research Foundation,* [7]*Harvard-Chan School of Public Health,* [8]*London School of Hygiene and Tropical Medicine,* [9]*Schizophrenia Research Foundation SCARF,* [10]*University of Ibadan,* [11]*King's College London,* [12]*Institute of Psychiatry, King's College London,* [13]*Centre for Society and Mental Health, King's College London,* [14]*Psychiatry Unit, Faculty of Medical Sciences, University of the West Indies*

Background: Several recent studies have shown variation in incidence between different regions in Europe with one of the risk factors so identified being cannabis use. Using data from INTREPID II – a research programme in three diverse settings in the Global South (i.e., Tamil Nadu [India], Oyo state [Nigeria], and northern Trinidad) – we sought to examine, between and within sites (a) variations in incidence and (b) variations in the distribution of cannabis use and associations with psychoses.

Methods: INTREPID II is a programme of research incorporating incidence, case-control, and cohort studies of psychoses. Baseline recruitment of untreated cases with a psychotic disorder and age-, sex-, and neighborhood-matched controls was conducted between May 2018 and September 2020 (n= 221 (India), 209 (Nigeria), 212 (Trinidad) pairs of matched cases and controls). 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. The Schedules for Clinical Assessment in Neuropsychiatry (SCAN) were used to confirm presence of a psychotic disorder and the MRC Sociodemographic Schedule and Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) to collect information on sociodemographic details and cannabis use.
Results: The incidence of psychotic disorders was higher in the site in Trinidad (incidence rate [IR] 61.3 per 100,000 person years; 95% CI 56.3-66.3)) compared with the sites in India (IR 20.8; 95% CI 18.3-23.3) and Nigeria (IR 14.5; 95% CI 12.4-16.6). This, in part, was due to a higher incidence of affective psychoses in Trinidad (i.e., 30% of cases diagnosed with affective psychoses in Trinidad compared with less than 10% in Nigeria and India) Within Trinidad, the incidence was higher for men compared with women (IR 71.5 vs. 55.1) and higher for African-Trinidadian compared with Indian-Trinidadian and mixed (IR 88.5 vs. 47.8 and 51.5). Further, the average age of onset was lower for cases in Trinidad compared with India and Nigeria (35.8 years in India, 31.1 Nigeria, 26.8 Trinidad).
Using controls as a proxy for population estimates, the prevalences of both lifetime and frequent (more than once per week) cannabis use were much higher in Trinidad compared with Nigeria and India. The proportions that reported lifetime cannabis use were 65% in Trinidad, 13% in Nigeria, and less than 1% in India; the proportions that reported using cannabis frequently (more than once per week) were 21% in Trinidad, 4% in Nigeria, and less than 1% in India. In Trinidad, the prevalence of frequent cannabis use was higher for men (28%) compared with women (10%) and higher for African-Trinidadians (24%) compared with Indian-Trinidadians (9%).

In Trinidad, lifetime cannabis use was associated with around a 1.5-fold increased odds of psychotic disorder (adj. OR of 1.5, 95% CI 0.8-2.7), frequent cannabis use was associated with around a two-fold increased odds (adj. OR 2.14 (95% CI 0.1-1.0), and the highest level of cannabis involvement (as measured by an ASSIST score of 27 or more) was associated with around a four- to five-fold increased odds (adj. OR 4.78 95% CI 1.1-20.0). The proportion of cannabis users in the other two sites were too small to allow reliable estimates of odds ratios.

Conclusions: We found evidence of wide variations in incidence between the sites, with the highest rates in Trinidad. We also found high levels of lifetime and frequent cannabis use and strong associations with psychoses in Trinidad. This is in line with findings from the EU-GEI study, which reported high levels of cannabis use in the areas with the highest incidence of psychoses. It is possible, then, that cannabis use may account, in part, for variations between Trinidad, India, and Nigeria and within Trinidad in the incidence, presentation, and mean age of onset of psychosis. However, this remains speculative and there is a need to both consider alternative explanations and directly test this in further analyses.

28.2 DRAMATIC INCREASE IN THE INCIDENCE OF SCHIZOPHRENIA IN SOUTH LONDON OVER FIFTY YEARS

Diego Quattrone*[1], Marta Di Forti[1], Robin Murray[1]

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

Background: The incidence rates of schizophrenia and psychotic disorders vary across places. Such variation is partly due to differences in exposure to environmental risk factors for psychosis, such as frequency of cannabis use and local availability of high-potency cannabis varieties. Hence, one would expect that schizophrenia incidence rates have likewise fluctuated over time within the same place, following local changes in the contexts and patterns of use of cannabis.

However, estimating the incidence variation of a psychiatric disorder over decades in the same place is a methodological challenge. The same standardised diagnostic criteria and procedure should be used and repeated over time, mapping the same geographic catchment area.

Methods: Between 1965 and 1997, we identified the records of all patients who presented to psychiatric services with a first-episode psychosis who were living in the old metropolitan borough of Camberwell, in South-East London. We applied the OPerational CRITeria (OPCRIT) system to the records to identify those who met the Research Domain Criteria (RDC) for schizophrenia. After a gap, the process was repeated for those similarly presented between May 1, 2010, to April 30, 2012, in the same geographic area, which we mapped in the current South-East London districts of Camberwell, Peckham, and Dulwich. Denominator populations for this area were estimated using Office for National Statistics (Census) data, thus enabling us to reliably calculate trends in the incidence of schizophrenia over 50 years.
Results: We will report OPCRIT RDC-based schizophrenia incidence rates by the time period in the geographic area corresponding to the old borough of Camberwell. Thus, we will show a progressive increase in the number of new cases of schizophrenia, up to three times from 1965 to 2012. We will further show that such increase has mirrored a higher frequency of cannabis use and greater availability of high-potency cannabis varieties in recent years.
Conclusions: We will discuss changes in the patterns of cannabis use in South-East London over 50 years that might be associated with the reported increase in the incidence of schizophrenia. Given the growing diffusion of high-potency cannabis on the one hand and the current tendency towards legalisation on the other hand, these findings may have implications for public health and primary prevention.

28.3 CANNABIS-INDUCED PSYCHOSIS: SCHIZOPHRENIA WITH A NEW NAME, OR A MODIFIABLE RISK FACTOR FOR SCHIZOPHRENIA?

Carsten Hjorthøj*[1], Marie Starzer[2], Merete Nordentoft[2], Maria Oku Larsen[2], Michael Eriksen Benros[2], Trine Madsen[2], Annette Erlangsen[2], Benjamin Arnfred[2], Silke Behrendt[3], Stine Bjerrum Møller[3]

[1]*Copenhagen Research Center for Mental Health - CORE,* [2]*Copenhagen University Hospital, Mental Health Center Copenhagen, Copenhagen Research Center for Mental Health - CORE,* [3]*University of Southern Denmark*

Background: More than 30 years of research have implicated cannabis as a possible cause for schizophrenia. However, the exact nature of the association is still poorly understood, and still debated to this day. Meanwhile, a diagnostic entity exists in both ICD-10 and DSM-5 called cannabis-induced psychosis. Defined as a psychotic disorder arising in the context of, or immediately after, use of cannabis, it would imply at least acute psychotogenic effects of cannabis. As such, a deeper understanding of cannabis-induced psychosis would likely yield insights into the actual link between cannabis and psychotic disorders persisting outside of the context of intoxication from cannabinoids, e.g. schizophrenia.
Methods: This presentation will synthesize a range of studies, both recently published and not-yet published, utilizing the unselected nationwide Danish registers.
Results: A range of results will be presented, including:

- The incidence of cannabis-induced psychosis has increased over time, and so has the incidence of schizophrenia with comorbid cannabis use disorder
- Cannabis-induced psychosis is associated with a range of poor outcomes, including progression to schizophrenia, bipolar disorder, all-cause and cause-specific mortality, anxiety, depression, etc.

- Separation of whether cannabis-induced psychosis is simply an initial misdiagnosis of schizophrenia, or its own disorder
- Cannabis-induced psychosis as a population-based modifiable risk factor for severe mental illness including schizophrenia

Conclusions: This presentation will show that cannabis-induced psychosis has important implications for the understanding of the association between cannabis and schizophrenia, possibly reflecting a cannabis-related subtype of schizophrenia. Further, cannabis will be firmly established as a modifiable risk factor with population-level benefits in terms of potentially dramatically reduced incidence of schizophrenia.

28.4 LEGALISATION OF MEDICINAL AND RECREATIONAL CANNABIS USE IN CANADA; IMPACT ON INCIDENCE OF CANNABIS-INDUCED PSYCHOSIS AND SCHIZOPHRENIA

Russell Callaghan[1], Robin Murray*[2]

[1]*Univ. of Northern B.C,* [2]*Institute of Psychiatry, King's College London*

Background: The varying use and legal status of cannabis in different countries, and changes in the latter, provide the opportunity to examine the effect of these on the incidence of psychosis. Canada provides a unique opportunity to address these issues. It has the highest cannabis use of any major country. Cannabis was legalised for medicinal reasons in 2001, and then for recreational purposes in 2018. Rates of inpatient hospitalisations in Canada with cannabis-induced psychosis tripled from 2006-2015. In a study led by Russ Callaghan, we investigated the impact of legalisation on emergency clinic presentations.
The Canadian study examines temporal effects of cannabis use on psychosis. The variation in cannabis use across Europe provides the opportunity for a comparison study of the geographical effects on psychosis incidence

Methods: We examined emergency department (ED) presentations aggregated across Alberta and Ontario, obtained from Canada records for April 1, 2015 till December 31, 2019). We employed Seasonal Autoregressive Integrated Moving Average (SARIMA) models to assess associations between Canada's cannabis legalization (via the Cannabis Act implemented on October 17, 2018) and weekly Emergency Clinic presentation counts of the following: ICD-10-CA-defined target series of cannabis-induced psychosis (F12.5; n = 5832) and schizophrenia and related conditions ("schizophrenia"; F20-F29; n = 211,661), as well as two comparison series of amphetamine-induced psychosis (F15.5; n = 10,829) and alcohol-induced psychosis (F10.5; n = 1884).
Results: Emergency Clinic presentations for cannabis-induced psychosis doubled between April 2015 and December 2019. However, across all four SARIMA models, there was no evidence of significant step-function effects associated with cannabis legalization for recreational use on post-legalization weekly ED counts of (a) cannabis-induced psychosis [0.34 (95% CI -4.1; 4.8; p = 0.88)]; (b) schizophrenia [24.34 (95% CI -18.3; 67.0; p = 0.26)]; (3) alcohol-induced psychosis [0.61 (95% CI -0.6; 1.8; p = 0.31); or (4) amphetamine-induced psychosis [1.93 (95% CI -2.8; 6.7; p = 0.43).
Conclusions: In Canada, the period when cannabis was legalised for medicinal reasons, presentations with cannabis-induced psychosis steadily increased. However, Implementation of cannabis legalization for recreational use in 2018 was not immediately associated with evidence of significant changes in cannabis-induced psychosis or schizophrenia ED presentations. Given the idiosyncratic rollout of Canada's cannabis legalization with varying

degrees of access to legal cannabis and the short period since legalisation, further research is required in Canada to definitively assess the effect.
Evidence from the EU-GEI Incidence study across 16 Europe sites shows that incidence was highest in the big Northern cities and lowest in rural areas in the North, and across. rural and urban centres in Southern Europe. This was partly explained by variations in use of cannabis and in particular high potency cannabis. The population attributable fraction for high potency cannabis use across all sites was 12% rising to 30% in London and 50% in AmsterdamEvidence from the EU-GEI study does suggest a relationship between use of high potency cannabis and incidence of psychosis.

The position in Portugal is also relevant. Cannabis use was decriminalised in 2001. From 2002 till 2015, the proportion of psychosis patients diagnosed as cannabis dependent rose from less than 1% to over 10% The increase in the proportion of psychosis patients diagnosed as having cannabis dependence in Portugal may be consequent upon decriminalisation but could also be because of increasng potency of cannabis.

29. THERAPEUTIC PATHWAYS FOR THOUGHT AND LANGUAGE DYSFUNCTION IN PSYCHOSIS

Lena Palaniyappan

University of Western Ontario

Overall Symposia Abstract: The rates of functional recovery from psychotic illness remains poor despite the provision of the state-of-art early interventions. Existing treatments predominantly focus on reducing delusions and hallucinations. Antipsychotics indeed reduce acute communication disturbances arising from thought/language disorder but have minimal effect on persistent language disturbances in psychosis. Paradoxically, persistent features such as negative symptoms, language disturbances and cognitive deficits that predict poor prognostic outcomes are made worse with existing therapies. Clinical trials focus on measuring only those symptoms that are likely to change; thus thought/language disorder has been a neglected area of therapeutic need. This is further compounded by the difficulties in recruiting a subject with language disturbances for interventional trials including psychotherapies, diminishing our ability to empirically evaluate the treatment effects on these core features of psychosis. We need to select and validate treatment targets in the thought/language domain, facilitate inclusion of patients with language deficits in ongoing trials and develop focussed remediation approaches to reduce key linguistic deficits that affect functional outcomes.
We approach this by directly examining the effects of focussed neurochemical manipulations involving dopamine (antipsychotics/methamphetamine), serotonin (psychedelics/MDMA), neuropeptides (oxytocin) and glutamate (ketamine) on speech.

- Drs. Sommer and de Boer highlight how dopaminergic treatments alter our utterances in a profound manner that enables us to identify the prescribed class of medications. This work focusses on the receptor-level specificity of linguistic readouts in schizophrenia and exposes the unmet therapeutic need in this area.
- Using an extensive multi-domain linguistic analysis in healthy adults under acute pharmacological perturbations, Dr. Bedi will report that the serotonergic enhancement (MDMA) increases, but dopaminergic enhancement (methamphetamine) reduces prosocial concepts. Oxytocin, on the other hand, had effects limited to affect-related acoustic features.

- Continuing with this 'perturb-and-measure' approach, Dr. Tagliazucchi will present the effects of 75mcg of intravenous LSD on speech markers. With its verbosity-enhancing but incoherence-inducing effects, the psychedelic LSD produces a mania-like effect on speech.
- Drs. Stein and Kircher will discuss ketamine-related glutamatergic effects and present a network-level systems model of thought disorder. The insights from their transdiagnostic sample of >1000 patients will form the foundation for discussing the next priorities in the field.

Dr. Corcoran will synthesize these neurochemical and circuit-level findings to discuss the utility of this knowledge for clinical trials.

The overall goal of this symposium is to present key observations that generate tenable hypothesis for therapeutic progress in this area of unmet need.

29.1 FORMAL THOUGHT DISORDERS: NEUROIMAGING OF MODEL PSYCHOSES WITH GLUTAMATERGIC SUBSTANCES AND TRANSDIAGNOSTIC FINDINGS IN PATIENTS WITH SZ, BD AND MDD

Frederike Stein*[1], Tilo Kircher[1]

[1]*Marburg University,*

Background: Formal thought disorder (FTD) refers to a construct describing deviant thinking, speech and communication. The pathophysiology of FTD has been investigated using, among others, structural and functional MR imaging, model psychoses using psychoactive substances and a combination thereof.
Methods: During our presentation, we will give an overview on this research and report on novel results on transdiagnostic brain correlates of FTD.
Results: Phenomenologically, FTD can be divided into positive and negative dimensions. Positive FTD correlate with the gray matter volumes (GMV) of the bilateral superior temporal gyri, inferior frontal gyri, amygdala-hippocampus complex, and the bilateral insula in SZ patients. In addition, the glutamate system is related to positive FTD. Hereof, we were able to show that ketamine-induced positive FTD correlate with the activation of the left superior temporal gyrus and the right inferior and middle temporal gyri during verbal fluency tasks, indicating strikingly similar results to those seen in SZ patients with positive FTD. Besides, since FTD has been traditionally linked to SZ patients, both psychopathology and particularly neurobiological markers remain largely elusive in other diagnoses (e.g. major depression, bipolar disorder). In recent studies of ours with N=1071 patients, we were able to show three transdiagnostic FTD dimensions being differentially associated with gray and white matter brain structure in language areas independent of SZ, MDD and BD diagnosis.
Conclusions: The studies reported in our talk might be a starting point for investigations on the treatment of FTD, since the presence of FTD is related to functional social outcome as well as general course of illness.

29.2 ACUTE EFFECTS OF METHYLENEDIOXYMETHAMPHETAMINE (MDMA) ON HUMAN SPEECH DETECTED BY AUTOMATED NATURAL LANGUAGE PROCESSING

Gill Bedi*[1], Guillermo Cecchi[2], Harriet de Wit[3]

[1]*University of Melbourne,* [2]*IBM Research,* [3]*University of Chicago*

Background: Methylenedioxymethamphetamine (MDMA; 'ecstasy') produces powerful effects on mental states that can motivate use. These changes appear to be produced via effects on both serotonergic and dopaminergic systems, with possible involvement of oxytocinergic signalling. Assessment of these effects via self-report is vulnerable to bias; automated natural language processing (NLP) may provide a more objective assay of mental state changes due to MDMA.
Methods: We will present two randomized, double-blind, within-subject laboratory studies which assessed the acute effects of MDMA compared to placebo and two active controls – methamphetamine (with primarily dopaminergic effects) and exogenous oxytocin – on speech in healthy adults as assessed with NLP. Study 1 compared speech on MDMA (0.75 mg/kg, 1.5 mg/kg), methamphetamine (20 mg) and placebo in 13 participants using latent semantic analysis. Study 2 used a double-dummy design to compare speech across multiple domains (acoustic, semantic, psycholinguistic) after MDMA (0.75 mg/kg, 1.5 mg/kg), oxytocin (20 IU), and placebo in healthy adults (N=31).
Results: In Study 1, speech on MDMA was semantically closer than placebo speech to prosocial concepts (1.5 mg/kg: friend, support, intimacy, rapport; 0.75 mg/kg: empathy). Relative to placebo, methamphetamine speech was semantically further from compassion. In Study 2, MDMA altered speech relative to placebo in acoustic, semantic, and psycholinguistic domains, whereas oxytocin's effects compared to placebo were limited to affectively-relevant acoustic features.
Conclusions: Results indicate that the acute effects of MDMA, and those of related substances, can be detected using NLP. Speech contains rich, multidimensional data that can be mined to further characterise the mental state effects of drugs like MDMA.

29.3 LANGUAGE DISTURBANCES IN SCHIZOPHRENIA: THE RELATION WITH ANTIPSYCHOTIC MEDICATION

Iris Sommer*[1], Alban Voppel[2], Sanne Brederoo[3], Frank Wijnen[4], Janna de Boer[5]

[1]*UMC Groningen,* [2]*University Medical Center Groningen,* [3]*University Medical Center Groningen, University Medical Center Groningen,* [4]*Utrecht University,* [5]*University Medical Center Groningen, University Medical Center Utrecht*

Background: Language disturbances are key aberrations in schizophrenia. Little is known about the influence of antipsychotic medication on these symptoms.
Methods: Using computational language methods, this study evaluated the impact of high versus low dopamine D2 receptor (D2R) occupancy antipsychotics on language disturbances in 41 patients with schizophrenia, relative to 40 healthy controls.
Results: Patients with high versus low D2R occupancy antipsychotics differed by total number of words and type-token ratio, suggesting medication effects. Both patient groups differed from the healthy controls on percentage of time speaking and clauses per utterance, suggesting illness effects. Overall, more severe negative language disturbances (i.e. slower articulation rate, increased pausing, and shorter utterances) were seen in the patients that used high D2R occupancy antipsychotics, while less prominent disturbances were seen in low D2R occupancy patients. Language analyses successfully predicted drug type (sensitivity = 80.0%, specificity = 76.5%).
Conclusions: Several language disturbances were more related to drug type and dose, than to other psychotic symptoms, suggesting that language disturbances may be aggravated by high D2R antipsychotics. This negative impact of high D2R occupancy drugs may have clinical

implications, as impaired language production predicts functional outcome and degrades the quality of life.

29.4 NATURAL LANGUAGE AS A WINDOW INTO THE PSYCHOTOMIMETIC PROPERTIES OF LSD, A CLASSICAL PSYCHEDELIC DRUG

Enzo Tagliazucchi*[1], Camila Sanz[1], Carla Pallavicini[1], Facundo Carrillo[1], Federico Zamberlan[1], Mariano Sigman[2], Natalia Mota[3], Mauro Copelli[4], Sidarta Ribeiro[3], David Nutt[5], Robin Carhart-Harris[5]

[1]*University of Buenos Aires,* [2]*Universidad Torcuato Di Tella,* [3]*Federal University of Rio Grande do Norte,* [4]*Federal University of Pernambuco,* [5]*Imperial College London*

Background: Serotonergic psychedelics have been suggested to mirror certain aspects of psychosis, and, more generally, elicit a state of consciousness underpinned by increased entropy of on-going neural activity. We investigated the hypothesis that language produced under the effects of lysergic acid diethylamide (LSD) should exhibit increased entropy and reduced semantic coherence, and how these changes relate to natural language alterations seen during different types of psychotic episodes.
Methods: Computational analysis of interviews were conducted at two different time points after 75 μg of intravenous LSD. Changes in natural language production (compared to the placebo condition) were investigated along semantic and non-semantic dimensions. For the first, we introduced a new metric of semantic coherence based on the fluctuations of semantic distance between consecutive words, obtained using a word embedding. The non-semantic analysis was conducted investigating the topological properties of speech graphs.
Results: Semantic and non-semantic analysis of speech organization revealed reduced coherence, increased verbosity and a reduced lexicon, changes that are more similar to those observed during manic psychoses than in schizophrenia, which was confirmed by direct comparison with reference samples. Features related to language organization allowed machine learning classifiers to identify speech under LSD with accuracy comparable to that obtained by examining semantic content.
Conclusions: Our results constitute a quantitative and objective characterization of disorganized natural speech as a landmark feature of the psychedelic state.

30. VIRTUAL-REALITY ASSISTED THERAPIES: A NOVEL PSYCHOTHERAPY WITH POTENTIAL FOR THE TREATMENT OF SCHIZOPHRENIA AND OTHER PSYCHOSES

Merete Nordentoft

Mental Health Centre Copenhagen

Overall Symposia Abstract: Schizophrenia is a heterogeneous disorder that calls for various pharmaceutical, psychosocial and psychological interventions. Our current treatment strategies for psychotic disorders do not work for everyone and many patients with schizophrenia continue to hear voices, suffer from delusions and experience difficulties in their every-day life even years after onset of psychosis. Alleviation from these symptoms are still a great unmet need for many of our patients.
Virtual reality-assisted therapy (VRT) – typically within a cognitive-behavioral framework - shows promise in patients who are treatment resistant as well as patient with first-episode psychosis. The VR technology provides clinicians with the means to bring the patient's reality

to the therapy room, thus allowing for both the possibility of a more directly shared experience as well as an accessible and acceptable form of exposure. In traditional cognitive behavioral therapy (CBT), exposure, training and experiments often play an important role. Real world experiments with a therapist are not always feasible and often require extra resources, and patients with psychoses may be reluctant to try it out alone out of fear. Using VRT, the therapist can modify the environment to provide an optimal exposure setting for the individual patient with respect to both their level of anxiety and proclivity to engage.

The current symposium will offer a state-of-the art presentation of current knowledge and studies aimed at different key aspects of psychotic disorders.

Clinical professor, psychiatrist Alexandre Dumais will open the symposium with findings from two studies targeting auditory hallucinations in patients with treatment-resistant schizophrenia. VRT showed a larger effect than gold-standard CBT and the effects remained 12 months after. VRT also significantly improved quality of life and affective symptoms. Afterwards, clinical psychologist Lisa C. Smith will give a more qualitative presentation of how VRT is carried out in the Challenge-trial – a large randomized control-study currently taking place in Denmark aimed at treatment of auditory hallucinations. Video will be used to give the audience a clearer sense of the therapy and how the sessions progress. Dr., clinical neuropsychologist Chris Geraets will follow with data on another VRT randomized control study aimed at delusions and paranoid ideation, comparing VRT with treatment as usual. A structured diary technique was used to assess affective states throughout the day. VRT was found to reduce paranoid symptoms and lower negative affect. Dr., clinical psychologist Matteo Cella will then present the first study focusing on the treatment of negative symptoms with VR. Negative symptoms are particularly difficult to treat, affects quality of life and is a factor in long-term disability and functional outcomes. VRT was found to be acceptable and well tolerated. Therapy effect will be reported descriptively.

Finally, Professor Tom Craig, principal investigator of the AVATAR-project, will serve as the discussant, putting the four presentations in perspective with regards to future research and clinical implementation of VRT.

30.1 THE EFFICACY OF VIRTUAL REALITY-ASSISTED THERAPY AND ITS POTENTIAL THERAPEUTIC PROCESSES FOR PATIENTS WITH TREATMENT-RESISTANT SCHIZOPHRENIA

Alexandre Dumais*[1], Laura Dellazizzo[2], Kingsada Phraxayavong[3], Stéphane Potvin[4]

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Background: Schizophrenia, especially treatment-resistant schizophrenia (TRS), is a disabling psychiatric disorder that poses significant therapeutic challenges. Auditory verbal hallucinations (AVH) are among the most debilitating symptoms. Although medication may be helpful to treat these symptoms, up to 50% of patients are resistant to antipsychotics. To potentiate effects, Cognitive Behavioral Therapy (CBT) for psychosis is the psychotherapy most largely recommended. Yet, only moderate effects may be achieved and around 50% are non-responsive. Given the limited benefits of existing gold-standard psychosocial treatments, therapy improvement is a must. Virtual reality (VR) therapies for AVH, such as AVATAR

Therapy and VR-assisted Therapy (VRT), are amid a new wave of relational approaches that may heighten effects. These comprise experiential and exposure-based interventions that permit the establishment of an intimate dialogue with patients' voice by means of an avatar controlled in real time by a therapist. The main objectives of this presentation are to showcase the efficacy of VRT as well as to discuss the potential therapeutic processes of the intervention.
Methods: To achieve this end, various methods have been used: (i) two pilot clinical trials were performed to evaluate the short-term and long-term efficacy of VRT versus treatment-as-usual and CBT in patients with TRS, and (ii) two qualitative content analyses of patients' and their corresponding avatars' discourse were analyzed.
Results: Our small partial crossover trial comparing VRT to TAU in 15 TRS patients as well as our one-year randomized trial comparing 9 sessions of VRT to the gold-standard CBT in 74 TRS patients showed that VRT produced larger effects on the severity of AVH at short-term follow-up, particularly for AVH-related distress. Effects were maintained at 12-month follow-up. VRT produced significant moderate improvements in depressive symptoms at post-treatment and at follow-up. Concerning symptoms of schizophrenia, effects of moderate magnitude were observed for VRT, with effects being larger for affective symptoms. A significant between-group effect for anxio-depressive symptoms were noted favoring VRT over CBT. Lastly, the trials showed that VRT produced significant improvements in quality of life. Concerning qualitative analyses to investigate therapeutic processes, results showed that patients respond to the avatar's words by using coping mechanisms or by expressing emotions, beliefs, self-perceptions or aspirations. The avatar's discourse was categorized into confrontational techniques (e.g., provocation) and positive techniques (e.g., reinforcement). A positive shift in the dialogue was additionally observed.
Conclusions: VRT highlights the future of patient-tailored approaches that may have advantages over conventional treatments. These types of holistic interventions using VR may have notable applications in several other psychiatric disorders. In light of these positive effects, our laboratory has been conducting distinct projects assessing the efficacy of VR interventions, their therapeutic processes and biomarkers associated to treatment response. Among the ongoing projects are: (i) a fully powered single-blind randomized controlled trial comparing VRT to CBT in TRS patients, (ii) a neuroimaging study evaluating changes in brain function associated to VRT, and (iii) a pilot trial assessing the efficacy of an adapted version of VRT for cannabis use disorder in patients with psychotic disorders.

30.2 WITH THE AID OF VIDEOTAPED SESSIONS, IT IS DELINEATED HOW VIRTUAL REALITY-ASSISTED PSYCHOTHERAPY TARGETING PERSISTENT AUDITORY HALLUCINATIONS IS CONDUCTED IN THE CHALLENGE-TRIAL.

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Background: Many patients suffering from schizophrenia spectrum disorders continue having distressing auditory hallucinations despite treatment with antipsychotic medication. The aim of the CHALLENGE-trial is to examine the effect of a targeted virtual reality-assisted psychotherapy for persistent auditory hallucinations in individuals with psychosis. It is

investigated whether 9 sessions of this type of therapy can decrease the severity, frequency and distress of auditory hallucinations and additionally, whether it can reduce clinical symptoms and enhance daily functioning in individuals with psychosis. The main objective of this presentation is to give a qualitative account of this new psychotherapeutic method as it is applied in the CHALLENGE-trial.

Methods: The CHALLENGE-trial is a randomised, assessor-blinded parallel-groups superiority clinical trial, allocating a total of 266 patients to either the experimental intervention or standard intervention. The trial is currently in its recruitment phase, thus quantitative data is not available yet.

The virtual reality-assisted psychotherapy applied in this trial rests upon cognitive behavioural and compassion focused theory. Participants create a virtual avatar that corresponds to their visual perception (or imagination) of the source of their voice, and by use of a software program the voice of the therapist is transformed to match the pitch and tone of the voice heard by the participant. Part of the therapy is conducted in virtual reality where the therapist initiates, encourages, and supports a dialogue between the patient and the avatar by alternating between talking as the avatar and as a supportive therapist. Emphasis throughout therapy is on enhancing the participants sense of power over the voice, their self-esteem and in the final phase: recovery.

Results: Qualitative data from the pilot study conducted prior to the CHALLENGE-trial in the form of a case will be presented. A patient gave consent that the psychotherapeutic intervention was videotaped and that her case (with video) is presented on SIRS 2021.

Conclusions: It is the impression from the presented case and from other participants in the trial, that this new psychotherapeutic method for some patients is a definite "game changer", i.e. some patients experience great relief from their voices and a markedly increase in quality of life after only 9 sessions. If the promising findings of the AVATAR-trial (Craig et al., 2018) can be replicated in several other studies (e.g. the CHALLENGE-trial) it is indeed an exciting new lead in the strive to find more effective psychotherapeutic methods for patients suffering from psychosis.

30.3 VIRTUAL REALITY BASED COGNITIVE BEHAVIORAL THERAPY FOR PARANOIA: EXPLORING MECHANISMS WITH ECOLOGICAL MOMENTARY ASSESSMENT

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Background: Many patients with psychotic disorders experience paranoid ideations. We examined the effects of Virtual Reality based cognitive behavioral therapy (VR-CBT) on paranoia and affective states (e.g., feeling down and anxious) in the flow of everyday life. Negative affective processes may contribute to the maintenance of paranoia and vice versa. Successful treatment could break these pathological symptom networks. Therefore, we investigated how VR-CBT influences momentary affective states, and whether VR-CBT changes the interplay between affective states and paranoia.

Methods: In total 91 patients with a psychotic disorder and paranoid ideation were randomized to 16-sessions of individual VR-CBT or treatment as usual (TAU). With ecological momentary assessment - a structured diary technique - affective states were assessed multiple times a day, for 6 to 10 days at baseline, posttreatment, and 6-month follow-up. Multilevel analyses were performed to establish treatment effects and time-lagged associations between affective states, that were visualized with networks.

Results: VR-CBT, but not treatment as usual, resulted in reduced levels of paranoia and negative affect (feeling anxious, down, and insecure). Baseline networks of affective states had few significant connections, with the most stable connections being autocorrelations of affective states. The interplay between affective states and paranoia did not change in response to treatment. A trend reduction in autocorrelations was found after VR-CBT, indicating that affective states may reinforce themselves less after treatment.
Conclusions: VR-CBT reduced paranoid symptoms and lowered levels of negative affect in daily life, but did not affect the extent to which affective states influenced each other. Thus, no evidence was found that negative affective states such as feeling down or lonely triggered paranoia in the next moment even at baseline. Further, these temporal relations between affective states did not change over time in response to treatment. Findings do suggest that as a result of treatment affective states regain flexibility.

30.4 VIRTUAL REALITY SUPPORTED THERAPY FOR NEGATIVE SYMPTOMS: A PILOT RANDOMISED CONTROLLED TRIAL

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Background: Negative symptoms are common in people with schizophrenia and linked to loss or reduction of normal functioning as a result of reduced motivation and pleasure experience. Despite their importance the development of interventions for negative symptoms has received very limited attention. This study aims to develop and evaluate a novel Virtual Reality (VR) assisted Therapy for the Negative Symptoms of schizophrenia (V-NeST) and assess its feasibility and acceptability.
Methods: A single blind randomised controlled study with two conditions: V-NeST plus treatment-as-usual (TAU) vs. TAU alone. Participants are people with psychosis under the care of community mental health services in the UK. Assessments is at baseline and 3-month post-randomisation. The primary outcome is client therapy goal achievement, secondary outcome are negative symptoms and a therapy hypothesised mechanism: reward learning. Acceptability is evaluated using interviews and content analysed qualitatively. Feasibility parameters are also assessed. The therapy effect is reported descriptively.
Results: Thirty participants were recruited in the study (15 randomised to V-NeST). Four participants dropped-out of the study (i.e. two in the active arm and two in TAU). Those attending therapy were able to attend 75% of the sessions offered. The main outcomes completion was over 80% and the study procedures feasibility was good. Participants' feedback suggested the therapy was acceptable and considered valuable. There was indication of positive changes in the study outcomes associated with V-NeST.
Conclusions: Psychological therapies for negative symptoms can benefit from using engaging and immersive digital technologies such as VR. The acceptability and ease of use of this technology is appropriate for people with schizophrenia experiencing negative symptoms and the study procedures and therapy were well tolerated. Further studies should continue to develop this approach and formally evaluate its efficacy.

31. THE INTERPLAY BETWEEN NEURONS AND GLIA AT THE SYNAPSE IN SCHIZOPHRENIA

Carl Sellgren

Karolinska Institute

Overall Symposia Abstract: Recent progress in basic science implies an important role of glia in neurodevelopment. Microglia and astrocytes display a plethora of developmentally regulated functions at the synapse that ultimately influence synaptic remodeling, a process by which maturing brain circuits optimize their connectivity during the transition from early adolescence to adulthood. Already in the early 1980s, it was proposed that schizophrenia (SZ) might be associated with anomalies in synaptic remodeling, ultimately leading to fewer synapses being spared. Four decades of postmortem brain tissue studies have then strengthened this hypothesis, but mechanistic evidence that directly link aberrant synaptic pruning to SZ is still lacking. With the knowledge about the role of glia cells in these processes, and recent technical advances, the last few years has seen a growing number of reports that imply disruptions in the interplay between microglia and synapses in SZ. Indeed, different methodological approaches, including GWAS of genetic risk variants, patient-derived cellular modeling and in-vivo research using animal models, have all identified a striking relationship between abnormalities in complement-dependent microglial synapse pruning and changes in brain and behavioral development pertaining to SZ. In parallel, the development of positron emission tomography radioligands targeting glial cells and synapses has yielded important in-vivo evidence for changes in glial cell density and reduced synapse density in SZ. However, with the complexity of these time- and space dependent interactions, and in light of the large polygenic contribution to schizophrenia risk, it has become evident that a multi-modal scientific framework is needed to adequately address the role of glial synapse remodeling in SZ. Importantly, this will not only require state-of-the-art techniques but also careful sampling of high-risk subjects and patients in early phases of the disorder. In the current symposium, leading researchers that investigate these mechanisms will provide up-to-date knowledge about the recent advances in each presented field. Simon Cervenka (Uppsala University, Sweden) will describe recent advances in the application of molecular imaging to study glial cell function in SZ and how the results relate to synaptic markers, as well as to provide an update on in-vivo studies of synaptic density in early stage psychosis. Urs Meyer (University of Zurich, Switzerland) will discuss behavioral, electrophysiological and immunohistochemical data from a novel mouse model of local and transient microglia depletion, suggesting that adolescence is a sensitive period for prefrontal microglia to act on cognitive development via synaptic remodeling. Corentin Le Magueresse (INSERM, Paris, France) will present results obtained from a mouse model of complement C4 overexpression showing that elevated C4 expression not only affects synapse turnover in the developing cortex, but also causes e.g., NMDAR hypofunction and alterations in GABAergic neurotransmission. Carl Sellgren (Karolinska Institutet, Sweden) will present data from microglia containing schizophrenia-derived 2D and 3D models (functional assays and single cell RNA sequencing), as well as to present data displaying increased C4A protein levels in cerebrospinal fluid obtained from first-episode psychosis patients. The discussion will be led by Romina Mizrahi (McGill University, Canada) and focus on how to cross-reference scientific data from independent methodological modules to better understand synapse remodeling in SZ, and in the next step to translate these insights into clinical practice.

31.1 ADOLESCENCE IS A SENSITIVE PERIOD FOR PREFRONTAL MICROGLIA TO ACT ON COGNITIVE DEVELOPMENT VIA SYNAPTIC REMODELING

Sina M. Schalbetter[1], Anina S. von Arx[1], Natalia Cruz-Ochoa[1], Kara Dawson[1], Andranik Ivanov[2], Flavia S. Mueller[1], Han-Yu Lin[1], René Amport[1], Daniele Mattei[3], Dieter Beule[4], Csaba Földy[1], Melanie Greter[1], Tina Notter[1], Urs Meyer*[1]

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Background: The prefrontal cortex (PFC) is one of the cortical brain regions known to be impaired in schizophrenia and related disorders. One distinctive feature of the PFC is its protracted adolescent maturation, which is necessary for acquiring mature cognitive abilities in adulthood. Here, we examined whether microglia, the resident immune cells of the brain parenchyma, contribute to the structural and functional maturation of the PFC. This was achieved by means of a transient loss-of-function approach in mice, in which microglia were depleted selectively from the PFC during a defined window of adolescence.
Methods: Brain region-specific and transient depletion of prefrontal microglia during adolescence was induced by a single, bilateral stereotaxic injection of clodronate disodium salt (CDS) into the medial portion of the PFC in 6-week old C57BL/6 mice. Control mice received a bilateral stereotaxic injection of phosphate-buffered saline (PBS). An additional group of mice receiving sham surgery, which involved the same surgical procedures but no stereotaxic injections, was included as a negative control group as well. The magnitude and specificity of microglia depletion was ascertained by post-mortem immunohistochemistry and transcriptomic profiling during the acute phase of microglia depletion. A combination of behavioral testing, electrophysiological recordings and confocal laser scanning microscopy was used to assess the long-term effects of transient prefrontal microglia depletion on synaptic structures and cognitive functions after full microglia recovery in adulthood.
Results: We show that a single intra-PFC injection of CDS is a suitable and efficient method to selectively deplete microglia without affecting astrocytes and neurons in-vivo, leading to a robust (~ 80% depletion) but temporary (~ 1 week) microglia deficiency in the adolescent PFC. Using this model, we demonstrate that prefrontal microglia deficiency during adolescence is sufficient to induce an adult emergence of PFC-associated impairments in cognitive functions, including deficits in social memory, temporal order memory and extinction of learned fear. We further find that CDS-induced microglia deficiency in the adolescent PFC leads to reduced densities in excitatory (Vglut1+/PSD-95+) and inhibitory (Vgat+/gephyrin+) synapses in the adult PFC, decreased dendritic complexity of adult prefrontal neurons and electrophysiological changes that are indicative of an excitatory-inhibitory imbalance in adult prefrontal circuits. Intriguingly, intra-PFC injection of CDS into the PFC during adulthood (12 weeks of age) did not induce such cognitive or synaptic dysfunctions.
Conclusions: Our data implicate microglia as a regulator of prefrontal maturation and suggest that adolescence is a sensitive period for prefrontal microglia to act on cognitive development via synaptic remodeling. Our model system offers a unique experimental tool to study the role of microglia-neuron interactions during specific stages of brain maturation, thereby taking into account cell type- and brain-region specificity. Therefore, this model system is expected to advance basic neurobiological knowledge pertaining to abnormal microglia-neuron interactions in schizophrenia and beyond.

31.2 THE COMPLEMENT SYSTEM AND SCHIZOPHRENIA: INSIGHTS FROM A NEW MOUSE MODEL

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Background: Accumulating evidence supports immune involvement in the pathogenesis of schizophrenia. In particular, high expression variants of C4A, a gene of the innate immune complement system, were shown to confer susceptibility to schizophrenia. Recent results have indicated that C4A contributes to synapse loss through the increased phagocytosis of synaptic material by microglial cells. However, how elevated C4A expression may impact brain circuits beyond synapse loss remains largely unknown. Here, we overexpressed C4, the mouse homolog of human C4A, in the mouse prefrontal cortex (PFC). We examined the consequences of elevated C4 on the turnover of dendritic spines and on the functional properties of excitatory synapses, in particular NMDA receptor function, and on inhibitory GABAergic neurotransmission. We also assessed the long-term consequences of C4-overexpression on working memory, a mechanism for the short-term maintenance and processing of information which is critically dependent on the PFC and is impaired in schizophrenia.
Methods: C4 overexpression selectively in layer 3 pyramidal cells of the PFC was achieved using in utero electroporation at embryonic stage E14.5 in timed pregnant C57Bl/6 mouse females. The C4 overexpression construct was co-electroporated with a tdTomato-expressing construct, in order to enable the identification of C4-expressing, tdTomato-positive neurons in vivo and ex vivo. We used a multidisciplinary approach combining ex vivo electrophysiology, optogenetics, in vivo two-photon microscopy, immunohistochemistry and behavioral studies to investigate the consequences of C4 overexpression on brain circuits and behavioral phenotypes that have been associated with schizophrenia.
Results: We found reduced glutamatergic input to pyramidal cells of juvenile and adult, but not of newborn C4-overexpressing (C4-OE) mice, together with decreased spine density, which mirrors spine loss observed in the schizophrenic cortex. Using time-lapse two-photon imaging in vivo, we observed that these deficits were associated with decreased dendritic spine gain and elimination in juvenile C4-OE mice, which may reflect poor formation and/or stabilization of immature spines. In juvenile and adult C4-OE mice we found evidence for NMDA receptor hypofunction, another schizophrenia-associated phenotype, and synaptic accumulation of calcium-permeable AMPA receptors. Alterations in cortical GABAergic networks have been repeatedly associated with schizophrenia. We found that functional GABAergic transmission was reduced in C4-OE mice, in line with diminished GABA release probability from parvalbumin interneurons, lower GAD67 expression and decreased intrinsic excitability in parvalbumin interneurons. These cellular abnormalities were associated with working memory impairment.
Conclusions: Our results substantiate the causal relationship between an immunogenetic risk factor and several distinct cortical endophenotypes of schizophrenia, and shed light on the underlying cellular mechanisms.

31.3 MODELING BRAIN DEVELOPMENT IN SCHIZOPHRENIA

Jessica Gracias[1], Susmita Malwade[1], Ana Oliveira[1], Funda Orhan[1], Neda Khanlarkani[1], Sophie Erhardt[1], Kaj blennow[2], Henrik Zetterberg[2], Simon Cervenka[3], Mikael Landen[2], Elin Hörbeck[2], Steven Sheridan[4], Roy Perlis[4], Carl Sellgren*[1]

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Background: Multiple risk factors for schizophrenia could alter neurodevelopmental trajectories and predispose an individual for developing the disorder. Patient-derived cellular

modeling based on induced pluripotent stem cells (iPSCs) has the capacity to recapitulate key events in brain development and provide mechanistic data on individual level. The use of patient-derived cells permits the study of non-deterministic genetic risk variants in the context of other risk variants. Experimental approaches can be based on cohorts of patients and controls as well as the use of isogenic lines. Recently, we developed models to recapitulate microglial and astrocytic synaptic pruning. In line with the regional decreases in synapse density in schizophrenia, we observed excessive synapse elimination in schizophrenia-based models. Genetic risk variants increasing complement component 4A (C4A) expression also caused increased neuronal complement deposition and increased microglial engulfment. In the current studies, we are now expanding on these initial findings and introduce more advanced 3D models as well as to provide mechanistic that more accurately capture the role of C4A in schizophrenia. Further, we present a method to measure C4A protein levels in cerebrospinal fluid and apply it to two independent cohorts of first-episode psychosis (FEP) patients.
Methods: 1. A directed forebrain protocol for organoids containing microglia and applied to monozygotic twins discordant for schizophrenia (single cell RNA sequencing and assessment of synaptic pruning).
2. 2D studies focusing on the interplay between C4A, cytokines, and the NMDAR antagonist kynurenic acid.

3. A novel mass spectrometry assay that can differ C4A and C4B unique peptides in cerebrospinal fluid.

Results: 1. Dorsal and ventral forebrain organoids with different percentages of microglia can be derived from patient-derived iPSCs and recapitulate in vivo gene expression as well as microglial and astrocytic synapse elimination. Patient versus control data will be available at the time of the meeting.
2. Kynurenic acid (increased in schizophrenia) decrease neuronal activity in patient-derived models and cause excessive synaptic pruning. Cytokines, that also induce the production of kynurenic acid, induce neuronal C4A expression.

3. FEP subjects that later on developed schizophrenia display higher C4A protein levels than controls, as well as FEP subjects receiving a non-schizophrenia diagnosis.

Conclusions: Our preliminary data further strengthen the hypothesis that targetable complement-dependent microglial functions at the synapse play a role in the observed decrease in synaptic density in schizophrenia. Studied risk factors, independent of the C4 locus, also seem to converge on this mechanism and contribute to excessive synapse elimination mediated by microglial engulfment of synapses.

31.4 MOLECULAR IMAGING OF GLIAL CELLS AND SYNAPTIC MARKERS IN SCHIZOPHRENIA

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Background: Several lines of research support a role for immune mechanisms in the pathophysiology of schizophrenia. During the last decade, a series of molecular imaging studies using radioligands for the glial marker translocator protein (TSPO) has yielded inconclusive results. Using the second generation TSPO radioligand [11C]PBR28 we showed lower TSPO levels in a cohort of antipsychotic naïve first episode psychosis (FEP) patients. Although the data suggests aberrations in glial cell activation in schizophrenia, the small sample size and limitations in the outcome measures used limit the interpretation. Moreover, recent data has highlighted a role for glial cells in synaptic remodelling, however, the relationship between TSPO and synaptic turnover as well as components of the complement system in cerebrospinal fluid has not been investigated.
Methods: Data from 7 different TSPO studies in first episode psychosis and schizophrenia were gathered and analyzed using a linear mixed-effects model. We then used a recently developed method for simultaneous estimation of non-displaceable binding (VND) (SIME) to disentangle contributions from VND and specific binding (VS) in our cohort of FEP patients. In follow-up studies, we assess the relationship between brain TSPO levels and the synaptic markers neurogranin, synaptosomal-associated protein 25 (SNAP25), synaptotagmin-1 as well as C4A measured in the cerebrospinal fluid. Finally, a new cohort of FEP patients are being examined with PET and the radioligand [11C]UCB-J, targeting synaptic vesicle glycoprotein 2A (SV2A).
Results: In the multi-centre individual-participant data meta-analysis of in total 99 patients and 109 healthy control subjects we corroborate the finding of lower levels of TSPO in psychosis and schizophrenia. Using SIME in FEP patients and controls, the signal was shown to correspond to lower levels of specific binding in patients. In a larger cohort, neurogranin, SNAP25 and synaptotagmin-1 did not differ between FEP patients and controls, whereas C4A levels were higher. Correlational analyses between these markers and brain TPSO levels will be presented, as well as preliminary data on SV2A binding in FEP patients.
Conclusions: Our results confirm aberrant glial cell function in schizophrenia. Combining these data with markers for synaptic turnover and complement function may shed further light on glial-neuronal interaction in patients. Furthermore, there is a need to investigate synaptic density in vivo in different disease stages of schizophrenia.

32. THE MULTIDIMENSIONAL PHENOMENON OF 'FELT PRESENCE'

Ben Alderson-Day

Durham University

Overall Symposia Abstract: Overall Abstract:
The experience of 'felt presence' (FP) in the absence of clear perceptual evidence has been described as a complex multimodal sensory experience that is both transdiagnostic and exists along a non-clinical and clinical continuum. FP occurs during periods of isolation, exposure to extreme elements, sleep paralysis, bereavement, religious experiences, anxiety, and psychosis. This symposium will unpack the multidimensional construct of FP within phenomenological, neurocognitive, social, and philosophical frameworks.

Dr. Alderson-Day will present on two studies from Durham University's Hearing the Voice project. First, a phenomenological survey of people experiencing early psychosis which showed a case rate of 52% for FP. Second, a comparison of FP across three online surveys,

featuring the general population; people from spiritual groups; and people who engage in solo/endurance sports. These show that while FP overlaps with other hallucinations, it can occur as standalone hallucinatory experience. Many accounts of FP involve a distinct identity, sense of familiarity, and occurring on multiple occasions. Survey data shows that FP frequency is consistently associated with general hallucination-proneness but not dissociation or social imagery. These findings highlight a common thread to FP experiences across diverse samples and contexts, with implications for clinical practice.

Dr. Rosen examined the interrelatedness of FP, self-disturbances (SD), and increased paranormal or magical ideation, mysticism, absorption, and enhanced imagery known as transliminality (TL). She also examined changes in sensory (visual, tactile, auditory, and olfactory) and perceptual experiences (sense of time, space, self-consciousness) during FP. Given that psychosis is associated with anomalous self-other processing and heightened absorption – implicating immersion in mental imagery– it is important to elucidate individual differences between FP, SD, and TL. Association and Network Analysis results show that as TL increased, all aspect of FP (frequency, distress, vividness) and SD increased. There were similar parallels between FP, increased TL, SD, and changes in the metaphysical construct of being, knowing, time, and space.

Dr. Park examined two distinct types of bodily self-disturbance– felt presence (FP) and out-of-body experiences (OBE)– in relation to psychosis-risk, social isolation and resilience in the general population. FP and OBE involve spatial body imagery associated with the temporoparietal cortex, but differ with respect to the perceived self-location and the social context of the experience.

Anxiety and stress were elevated in the FP and OBE groups but not depression. While the OBE group reported elevated trauma and lower resilience, the FP group reported increased spirituality. Co-occurrence of FP and OBE significantly increased psychosis-risk, but FP and OBE differentially shaped the key aspects of self-disturbances that may contribute to schizophrenia.

Dr. Barnby will present on how generalised prior knowledge about social partners serves as a starting point for beliefs about others, and the unresolved question of whether we use similar mechanisms when interpreting FP as one generically learns about others. He examined formal mechanisms used to learn about social partners in the absence of immediate evidence, and how a frequent corollary of unusual experiences in clinical populations – paranoia – may bias this process. He will also present parallel work suggesting a common computational mechanism that ties together how we learn about others and learn about FP experiences.

32.1 THE METAPHYSICS OF FELT PRESENCE, SELF, AND TRANSLIMINALITY: GOING BEYOND THE THRESHOLD

Cherise Rosen*[1], Sohee Park[2], Tatiana Baxter[2], Michele Tufano[1]

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Background: "It knows that I'm aware of it." The complex, multimodal, sensory experience of 'felt presence (FP)' in absence of clear sensory or perceptual evidence is a transdiagnostic and subjectively meaningful experience that emerges during periods of isolation, exposure to extreme elements, sleep paralysis or bereavement but FP is most closely associated with the

schizophrenia-spectrum. Within a phenomenological framework, FP is a form of mental imagery or hallucination involving the bodily self. Along with increased paranormal or magical ideation, mysticism, absorption and enhanced imagery, individuals with psychosis are also prone to facilitated transference between unconscious and conscious processing, known as transliminality. Given that individuals with psychosis experience anomalous self-other processing and heightened absorption that implicates immersion in mental imagery, it would be important to elucidate the relationship between FP, self-disturbances and differences in transliminality. Thus, the primary aims of this study were to examine the metaphysical construct of being, knowing, identity, time, and space within the framework of FP, self, and transliminality.

Methods: Participants were recruited through an anonymous mixed-methods internet survey. Validated self-report measures of FP (Barnby and Bell, 2017), self-disturbance (Ising et al., 2012) and transliminality (Thalbourne and Houran, 2000) were administered. We also included questions pertaining to changes in sensory (e.g. visual, tactile, auditory, and olfactory) and perception (changes in sense of time, space, increased self-consciousness) experienced during FP.

Results: Pearsons bivariate correlations with bootstrapping at 1000 iterations were conducted to determine association between FP, sense of self, and transliminality. A Network Analysis was included to explore the centrality of these constructs to identify core features of interrelatedness and to reveal the most central underlying structures. There was a significant positive association between the dimensions of FP (frequency, distress, vividness, sum), and self-disturbance ($p \leq 0.001$) and transliminality ($p \leq 0.001$). We also examined the association between FP and sensory experiences. There was a positive association between the sensory experience of touch and FP frequency ($p=0.009$), vividness ($p=0.001$), sum ($p=0.002$) but not FP distress ($p=0.89$). We also found a significant association in alterations in auditory experiences and FP frequency ($p=0.004$), vividness ($p \leq 0.001$), and sum ($p \leq 0.001$), but not distress ($p=0.56$). There was no association between olfactory experiences and any dimension of FP. The Network analysis found that FP distress and FP sum had the greatest strength and the most influence. The closeness in the network highlighted two groups: changes in auditory and visual experiences, and increased self-consciousness and the sensory experience of touch. Lastly, the network analysis showed two distinct pathways: a positive association between FP distress, self-disturbance, and transliminality and a positive association between FP vividness, sensory experiences (tactile, auditory, visual) and perceptual changes (sense of time, location of FP, and increased self-consciousness).

Conclusions: Despite the prevalence of FP in psychosis and in the general population, the underlying mechanisms that give rise to FP are poorly understood. We explored the role of transliminality in FP in relation to self-disturbance and found that as transliminality increased so did all aspect of FP and self-disturbance. There were similar parallels between FP, increased transliminality, self-disturbance, and changes in the metaphysical construct of being, knowing, identity, time, and space.

32.2 THE VARIETIES OF FELT PRESENCE: SAME OR DIFFERENT?

Ben Alderson-Day*[1]

[1]*Durham University*

Background: Felt presence (FP) represents one of the most unusual hallucinatory phenomena known to psychiatry. Being largely devoid of sensory content, cases of FP test the definition of hallucination as an experience based in perception. At the same time, FP are often ill-fitted to typical understandings of delusion, being experienced in a visceral and yet nevertheless

ineffable manner. Notably FP occur across a range of diverse clinical and non-clinical contexts, including in schizophrenia, Parkinson's disease, survival situations, bereavement, and spiritual practice. This raises the question of whether a comparative approach can shed light on the nature and basis of FP, and whether such cases reflect a singular kind of experience, or a family of similar but dissociable phenomena.

Methods: This symposium talk will focus on two studies from Durham University's Hearing the Voice project, a 10-year interdisciplinary project on hallucinations. The first study involved a phenomenological survey of 40 patients with first episode psychosis (Alderson-Day, Woods et al,, 2021, Schiz. Bull). Within psychosis, a working hypothesis is that FP could arise from delusional elaboration and expectations about simpler hallucinatory phenomena (such as hearing voices and seeing visions). Here, I will present an in-depth analysis of the presences reported in first episode psychosis and their relation to voice identity, paranoia, command hallucinations, and feelings of embodiment. The second study (Alderson-Day et al., forthcoming) compared accounts of FP in three online surveys: a self-selecting sample of the general population (n = 75), a sample of people from spiritual communities with frequent FP (n = 47), and a sample of individuals who engage in endurance sports and solo activities associated with FP (n = 84). In a multidisciplinary team we coded FP experiences for their phenomenological features and explored how individual differences in general hallucination-proneness, paranoia, dissociation, and social imagery related to FP frequency.

Results: In study 1, we identified a case rate of 52% for felt presence experiences. In my presentation I will provide an overview of the main overlaps and dissociations between FP, expectations, and voices, highlighting how minimal FP can occur as standalone hallucinatory experiences. Our results from study 2 demonstrated considerable overlap across the three samples, with the many accounts involving a distinct identity, with a sense of familiarity, and occurring on multiple occasions. Feelings of paranoia and effects of gender (in favour of females) distinguished more negative and distressing FP, while spiritual FP were distinguished by being in immersive states. FP in self-described voice-hearers was more likely to involve tactile components, suggesting an embodied basis for FP linked to auditory hallucinations, but diagnostic status was not associated with any qualitative differences in FP phenomenology. FP frequency, in all groups, was predicted by general hallucination-proneness but not dissociation or social imagery measures.

Conclusions: Together, these findings highlight a common thread to FP experiences across diverse samples and contexts. While associated with other hallucinations (such as voices), FP can occur as a minimal form of hallucination characterised by identity and familiarity. This implicates social cognitive processes in the psychological and neurological basis of this mysterious phenomenon. See recent publication for additional information https://psyarxiv.com/n4kth.

32.3 FELT PRESENCE AND OUT-OF-BODY EXPERIENCE IN RELATION TO PSYCHOSIS-RISK: IS THERE ANYBODY OUT THERE, OR AM I OUT THERE?

Sohee Park*[1], Tatiana Baxter[1]

[1]*Vanderbilt University*

Background: Felt presence (FP), the feeling that somebody is nearby when no one is present, is the most common form of hallucination among the general population (Laroi et al, 2019) and is reported by 46% of people with schizophrenia (Llorca et al, 2016) but has been neglected in psychiatry. FP involves anomalous mental imagery about the bodily self, is associated with the temporoparietal cortex, but is distinct from other bodily hallucinations such as the out-of-body experience (OBE) in which the self is disembodied. Whilst FP and OBE differ with

respect to perceived self-location, embodiment, social context, and phenomenology, they are both disorders of the spatial self, closely related to anomalous self-other distinction that lies at the core of schizophrenia. However, FP and OBE have not been examined together in the psychosis-spectrum conditions. We investigated these two distinct types of bodily self-disturbance in relation to psychosis-risk, other forms of psychopathology, and the role of social-environmental context. Furthermore, we catalogued the phenomenology of FP to understand potential promotive and risk factors in the general population.

Methods: We conducted an online survey that included the Prodromal Questionnaire-16 (Ising et al, 2012), Depression, Anxiety and Stress Scale-21 (Henry and Crawford, 2005), UCLA Loneliness Scale (Russell, 1996), Brief Trauma Questionnaire (Schnurr et al, 1999), Sensed Presence Questionnaire (Barnby and Bell, 2017), Brief Resilience Coping Scale (Sinclair and Wallston, 2004), Daily Spiritual Experiences Scale (Underwood, 2011). Qualitative information about the physical and social characteristics of the presence was also collected. The survey was distributed by social media and email.

Results: Of 211 participants, 122 reported FP, 87 reported OBE, and 61 reported both. 56% of those with FP also had OBE; 78% of those with OBE reported FP. We then compared individuals with FP only (FP+), OBE only (OBE+), FP+OBE, and those without (CO).

Those with FP and OBE were significantly more psychosis-prone than either FP+ or OBE+ who, in turn, showed greater psychosis-risk than CO. Frequency, distress and vividness of the FP, and frequency of OBE were significantly associated with increased psychosis-risk

Anxiety and stress were elevated in FP+, OBE+ and FP+OBE groups compared with CO but there was no difference in depression. Compared with CO, FP+ reported more past trauma and loneliness, but also showed increased resilience. Compared with CO, OBE+ had more past trauma but there were no differences in loneliness or resilience. FP+ were lonelier but more resilient than OBE+. OBE+ reported more past trauma than FP+. Both FP+ and OBE+ reported increased closeness to God than CO.

FP+OBE group reported more vivid social and physical experiences of the presence than the FP+ group. 75% of those with FP could locate the presence, which was equally distributed between left and right sides, and between front and back. It was rare for the FP to touch, talk or move but the range of bodily sensations and interpretations of the experience was vast.

Conclusions: Co-occurrence of FP and OBE significantly increases psychosis-risk, but FP and OBE may uniquely shape key aspects of self-disturbances. Disembodiment in OBE suggests a complete loss of the self-boundary whereas in FP, the hallucinated 'other' in extra-personal space may shape the self-other boundary. Importantly, despite increased anxiety and stress, those with FP were also more resilient than CO, which is suggestive of a potential adaptive role. Although notable gaps remain with respect to the time course of these phenomena and their contributions to clinical symptoms in schizophrenia. Nevertheless, these results suggest that FP and OBE each have distinct roles in shaping the self-disturbances that lie at the core of schizophrenia phenomenology.

32.4 SEEING OURSELVES IN THE SHADOWS: THE ROLE OF PERSONAL PREFERENCES IN FELT PRESENCE EXPERIENCES.

Joseph M Barnby*[1]

[1]*Queensland Brain Institute*

Background: Previous work offers formal theory and experimental evidence on how we might generalise prior knowledge of environments as a starting point to learn about new ones. New

work has now suggested that we learn about our social partners in the same way, drawing upon our own preferences as a starting point for our beliefs about others. Given the detailed work on the frequent residence of interactive social characters in the auditory verbal hallucinations and felt presences, it is an unresolved question as to whether we use similar mechanisms when interpreting these phenomena as we do to generically learn about others.
Methods: I present a computational method to model social-value orientations of participants and simultaneously their beliefs about interaction partners using formal Bayesian mathematics. All data, code (https://github.com/josephmbarnby/Barnby_etal_2021_SVO), and preprint (https://psyarxiv.com/an5kp) materials are available online.
Results: I will present novel data that speaks to the formal mechanisms we might use to learn about social partners when there is an absence of immediate evidence, and how a frequent corollary of unusual experiences in clinical populations – paranoia – may bias this process. I then present parallel work that may hint toward a common computational mechanism employed that tie together how we learn about others and learn about sensed presence experiences.
Conclusions: I finally lay the foundations for experimental and observational designs that may help answer test these hypotheses in the future and outline some methodological challenges the field might face in answering these questions.

33. MMP9, A NOVEL ACTOR IN NEUROINFLAMMATION: FROM MOLECULAR MECHANISM TO BIOMARKER IN SCHIZOPHRENIA

Marek Kubicki

Brigham and Women's Hospital Harvard Medical School

Overall Symposia Abstract: MMPs are a group of extracellular acting zinc-dependent proteases that are essential regulators of extracellular matrix, neuronal growth and plasticity. Specifically, they can remodel and control perineuronal nets (PNNs), the areas of condense extracellular matrix enveloping several specific subgroups of neurons, most notably parvalbumin interneurons (PVIs). MMP-9 is the largest, most complex, and best described MMP in the central nervous system. MMP-9 is expressed in the brain mostly in the hippocampus, choroid plexus (ChP), and the prefrontal cortex (PFC), and besides its role in neuronal growth and plasticity (through modulation of PNNs), it also plays a pivotal role in modulating central inflammatory response. Because of its role in PVI development, relationship with PNNs, and involvement in neuroinflammation, MMP-9 has recently attracted the attention of schizophrenia researchers.
This symposium cuts across the disciplines of systems neuroscience, cellular and molecular neurobiology, clinical psychiatry and neuroimaging, to explore the mechanisms, in which MMP-9 is involved in the emergence of psychotic symptoms in schizophrenia. The first of our four presenters, Dr. Leszek Kaczmarek, Head of the Laboratory of Neurobiology, Nencki Institute, Warsaw, will introduce the MMP-9 function, its brain expression and its role in synaptic plasticity. His talk will also cover the newest developments in MMP-9 gene polymorphisms in schizophrenia. This talk will be followed by Dr. Wilson Woo, a founding Director of Laboratory of Cellular Neuropathology at McLean Hospital, Harvard Medical School, who will present his recent findings regarding MMP-9 gene expression, cellular and enzymatic activity in postmortem schizophrenia brain tissue, blood and CSF. These two talks from senior researchers will set up the stage for the last two presentations, given by talented, junior faculty members. First of those talks will be given by Dr. Johanna Seitz-Holland, Psychiatry Resident at Ludwig-Maximilians-University Munich Clinic for Psychiatry and

Psychotherapy, and an Instructor at Psychiatry Neuroimaging Laboratory, Harvard Medical School, and will focus on the evidence of neuroimaging correlates of peripheral MMP-9 upregulation in schizophrenia. The last talk will be given by Dr. Daniella Dwir, Research Associate at the Center for Psychiatric Neuroscience, Department of Psychiatry Lausanne University Hospital. Daniella will present results of her translational research in animals and patients with schizophrenia investigating RAGE/MMP-9 neuroinflammation-redox mechanistic model, in the context of clinical and cognitive deficits. These presentations will be followed by an in-depth discussion (led by Dr. Daniel Umbricht, Associate Professor at University of Zurich and Distinguished Scientist at Roche) on the role of MMP-9 in psychosis psychopathology, its potential as diagnostic biomarker and treatment target.

Altogether, this symposium is expected to stimulate discussions on the possible mechanistic basis of schizophrenia onset and thereby rational, neurobiologically-inspired, evidence-based treatment, early intervention and prevention approaches.

33.1 EXTRASYNAPTIC PROTEOLYSIS IN SCHIZOPHRENIA

Leszek Kaczmarek*[1]

[1]*Nencki Institute*

Background: Matrix metalloproteinase 9, MMP-9 is an extracellularly operating enzyme that has been demonstrated as important regulatory molecule in control of synaptic plasticity, learning and memory.
Methods: We have shown that either genetic or pharmacological inhibition of MMP-9 impairs late phase of long-term potentiation at various pathways, as well as appetitive and spatial memory formation, although aversive learning remains apparently intact in MMP-9 KO mice. MMP-9 is locally translated and released from the excitatory synapses in response to neuronal activity. Extrasynaptic MMP-9 is required for growth and maturation of the dendritic spines to accumulate and immobilize AMPA receptors, making the excitatory synapses more efficacious.
Results: Our studies have implicated MMP-9 in such neuropsychiatric conditions as schizophrenia. In particular, we have demonstrated that functional MMP-9 gene polymorphisms, capable of modulating the protein expression levels, correlate with the schizophrenia disease symptoms and these data are supported by studies on genetically modified mice.
Conclusions: In aggregate, since schizophrenia might be considered as a synaptopathy, the understanding the role played by MMP-9 in the synaptic plasticity may allow to elucidate the underpinnings of this major neuropsychiatric disorder.

33.2 MMP-9 IN SCHIZOPHRENIA PATHOPHYSIOLOGY

T. Wilson Woo*[1]

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

Background: The “two-hit model” of schizophrenia posits that insults (e.g., infection) occurring in utero (i.e., first hit) elicit neuroinflammation that persists into postnatal life and thereby increases the susceptibility to a second-hit (e.g., stress), which then leads to schizophrenia onset. We hypothesize that production of the homeoprotein OTX2 in the choroid

plexus and its availability in the brain parenchyma are impaired in schizophrenia as a result of MMP-9-mediated neuroinflammation that begins in utero. The persistent elevation of MMP-9 and deficits of OTX2 into postnatal development can lead to the impairments of parvalbumin (PV)-containing inhibitory neurons and perineuronal nets (PNNs), which together contribute to cortical circuitry dysmaturation and thus the onset of schizophrenia.
Methods: We used in situ zymography and immunohistochemistry to investigate MMP-9 activity and expression, Western blot and enzyme-linked immunoassay to measure OTX2, and immunohistochemistry to study OTX2 expression in postmortem schizophrenia brains. We determined the neurobiological consequences of elevated MMP-9 in Mmp9-overexpressed mice and that of OTX2 deficits that emerge in utero using Otx2creERT2/flox mice.
Results: We found that MMP-9 enzymatic activity and protein expression are elevated whereas OTX2 levels in choroid plexus, cerebrospinal fluid and brain parenchyma are decreased in schizophrenia. Furthermore, increased MMP-9 not only caused OTX2 deficits but also schizophrenia pathologies, such as deficits of PV neurons and PNNs. Finally, in Otx2creERT2/flox mice where OTX2 deficits were induced in utero, the development and maturation of PV neurons and PNNs were impaired.
Conclusions: These findings provide experimental support for the hypothesis that increased MMP-9 can lead to OTX2 deficits, which can in turn contribute to schizophrenia pathologies. Furthermore, it appears that MMP-9 elevation itself can also directly result in these pathologies. Thus, MMP-9-mediated neuroinflammation may be an upstream event that triggers the schizophrenia pathophysiological cascade.

33.3 NEUROIMAGING CORRELATES OF PERIPHERAL MMP-9 UPREGULATION IN SCHIZOPHRENIA

Johanna Seitz-Holland*[1], Daniella Dwir[2], Kim Do[2], Kang Ik Kevin Cho[3], Carina Heller[3], Zora Kikinis[3], Ofer Pasternak[3], Tomas Kasparek[4], Jan Losak[4], Marek Kubicki[3]

[1]*Brigham and Women's Hospital, Harvard Medical School, Ludwig-Maximilians-Universität,* [2]*Center for Psychiatric Neuroscience, , University Hospital of Lausanne - CHUV Cery,* [3]*Brigham and Women's Hospital, Harvard Medical School, * [4]*Faculty of Medicine, Masaryk University and University Hospital Brno*

Background: Matrix Metalloproteinase 9 (MMP-9) is the most prevalent matrix metalloproteinase in the central nervous system (CNS), where it can be found in several brain regions, most notably in the hippocampus. It is critical for controlling dendritic and synaptic development and pruning of parvalbumin neurons, a physiological readout of neuroplasticity that reflects the functional ability for memory acquisition and storage. In addition, it is vital in initiating and modulating the neuroinflammatory response, and MMP-9 upregulation has been linked to blood-brain barrier (BBB) disruptions. Given that neuroplasticity abnormalities, neuroinflammation, and BBB disruptions are among key pathologies in schizophrenia (SCZ), MMP-9 has attracted the attention of SCZ researchers. Previous studies demonstrated an upregulation of MMP-9 in the blood of individuals with SCZ. However, only a few studies to date have investigated the relationship between peripheral MMP-9 upregulation and the CNS in SCZ. Here, we present our recent findings utilizing state-of-the-art imaging methods to explore the link between peripheral MMP-9 upregulation in SCZ and the hippocampus.
Methods: Given that the hippocampus plays a crucial role in neuroplasticity, and given the known expression of the MMP-9 in this structure, we investigated the relationship between MMP-9 plasma activity and several neuroimaging measures of hippocampal micro and macrostructural integrity. In this symposium, we will present the results of two independent studies. First, we will show the structural MRI, and automated analysis of hippocampal volume

and shape and its relation to MMP-9 plasma levels in an SCZ sample collected at Brno, Czech Republic (34 healthy individuals, 30 individuals with SCZ). We will then show the results of a free-water imaging study, a diffusion MRI-based method sensitive to extracellular space free water volumes (FW), which was previously associated with neuroinflammation. This method was applied to a first episode sample acquired at the University of Lausanne, Switzerland (45 healthy individuals, 46 individuals with SCZ).
Results: An increase of peripheral MMP-9 activity was found in SCZ (both data sets, $p<.00001$) and was associated with more severe negative symptoms in the Brno data set 1 ($R=0.39$, $p=.035$). In addition, individuals with SCZ demonstrated lower hippocampal volumes (total and subtotal) and increased FW. Importantly, for individuals with SCZ, higher peripheral MMP-9 values were related to hippocampal volume loss (left hippocampus: $R=-0.39$, $p=.034$; right hippocampus: $R=-0.37$, $p=.046$) and FW increase (left hippocampus: $R=0.50$, $p=.001$, right hippocampus: $R=0.72$, $p<.0001$).
Conclusions: Our finding of abnormal MMP-9 levels in SCZ aligns with previous studies that suggested that MMP-9 might be a key player in the pathophysiology of this disorder. Interestingly, we see that peripheral MMP-9 levels are related to negative symptoms, which supports previous claims that MMP-9 deficits might be particularly relevant for deficit SCZ. In addition, the highlighted findings provide evidence for the association between peripheral MMP-9 levels and the hippocampal micro-, and macrostructural pathology. In line with animal research, our imaging studies suggest that MMP-9 might be essential for the crosstalk between periphery and CNS, modulating neuroplasticity and neuroinflammatory response. Thus, while future studies are needed to understand the biological nature, the results provide an exciting avenue towards developing in-vivo markers, understanding the neuropathology of the disorder, and potentially novel treatment options.

33.4 ROLE OF MMP9/RAGE MECHANISM IN THE DEVELOPMENTAL PSYCHOPATHOLOGY OF SCHIZOPHRENIA: A PROMISING TARGET FOR EARLY INTERVENTION IN EARLY PSYCHOSIS PATIENTS

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

[1]*Center for Psychiatric Neuroscience, CHUV,* [2]*Center for psychiatric neuroscience, CHUV,* [3]*Center for Biomedical Imaging, EPFL,* [4]*Service of General Psychiatry, CHUV*

Background: A hallmark of the pathophysiology of schizophrenia (SZ) is a dysfunction of parvalbumin-expressing fast-spiking interneurons (PVI), which are essential for neuronal synchrony during sensory and cognitive processing. Oxidative stress (OxS) and inflammation, as observed in SZ, affect the highly metabolically active PVI. GSH dysregulation, by increasing vulnerability to OxS and inflammation during early development leads to impaired cortical circuitry, specifically the PVI and the perineuronal nets (PNN) that surround them. In a translational approach both in an animal model and in early psychosis patients (EPP), we aimed (1) to identify a precise mechanism inducing the interaction between OxS and neuroinflammation, 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/PNN maturation.
Methods: This study was conducted on a transgenic mouse model of GSH deficit (GCLM KO) with SZ related phenotype and on EPP. Mice were treated with a dopamine reuptake inhibitor, the GBR-12909 dihydrochloride (GBR), to mimic a social stress, from postnatal day (P)10 to 20. GBR-mice were subjected to NAC and EE during juvenile/adolescent period and

morphological/functional analysis were conducted on adult animals. EPP underwent blood sampling, magnetic resonance spectroscopy (MRS) and clinical assessment. This cohort is composed of N=68 healthy controls (37% females; 14.7% ethnic minority) and N=111 EPP (25% females; 30% ethnic minority). A part of this cohort joined a double-blind, randomized, placebo-controlled clinical trial of NAC supplementation for 6-months and underwent blood sampling, MRS and clinical assessment at baseline and after treatment. This cohort is composed of N=16 placebo (44% females; 31% ethnic minority) and N=15 NAC (14% females; 26% ethnic minority).

Results: An additional OxS (GBR) in early postnatal days (P10-20) leads to long-lasting effects in adult GCLM KO: increased OxS, microglia activation, and PVI/PNN impairments. We identified during peripubertal stage of GCLM KO a vicious cycle of processes involving activation of MMP9 by OxS, leading to RAGE shedding, NFkB activation, secretion of pro-inflammatory cytokines, microglia activation, further ROS production and OxS, inducing long-term impairment of PVI maturation. Peripubertal inhibition of MMP9 prevents RAGE shedding and the feedforward loop induced impairment of PVI in adulthood. Moreover, these effects were completely reversed by the combination of NAC treatment and EE. This recovery is mediated by NAC, possibly via the inhibition of OxS induced MMP9/RAGE pathway. NAC interrupts this deleterious feedforward mechanism that maintains high levels of OxS and neuroinflammation, allowing PVI/PNN maturation. A subsequent EE during adolescence promotes the final maturation of PVIs, providing a long-term neuroprotection to PVI/PNN network. The fast-rhythmic oscillations reflecting neuronal synchronization of PVI was decreased in the GBR-treated GCLM KO, and recovered by NAC/EE.

In EPP with a genetic vulnerability to OxS, an increase in RAGE shedding, measured as soluble form of RAGE (sRAGE) in the plasma, was associated with low prefrontal GABA levels, potentially predicting a central inhibitory/excitatory imbalance, in line with our preclinical model. Interestingly, 6-month NAC treatment decreased RAGE shedding in the plasma of EPP, in association with increased prefrontal GABA level, improvement of cognition and clinical symptoms, suggesting similar neuroprotective mechanisms.

Conclusions: MMP9/RAGE pathway represents a key regulatory mechanism by which OxS interacts with neuroinflammatory conditions, which is particularly damaging to PVI/PNN. The long-lasting effects on PVI/PNN can be reversed by a combined NAC/EE, even after the challenge. In analogy, patients carrying genetic risks to redox dysregulation potentially vulnerable to early-life insults could benefit from a combined pharmacological and psycho-social therapy. Our translational study establishes sRAGE as a peripheral marker for CNS inhibitory circuit impairments. The activation of MMP9 by OxS, on its redox-sensitive site, represents a mechanism-based peripheral proxy for brain neuroinflammation and OxS. Our findings highlight the MMP9/RAGE pathway as a promising target for novel drug development in psychiatry.

Plenary VI: Eric Chen

1:45 p.m. - 2:45 p.m.

34. CAN WE IMPROVE LONG-TERM OUTCOMES OF PSYCHOTIC DISORDERS THROUGH EARLY INTERVENTION?

Merete Nordentoft

Mental Health Centre Copenhagen

Overall Abstract: This plenary talk will provide an overview of the current evidence for the possibilities for early intervention services to improve long term outcome

34.1 CAN WE IMPROVE LONG-TERM OUTCOMES OF PSYCHOTIC DISORDERS THROUGH EARLY INTERVENTION?

Eric YH Chen

The University of Hong Kong

Individual Abstract: Early intervention (EI) has increasingly been recognized as an established clinical paradigm. Studies of sustained long-term outcome requires appropriate contextualization to appreciate. We review these issues with data from a population-based program in Hong Kong.

EI involved three interacting components: early detection, phase-specific intervention, and indicated prevention. EI programs also enhance other mental health programs in the population (a ripple effect involving the sharing of knowledge, paradigm, and human resources).

Based on a series of outcome studies in Hong Kong, EI has resulted in a shortening of DUP for the adult patients but not youth patients. The multi-disciplinary EI team improved functioning and reduced hospitalization. Beyond the direct program effects, there are sustained long-term effects for up to 10 years. In addition, there was a significant and sustained reduction in suicide. These data supported the critical period hypothesis: better outcome in the initial years of the disorder can be sustained after the patients have exited to generic service, for a period of up to 10 years. This is despite there being concurrent improvement in generic services (partly as a result of the ripple effect). This reinforced the role of EI programs in leading continuous cycles of quality improvements. Accordingly, we explored opportunities where further outcome improvements could be targeted.

Maintenance therapy after first episode psychosis is a complex area under intense investigations. Data from our cohort suggest that for first episode patients with a good post-episode outcome (no residual psychosis, no early relapse) continuation of maintenance for up to year 3 leads to a sustained good outcome in 10 years. Those who stopped maintenance between year 2 and year 3 ended up with a less favourable outcome comparable with those that did not have the most favourable initial outcome. Fine-tuning maintenance strategy to individual circumstances and needs.

Another important areas of opportunity is in improving outcome through cognitive function enhancement. Our studies showed that mind-body exercise (Yoga) as well as aerobic exercise could significantly improve attention and memory, with corresponding brain changes. To enhance the establishment of exercise habits. It has been shown that a motivational coaching program can be a useful augmentation to exercise intervention programs.

Our data showed that EI paradigm can improve long-term outcome of psychosis patients which are sustained beyond the period of intervention. This highlights the importance of timely intervention and securing the best possible outcome during the critical period. Early psychosis programs produce ripple effects on generic services which may complicate long term outcome comparison. EI service are well positioned to lead continuous cycles of outcome improvements for psychotic disorders.

Concurrent Symposia

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

35. SOCIAL COGNITIVE IMPAIRMENTS IN SCHIZOPHRENIA SPECTRUM DISORDERS: FROM NEURAL MECHANISMS TO THERAPEUTIC TARGETING IN CLINICAL TRIALS

Robert Buchanan

University of Maryland School of Medicine

Overall Symposia Abstract: Social cognitive processes exist as part of a greater framework, in which interactions occur with neurocognition, physiology and the overall functioning of the individual. Furthermore, while social cognitive performance is dependent on neural circuit function, evidence is emerging that subgroups of individuals may use different circuits or may have different network interaction profiles related to performance. In combination, an increased understanding of the core circuitry of social cognition in people with schizophrenia spectrum disorders (SSDs), along with subgroup variability and even individual profiles, can facilitate the design of prospective clinical trials targeting such circuitry with the aim to improve performance and, ultimately, social functioning. The four proposed presentations address these themes through the analysis of data collected from the large multi-center Social Processes Initiative in Neurobiology of the Schizophrenia(s) (SPINS); the examination of the neural circuitry of a transcranial magnetic stimulation marker of motor inhibition; and the examination of the effect of transcranial magnetic stimulation on cognitive test performance. Dr. Lindsay Oliver will discuss results using a data-driven, multivariate approach to identify relationships between functional neural connectivity during a social processing task and social and non-social cognitive performance in people with SSDs and healthy controls. The delineation of social cognitive constructs is of particular interest given the relationship of these constructs with social functioning and the need to identify treatment targets. The two significant latent variables suggested that: 1) a general pattern of increased connectivity may be related to better overall cognitive performance across groups, and 2) whereas the second latent variable appeared to delineate functional connectivity patterns associated with lower-level social cognitive performance. Dr. Sunny Tang will discuss predictors of role, social and independent functioning. In a discovery sample from the SPINS study and in an independent validation sample, hierarchical cluster analysis revealed three clusters: Cluster 1 was comprised of participants with low functioning in all areas; Cluster 2 was characterized by mixed functioning; and Cluster 3 was characterized by high functioning in all areas. The validation sample showed the same pattern. Machine learning was then used to examine prediction of cluster membership from among 65 demographic and clinical variables. Social cognition, negative symptoms, and structural measures were the primary predictors of functional outcome cluster. Dr. Stephanie Hare will discuss how resting functional connectivity profiles relate to short-interval intracortical inhibition (SICI), a TMS marker of motor inhibition that is consistently reduced in people with SSDs. She will discuss how these findings might inform development of novel neuromodulatory interventions designed to normalize SICI, and the need for future studies to probe the relationship between reduced SICI in SSDs and cognitive impairments. Finally, Dr. Colin Hawco will present data from two randomized double-blind, sham-controlled, rTMS studies designed to improve cognitive performance by targeting the dorsolateral prefrontal cortex. He will then describe a novel method for incorporating both individual functional variability and e-fields for optimal coil targeting, and its application in a newly funded multi-center clinical trial targeting dorsomedial prefrontal cortex, functional connectivity and social cognitive performance.

35.1 MULTIVARIATE RELATIONSHIPS BETWEEN FUNCTIONAL CONNECTIVITY AND SOCIAL COGNITIVE PERFORMANCE ACROSS SCHIZOPHRENIA SPECTRUM DISORDERS AND HEALTHY CONTROLS

Lindsay Oliver*[1], Colin Hawco[2], Navona Calarco[2], Iska Moxon-Emre[3], Thomas Tan[4], James Gold[5], George Foussias[2], Pamela DeRosse[6], Miklos Argyelan[6], Robert Buchanan[5], Anil Malhotra[6], Aristotle Voineskos[2]

[1]*Centre for Addiction and Mental Health, Toronto,* [2]*Centre for Addiction and Mental Health, University of Toronto,* [3]*Centre for Addiction and Mental Health,* [4]*Centre for Addiction and Mental Health,* [5]*Maryland Psychiatric Research Center,* [6]*Zucker Hillside Hospital*

Background: Schizophrenia spectrum disorders (SSDs) often feature social cognitive deficits, associated with functional outcome. Social cognition can be divided into lower-level (e.g., emotion recognition) and higher-level (e.g., theory of mind) processes, subserved by partially dissociable neural networks. Recent work suggests that neural activation patterns during social processing may relate to cognitive performance rather than diagnosis across SSDs and healthy controls. Our objective was to identify multivariate relationships between functional connectivity during a social processing task and social and non-social cognitive performance across individuals with SSDs and healthy controls. We hypothesized that functional connectivity in relevant regions would covary with specific behavioral domains, perhaps reflecting the delineation of lower- and higher-level social cognitive and non-social cognitive constructs.

Methods: Data come from the Social Processes Initiative in the Neurobiology of the Schizophrenia(s) (SPINS) study. Across three sites, 197 people with SSDs and 157 healthy controls (216 males, 138 females) completed the Empathic Accuracy task during functional magnetic resonance imaging, a naturalistic social processing task. Participants also completed measures of lower- and higher-level social cognition and non-social cognition outside the scanner. Partial least squares correlation (PLSC) was used to identify latent variables capturing multivariate brain-behavior relationships with maximal covariance from a 'brain set' of functional connectivity metrics (between 392 regions of interest) and a 'behavior set' of cognitive performance measures (9 social cognitive and 6 non-social cognitive metrics). Permutation testing (1000 iterations) and bootstrap resampling (1000 iterations) were used to evaluate the significance of identified latent variables, and the reliability of contributing brain and behavior measures, respectively.

Results: PLSC followed by permutation testing identified two significant latent variables ($p < .05$), explaining 74% and 10% of the variance, respectively. The first latent variable was characterized by an association between connectivity across much of the brain, including frontal, occipital, temporal, parietal, and subcortical regions, and better performance across both lower- and higher-level social and non-social cognitive measures. The second latent variable was characterized by an association between frontal-parietal and temporal-parietal connectivity, among other regions, and worse social cognitive performance on a subset of lower-level social cognitive measures.

Conclusions: The data-driven delineation of social cognitive constructs is of particular interest given its relationship with functioning and the need to identify treatment targets in SSDs. Our results suggest that patterns of functional connectivity during social processing are associated with both social and non-social cognitive performance across people with SSDs and healthy controls. A general pattern of increased connectivity may be related to better overall cognitive performance across groups. Interestingly, lower-level social cognitive performance also

appears to be negatively associated with increased connectivity in a subset of regions, indicative of functional connectivity patterns that may delineate this aspect of social cognitive processing.

35.2 BIOPSYCHOSOCIAL CONTRIBUTIONS TO FUNCTIONAL OUTCOMES IN SCHIZOPHRENIA: A DATA-DRIVEN MACHINE LEARNING APPROACH

Sunny Tang*[1], Katrin Hänsel[2], Lindsay Oliver[3], Colin Hawco[3], Erin Dickie[3], Majnu John[2], Miklos Argyelan[2], Pamela DeRosse[2], Robert Buchanan[4], Aristotle Voineskos[3], Anil Malhotra[2]

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Background: Schizophrenia spectrum disorders (SSD) are associated with significant functional impairment on average. However, individuals are not affected uniformly. Some resilient individuals achieve high levels of social and role functioning despite their diagnosis. In this study, we used data-driven methods to characterize patterns in functional outcomes among individuals with SSD and determine the key biopsychosocial correlates of these functional outcomes. We hypothesized that social cognition would be an important predictor of functional outcomes in SSD.

Methods: The primary cohort (N=282) was derived from the Social Processes Initiative in the Neurobiology of the Schizophrenias (SPINS). Functional outcomes were assessed with the Birchwood Social Functioning and Quality of Life scales. Social cognition was assessed across three domains: Emotion Recognition, Theory of Mind, and Social Perception. Neurocognition was evaluated with the MATRICS consensus battery. Participants also underwent multimodal MRI, including structural scans. An independent validation sample of 317 SSD were derived from a separate study where functional outcomes were evaluated with different measures assessing convergent constructs (including Multidimensional Scale of Independent Functioning, Social Adjustment Scale). Hierarchical clustering was used to group participants into 3 functional clusters in both the SPINS and validation samples. To select for key biopsychosocial correlates, we employed two novel machine learning methods based on latent discriminant analysis (LDA) using forward- and backward-selection principles. Predictors were selected without a priori assumptions from among 65 variables describing the participants' demographics, general cognition, social cognition, clinical ratings, perception of self, and brain structure. We verified the LDA results using binomial LASSO regression. Analyses were done in R.

Results: We found convergent results for three clusters across both the primary and the independent validation sample. Cluster 1 was low functioning in all areas, and Cluster 3 was high functioning in all areas. Cluster 2 showed a more nuanced pattern with poor role functioning (Cohen's d=0.24 [-0.06, 0.55] vs. low-functioning) but intermediate social (Cohen's d=2.02 [1.57, 2.47]) and independent functioning (Cohen's d=1.21 [0.84, 1.57]). Our novel machine learning approaches examined over 20 million combinations of potentially predictive variables for classifying participants into one of the 3 clusters. Final accuracies were 74% for the backward selection approach and 73% for forward selection. Both approaches consistently found that avolition, anhedonia, social cognition, hippocampal volume, and subjective interpersonal experience were the principal predictors of functional outcome cluster. These results were consistent with the LASSO models, which predicted the clusters with 54% accuracy.

Conclusions: There may be a group of individuals with SSD who have poor role functioning but relatively preserved social and independent functioning, which has not been broadly

recognized. Social cognition was among the key predictors of functional cluster membership, along with brain structure, negative symptoms, and subjective experience of social interactions. Importantly, positive symptoms of psychosis were not among the main variables of interest.

35.3 A RESTING FMRI INVESTIGATION OF TMS-RELATED INHIBITION REDUCTION IN SCHIZOPHRENIA

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Background: The short interval intracortical inhibition (SICI) can be measured non-invasively using paired pulse transcranial magnetic stimulation (TMS). Conventionally applied to the motor cortex, SICI is measured as the ratio of the electromyographic (EMG) response in muscle to a pair of pulses separated by a short (1-4 ms) interval relative to a single, excitatory suprathreshold test pulse. Higher SICI ratios (indicating reduced inhibition) are readily replicated in studies of chronic schizophrenia and first-episode patients with limited antipsychotic medication exposure. Yet the neural mechanisms underlying reduced intracortical inhibition in schizophrenia remain elusive.

Methods: Our study investigated local and long-distance resting state functional connectivity (rsFC) markers of SICI in a sample of N=23 patients with schizophrenia spectrum disorders (SSD) (16 male/7 female) and N=29 controls (15 male/14 female) using TMS and functional magnetic resonance imaging (fMRI). Each participant's resting motor threshold (RMT) was determined as the minimum TMS intensity to elicit a motor evoked potential (MEP) of .50 mV in at least 5 of 10 consecutive stimuli. For paired-pulse TMS, a subthreshold conditioning stimulus (80% RMT) was followed by a suprathreshold stimulation (120% RMT) separated by a brief interval (1ms and 3ms trials were merged). SICI was calculated as ratio of the peak-to-peak EMG response to paired-pulse TMS relative to the EMG response to a single suprathreshold pulse (120% RMT). Local connectivity was estimated using regional homogeneity (ReHo) analysis; long-range connectivity was estimated using rsFC analysis. Direct and indirect effects of connectivity measures on SICI were modeled using mediation analysis.

Results: Higher SICI ratios (indicating reduced inhibition) were associated with lower ReHo in the right insula ($t = -2.74$, $P=0.01$) in SSD patients after controlling for effects of age, sex, and motion. We applied a regression validation method to assess the reliability of our estimate of the association between right insula ReHo and SICI (Harrell 2015). The results showed that the 95% bootstrap confidence interval of the adjusted correlation between SICI and ReHo is (-0.73, -0.19) based on 5000 bootstrap samples; these results suggest the association between right insula ReHo and SICI was reliable. In SSD patients, higher SICI ratios (indicating reduced inhibition) were strongly associated with reduced connectivity between right insula and hubs of the corticospinal pathway: sensorimotor cortex ($r = -0.83$, $P<0.001$) and basal ganglia ($r = -0.89$, $P<0.001$). Mediation analysis supported a model in which the direct effect of local insular connectivity strength on SICI is mediated by the interhemispheric connectivity between insula and left sensorimotor cortex (Sobel test statistic = -3.04, $P=0.002$) (Permutation-Based Results: Effect = -2.96, Std Error = 0.89, Lower CI = -4.89, Upper CI = -1.28).

Conclusions: Despite the fact that abnormal SICI in SSD provides direct evidence of altered excitatory/inhibitory balance in the motor system, little is known regarding SICI's relationship to clinical symptoms and cognitive functions, which rely heavily on appropriate excitatory/inhibitory balance. There is also a lack of evidence about the neural systems related to SICI. Our preliminary findings suggest that reduced inhibition in SSD may be related to

reduced connectivity with a distant brain region outside of the traditionally studied corticospinal pathway: the right insula. The broader clinical implications of our findings are discussed with emphasis on how these findings might inform novel interventions designed to restore or improve SICI in SSD and deepen our understanding of motor inhibitory control and the impact of abnormal signaling in motor-inhibitory pathways in SSD. We also discuss the need for future studies of SSD to probe the relationship between SICI and both clinical symptoms and cognitive impairments.

35.4 CHANGES IN VARIABILITY OF BRAIN FUNCTIONAL CONNECTIVITY OR ACTIVITY RELATED TO RTMS RESPONSE: IMPLICATIONS FOR INDIVIDUALIZED TARGETING

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Background: Repetitive Transcranial Magnetic Stimulation (rTMS) is a neuromodulatory approach which has been applied to improving outcomes in psychiatric disorders. Ongoing work seeks to examine the utility for improving cognitive domains such as working memory or social cognition. Most rTMS protocols use a 'one-size-fits-all' approach to identifying a target site for brain stimulation. There has been growing evidence that psychiatric populations can show greater variability in brain functional topology than control groups. In recent work, our group demonstrated greater variability in brain functional topology in subsets of patients with schizophrenia spectrum disorders (SSD) or autism spectrum disorder (ASD). Here we present data from two studies examining changes in brain function following rTMS, focusing on individual variability. These results will be considered in the context of individualized targeting in rTMS trials.

Methods: Functional magnetic resonance imaging (fMRI) data was examined from double-blind rTMS trials (20 Hz or sham rTMS to the bilateral dorsolateral prefrontal cortex) to improve executive function. Study 1 included data from 42 SSD who completed a letter sequence Nback fMRI task both pre and post treatment; Nback task activation maps (3back - 1back) were created. Study 2 included 37 ASD who completed a resting state fMRI pre and post rTMS; seed connectivity maps to the rTMS target were created. For both studies, individual variability in brain activity or connectivity was quantified by creating a correlational distance matrix for each group, and taking the average distance for a participant to all other participants (high distance means more 'idiosyncratic' response). Changes in variability pre-post treatment were examined within and between the active and sham groups, and changes in variability were related to changes in working memory following treatment.

Results: In Study 1, the active group showed a reduction in variability in Nback task-related activity following treatment ($p<0.001$), which was greater than the change in the sham group ($p<0.001$). The change in variability was not significantly related to change in 3back accuracy ($p=0.11$), but interestingly decreased variability was associated with reduction in 3back misses ($p=0.014$) as well as improvements in out-of-scanner attention (continuous performance test; $p=0.0089$). In Study 2, variability was observed to decrease in the active rTMS group ($p=0.04$), and increase in the sham group ($p<0.001$). Although overall changes in working memory performance were not observed in the active group ($p=0.07$), in the active group only there was a significant correlation with change in variability and improvement in task performance ($p=0.03$).

Conclusions: In both studies, we observed changes in functional individual variability in the active rTMS group which related to behavior, suggesting that participants who showed decreases in individual variability (i.e. normalization of brain function) following treatment also showed improved working memory. This highlights the importance of variation in individual functional brain topology in rTMS. These results will be discussed with relevance to individual targeting in rTMS, and an ongoing trial using individually derived functional target and electric-field models to optimize engagement of social cognitive networks in SSD. Personalized targeting may improve the overall efficacy of rTMS.

36. MITOCHONDRIAL DYSREGULATION IN PSYCHOTIC DISORDERS

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Overall Symposia Abstract:

This symposium will present cutting-edge data on mitochondrial dysregulation in psychotic disorders such as schizophrenia and bipolar disorder with psychotic features. Several lines of evidence suggest that mitochondrial function is impaired in these disorders, but the underlyiing mechanisms as well as its downstream implications are unclear. Mitochondria play keys roles in energy metabolism, redox regulation, compartmentalization of glutamate, and several other domains critical for brain function. Therefore, better understanding of mitochondrial dysregulation in psychotic disorders is likely to give rise to novel targets for intervention to improve brain function. In this symposium, we present newly emerging evidence from experiments using patient-derived induced pluripotent stem cells, postmortem brains from individuals with psychotic disorders, in vivo magnetic resonance spectroscopy (MRS) in animal model and finally translational research both in model and patients towards exosomal biomarkers needed for patients stratification. Dorit Ben-Shachar will provide experimental evidences for a direct link between the mitochondria and schizophrenia-related pathologies. She will show that both in schizophrenia derived iPSCs and in rat brain, transplantation of healthy mitochondria improves mitochondrial function, neuronal sprouting and schizophrenia related behaviour. Lijing Xin will present in vivo data from state-of-the-art 13C-MRS-study in a redox-dysregulated mice model during neurodevelopment, showing altered brain energy metabolism, specifically reduced TCA cycle and trans-mitochondrial transport activity. Furthermore, she will show mitochondrial dysfunction in early-psychosis patients, highlighting reduced levels of mitochondrial markers in both oxidative-stress-stimulated fibroblasts and brain MRS. An tight association between brain and peripheral mitochondrial markers in patients, combined with their link with brain glutathione suggest that a coupling between redox and mitochondrial functioning is limiting in early psychosis. Dr Khadimallah will show, both in early-psychosis patients and in redox-dysregulated-mice model, that alterations of mitochondrial miR-137 and COX6A2 plasma exosome levels represent proxy markers of parvalbumin interneuron cortical microcircuit impairment. Mitochondrial impaired patients' subgroup, having high-exosomal miR-137 and low COX6A2 levels, exhibited impaired gamma oscillations in correlation with worse psychopathology, neurocognition and functioning. Jill Glausier will present transcriptomic profiling data of a gene set indexing the variety of mitochondrial functional pathways in DLPFC grey-matter, and layer-3 and layer-5

glutamatergic pyramidal cells, in subjects with schizophrenia or bipolar disorder. She will show that mitochondrial perturbations are present in both disorders and the presence of psychosis may contribute to some similarities. The effect in schizophrenia is however strongest and shows a selective effect on energy producing pathways. These projects run the gamut from molecular and cellular research to in vivo biochemistry and cognition in both patients and models. The findings are complementary across levels and present an emerging picture of mitochondrial dysfunction in psychotic disorders. This symposium will highlight exciting developments and reveal mechanism-based biomarkers leading to patients stratification needed for treatments targeting mitochondria dysregulation. Ultimately, new treatment interventions may be developed to exploit this under-examined area of psychotic disorders.

36.1 EXPERIMENTAL EVIDENCE FOR A DIRECT LINK BETWEEN MITOCHONDRIA AND DISEASE-DEPENDENT BENEFICIAL OR DETRIMENTAL CELLULAR AND BEHAVIORAL OUTCOMES: IMPLICATIONS FOR SCHIZOPHRENIA

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Background: Multifaceted dysfunction in mitochondria in schizophrenia (SZ) is repeatedly reported. Mitochondrial abnormalities include structural deformation, genetic and molecular changes specifically in the oxidative phosphorylation system of which complex I is mostly affected as well as reduced cellular respiration, mitochondrial membrane potential ($\Delta\psi m$) and altered mitochondrial network dynamics. In addition, we have shown that mitochondrial malfunction is associated with impaired ability of neurons to differentiate from SZ-derived induced pluripotent stem cells (iPSCs) into neurons. Here we show a direct link between mitochondria and SZ related pathologies.

Methods: Isolated active normal mitochondria (IAN-MIT) were transplanted once into SZ and healthy subjects-derived iPSCs or lymphocyte cell lines (hLCLs) as well as into the medial prefrontal cortex (mPFC) of the maternal immune activation poly I:C and control rats in adolescence. The long-term effects at the cellular, molecular, mitochondrial and behavioral levels were studied.

Results: In cells, IAN-MIT transplantation showed improved mitochondrial function associated with enhanced ability of neurons to differentiate from SZ-derived iPSCs into neurons. In Poly I:C rats, a single injection of IAN-MIT into the mPFC in adolescence restored in adulthood mPFC regulated behaviors. This was associated with normalization of mitochondrial function, alterations in monoamines levels and turnover rates, improved neuronal sprouting and enrichment of proteome profiles related to metabolism and neuronal development and plasticity. Unexpectedly, in healthy rats IAN-MIT transplantation induced detrimental effects in all of the above parameters. A similar phenomenon was observed in healthy subjects derived LCLs.

Conclusions: This study strongly support the potential of manipulating mitochondria as a novel treatment for neurodevelopmental disorders and diseases with bioenergetics deficits such as SZ, as long as mitochondrial toxic potential is taken into account.

36.2 MITOCHONDRIAL DYSFUNCTION AND ITS COUPLING WITH REDOX REGULATION IN EARLY PSYCHOSIS

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Background: Mitochondria play a pivotal role in regulating cellular functions including energy production, calcium homeostasis, redox signaling, and apoptosis, which are all crucial for neuronal maturation and function. Impaired mitochondrial function and energy metabolism have been suggested in patients with schizophrenia (SZ). As oxidative stress appears as a common hub in SZ pathophysiology, it is key to understand the interplay between mitochondrial dysfunction, energy metabolism and redox impairments, and to clarify if redox susceptibility confers a predisposition to mitochondrial impairments in SZ patients. Therefore, in this study we first investigated in vivo brain energy metabolism in an animal model of SZ with redox-dysregulation and additional oxidative stress challenges during the early developmental period; then we studied the effect of oxidative stress on the mitochondrial complex I marker in fibroblasts from early psychosis (EP) patients and healthy controls, and also their associations with brain mitochondrial and redox metabolites.

Methods: Two groups of 30 days old C57BL6/J mice were used in this study: GCLM-KO mice (n=13, 7 females) with the early postnatal oxidative challenge by administration of dopamine uptake inhibitor GBR12909 during postnatal development, and wild type mice (n=10, 6 females). [2-13C] acetate was infused in combination with 13C MRS experiments performed on a 14.1T magnet. Two-compartment modeling was applied to extract metabolic fluxes including: the glial tricarboxylic acid (TCA) cycle flux Vtcag, the neuronal TCA cycle Vtcan, the transmitochondrial transport Vx (representation of glutamate dehydrogenase, aspartate transaminase and transport across the membrane of the mitochondria), the glutamate-glutamine cycle Vnt, and glial Vgtg and neuronal Vgtn glutamate turnover fluxes (composite flux of Vx and Vtca).

39 EP patients (46 % women) and 31 control subjects (32 % women) participated in this study. All participants gave informed written consent prior to the study according to ethical guidelines of the University Hospital of Lausanne. Their fibroblasts were fractioned; mitochondrial and cytosolic fractions were used separately to assess mitochondrial markers (specifically NADH Dehydrogenase Ubiquinone Flavoprotein 2, NDUFV2) using Western blot analysis, in basal and oxidative stress conditions. Metabolites levels from the medial prefrontal cortex were measured by 1H magnetic resonance spectroscopy at a 3T MR scanner with the SPECIAL localization sequence and quantified by LCModel. $P<0.05$ was used to reject the null hypothesis.

Results: By modeling the 13C-labeling time courses, we showed that the redox-dysregulated mice model presented reduced glial glutamate turnover flux (Vgtg), suggesting a mitochondrial oxidative metabolism slowdown in the astrocyte resulting from early developmental oxidative stress. Furthermore, in EP patients we observed reduced levels of the mitochondrial marker (NDUFV2) in oxidative-stress-stimulated fibroblasts-mitochondrial fraction and brain mitochondrial marker (N-acetylaspartate), respectively. Strikingly, a tight association between the brain and the peripheral mitochondrial marker is exclusively established in EP patients.

Lastly, brain glutathione levels are shown to be correlated with the extent of mitochondrial responses to oxidative stress in EP patients, suggesting that a coupling between redox and mitochondrial functioning could be a limiting factor in early psychosis.
Conclusions: Current findings in the animal model and EP patients suggested redox homeostasis is a limiting factor for mitochondrial functioning in early psychosis. The brain antioxidant assessment together with the peripheral mitochondrial marker profiling may therefore potentially contribute to patients' stratification.

36.3 MITOCHONDRIAL, EXOSOMAL MIR137-COX6A2 AND GAMMA SYNCHRONY AS BIOMARKERS OF PARVALBUMIN INTERNEURON AND COGNITIVE IMPAIRMENTS IN SCHIZOPHRENIA

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Background: Molecular and cellular mechanism underlying mitochondrial bioenergetics is still unclear in schizophrenia. In redox dysregulated mice (Gclm-KO±GBR), prefrontal parvalbumin immunoreactive interneurons (PVI) showed higher extranuclear 8-oxo-dG (a DNA oxidative-stress marker) immunolabeling, suggesting mitochondrial DNA damage. We hypothesized that miR-137 overexpression, by inhibiting mitophagy via the regulation of the expression of two mitophagy receptors (NIX and FUNDC1), prevented damaged mitochondria elimination.
Methods: Blood exosomal mitochondrial markers levels (miR 137, COX6A2, mitophagy markers), EEG 40-Hz auditory-steady-state-response (ASSR), psychopathology (PANSS), neurocognition (MATRICS) were assessed in early psychotic patients EPP, n=138; 26.1% women; 26.1% ethnic-minorities), controls (n=134; 34.3% women; 16.9% ethnic-minorities). In Gclm-KO similar prefrontal and blood markers were measured using immunohistology, electron-microscopy and protein quantification. Statistics: SAS-JMP-N,Version-12.1; Pearson-correlation; Adjusted p-values for multiple ANOVAs.
Results: In prefrontal cortex and blood of Gclm-KO±GBR mice, oxidative-stress induced miR-137 exosomal level increases, COX6A2 and mitophagy markers (NIX/Fundc1/LC3B) decreases and PVI accumulation of damaged mitochondria, all these processes were rescued by a mitochondrial-targeted antioxidant (MitoQ), which implied an oxidative stress-induced mitophagy deficit as underlying mechanisms. Translating to EPP, blood exosomal miR-137 increases and COX6A2 decreases, combined with mitophagy markers alterations, suggested that observations made centrally and peripherally in animal model were reflected in patients' blood. Higher exosomal miR-137 and lower COX6A2 levels were associated with ASSR deficit for both evoked power (POW) and inter trial phase coherence (ITC). As ASSR requires proper PVI circuitry, exosomal miR-137/COX6A2 level alterations may represent proxy markers of cortical PVI-microcircuit impairments. EPP were stratified in two subgroups:(a) no/low mitochondrial impaired "Psy-ND" subgroup, having miR-137 and COX6A2 levels similar to controls; (b) patients' group with mitochondrial dysfunction "Psy-D" patients, having high-exosomal miR-137 and low COX6A2 levels, exhibited more impaired ASSR

responses associated with worse psychopathological status, neurocognitive performance and global and social functioning. Discrimination performance: Receiver-operating-characterisc (ROC) curve and corresponding area under the curve (AUC) provide us an overall profile of the cutoff-based clustering. The AUC of Psy-D subjects (AUC=0.96) was higher than that of both Psy-ND (AUC=0.63) and control subjects (AUC=0.74), showing that the combined detection of miR-137 exosomal levels and COX6A2 protein levels allowed an optimal identification of Psy-D patients, with the highest sensitivity and specificity.
Conclusions: Our findings revealed mechanism-based biomarkers allowing selective and specific patients selection needed for treatments targeting brain mitochondria dysregulation and capture the clinical and functional efficacy of novel drug trials.

36.4 UNIQUE DIAGNOSIS- AND CELL TYPE-SPECIFIC MITOCHONDRIAL TRANSCRIPTOMIC ALTERATIONS IN DORSOLATERAL PREFRONTAL CORTEX OF INDIVIDUALS WITH PSYCHOTIC DISORDERS

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Background: Schizophrenia (SZ) and bipolar disorder (BD) share some risk factors and clinical features, such as psychosis. These shared factors and features may be linked via similar brain alterations, many of which have been associated with mitochondrial dysfunction. However, the severity of mitochondrial dysfunction, and/or the specific mitochondrial functional pathways affected, might differ between diagnoses and/or presence of psychosis, especially at the level of individual cell types.
The primary role of mitochondria is ATP synthesis via oxidative phosphorylation (OXPHOS). Mitochondria also participate in other biological processes integral to neuronal functioning, including mediating oxidative stress, Ca2+ buffering and apoptosis. Although mitochondrial perturbations are reported in both SZ and BD, the severity of these alterations and/or the affected mitochondrial functions are unclear. Further, because mitochondria are responsible for multiple distinct but interdependent biological processes, analysis of the higher-order gene expression relationships within and between biological pathways may prove informative across SZ and BD. Finally, accumulating data suggests that the presence of psychosis may contribute to molecular similarities between diagnoses. Thus, we explored whether analysis of mitochondrial-related gene expression and co-expression relationships would provide insight into the nature of mitochondrial alterations in these disorders and psychosis.

Methods: Dorsolateral prefrontal cortex (DLPFC) grey matter data were analyzed from RNA sequencing studies completed as part of the CommonMind Consortium from the SZ (N=57), BD (N=35, n=11 with psychosis), and unaffected comparison (UC; N=82) subjects obtained from the University of Pittsburgh. We analyzed data from two previously published microarray studies of DLPFC layer 3 pyramidal neurons (L3PNs) and L5PNs. The first study included 36 pairs of UC and SZ subjects, and the second study included 19 triads of UC, SZ and BD (11/19 with psychosis).
Genes within the pathway defined by Gene Ontology (GO) as ‘mitochondria’ (GOMito) were included for analysis. DEG analysis was performed in grey matter using a basic linear regression model with covariate correction and was performed in PNs using a random intercept model with variable covariate selection. The co-expression network for UC subjects was constructed using weighted gene co-expression analysis (WGCNA).

Results: In DLPFC grey matter, 41% of GOMito genes were differentially expressed in SZ whereas only 8% were differentially expressed in BD (all $q<0.05$). In SZ, 83% of DEGs were lower, whereas in BD, 99% of DEGs were lower. DEGs in SZ subjects were enriched for OXPHOS, mitochondrial dysfunction and sirtuin signaling pathways. In contrast, no pathways were identified as significantly enriched for DEGs in BD subjects. However, comparison of differential-expression test statistics showed a moderate correlation between SZ and BD subjects ($r=0.53$). This relationship was largely driven by BD subjects with psychosis ($r=0.63$), as only a very weak correlation was present between SZ and BD without psychosis ($r=0.17$). WGCNA identified five co-expression modules in UC subjects which were all preserved in SZ and BD .
In L3PNs and L5PNs, 28% and 25% of of GOMito genes were differentially-expressed (all $q<0.05$), respectively, in SZ subjects. In both cell populations, 97% of DEGs were lower, and were enriched for OXPHOS, mitochondrial dysfunction and sirtuin signaling pathways. In L3PNs and L5PNs from BD subjects, no GOMito genes were differentially-expressed. Comparison of test statistics showed that, unlike in DLPFC grey matter, very weak ($r=0.16$) to weak ($r=0.28$) correlations existed between SZ and BD subjects in L3PN and L5PNs, respectively. WGCNA in PNs from UC subjects were preserved in SZ and BD subjects.

Conclusions: Pathways related to energy production are selectively and significantly downregulated in DLPFC grey matter, L3PNs and L5PNs in SZ subjects. Higher-order co-expression networks were maintained, demonstrating a coordinated reduction in these genes. Threshold-free analyses suggest a similar pattern in BD subjects with psychosis that is present in DLPFC grey matter, but not PNs. Together, these findings support the presence of mitochondrial perturbations in DLPFC in SZ and BD, but that the severity, nature and cell type-specificity differ across diagnosis and presence of psychosis.

37. SOCIAL DISADVANTAGE AND HEALTH INEQUITIES IN EARLY PSYCHOSIS: TIME TO ACT

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Overall Symposia Abstract: The association between social disadvantage and psychosis has been identified across diverse cultural, social, and demographic contexts. Within this symposium, we will bring together data across the globe to illustrate disparities in health care and outcomes for underserved populations. We wish to demonstrate that these inequalities and complex contextual factors not only affect the individual's predisposition for developing psychosis, but may also serve to drive enduring impairment. We make the case for change, and for services to adapt to the needs of these individuals whose illness is contextualised within disadvantaged social settings.
First, data from an Australian ultra-high risk for psychosis (UHR) cohort (N=461) study will present evidence supporting a causal link between neighbourhood deprivation and identification of UHR individuals and transition to psychosis. The findings will provide support that Early Intervention Services (EIS) should be funded as per the expected incidence of psychotic disorders.

Second, longitudinal cohort data from Swedish registers of 1.5m people living in Stockholm will provide evidence of an effect modification of parental region-of-origin on social capital and psychosis risk. Neighbourhood levels of personal trust – a form of bonding social capital

– appears protective for those of Swedish and European descent but serves to increase risk for those of African and Middle Eastern and Sub-Saharan African descent. These patterns reveal the highly context-dependent nature of designing area-level intervention strategies to improve psychosis outcomes, and potentially unintended public health consequences.

Next, long term recovery outcomes from a large UK EIS cohort (N=1027) of young people with first episode psychosis (FEP) will be presented. Here, we present evidence of disparities in a range of recovery outcomes for individuals with ethnic minority status at two years following discharge from EI services. Despite receiving gold standard EIS care, individuals of Black and Asian heritage showed less improvement in their long term social and clinical recovery, compared to their white counterparts. Social deprivation also contributed to the disparities in recovery outcomes. These findings highlight the need for improved service provision and targeted care to mitigate the effects of social deprivation on ethnic minority individuals following FEP.

Finally, the concluding talk will provide a qualitative exploration of help seeking events prior to the receipt of early psychosis services, and barriers and facilitators to specialized services for psychosis in the U.S. Difficult and negative experiences on the path to specialized services can lead to extended duration of untreated psychosis and lack of engagement among service users and their families. Improving experiences and interactions with formal and informal sources within the community is imperative to reducing racial inequities in mental health. The findings presented here have the potential to provide much needed support on the pathway to and step down from specialized services for those from ethnically diverse backgrounds.

37.1 THE ASSOCIATION BETWEEN SOCIAL DEPRIVATION AND THE RATE OF IDENTIFICATION OF INDIVIDUALS AT ULTRA-HIGH RISK FOR PSYCHOSIS AND TRANSITION TO PSYCHOSIS

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Background: It has been well established that a higher incidence of psychotic disorders exists in neighbourhoods of greater social deprivation. However, it is not known whether this represents a causal relationship, as the stage at which social deprivation exerts its influence on the development of psychotic disorders is yet to be elucidated. We aimed to investigate the association between neighbourhood-level social deprivation and the rate of identification of individuals at Ultra-High Risk for psychosis (UHR), as well as the rate of transition to psychosis in UHR individuals.

Methods: The cohort included all young people aged 15–24 identified as UHR attending an Early Intervention clinic at Orygen in Melbourne, from a geographically defined catchment area comprising Northern and Western Melbourne, over a five-year period (2012–16). Australian census data were used to obtain the at-risk population and social deprivation information according to postcode of residence. Levels of social deprivation were ordered into quartiles. Poisson regression was used to calculate rate ratios and Cox regression analysis determined hazard ratios.

Results: Of the 461 young people identified as UHR, 11.1% (n=49) lived in the most affluent neighbourhoods (Quartile 1) compared to 36.7% (n=162) in the most deprived neighbourhoods

(Quartile 4). There was a 35% higher rate of identification of young people who were UHR from the most deprived neighbourhoods (aIRR=1.35, 95% C.I. 0.98-1.86). Over a median follow-up of approx. 10 months (308 days (I.Q.R. 188–557), 17.5% (n=77) were known to have transitioned to a full-threshold psychotic disorder. When controlling for age, sex and substance use, young people from the neighbourhoods of above average deprivation (Quartile 3), the hazard ratio for transition was 2.05 (95% CI 0.88-4.80).
Conclusions: These findings provide more support that EI services should be funded as per the expected incidence of psychotic disorders.

37.2 LONGITUDINAL ASSOCIATION BETWEEN NEIGHBOURHOOD-LEVEL SOCIAL CAPITAL AND INCIDENCE OF PSYCHOTIC DISORDERS: A COHORT STUDY OF 1.5M PEOPLE IN STOCKHOLM COUNTY, SWEDEN

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Background: Better neighbourhood-level social capital may be protective for people at risk of first episode psychosis, but longitudinal evidence is missing. We also do not know (i) whether this is specific to psychosis or extends to other forms of severe mental illness (SMI), or; (ii) whether these effects are protective for all groups equally, including people with and without a parental history of immigration. To investigate these issues, we used longitudinal cohort data from linked Swedish registers of 1.5m people living in Stockholm County, linked to prospectively-collected, population-based ratings of neighbourhood social capital.
Methods: All Swedish-born people living in Stockholm County between 2002-2016 while aged 14-64, were followed from earliest residency in Stockholm County after 14 years old until diagnosis of ICD-10 non-affective psychotic disorder (NAPD; F20-29), affective psychotic disorder (APD; F30/1.2, F32/3.3) or non-psychotic bipolar disorder (NP-BPD; F30/1.x except APD codes), emigration from Stockholm County, 65th birthday, death, or 31 December 2016, whichever was sooner. We developed empirical estimates of neighbourhood social capital (political trust, welfare trust, personal trust) independently-rated in the Stockholm County Public Health (SPHC) survey (N=23,510) in 2002. Social capital domains were estimated using factor analysis and multiple imputation to handle missing survey data. We used directed acyclic graphs to guide confounder choice, which included age, sex, parental region-of-origin, parental history of severe mental illness, family disposable income quintile at cohort entry, deprivation quintile and population density quintile. We ran multilevel survival analyses with time-varying covariates for each social capital measure, deprivation and population density, to model exposure to area-level factors over follow-up. A priori interactions between each social capital measure and parental region-of-origin were tested.
Results: Our cohort included 1,467,128 participants, of whom 17,760 (1.2%) were diagnosed with SMI for the first time during follow-up. Compared with cohort participants, SPHC survey respondents were more likely to be of Swedish or European origin ($p<0.001$). In full multivariable models, a one standard deviation increase in neighbourhood-level personal trust was associated with reduced incidence of NAPD (hazard ratio (HR): 0.89; 95%CI: 0.83-0.95) and NP-BPD (HR: 0.92; 95%CI: 0.86-0.98), with a trend-level effect for APD (HR: 0.92; 95%CI: 0.83-1.01; $p=0.09$). For NAPD and NP-BPD there was strong evidence of effect modification by parental region-of-origin (both $p<0.001$); thus, neighbourhood-level personal trust appeared protective for participants of Swedish and European descent (i.e. NAPD: Swedish HR: 0.88, 95%CI: 0.82-0.95; European HR: 0.85, 95%CI: 0.74-0.97), but increased incidence for participants of North African and Middle Eastern (HR: 1.61; 95%CI: 1.17-2.02)

and Sub-Saharan African (HR: 1.84; 1.09-3.09) descent. Political and welfare trust were not associated with NAPD or APD, although had a weak protective effect (HR: 0.88; 95%CI: 0.77-1.00; p=0.05) and risk-increasing effect (HR: 1.14; 95%CI: 1.02-1.28), respectively, on incidence of NP-BPD.
Conclusions: Neighbourhood levels of personal trust – a form of bonding social capital, here disproportionately rated by people of Swedish and European descent – was longitudinally associated with protective effects against SMI, but only for these groups, and actually served to increase risk for those of African and Middle Eastern descent. These patterns reveal the highly context-dependent nature of designing area-level intervention strategies to improve SMI, and potentially unintended public health consequences.

37.3 LONG-TERM SOCIAL AND CLINICAL OUTCOMES ACROSS ETHNIC GROUPS IN THE UK FOLLOWING A FIRST EPISODE OF PSYCHOSIS

Sian Lowri Griffiths*[1], James Kirkbride[2], Swaran Singh[3], Tumelo Bogatsu[1], Mrunal Bandawar[1], Mia Longhi[1], Beel Alexander[1], Emily Butler[1], Nick Freemantle[4], Peter Jones[5], David Fowler[6], Joanne Hodgekins[7], Tim Amos[8], Max Marshall[9], Paul McCrone[10], Vimal Sharma[11], Linda Everard[12], Max Birchwood[1], Rachel Upthegrove[1]

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Background: Psychosis is disproportionally high within ethnic minority groups in high-income countries, and inequalities in accessing care is also evident. Yet evidence of disparities in recovery outcomes for ethnic minority groups following a First Episode Psychosis (FEP) is less conclusive. It is imperative to understand the factors that predispose these individuals to illness, but also whether such underlying factors hold risk for continuing poorer outcomes even after receiving specialised care under Early Intervention Services (EIS).
Aims: We sought to investigate the longitudinal clinical and social outcomes of young people with FEP from different ethnic groups following treatment within UK early intervention services (EIS).

Methods: Data were used from the NIHR SUPEREDEN study, a longitudinal study of young people with FEP, across 14 EIS centres in the UK. Participants (n=1027) were initially assessed over the first 12 months of service, and subsequently at yearly follow-ups from EIS discharge (approximately 3 years from baseline) to 2 years post-discharge. Validated assessment tools quantifying social and clinical recovery were used, alongside a covariate, social index score. A linear mixed effects model was used for statistical analysis.
Results: Participants showed general improvement on recovery outcomes post EIS. Compared to their white counterparts (n=750), individuals of Black (n=71) and Asian (n=157) heritage showed less improvement in positive psychosis symptoms (F=21.11; p= <0.001), depressive (F=20.77; p= <0.001), and general symptoms (F=13.89; p= <0.001), and made less gains in their social functioning (F=11.26; p= <0.001). There were no group interaction effects for negative symptoms (F=0.55; p= 0.579) and total number of relapses (F=2,83; p=0.06). When a social deprivation index was added as a covariate in the models, social deprivation independently contributed to the variance in outcomes for positive (p<.001, 95% CI [.267, .803]), general symptoms (p<.001, 95% CI [.323, 1.234]), and social outcomes (p<.001, 95% CI [-4.891, -3.212]). This was not seen for the depression outcomes. Ethnicity retained its significance across all outcome models.

Conclusions: Despite receiving gold standard EIS care, individuals of Black and Asian heritage showed less improvement in their long term social and clinical recovery, compared to their white counterparts. Social deprivation in part contributed to this disparity. Improved service provision and targeted care to mitigate the effects of social deprivation on ethnic minority individuals is needed to promote recovery following FEP.

37.4 QUALITATIVE EXPLORATION INTO COMMUNITY SUPPORT AND SERVICES FOR EARLY PSYCHOSIS BASED ON RACIAL AND ETHNIC MINORITY FAMILY MEMBER EXPERIENCES

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Background: Racially and ethnically diverse family members' experience aversive pathways to early psychosis services and across the continuum of care. Difficult and negative experiences on the path to specialized services can lead to extended duration of untreated psychosis and lack of engagement among service users and their family members. However, the complexity of these pathways across the continuum of care for racially and ethnically diverse families has not been well documented in the U.S.
Methods: To date, 31 self-identified racially and ethnically diverse family members have participated in an ongoing online survey and completed quantitative and qualitative responses that explored help seeking events prior to the receipt of early psychosis services and barriers and facilitators to specialized services for psychosis in the U.S.
Results: Family members self-identified as 40% Latinx, 30% Black, 14% Multi-racial, 10% Asian, and 3% American Indian/Alaska Native. Sixty-seven percent were female, and the average age was 46 years (SD=11.08). Majority (67%) of family members were parents, followed by siblings (11%). Family members reported participating in an average of four (SD=5.09) mental health programs prior to current services. Among the majority of family members' the help-seeking catalyst began with hospitalization and the first source of support occurred at the interpersonal level (e.g., relative or friend). At the community level, only one family members' pathway involved interaction with police as a source for help, yet five pathways included contact with a spiritual leader, as early as the second point of contact. The most reported contact with professional staff were with primary care doctors or nurses, followed by school counselors. Family members experiences prior to receiving specialized services were shaped by support (e.g., connections with other families with similar experiences), access (e.g., timely referrals, available services, bilingual staff), communication (e.g., being valued and listened to by clinicians), and knowledge (e.g., understanding of diagnosis, clinician awareness of community climate for racially diverse groups).
Conclusions: Family members sources for support were embedded with certain social groups and the services sought first were from non-mental health professionals. To improve help-seeking experiences and outcomes, concerted efforts should be made with disseminating information (e.g., early intervention resources in communities) to religious congregations, primary care professionals, school/college personnel, and employers. This has the potential to provide much needed support on the pathway to and step down from specialized services. Improving experiences and interactions with formal and informal sources within the community is imperative to reducing racial inequities in mental health. As such, additional research is needed to explore how these community contacts and places of support outside of early intervention programs are associated with individual outcomes. Supported by NIMH K01MH117457.

38. THE WORLDWIDE CHALLENGE OF COVID-19, SCHIZOPHRENIA, AND OTHER SERIOUS MENTAL ILLNESSES

Robert Yolken

Johns Hopkins University School of Medicine

Overall Symposia Abstract: The COVID-19 pandemic caused by the Coronavirus SARS-CoV-2 has presented major challenges in virtually every area of the world. These challenges are particularly daunting for persons with schizophrenia and other serious mental illnesses (SMI) as well as for families, health care providers, and policy makers. This session will describe the experience of COVID-19 among persons with schizophrenia and other SMI in 3 countries from around the world. The session will focus on clinical, demographic and psychiatric factors associated with rates of exposure, hospitalization, and vaccine response in persons with schizophrenia and other SMI during the COVID-19 pandemic.

Dr. Katlyn Nemani from New York, USA will present an analysis of the association between antecedent psychotropic use and risk of COVID-19 among 1958 people with SMI in a statewide psychiatric hospital system in New York between March 1 and July 1, 2020. She will discuss the high incidence of infection (50%) and case fatality (4%) in this cohort and report that decreased risk of infection was observed in association with second-generation antipsychotics and increased risk was found with valproic acid.

Dr. Mark Weiser from Tel Aviv, Israel will present the results of a nationwide study of testing, SARS-CoV-2 infection, hospitalization for COVID-19 disease, mortality, and rate of vaccinations, in patients with SMI. His study is based on 125,273 adults with SMI hospitalized in a psychiatric facility as compared to the age-adjusted national population. He will show that persons with SMI were less likely to be tested for COVID-19 infection and had lower rates of infection. However, among those individuals with SMI who were infected, the risks of COVID-19 hospitalization and attributed mortality were increased. Furthermore, age-adjusted rates of vaccination were lower in persons with SMI, particularly in those with non-affective psychotic disorders.

Dr Livia De Picker from Antwerp, Belgium will present an account of how the first scientific evidence of increased COVID-19 mortality risks in patients with severe mental illness became translated into national health policies across Europe. Meta-analytic results have convincingly demonstrated that patients with SMI are at increased risk for severe or fatal COVID-19 infection. These results have warranted an international call for action, including the launch of campaigns advocating for the priority vaccination. Psychiatrists and psychiatric researchers have played an important role in influencing policy. Furthermore, Dr. De Picker will present the results of a 1-year SARS-CoV-2 seroprevalence study among newly hospitalized psychiatric patients, linking exposure to COVID-19 to acute psychiatric presentations.

Dr. Faith Dickerson from Baltimore, USA will present an update of the effects of Coronaviruses and the COVID-19 pandemic in a cohort of persons with SMI and those without a psychiatric disorder. She will show that while persons with schizophrenia had increased levels of exposure to the seasonal Coronavirus OC-43, their rate of serological evidence of infection to SARS-CoV-2 did not differ from that of the other groups. In addition, persons with schizophrenia had a rate of completed immunization regimens and attained levels of antibody to SARS-CoV-2 similar to those of the persons without a psychiatric disorder. There was a significant decline in antibodies to SARS-CoV-2 in all of the groups over time indicating the likely need for booster doses.

The discussion will focus on similarities and differences among the populations with the goal of identifying shared risk factors, challenges, and goals for ongoing studies about the effects of COVID-19 in persons with schizophrenia and other SMI.

38.1 THE ASSOCIATION BETWEEN PSYCHOTROPIC MEDICATIONS AND COVID-19 RISK AMONG PEOPLE WITH SERIOUS MENTAL ILLNESS IN NEW YORK

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Background: Schizophrenia is associated with increased mortality in the setting of Covid-19 infection, and risk of viral exposure is increased in the enclosed milieu of inpatient psychiatric facilities. Psychotropic medications may contribute to risk of infection or adverse outcomes. We did not find increased risk of COVID-19 mortality associated with antipsychotic use in a cohort of adults with serious mental illness (SMI). However, individual medications may be associated with differences in risk of infection and adverse outcomes. We aimed to assess risk of COVID-19 infection and mortality associated with psychopharmacologic medications among patients in a statewide psychiatric hospital system during the peak of the pandemic in New York.

Methods: We conducted a retrospective cohort study of adult inpatients with SMI (including schizophrenia, schizoaffective disorder, and mood disorders with psychotic features) across 18 psychiatric hospitals operated by the New York State (NYS) Office of Mental Health (OMH). Patients who were continuously on census between March 1 and July 1, 2020 and received COVID-19 testing were included. Logistic regression was used to estimate the association between exposure to psychotropic medications and 1) risk of infection, the primary outcome 2) death, the secondary outcome after adjusting for demographic and medical risk factors.

Results: The sample included 1958 patients; 1442 (73.7%) were male and 516 (26.4%) female; mean age 51.4 years (SD 14.3). A total of 969 (49.5%) patients had laboratory-confirmed infection and of those, 38 (3.9%) died. Decreased risk of infection was observed in association with paliperidone (OR 0.53, 95% CI 0.37—0.76), p<.001), risperidone (OR 0.73, 95% CI 0.56—0.96, p=.02) and olanzapine (OR 0.77, 95% CI 0.61—0.96, p=.02), while valproic acid was associated with increased infection risk (OR 1.51, 95% CI 1.20—1.89, p<.001). First generation antipsychotics, clozapine, antidepressants, and benzodiazepines showed no significant association with infection or death in the fully adjusted model.

Conclusions: Risk of COVID-19 infection within inpatient settings is high; this is of particular concern among people with schizophrenia spectrum disorders who are at increased risk of fatal infection. Differences in risk of infection were observed in association with individual psychotropics in this cohort of inpatients with SMI. Further research is needed to understand the mechanism that underlies these findings and develop strategies to mitigate risk.

38.2 COVID-19 AND SEVERE MENTAL ILLNESS: TESTING, INFECTION, HOSPITALIZATION, MORTALITY AND VACCINATION RATES IN A COUNTRYWIDE STUDY

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Background: Previous studies on COVID-19 in persons with severe mental illness (SMI) have reported a more severe course of disease and higher rates of mortality compared with the general population. The objective of the current study was to assess rates of testing, infection, hospitalization for COVID-19, mortality, and vaccinations, in patients with SMI.
Methods: This cohort study linked Israeli national databases, including all persons ever hospitalized in a psychiatric ward for SMI, and COVID-19 testing, infection, hospitalization, mortality, and vaccinations, between March 1st 2020 and March 31st 2021. We used registries including the entire population of Israel, and included 125,273 persons aged 18 and above ever hospitalized in a psychiatric facility with SMI (ICD-10 F10-F69 or F90-F99), compared to the total population, n=6,143,802. The main outcome was rates of testing for and infection with COVID-19, COVID-19 hospitalization, mortality attributed to COVID-19 and all-cause mortality among the infected, and rates of vaccination. Analyses were age and sex specific, and adjusted for age. Relative risk for these outcomes was assessed using logistic regression.
Results: Compared with the total population, persons with SMI were less likely to be tested for COVID-19, 51.2% (95% CI: 50.8-51.7) vs 62.3% (95% CI 62.2-62.4) and had lower rates of infection with COVID-19, 5.9% (95% CI: 5.8-6.1) vs 8.9% (95% CI: 8.9-8.9). Among those infected, risks for COVID-19 hospitalization, COVID-19 attributed mortality and all-cause mortality were higher for persons with SMI than those without, adjusted odds ratios were 2.10; (95% CI: 1.96-2.25), 1.76; (95% CI: 1.54-2.01) and 2.02; (95% CI: 1.80-2.28), respectively. These risks were even higher for persons with non-affective psychotic disorders and bipolar disorder. Age adjusted rates of vaccination were lower in persons with SMI, 60.4% (95%CI: 59.9-60.8) vs 74.9% (95%CI: 74.8-75.0) in the total population, and particularly low for persons with non-affective psychotic disorders, 56.9% (95% CI: 56.3-57.6).
Conclusions: This study highlights the need to increase testing for COVID-19 in persons with SMI, closely monitor those found positive, and to reach out to encourage vaccination.

38.3 PROTECTING PATIENTS WITH SERIOUS MENTAL ILLNESS AGAINST COVID-19 RISKS: TARGETED ACTIONS IN EUROPE

Livia De Picker*[1], Benedetta Vai[2], Mario Gennaro Mazza[3], Kawtar El Abdellati[4], Robert Yolken[5], Alexandre Lucas[6], Steven Fried[6], Violette Coppens[4], Manuel Morrens[4], Marion Leboyer[7]

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Background: The first SARS-CoV-2 vaccine was approved by the European Medicines Agency on December 21st 2020 for authorization across the European Union, a second one on January 6th 2021. By then the first scientific evidence had emerged indicating that patients with serious mental illness (SMI) are at increased risk for severe or fatal COVID-19 infection, but it was unclear if policymakers would take note of these risks and include patients with

serious mental illness as high risk group eligible for priority vaccination against COVID-19. We initiated a European scientific initiative, which received endorsements and input from the five major European psychiatric organizations (ECNP, EPA, EUFAMI, GAMIAN-Europe and UEMS Psychiatry), with the aims of actively monitoring the state of the evidence on COVID-19 risks in patients with pre-existent SMI, and to ensure adequate translation of these findings into public health policy.

Methods: We systematically (1) reviewed national COVID-19 vaccine deployment plans across 20 European countries until February 10, 2021; and (2) searched Web of Science, Cochrane, PubMed, and PsycINFO databases between Jan 1, 2020, and March 5, 2021, for original studies reporting data on COVID-19 outcomes in patients with pre-existent psychiatric disorders compared with controls. We modelled random-effects meta-analyses to estimate crude and adjusted odds ratios for mortality after SARS-CoV-2 infection as the primary outcome, and hospitalization and ICU admission as secondary outcomes.

Finally, in order to gauge the burden of COVID-19 infections on acute psychiatric morbidity, we performed a SARS-CoV-2 seroprevalence timeseries analysis of acute psychiatric hospitalizations to a large university psychiatric hospital in Belgium (UPC Duffel). All patients admitted to the hospital between May 5, 2020 and April 1, 2021 were included in the study. Serological evidence of prior COVID-19 exposure was investigated at John Hopkins University, Baltimore, USA and at INSERM, Paris, France.

Results: Until February 10, 2021, while the European vaccination campaign was ongoing, only eight of 20 countries explicitly mentioned psychiatry or mental illness in their national vaccine strategy documents. Several countries prioritized institutional residents regardless of any diagnosis, but only four countries had some form of higher vaccination priority for outpatients with SMI. These findings prompted an international call for action and advocacy campaign, which resulted in policy changes in several countries. The systematic literature search identified 841 studies, of which 33 were included in the systematic review and and 23 in the meta-analysis. SMI patients had significantly higher adjusted mortality estimates (aOR 1·55 [1·30–1·85]) than did patients with other mental disorders (aOR 1·09 [0·92–1·29]). No significant differences were identified in the incidence of hospitalization and ICU admission. 707 patients were included in the seroprevalence study, of which 336 with SMI. Our findings indicate 65,4% of all patients admitted between January 1 and April 1, 2021 had been exposed to COVID-19.

Conclusions: Meta-analytic results have convincingly demonstrated that patients with SMI are at increased risk for severe or fatal COVID-19 infection. These results have warranted an international call for action, including the launch of campaigns advocating for the priority vaccination for these persons. Psychiatrists and psychiatric researchers continue to play an important role in influencing and shifting health policies for SMI patients.

38.4 EXPOSURE TO CORONAVIRUSES AND RESPONSE TO THE COVID-19 VACCINE IN PERSONS WITH SCHIZOPHRENIA AND OTHER SERIOUS MENTAL ILLNESSES

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

Background: Prior to the current COVID-19 pandemic, we showed that individuals with serious mental illness had an increased prevalence of infections due to several strains of seasonal, non-SARS Coronaviruses. In the current study, we measured antibodies to both

seasonal non-SARS and SARS-2 Coronaviruses in a cohort of persons with schizophrenia, with other serious mental illnesses, and without a psychiatric disorder.

Methods: A total of 325 blood samples were obtained from 196 persons in the period Sept 2017 – Sept 2021. Participants included 37 persons with schizophrenia, 64 with bipolar disorder, 62 with major depression and 33 without a psychiatric disorder. Of these 196 persons, a total of 151 had at least one sample obtained after the start of the COVID-19 pandemic in February 2020. Following the introduction of the COVID-19 vaccines in December 2020, information was collected about the date and type of vaccine received. In this same time period, a total of 179 blood samples were obtained from 77 persons including 24 with schizophrenia, 19 with bipolar disorder, 18 with major depression, and 16 without a psychiatric disorder.

Antibodies to Coronaviruses were measured by means of chemiluminescent immunoassays. The seasonal Coronaviruses studied included OC43, 229E, NL63, and HKU1, the predominant strains in the US population. We also measured antibodies to 3 antigens on the SARS-2 virion surface (S1 RBD, S1 NTD, and spike) as well as the SARS-2 nucleoprotein. Chemiluminescence assays were also used to measure the circulating levels of 19 cytokines and chemokines in the serological samples.

The relationships between antibody levels, clinical diagnosis, and vaccine administration were analyzed by means of mixed effects models employing age, sex, and race as covariates. Since the Covid-19 vaccines only generate antibodies to the SARS-2 surface proteins, natural infection was defined by elevated levels of antibodies to both the SARS-2 surface and nucleocapsid proteins.

Results: Persons with schizophrenia had increased levels of antibodies to Coronavirus OC-43 ($t=2.3$, $p=.012$) compared to the other groups. The levels of antibodies to OC-43 were correlated positively with levels of the cytokine TNF-alpha and negatively with IL-1 beta (both $p<.001$).

Serological evidence of natural SARS-2 infection was documented in 23.5% of the non-psychiatric participants but only 10.7% of the persons with schizophrenia, 8.6% with bipolar disorder, and 4.9% with major depression. None of these infections resulted in hospitalization.

Complete COVID-19 immunization regimens were achieved in 88.2% of the non-psychiatric participants, 81.5% of the persons with schizophrenia, 60.0% of those with bipolar disorder and 41.7 % of those with major depression. The levels of antibodies following complete immunization regimens did not differ significantly among the groups.

There were not significant differences among groups in the type of vaccine used. There was a significant decline in antibody levels over time (coef.- 016, 95% CI -.02, -.008, $p<.001$). The levels of the cytokines IL-1-beta and IL-12p70 were significantly associated with receipt of a vaccine ($t=3.28$, $p<.002$; $t=2.8$, $p<.005$, respectively).

Conclusions: Persons with schizophrenia had higher levels of exposure to the seasonal Coronavirus OC43 but were less likely to show evidence of natural infection with the SARS-2 Coronavirus than the non-psychiatric group. Individuals with schizophrenia had a high rate of completed COVID-19 vaccination regimens, similar to that of the non-psychiatric group. Continued surveillance of these populations is warranted including the possible immune effects of the vaccines and declines in the levels of antibodies to SARS-2 that would suggest a need for vaccine booster doses.

39. BROADENING THE VIEW ON RISK FACTORS AND THE CLINICAL IMPACT OF PSYCHOTIC EXPERIENCES IN YOUNG PEOPLE

Sara van der Tuin

UMCG

Overall Symposia Abstract: The development of psychosis is complex. Psychotic disorders develop gradually over time with expressions of psychosis already present before onset of clinical illness. Psychotic experiences are subclinical experiences of psychotic symptoms such as hallucinations and delusions that can exist outside the context of a clinical disorder. When distressing or persistent, psychotic experiences index an increased risk for later psychotic disorder. Better understanding of the nature of such psychotic experiences, as well as of factors that increase the risk of persistence of such experiences, is crucial in developing better and timely interventions for psychosis. As psychotic disorders often emerge in young adulthood, this research is especially relevant in young people. The four presentations in the current symposium examine risk factors and the potential clinical impact of early psychosis expression in young people in different contexts.

Dr. Koen Bolhuis will present data from the Generation R study encompassing of 3068 mother-offspring dyads. He found that maternal history of childhood adversity increases the risk of psychotic experiences in offspring through offspring exposure to childhood adversity. In other words, intergenerational transmission of adverse life events influences the etiology of psychosis vulnerability. This study highlights the need for a broad take on risk factors for psychotic symptoms by showing the importance of a familial-based approach.

Dr. Salma Khaled will present results from her study on the relationship between stress reactivity and psychotic experiences, insomnia and depression-anxiety symptoms in a non-clinical sample of students in Qatar. She found direct associations between insomnia and depression-anxiety with psychotic experiences, but no direct association between psychotic experiences and perceived social stress. Possibly, social stress shares common pathways with psychotic experiences that are predominantly emotion-based. These results can have important implications for early detection and prevention of severe mental illness in non-clinical individuals in Qatar.

Dr. Martin K. Rimvall will present secondary analyses from the Mind My Mind (MMM), a randomized controlled trial of a transdiagnostic cognitive behavioral therapy intervention encompassing 396 youths aged 6-17 years. The intervention was found effective in reducing the impact of common mental health problems. Results from the secondary analyses regarding psychotic experiences show that psychotic experiences at baseline did not moderate the positive effects of the treatment, providing evidence that psychotherapeutic interventions should be offered to help seeking youths, irrespective of the co-occurrence of psychotic experiences.

Sara van der Tuin, PhD candidate, will present her work on dynamics between transdiagnostic symptoms in individuals in early clinical stages for psychosis from the Mapping Individual Routes of Risk and Resilience (Mirorr) study. She examined whether certain symptom dynamics are clinical stage specific (top-down) and, whether certain symptom dynamics can meaningfully cluster individuals (bottom-up). Theory-based subgroups distinguish between individuals based on psychotic severity while data-driven subgroups distinguish individuals based on overall psychopathological severity.

The symposium will be chaired by Sara van der Tuin and co-chaired by dr. Johanna Wigman. Dr. Ian Kelleher will be discussant. Both Dr. Wigman and Dr. Kelleher are well-established researchers in the field of early psychosis.

39.1 A PROSPECTIVE COHORT STUDY ON THE INTER-GENERATIONAL TRANSMISSION OF CHILDHOOD ADVERSITY AND SUBSEQUENT RISK OF PSYCHOTIC EXPERIENCES IN ADOLESCENCE

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Background: Intergenerational transmission of adversity refers to the observation that parents who have been exposed to childhood adversity are more likely to have children who will also be exposed to adversity. This cycle of trauma can have negative consequences for the development of mental health problems in offspring, including psychotic symptoms. This is particularly relevant since previous studies have suggested a potentially causal relationship between adversity in childhood and psychotic symptoms and illness. However, the role of familial risk, i.e. intergenerational transmission of adversity, in the relationship between adverse life events and psychosis vulnerability remains to a large extent unclear. In this study, we explored whether offspring childhood adversity mediated the relationship between maternal childhood adversity and offspring psychotic experiences. Furthermore, we examined the role of maternal psychopathology in this relationship as an additional mediating mechanism.
Methods: This study was embedded in the Generation R Study, including 3068 mother-offspring dyads. Maternal childhood adversity was assessed using the Childhood Trauma Questionnaire and offspring childhood adversity was assessed with a mother-reported interview about a range of adverse events when the child was on average ten years old. Child hallucinatory and delusional experiences were examined using self-report questionnaires at mean age 14 years. Maternal psychopathology was assessed prenatally as well as at 3 months post-natal. Structural equation mediation models were conducted to explore whether offspring childhood adversities and maternal psychopathology mediated the relationship between maternal childhood adversity and offspring psychotic experiences.
Results: Hallucinatory and delusional experiences were reported by approximately 12% of the sample, and 24.2% and 5.2% of the offspring were exposed to 1-2 or 3 or more events, respectively. Offspring exposure to adversities mediated the association of maternal childhood adversity with offspring hallucinations (indirect effect: $\beta = 0.011$, $p < 0.001$; proportion mediated = 0.21) and delusions (indirect effect: $\beta = 0.010$, $p = 0.001$; proportion mediated = 0.16). In a serial mediation model of the association between maternal childhood adversity and offspring psychotic experiences mediated through maternal psychopathology and subsequently via offspring childhood adversity, there was a significant mediation effect on offspring hallucinations – but not delusions – as the outcome (indirect effect: $\beta = 0.003$, $p = 0.001$; proportion mediated = 0.07).
Conclusions: Maternal history of childhood adversity increases the risk of offspring psychotic experiences through offspring exposure to childhood adversity, suggesting that intergenerational transmission of adverse life events is of great importance in the aetiology of psychosis vulnerability. The current results contribute to a more complete understanding of the familial risk factors pertaining to psychotic symptoms across development. Furthermore, these

findings call for a familial-based approach in the treatment as well as screening and prevention of psychotic symptoms in childhood and adolescence.

39.2 PSYCHOTIC EXPERIENCES AS EFFECT MODIFIERS IN YOUTHS WITH COMMON MENTAL HEALTH PROBLEMS REFERRED TO TRANSDIAGNOSTIC COGNITIVE AND BEHAVIORAL THERAPY: SECONDARY ANALYSES FROM THE MIND-MY-MIND RANDOMIZED TRIAL

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Background: Psychotic experiences (PEs), characterized by hallucinations, delusions and subjective thought disturbances that do not conform to psychotic disorders, are common in youths with emotional and behavioral mental health problems. PEs have been increasingly well-described as a marker of more severe general psychopathology. However, few studies have examined the significance of PEs in clinical and help-seeking populations. Our objective was to examine whether PEs are associated with a differential response to early intervention with transdiagnostic cognitive and behavioral psychotherapy (CBT) directed towards non-psychotic mental health problems and disorders.

Methods: This study reports secondary analyses from the randomized Mind My Mind (MMM) trial, randomizing 396 help-seeking youths with emotional and behavioral problems aged 6-17 years to either CBT (MMM) or community management as usual (MAU). The MMM intervention consisted of 9-13 CBT sessions delivered by community psychologists, whereas MAU received 2 coordination visits in addition to usual care. Findings from the RCT showed that MMM was superior to MAU in reducing parent-reported impact of the child's mental health problems (primary outcome) using the Strengths and Difficulties Questionnaire (SDQ), as well as various other measures of psychopathology and functioning.

Presence (PE+) or absence (PE÷) of PEs during the last four weeks and/or lifetime before were assessed by clinical interviews at baseline performed by trained psychologists. Four types of PEs (auditory verbal hallucinations, visual hallucinations, delusional ideation and subjective thought disturbances) were evaluated. Based on the parent-reported SDQ: impact of child's mental health problems (primary outcome, rated 0-10), response (≥1-point reduction in SDQ Impact score), and total difficulties score (rated 0-40) at week 18 for the intention-to-treat population, we estimated PE-subgroup differences using analysis of covariance (ANCOVA) model estimates for the continuous (SDQ) outcomes, and risk difference for the dichotomous (number of SDQ responders), and assessed if any of four different PE-scenarios could effect-modify the overall beneficial effects of MMM versus MAU

Results: Lifetime rating of any PE was present in a subgroup amounting to 19% of the young people at baseline. None of the effects of MMM versus MAU were moderated by the presence of PEs at baseline. The differences in mean change from baseline to week 18 (net benefits) in SDQ impact for PEs+ -0.89 (95%CI -1.77 to -0.01) and for PE÷ -1.10 (95%CI -1.52 to -0.68), corresponding to a between subgroup difference of 0.21 [95%CI -0.77 to 1.18], p-value for

interaction 0.68; SDQ total score for PEs+ -2.19 (95%CI -4.12 to -0.26) and for PE÷ -2.01 (95%CI -2,94 to -1.09), between subgroup difference -0.18 [95%CI -2.32 to 1.96] p-value for interaction 0.87); and risk differences for SDQ response for PEs+ 0.28% (95%CI 0.07% to 0.49%) and for PE÷ 0.26% (95%CI 0.16% to 0.36%), between subgroup difference 0.02% [95%CI -0.22% to 0.25%], p-value for interaction 0.89). The overall findings did not differ when considering the presence of PEs restricted to the last four weeks, or only auditory verbal hallucinations in in the last four weeks or ever.
Conclusions: We explored whether PEs moderated the treatment effects of a transdiagnostic CBT intervention aimed at common mental health problems and found no evidence suggesting that young people with PEs should be treated differently. The beneficial effects of the transdiagnostic CBT program did not differ by the presence or absence of PEs at baseline; and youths who seek help for emotional and behavioral problems and disorders should be offered psychotherapeutic interventions irrespective of co-occurring PEs.

ClinicalTrials.gov Identifier: NCT03535805

39.3 SOCIAL STRESS REACTIVITY AS A VULNERABILITY TRAIT TO PSYCHOTIC EXPERIENCES IN YOUNG ADULTS OF A RAPIDLY DEVELOPING COUNTRY: AN EXPLORATORY STUDY

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Background: Increased daily life stress reactivity maybe an important endophenotype for psychotic disorders. Most available literature shows strong associations between sleep- and emotional-based reactivity and psychotic experiences, but less is known about the role of social stress reactivity in vulnerability for psychotic symptoms including hallucinations and delusions in non-clinical samples. Qatar is a small, rapidly developing nation in the Arabian Peninsula with a relatively younger population (median age 34) than most developed countries.
Methods: A cross-sectional probability sample of male and female participants (N=2000) were invited to participate in the study via survey between October 2019 and February 2020. A total of 598 participants completed the survey. Subscales from the Specific Psychotic Experiences Questionnaire (SPEQ) were used to assess paranoia (15 items) and hallucinations (9 items). The 8-item Sleep Condition Indicator (SCI) was used to index insomnia symptoms with lower scores indicating poor sleep. Ultra brief measures of depression (Physician Health Questionnaire 2-item: PHQ2) and anxiety (Generalized Anxiety Disorder 2-item: GAD2) were also used to assess mood-related symptoms. The 23-item Perceived Stress Reactivity Scale (PSRS) were used to assess five dimensions of social stress reactivity including prolonged reactivity (ProlReac), work-load reactivity (WlodReac), social conflict reactivity (SconReac), failure reactivity (FailReac), and social evaluation reactivity (SevlReac). These five dimensions of stress reactivity were regressed on hallucinations, delusions, insomnia, and depression-anxiety in addition to standard demographic variables of age, gender, and nationality. Standardized beta coefficients and corresponding p-values are reported. All analyses were conducted in MPlus version 8.0.
Results: Results A confirmatory measurement model without regression paths fitted the data well: the Root Mean Square Error Of Approximation (RMSEA) = 0.03 (90%CI 0.028 to 0.033), the comparative fit index (CFI) = 0.926, the Tucker–Lewis index (TLI) = 0.920, and the Standardized Root Mean Square Residual (SRMR) = 0.048. Hallucinations were significantly correlated with paranoia (r=0.539, p< 0.0001) SCI (r=-0.247, p< 0.0001), and depression-anxiety (r =0.422, p< 0.0001). Neither hallucinations nor paranoia were significantly associated

with any of the PSRS subscales. Both SCI (β = -0.263, p=0.001) and depression-anxiety (β = 0.273, p< 0.0001) were significantly associated with prolonged reactivity. Only depression-anxiety were significantly associated with WlodReac (β =0.575, p< 0.0001), SconReac(β =0.428, p< 0.0001), FailReac (β =0.334, p< 0.0001), and SevlReac (β =0.459, p< 0.0001).
Conclusions: Insomnia and depression-anxiety were associated with experiences of paranoid delusions and hallucinations. However, no direct association between positive psychotic symptoms and any subtype of perceived social stress was found. Insomnia was only associated with prolonged stress reactivity. Depression-anxiety were significantly associated with all PSRS subscales. These initial findings suggest that social stress share common pathways with hallucinations and paranoid delusions that are predominately emotion-based with potentially important implications for early detection and prevention of severe mental illness in Qatar's context.
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39.4 GROUP, SUBGROUP AND PERSON SPECIFIC SYMPTOM ASSOCIATIONS IN INDIVIDUALS AT DIFFERENT LEVELS OF RISK FOR PSYCHOSIS: A COMBINATION OF THEORY-BASED AND DATA-DRIVEN APPROACHES

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Background: Understanding more about the development of psychosis, and more specifically, the risk of developing psychosis may help us to better detect and treat individuals along the psychosis continuum. The clinical stating model proposes that psychosis does not emerge abruptly, but rather gradually through different stages of severity. What drives this progression is not yet fully understood. Dynamics between symptoms may reveal insights into mechanisms through which individuals progress through the clinical stages. In this study, we combined a top-down (theory-based) and bottom-up (data-driven) approach to examine which dynamics between symptoms arise on group-level, on subgroup levels, and on individual levels in individuals in the early clinical stages for psychosis.
Methods: Data came from N=96 individuals, aged 18-35, at different levels of risk for psychosis divided over four theory-based subgroups (n1=25, n2=27, n3=24, n4=20). Each subsequent subgroup represented a higher risk for psychosis based on the early clinical stages (stages 0-1b). All individuals completed 90 days of daily diaries, totaling 8640 observations. Confirmatory Subgrouping Group Iterative Multiple Model Estimation (CS-GIMME) and subgrouping (S-)-GIMME were used to examine group-level associations, respectively theory-based and data-driven subgroups associations, and individual-specific associations between daily reports of depression, anxiety, stress, irritation, psychosis and confidence.
Results: One contemporaneous group path between depression and confidence was identified. CS-GIMME identified several subgroup-specific paths and some paths that overlapped with other subgroups as well as additional paths that were unique to specific individuals. S-GIMME identified two data-driven subgroups, with one subgroup reporting more psychopathology and lower social functioning. This subgroup contained most individuals from the higher stages and those with more severe psychopathology from the lower stages, and shared more connections between symptoms.

Conclusions: Although subgroup-specific paths were recovered, no clear ordering of symptom patterns was found between different early clinical stages. Theory-based subgrouping distinguished individuals based on psychotic severity, whereas data-driven subgrouping distinguished individuals based on overall psychopathological severity. The early clinical stages might be more transdiagnostic, with psychotic symptomatology only becoming more prominent in later stages. Future work should compare the predictive value of both approaches, i.e. theory-based, focusing on psychotic symptomatology or data-driven, based on general psychopathology.

40. LEVERAGING BASIC AND CLINICAL SCIENCES TO UNDERSTAND SOMATIC AND PSYCHOPATHOLOGICAL MANIFESTATIONS IN SCHIZOPHRENIA SPECTRUM DISORDERS

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University Medical Center Utrecht

Overall Symposia Abstract: While the etiology of schizophrenia spectrum disorders (SSDs) is unknown, accumulating evidence suggests existence of premorbid systemic inflammation and disturbances in metabolism, including insulin resistance and increased adiposity. Recent work has focused on hypotheses related to neuroinflammation and dysfunctional bioenergetics in neurons and glia linked to illness psychopathology, which intriguingly may overlap with brain pathways that control metabolic homeostasis. Despite these promising new insights, progress in the field is hindered by the difficulty of disentangling the relative contributions of illness biology, lifestyle factors, and antipsychotic drug (APD) treatment. Importantly, APDs may impact neuronal control of metabolism, brain bioenergetics and neuroinflammation, making assessment of dependent measures as well as the development of disease and treatment response biomarkers difficult. To address this timely and clinically relevant issue, we propose an innovative panel, chaired by Dr. Wiepke Cahn (Utrecht University, NL) with the following presentations:

1) Dr. Bjorn Ebdrup (University of Copenhagen, Denmark) will present data on a novel serum panel of biomolecules, proteoglycans and glycosaminoglycans capable of discriminating with high accuracy antipsychotic-naïve individuals with SSDs from healthy controls. These novel findings support disruptions in the blood brain barrier and neuroinflammation as a biomarker of schizophrenia which precedes APD treatment, and which may map on to specific domains of psychopathology.

2) Dr. Margaret Hahn (University of Toronto, Canada) will present novel findings examining adiposity-independent effects of APDs on leptin action in the brain of rodents in relation to energy and feeding homeostasis. These data support that olanzapine spares central leptin activity in control of feeding and metabolic flexibility, but that conversely leptin is unable to overcome olanzapine-induced glucose dysregulation.

3) Dr. Anthony Vernon (Kings College London, UK) will present novel data on the effects of APDs on synaptic engulfment, using an in vivo rodent model of clinically comparable antipsychotic exposure. These data support the view that whilst APDs modulate microglia form and function, they do not appear to elicit microglial-driven synaptic refinement.

4) Dr. Rob Mccullumsmith (University of Toledo, USA) will present data on off-targets effects of APDs, demonstrating that perturbations of bioenergetic and neuroinflammatory systems in

patients with schizophrenia may be secondary to serine and threonine protein kinase modulatory effects of APDs.

Taken together, this fresh look at markers of neuroinflammation in SSDs and the role(s) of APDs on related novel central pathways will provide new insights into pathophysiology underlying the somatic and clinical manifestations of this devastating disorder. Discussion on how to integrate the existing lines of investigation and the implications for therapeutic interventions moving forward will be led by Dr. Laura Rowland (Division of Translational Research, National Institutes of Mental Health, USA).

40.1 SHEDDING PATTERNS OF GLYCOCALYX IN PLASMA: A NOVEL BLOOD MARKER FOR PSYCHOSIS?

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Background: Glycocalyx (GLX) is a layer of proteoglycans and glycosaminoglycans on the endothelial luminal surface and plays a vital role in blood-brain barrier (BBB) function. A loss of GLX, denoted 'shedding', can result from inflammation, and lead to BBB disruption. Shedding of GLX is increased in response to brain insults and in neuroinflammatory disorders. The etiology of schizophrenia is largely unknown, but infection and autoimmune disease are well-established risk factors for schizophrenia spectrum disorders. Peripheral inflammation, neuroinflammation, and BBB dysfunction in schizophrenia could be linked through a loss of GLX components in the neuroendothelia.

We investigated whether a panel of 15 GLX molecules in plasma can discriminate antipsychotic-naïve, first-episode schizophrenia spectrum patients from healthy controls (HC).

First, we tested if the GLX shedding patterns, denoted 'the composite GLX signal', could classify groups. Next, within the patient group only, we explored whether the composite GLX signal could classify high vs. low symptom severity.

Methods: Patients (n=49) fulfilled ICD-10 criteria for schizophrenia spectrum disorder and were lifetime naïve to antipsychotic exposure. HC (n=51) were matched to patients on gender, age, and parental socioeconomic status.
Blood samples were collected, plasma isolated, and the hydrophilic layer extracted. From this, 15 GLX markers were detected with immunoblotting using optimized protocols. Signals were imaged, background corrected, and analyzed for optical density.

Patients' psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS).

Seven machine learning (ML) models were run separately using nested cross-validation to reduce overfitting. Models yielded estimates of diagnostic (classification) accuracy.

Within patient group, we explored associations between the composite GLX signal and psychopathology. PANSS subcategories and total scores were split by the mean score to classify either 'high' or 'low' impact of psychopathology. Gender, CRP levels, body mass index and smoking status were included as covariates.

Significance of the classification accuracies were tested with a Wilcoxon nonparametric test against a dummy model representing randomness. Differences were deemed significant when $p<0.05$ after Holm-Bonferroni correction.

Results: Univariately, five of the 15 GLX markers were significantly increased in patients compared to HC ($p<0.0001$), passing Holm-Bonferroni correction.
In the ML models of the composite GLX signal, the mean diagnostic classification accuracy was 82% (range 89-72%; $p= <0.00001$ to 0.009). All models remained statistically significant after Holm-Bonferroni correction.

Regarding psychopathology, the composite GLX signal significantly classified patients with high vs low PANSSpositive, and PANSSnegative subscores, however, these results did not survive Holm-Bonferroni correction.

Conclusions: To our knowledge this is the first study to investigate the impact of GLX shedding patterns in patients with schizophrenia spectrum disorder. We find that composite GLX signal from plasma differentiates antipsychotic-naïve patients from HC with high accuracy. Although not significant after correcting for multiplicity, our findings suggest that the GLX signal may map onto core symptom domains, i.e. positive and negative symptoms in schizophrenia spectrum patients.
Biologically, the collective pattern of increase in GLX related markers in plasma indicates a thinning of the GLX layer, which may in turn be associated with BBB disruption and neuroinflammation.

40.2 EFFECTS OF ACUTE OLANZAPINE EXPOSURE ON CENTRAL LEPTIN-MEDIATED REGULATION OF ENERGY HOMEOSTASIS

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Background: Effects of illness biology, life-style factors, and metabolic adverse effects of antipsychotic drugs (APD)s contribute to exceedingly high rates of metabolic comorbidity in schizophrenia spectrum disorders (SSDs). Leptin is a key metabolic hormone secreted from adipose tissue, which acts through central and peripheral mechanisms to regulate metabolism. Hyperleptinemia has been observed in SSDs. However, it is unknown if APDs cause leptin resistance, and whether this occurs through direct impairments of leptin action in the brain, or as a secondary effect of APD-induced increased adipose mass. In the present study, we set out to explore whether the APD olanzapine, prior to increased adiposity, could interfere with intracerebroventricular (ICV) leptin-mediated regulation of food intake and energy homeostasis.

Methods: Male Sprague Dawley rats were assigned to 4 treatment groups (ICV-peripheral): Vehicle (VEH)-VEH (n =6), Leptin (LEP)-VEH (n = 6), LEP-olanzapine (OLZ) (n = 7), VEH-OLZ (n = 6). Following acclimatization to metabolic cages, rats received acute injections of LEP (3ug) or VEH into the 3rd ventricle, and OLA (2mg/kg) or VEH subcutaneously at the beginning of the light (8AM, t=0) and dark (8PM, t=12h) cycles. Indirect calorimetry was used to calculate respiratory exchange ratio (RER), and heat production. RER is indicative of substrate utilization, with higher values representing greater carbohydrate utilization. Cumulative food intake was measured at 12 hour intervals (t=12h and 24 h). Intraperitoneal glucose tolerance tests (IPGTTs) were performed in overnight fasted rats.
Results: Treatment with OLZ (VEH-OLZ) in the light cycle resulted in a rapid decrease in RER ($p<0.05$, vs. VEH-VEH), recovering to levels of VEH-treated rats, approximately 3 hours post-treatment. During the dark cycle when rats are feeding and should be shifting to carbohydrate utilization, OLZ resulted in a rapid and sustained reduction in RER in the absence of changes in food intake, suggesting an inappropriate shift to fat utilization ($p<0.05$, vs VEH-VEH). Treatment with ICV-leptin resulted in a gradual reduction in RER in the light cycle (LEP-VEH, vs VEH-VEH, $p<0.05$), which was sustained throughout the dark cycle. This was also accompanied by reductions in food intake. Similar to LEP-VEH animals, co-treatment with LEP and OLZ resulted in sustained reductions in RER as compared to VEH-VEH ($p<0.05$) in the light and dark cycle, and were also accompanied by reductions in food intake. Leptin (LEP-VEH) and LEP-OLZ treated animals demonstrated reduced cumulative food intake in the dark cycle relative to VEH-VEH and VEH-OLZ groups ($p<0.01$). During IPGTTs, acute OLZ exposure resulted in significantly higher blood glucose levels in both VEH-OLZ and LEP-OLZ groups compared to VEH-VEH and LEP-VEH groups ($p<0.01$).
Conclusions: Both LEP and OLZ reduce RER during the light and dark cycles, suggesting a shift in fuel preference from carbohydrates to fats. In the case of OLZ, this occurred independently of changes in food intake, and has previously been shown to represent an inappropriate response given simultaneous impairment of lipolysis and reduced availability of fat as a substrate. Intriguingly, we demonstrate that central LEP is able to reduce food intake in the presence of OLZ, suggesting feeding regulation mediated by LEP signalling in the brain is not acutely impaired by antipsychotics. Conversely, LEP is unable to mitigate OLZ-induced dysglycemia, suggesting involvement of disparate pathways regulating feeding and glucose homeostasis, and possible induction of acute LEP resistance by OLZ.

40.3 EXAMINATION OF DIFFERENTIAL CANCER RATES IN SCHIZOPHRENIA: OFF TARGET EFFECTS OF ANTIPSYCHOTIC DRUGS ON PROTEIN KINASES INVOLVED IN BIOENERGETIC HOMEOSTASIS AND NEUROINFLAMMATION

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Background: Overall cancer rates in schizophrenia are lower than the general population, but previous epidemiological studies of cancer rates in schizophrenia did not fully account for confounding variables such as smoking and substance abuse. We sought to confirm lower cancer rates in schizophrenia and explore mechanisms responsible for this unexpected observation. Gene expression analyses of cancer cells treated with antipsychotic drugs found decreased expression of protein kinases involved in cell survival, proliferation, neuroinflammation, and bioenergetic homeostasis. While most cell culture studies have focused dopamine 2 receptor antagonism as a mechanism of action for lower cancer rates in schizophrenia, we postulate that "off-target" effects of antipsychotic drugs include inhibition

of AKT and PIM kinases, accounting for this interesting observation. We applied a three-pronged approach to test this hypothesis: 1) epidemiological confirmation of reduced cancer incidence rates in patients with schizophrenia, 2) bioinformatic analyses of perturbagen/drug structural moieties and gene expression data, and 3) in vitro protein kinase activity-based drug screening.
Methods: The Healthcare Cost and Utilization Project (HCUP) dataset was used to identify health outcomes for patients with schizophrenia. Schizophrenia patients were matched to controls by age and sex (n=140476/group). TriNetX, an international administrative healthcare dataset, was used as a confirmation dataset. A stratified analysis was conducted to determine cancer risk among patients with schizophrenia (N=36,695) as compared to controls (N=237, 488). Structure-Activity relationship analyses were conducted to assess antipsychotics antineoplastic properties. 53 antipsychotics were virtual screened for similarity in gene expression across a library of 41,000 small molecules. Chemical similarity was determined across the same library to identify shared moieties between antipsychotics and library compounds. Protein kinase activity arrays and biochemical protein kinase assays were used to assess the effects of study drugs on recombinant PIM1 protein kinase activity.
Results: Cancer incidence risk for patients with schizophrenia were decreased across all cancer subtypes in the HCUP dataset despite patients with schizophrenia having higher smoking rates (Imputed lung cancer RR = 0.15). The TriNetX dataset confirmed decreased cancer incidence among patients with schizophrenia with an especially pronounced decrease in bladder and lung cancer when accounting for smoking (RR = 0.24 and 0.22, respectively). In our bioinformatics analyses, a known PIM and AKT inhibitor, 10-DEBC, was identified as structurally and transcriptionally similar to several phenothiazine antipsychotics. The Tanimoto structural similarity coefficient for thioridazine versus 10-DEBC was 0.87 and the transcriptional similarity in A549 NSCLC cells was 0.475. PIM1 activity was inhibited on the protein kinase activity array in a concentration dependent manner by thioridazine.
Conclusions: Epidemiological data confirmed reduced risk of cancer incidence in patients with schizophrenia when accounting for age and smoking rates using the Healthcare Cost and Utilization Project (HCUP). Bioinformatics analyses of perturbagen structure and transcriptional profiles suggest a medication effect, as opposed to genetic factors (such as single nucleotide polymorphisms risk alleles for schizophrenia), as a main contributor to the observed decrease in cancer rates. In vitro kinase activity studies using a microarray platform indicate an inhibitory effect of our study drugs on PIM1 kinase in vitro. Importantly, PIM1 kinase is a known regulator of neuroinflammatory and bioenergetic processes, suggesting that antipsychotic drugs may be impacting cancer risk by modulating these pathways.

40.4 OLANZAPINE ALTERS MICROGLIAL MORPHOLOGY WITHOUT IMPACTING SYNAPTIC ENGULFMENT IN THE RAT BRAIN

Mrityunjoy Mondal[1], Shiden Solomon[1], Els Halff[2], Marie-Caroline Cotel[3], Jacqueline Mitchell[3], Lawrence Rajendran[1], Anthony Vernon*[4]

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Background: Positron emission tomography (PET) studies using the radioligands [11C]-UCB-J and [11C]-PBR28 specific for synaptic vesicle glycoprotein 2A (SV2A) and translocator protein (TSPO), provide in vivo evidence for both synaptopathy and putative

gliosis in the cingulate and frontal cortex of individuals with schizophrenia. To what extent antipsychotics may or may not contribute to synaptopathy, gliosis and glia-dependent synaptic remodelling however, remains unclear.

Methods: To address these gaps in our knowledge, we examined the effect of chronic olanzapine exposure on PSD-95 engulfment by microglia in vivo. Naïve male Sprague-Dawley rats were exposed to Olanzapine using osmotic mini pumps for 28 days (7.5 mg/kg/d; n=4) or a common drug vehicle (n=4) as previously reported (Onwordi et al. Nat Comn 2020). This exposure resulted in a terminal drug plasma concentration of 16.3-26.9 ng/mL. Using immunostaining and confocal microscopy of we examined the morphology of Iba1+ microglia and the volume of PSD-95 engulfment by Iba1+ microglia in the rat somatosensory cortex with IMARIS software. This region was selected on the basis of prior work suggesting that chronic Olanzapine exposure causes an increase Iba1+ microglia density and amoeboid morphology in this region of the rat brain (Cotel et al., Eur. Neuropsychopharm. 2015).

Results: In our rat model, we observed that Iba1+ microglia from chronic (28 day) olanzapine-exposed rats were less ramified and had reduced volume, compared with vehicle-exposed controls ($p<0.01$), consistent with and confirming our previous observations (Cotel et al., Eur. Neuropsychopharm. 2015). There were however no statistically significant increases in the volume of PSD-95 within the Iba1+ microglia when comparing Olanzapine- and vehicle-exposed rats ($p>0.05$).

Conclusions: We provide evidence that, under the conditions tested, olanzapine does not induce microglia-driven synaptic remodelling. These data are consistent with and extend our previous observations that olanzapine does not impact on either SV2A radioligand binding or SV2A+ synaptic puncta in vivo (Onwordi et al. Nat Comn 2020; Halff et al. Brain Behav. Res. 2021). Consistent with our prior work however, we confirmed that chronic olanzapine exposure alters rat microglia morphology, but the functional impact remains unclear. Hence whilst olanzapine exposure is unlikely to account for synaptopathy in schizophrenia, further work is required to understand the effect on microglial cells.

Workshop: Evolving Concepts of Schizophrenia: Time to Revisit Its Name?

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

41. EVOLVING CONCEPTS OF SCHIZOPHRENIA: TIME TO REVISIT ITS NAME?

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Harvard University

Overall Symposia Abstract: Schizophrenia, ("split mind" in Greek) is a confusing term coined by Eugene Bleuler over a century ago to the disease earlier called dementia praecox by Emil Kraepelin. There has been a recent and growing interest to change the name of this illness for several reasons. First, this term has been stigmatized and associated with terms such as insanity, hopelessness, and violence. Second, uncertainty about what the core aspects of this syndrome are, and its enormous heterogeneity have even led to views that the term schizophrenia should be abandoned altogether. Third, several countries such as Japan, South Korea and Taiwan have already implemented alternative names for this entity designed primarily in an effort to reduce stigma, and a groundswell of stake-holder support is emerging for a name change in the US and Europe. Renaming will avoid use of the term schizophrenia as an adjective or metaphor, may increase help seeking and may reduce stigma and discrimination. However, renaming the illness requires serious consideration of what it

represents conceptually. Any effort to change the name of a major disorder requires considerable Introspection and debate about the nature of the illness. Is it a syndrome, disease, simply a deviation or a spectrum of diverse disorders? What is the core feature of this entity: is it cognitive dysfunction, reality distortion, a self disorder, or a combination of all those? In this symposium we will discuss the currently fuzzy conceptual underpinnings of the entity we call schizophrenia, and critically evaluate the various models in light of accumulating scientific knowledge. Once the concept of SZ is revised and accepted by the international community, then the name of schizophrenia can be "re-invented" to reflect the core features of the syndrome. The symposium will be interactive, and will engage the audience in a constructive discussion and generating potential areas of consensus.

41.1 A NEW NAME FOR SCHIZOPHRENIA SHOULD MIRROR A CHANGE IN THE CONSTRUCT ITSELF

Henry Nasrallah*[1],

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Background: Renaming schizophrenia to shed the stigma is currently gaining significant momentum among multiple stakeholders. Over 3 decades ago, early, misguided efforts to erase the stigma of schizophrenia began by abandoning the term "patients" to absurd terms like "clients" or "consumers", which ironically undermined the rapidly evolving neurological basis of schizophrenia.
Methods: Side by side with the accelerating wish for a new name for schizophrenia, researchers are seeking to re-invent the now frayed and archaic construct of schizophrenia to update this century old name and to portray this medical condition as the etiologically and clinically heterogeneous and complex syndrome it is. This will not be an easy task but very much worth undertaking.
Results: It is important to link a new name with a new construct for schizophrenia. However, the lay and other constituencies seeking a new name will have to collaborate with schizophrenia investigators to settle on a name that not only evades stigma, but accurately reflects the scientific and clinical essence of what schizophrenia is now being conceptualized by researchers. This won't be easy because there are numerous opinions of what the new name should be, irrespective of what the scientific advances have established. However, this dual task of renaming schizophrenia and re-inventing its construct is too important a process to take lightly and a thoughtful strategy must be developed to make it succeed.
Conclusions: This presentation will address this challenge and suggest some approaches to ensure a win-win-win outcome for patients, clinicians, and researchers

41.2 THE NAMING PROJECT: SURVEYING A POTENTIAL NAME CHANGE FOR SCHIZOPHRENIA

Raquelle Mesholam-Gately*[1]

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Background: About one in 100 people, worldwide, experience a condition called schizophrenia. There is widespread disagreement regarding what should be the appropriate name for this condition. Those advocating for a name change point to the stigma and discrimination associated with the name "schizophrenia", as well as how the name poorly characterizes features of the illness. The purpose of this project was to collect opinions from a

broad, diverse sample of stakeholders about possible name changes for schizophrenia in the U.S.

Methods: The Naming Project represented a partnership between researchers, clinicians and those with lived mental health experience (the Consumer Advisory Board (CAB), a mental health consumer-staffed policy and research group, at Massachusetts Mental Health Center/Beth Israel Deaconess Medical Center). Through collaborative efforts, the group developed a survey to assess opinions about the name schizophrenia as well as potential alternate names. These alternative names were derived from a combination of new names being used for schizophrenia across the world, a literature review of names proposed by researchers, and a name suggested by a CAB member. Both paper and online versions of the survey were developed to target a broad array of community stakeholders, including those with lived experience, family members, clinicians, researchers, and the general public. The survey captured non-identifiable demographic information (including which stakeholder group the respondent identifies with), a question about whether schizophrenia should be re-named and how stigmatizing the name is, ratings of proposed alternate names for schizophrenia as well as schizophrenia itself, and a request for additional feedback including any other potential alternate names.

Results: We accumulated 1,190 responses from a broad, diverse group of stakeholders. Findings indicated that the majority of respondents, 74.1%, favored a name change for schizophrenia. Most (71.4%) found the name schizophrenia stigmatizing. Of the proposed alternate names, those with the most support included “Altered Perception Syndrome”, Psychosis Spectrum Syndrome”, and “Neuro-Emotional Integration Disorder”.

Conclusions: Survey findings suggest strong support for renaming schizophrenia. Most expressed hope that a name change will reduce stigma and discrimination. These U.S.-based survey results reinforce the growing international momentum for renaming schizophrenia, and may be viewed as a pilot for a potential broader worldwide survey with commitment from all parties to accept the results.

41.3 "SCHIZOPHRENIA" IN THE MORAL ERA OF MEDICINE

Jim van Os*[1], Sinan Guloksuz[2], Bart Rutten[3], Jurjen Luykx[4], Maarten Bak[5], Lotta-Katrin Pries[6], Gunter Kenis[5]

[1]*Utrecht University Medical Centre,* [2]*MHeNs, Maastricht University,* [3]*Maastricht University Medical Centre,* [4]*University Medical Center Utrecht,* [5]*Maastricht University,* [6]*School for Mental Health and Neuroscience, Maastricht University Medical Centre*

Background: The moral era of medicine refers to the fact that diagnosis and treatment should not be based only on what clinicians consider important, but also on what patients and their relatives consider important. Given that psychiatry is lacking fundamental knowledge about the origins, predictability and treatability of mental variation, it is necessary to find ways to co-create language and terminology that reflect the values of both patients and clinicians.

Methods: Psychiatrists consider it important to observe mental suffering through the prism of the basic medical model of finding the right medication for the right diagnosis and finding the correct cerebral abnormality causing the corresponding illness. The term "schizophrenia" relfects these values. Patients consider it important to understand the unique context, meaning and history of their mental suffering. To date, no diagnostic framework exists that allows for co-creation to also incorporate patient values.

Results: A transdiagnostic and contextual framework of ‘clinical characterization’, combining personal, existential, recovery-related, clinical, psychopathological, sociodemographic,

aetiological and other personal contextual data, may provide the right framework for co-creation of a diagnostic formulation that reflect both traditional psychiatric and patient values.
Conclusions: We examined a contextual clinical characterization diagnostic framework in a prospective general population cohort (n=6,646 at baseline), interviewed four times between 2007-2018 (NEMESIS-2) and showed that this has more clinical value than categorical algorithm-based diagnosis.
A transdiagnostic framework of contextual clinical characterization is of more value to patients than a categorical system of algorithmic ordering of psychopathology.

41.4 THE NAMING PROJECT: GUIDELINES FOR ADOPTING A NEW NAME

Elyn Saks*[1]

[1]*University of Southern California*

Background: I am a Mental Health Law Professor with four decades of lived experience with schizophrenia. I am fortunate to have responded well to treatment, and to have the resources that have afforded me excellent care.
Methods: I am hugely pleased to see Harvard Medical School emphasize the role of people with lived experience in this project. I have been honored to work with the outstanding Consumer Advisory Board. The collaboration on the Renaming Project between Harvard faculty and people with lived experience is a model.
Results: As a law professor, I focus on rules and decision making. My talk will examine what guidelines we might adopt to choose among names. A popular vote?
Conclusions: A popular vote but with added weight to some voices, e.g., those of consumers and their families? Should a new name be based on history, on descriptive power, On our current knowledge of the pathophysiology underlying this illness, phenomenology, or on stigma-reducing effects? And who should decide these important questions? My talk will incorporate data from the Renaming Project's survey to shed light on how we think about the process of changing the name, "schizophrenia

Sunday, April 10, 2022

Plenary VII: Kim Do

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

42. TRANSLATING NEW DEVELOPMENTS IN NEUROBIOLOGY TO EFFECTIVE INTERVENTION IN SCHIZOPHRENIA RESEARCH; FROM PRECISE TARGETING TO GLOBAL SOLUTIONS

Gemma Modinos

King's College London

Overall Abstract: Dr. Kim Do's laboratory is at the forefront of translational research in schizophrenia. In this plenary session, she will discuss a novel translational programme bridging fundamental and clinical research to enable mechanism-based, personalised early detection and intervention strategies in schizophrenia. Her research integrates knowledge

across scales, from molecules and proteins to whole-brain neuroimaging to psychopathology and functioning, and holds great promise to break new ground in both our understanding of the pathophysiology of schizophrenia and the discovery of new therapeutic targets.

42.1 TRANSLATING NEW DEVELOPMENTS IN NEUROBIOLOGY TO EFFECTIVE INTERVENTION IN SCHIZOPHRENIA RESEARCH; FROM PRECISE TARGETING TO GLOBAL SOLUTIONS

Kim Do

Unit for Research in Schizophrenia, Center for Psychiatric Neuroscience, Lausanne University Hospital

Individual Abstract: Dr Kim Do will discuss a translational program aimed at early detection and intervention in schizophrenia. It requires mechanism-based biomarkers that capture neural circuitry dysfunction, allowing better patient stratification, personalization of treatment and monitoring of disease progression. She will show how interaction of genes and environment risk factors during neurodevelopment converge on a hub consisting of neuroinflammation, NMDA receptor hypofunction, dysregulation of mitochondria, dopamine, and redox balance, inducing oxidative stress and reinforcing each other in a damaging feedforward mechanism. This affects parvalbumin interneurons (PVI), including their associated gamma synchronization, and impacts myelination, thus leading to structural and functional alterations of local microcircuits and long-range connections, essential for cognitive, affective and social functioning. Animal models showed that additional insults at peripuberty, but not in adults, lead to PVI impairments that persist until adulthood. NAC application, only when it is followed by an environmental enrichment, leads to normalization of adult PVI (Dwir and al 2021). Reverse translation allowed mechanism-based stratification of patients towards early detection and novel treatments. The potential therapeutic effect of the antioxidant N-acetyl cysteine (NAC) observed in models was tested in patients with chronic schizophrenia, and improved negative symptoms, NMDA and related potentials in EEG. In early psychosis patients, NAC improved cognition (Conus and al 2018), as well as structural (Klauser and al 2018), and functional connectivity (Mullier and al 2019). Two blood exosomal markers, elevated miR137 and decreased COX6A2, allow to characterize the oxidative status of PVI mitochondria and to correlate it with a reduction of ASSR gamma EEG oscillations and with worse psychopathological status, neurocognitive performance, and global and social functioning (Khadimallah and al 2021). This stratification would allow the specific selection of patients for treatments targeting brain mitochondria dysregulation, and the investigation of the clinical and functional efficiency of future clinical trials.

Concurrent Symposia

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

43. PERCEIVED THREAT: ADVANCES IN UNDERSTANDING PSYCHOLOGICAL, NEUROBIOLOGICAL AND COMPUTATIONAL FACTORS OF PARANOIA

Katharina Stegmayer

University Hospital of Psychiatry, University of Bern

Overall Symposia Abstract: Paranoia, “the unfounded fears that others intend harm to the individual”, is a central and disabling experience of schizophrenia. It is described as a spectrum of distressing experiences including mistrust, suspiciousness, ideas of reference, feelings of persecution, and delusions. The extreme end of this spectrum includes persecutory delusions

that are held with great conviction. Paranoia profoundly disrupts interpersonal functioning, and the experience of paranoia may trigger safety behaviors, such as avoidance. It is highly prevalent (i.e. in about 50% of individuals with schizophrenia seeking initial help). Factor analytic studies indicate that paranoia is an independent experience. It is associated with poverty, poor physical health, aggressive behaviour, youth, suicidal ideation and poor social outcome. However, paranoid experience is in some cases hard to detect in the clinical interview. Researchers are just starting to understand the complex pathobiology of paranoia in psychosis. In fact, paranoia requires further understanding of its neural, psychological, and sociological mechanisms. Likewise, we do not know how paranoia precisely relates to poor functional outcome.

This symposium will give an overview of the current developments. We aim to elucidate neural, psychological, and computational mechanisms of paranoia. Central psychological aspects of paranoia, i.e. having distressing feelings of being watched by others, and initial evidence for the impact of these aspects on deficits in interpersonal functioning will be presented. Densely sampled EMA data will also be used to examine the daily effects of paranoia on mood and activity. Such findings will stimulate research on specific training to aid social functioning. While researchers are beginning to unravel the cognitive and emotional factors of delusion formation across different diagnoses, a neurobiological model of paranoia is still missing. Thus, the symposium will also cover neurophysiology and brain imaging of paranoia. Experiences of paranoid threat were associated with structural and functional alterations of the limbic system, suggesting that altered neural structure and activity in the limbic system (i.e. amygdala) may reflect neural responses to the paranoid experience of threat. Such findings provide evidence for the hypothesized association between limbic dysfunction and the clinical presentation of paranoid threat and persecutory delusions. Finally, the symposium will provide an overview of computational psychiatry applications to paranoia involving machine learning, reinforcement learning theory, and neural circuit models. Results highlight mechanisms which are suggested to cause, contribute to, or modulate the genesis and formation of delusions and paranoia. Importantly, understanding the psychological and computational mechanisms of paranoia, understanding which neural mechanisms underpin them, and how this is related to functional outcome may help to determine the pathophysiology underpinning paranoia and may help in the future to tailor treatment approaches aimed at that pathophysiology.

43.1 PARANOIA AND FACIAL TRUSTWORTHINESS JUDGMENTS - EYE - TRACKING AND EXPERIENCE SAMPLING STUDY

Michal Hajdúk*[1], Alexandra Straková[1], Jakub Januška[1], Daniel Dančík[1], Dana Krajčovičová[1], Ľubica Forgáčová[2], Barbora Vašečková[2], Anton Heretik[1]

[1]*Comenius University in Bratislava,* [2]*Slovak Medical University*

Background: Intensive paranoid thoughts are highly distressing and have a substantial impact on social functioning. Furthermore, paranoid thinking makes an individual more alert and suspicious toward others and overall social threat processing is aberrant. The present study aims to examine associations between paranoia and facial trustworthiness ratings. A secondary aim was to examine how behavioral measures and eye movements parameters are related to social interactions in the real-world setting.

Methods: The sample consisted of 40 healthy participants and 47 patients with schizophrenia, bipolar disorder, or depression. The first task consisted of two sets of 24 computer-generated faces balanced for trustworthiness levels. The sets represented two conditions (neutral and social stress). We elicited social stress by playing noisy street sounds, including cars and loud human conversations. The second task consisted of 24 real face photographs showing neutral expressions. During the tasks, eye movements were recorded. A subsample (N = 42) of participants underwent a follow-up 6-day experience sampling protocol. Paranoia was measured with the Paranoia scale and psychopathology with a 24-item version of the BPRS.
Results: We found small associations between paranoia and perception of faces as less trustworthy in both groups. Next, paranoia was unrelated to the number of face or mouth fixations in healthy controls. In patients, the number of fixations on eyes was negatively associated with negative symptoms (r_s = -0.330, p = 0.049) and positive symptoms were negatively associated with fewer fixations on the mouth region (r_s = -0.352, p = 0.032). Trust judgments on real faces were unrelated to fixations on socially salient face features. In the follow-up, we found that higher laboratory trust judgments under stress conditions were associated with perceiving real-life social interactions as more pleasant (r_s = 0.337, p = 0.029). On the other hand, higher number of fixations on the eye region was associated with the perception of social interactions as less pleasant (r_s = -0.402, p = 0.008).
Conclusions: Our results showed that subjectively rated paranoia is related to facial trustworthiness. Interestingly, overall judgments were not related to eye movement parameters, suggesting that top-down modulation might be more important in forming final trust judgments. Furthermore, the results in the patient subsample suggested that the perception of facial trust might be influenced by a complex interplay of positive and negative symptoms. Finally, trust judgments and specific eye-movement parameters were associated with the pleasantness ratings of real-life social interactions, implying the importance of trust perception in everyday functioning.
Supported by the VEGA 1/0184/19 and APVV: 20-0185.

43.2 WITHIN- AND BETWEEN-PERSONS EFFECTS OF PARANOIA ON DAILY MOOD AND ACTIVITY

Amy Pinkham*[1], Robert Ackerman[1], Colin Depp[2], Raeanne Moore[2], Philip Harvey[3]

[1]*The University of Texas at Dallas,* [2]*UC San Diego,* [3]*Leonard M. Miller School of Medicine, University of Miami*

Background: Severity of paranoia is typically assessed via clinical interviews that query timeframes of one week or more. While helpful, this strategy makes it difficult to examine the daily effects of paranoia and hampers the development of mechanistic models of paranoid ideation. Here, we used Ecological Momentary Assessment (EMA) to densely sample feelings of paranoia over 30-days.
Methods: One hundred forty-three individuals with schizophrenia spectrum illnesses (N=66 schizophrenia and N=77 schizoaffective disorder) completed 3 EMA surveys per day for 30 days. Each survey queried feelings of paranoia, sadness, happiness, nervousness and being bothered by voices on a scale from 1-7 with higher scores indicating greater severity. Each survey also asked participants who they were with and what they were doing.
Results: Preliminary results indicate marked variability in paranoia with an average standard deviation of 0.97 across time. Significant within-person effects also indicate that increased paranoia relative to one's average over the 30-day period is associated with relatively greater sadness (b=.29; p<.001), nervousness (b=.28, p=.002), and voices (b=.21, p=.03). Between-

persons, those individuals who are more paranoid on average are also sadder (b=.47, p<.001), more nervous (b=.53, p<.001), and more bothered by voices (b=.41, p<.001). They are also less happy (b=-.34, p<.001). Being alone (vs. with others) does not show a within-persons association with paranoia (OR=1.01, 95% CI: .95, 1.09); however, across persons, being more paranoid on average is related to a greater likelihood of being alone (OR=1.33, 95% CI: 1.11, 1.58).

Conclusions: Severity of paranoia appears to vary considerably over short periods of time and tracks with concurrent changes in mood and anxiety. Somewhat surprisingly however, feeling more paranoid than usual was not associated with being alone. Additional analyses will examine how paranoia relates to engagement in productive vs. unproductive activities and time-lagged associations between paranoia, mood, and activity.

43.3 THE LIMBIC BRAIN AND PARANOIA: STRUCTURAL AND FUNCTIONAL ALTERATIONS IN THE LIMBIC SYSTEM IN SCHIZOPHRENIA PATIENTS WITH PARANOIA

Katharina Stegmayer*[1], Frauke Conring[1], Nicole Gangl[1], Sebastian Walther[1]

[1]*University Hospital of Psychiatry, University of Bern*

Background: Paranoia is a frequent and highly distressing experience in schizophrenia. Modern models of paranoia suggest the limbic system to be involved in the formation of paranoia. Importantly, paranoid experience is in some cases hard to detect in the clinical interview. In contrast, personal space measures detected patients with paranoid threat with excellent sensitivity and specificity. Thus, personal space is an interesting model to study the biological mechanism underlying paranoid experience. We aim to demonstrate weather alterations are found within the limbic network, particularly the amygdala, hippocampus and orbitofrontal cortex in patients with current paranoia, compared to patients without paranoia and controls.

Methods: MRI data was collected in two studies including 165 subjects (89 patients) in the first, and 151 subjects (101 patients) in the second study. Paranoia was assessed using a Positive And Negative Syndrome Scale (PANSS) composite score as well as specific paranoia scales respectively. Safety behavior was assessed with the interpersonal distance task.

To measure functional changes in rs-fc, we compared the functional connectivity at the region of interest (ROI) level using both ROI-to-ROI and ROI-to-voxels analyses and at the whole-brain level using independent component analysis in the first study. In detail, we tested rs-fc between bilateral nucleus accumbens, hippocampus, amygdala and orbitofrontal cortex between groups and as a function of paranoia severity. We set the significant threshold as a cluster threshold p-value qFDR corrected < 0.05.

In the second study we tested the effect of interpersonal distance on grey matter volume applying an interpersonal distance test. We separated our patient sample into subgroups of patients with low and high interpersonal distance, and performed whole brain voxel-based morphometry between healthy controls and patient subgroups. Likewise, we tested differences in basal ganglia volume in these groups. We calculated group effects using one-way ANCOVAs and post-hoc tests using t-contrasts. Results were corrected for multiple comparisons (p (FWE) < .05).

Results: In the first study we found increased rs-fc between hippocampus and amygdala in patients with compared to without paranoia. This increase in rs-fc between bilateral hippocampus and amygdala was also linked to the severity of paranoia. In additional seed-to-voxel analyses, we found the left OFC to be connected to right BA47 in patients with paranoia,

and patients with paranoia had increased functional connectivity in prefrontal areas of the DMN when compared to healthy controls.
In the second study, paranoid threat increased interpersonal distance two-fold in the stop-distance paradigm, and reduced comfort ratings in the fixed-distance paradigm replicating our prevous results. Furthermore, we revealed significant differences between groups (controls and patients with low and high interpersonal distance) in grey matter volume within the limbic system including bilateral hippocampus, amygdala, ventral tegmentum, and thalamic nuclei. Post-hoc comparisons, revealed significantly reduced volumes in hippocampus in patients with high IPD compared to patients with low IPD and healthy controls. In contrast, no differences in grey matter volume were observed between healthy controls and patients with low IPD.

Conclusions: Our results suggest the limbic system to be relevant for the formation of the experience of paranoia. In particular, reduced grey matter volume of the hippocampus associated with high interpersonal distance in patients with schizophrenia supports animal models of delusion formation and further demonstrate that grouping patients according to a marker of territorial behavior allows for testing structural abnormalities in the limbic network related to paranoia in psychoses. In addition, functional over-excitation in the hippocampus-amygdala pathway could result from chronic neural alterations, as suggested by converging animal models and neuroimaging studies. Therapeutic efforts may aim at reducing neural hyperconnectivity and hyperactivity in this pathway.

43.4 A BIO-PSYCHO-SOCIAL COMPUTATIONAL ACCOUNT OF PARANOIA

Philip Corlett*[1]

[1]*Yale University*

Background: Some current strategies for teaching and practicing the biopsychosocial approach appear to suggest that suggest that biological, psychological, and social factors can be understood independently. But these are better understood as interacting pillars that holistically structure experience – when one is compromised, the others compensate – often in ways that compound the challenges that must be managed, fostering forms of distress that can become deeply entrenched and resistant to revision. These insights were present in Engel's original formulation of the biopsychosocial model, and in the work that inspired it.
Methods: I will explore the ways in which these factors interact, in ways that reveal a much wider range of possibilities for navigating the kinds of psychiatric challenges that people face. I would like to illustrate those interactions with reference to a specific phenomenon – paranoia – using the language of computation to provide a bridge linking the three pillars of the biopsychosocial model.
Results: Although paranoia has clear biological, psychological, and social determinants, each is relatable to the computational mechanisms of belief updating; and, we will argue that when one of those pillars is altered (at an individual level by brain damage or drug intake, at the social level by the descent of a pandemic), the computational mechanisms change in ways that modulate the behavior of the other pillars to preserve as much stability as is possible though that change.
Conclusions: Computational analysis may seem arcane and academic, but it appears to offer bridging insights - between biological, psychological, and social contributions to paranoia. The intersection between prior beliefs about and learning from volatility seems sensitive to all three of these factors, proffering new insights in to risk for and relief from paranoia.

44. CANNABIS AND PSYCHOSIS: WHERE ARE WE AT?

Marta Di Forti

SGDP, Institute of Psychiatry, KCL

Overall Symposia Abstract: While epidemiological evidence consistently support a causal association between heavy cannabis use and psychosis phenotypes, recent genetic studies have disputed the direction and the causal nature of this association. The recent large Genome-Wide Association Studies (GWAS) of cannabis initiation, cannabis use disorder and schizophrenia have allowed to explore the genetic overlap between these phenotypes. Polygenic risk scores for schizophrenia (SZ PRS) seem to explain a small, but significant, proportion of the variance in cannabis use initiation and in CUD but Mendelian Randomisation studies have yet failed to clarify the direction of causality between cannabis use and schizophrenia. Indeed, many questions remain unanswered about the impact of cannabis use on mental health. The work we propose to present combines the analyses of genetic, cognitive, behavioural and physiological data to add important and novel evidence to the effect of cannabis use on mental health and beyond.

Dr Isabelle Austin-Zimmer will start presenting data from the EUGEI multisite study and from the UKBiobank. Using the data available from the latest Schizophrenia Psychiatric Genomic Consortium her work aims to investigate a) the role of SZ PRS in predicting cannabis use and pattern of use in a European general population sample and replicate it in the UKBiobank b) the combined and independent effect of SZ PRS and heavy cannabis use on risk for psychotic disorder in both dataset. These analyses will be carried out using the latest bioinformatic tools to allow the inclusion of participants from diverse ethnic background, to produce results that represent the diversity of the world population.

Dr Laura Ferraro, using a two-step Cluster Analysis of the premorbid adjustment and current IQ data available in the EUGEI study, will show three main patterns of changes in cognitive function. Participants with first episode psychosis (FEP), who present with a deteriorating pattern before psychosis onset, have the lowest SZ PRS but they are more likely to have started using cannabis in early adolescence and to have used high potency types. This novel findings suggest that in some individuals the cognitive deterioration observed before psychosis onset, is not pre-determined by SCZ genes but could be prevented informing about the risk of early and high potency cannabis use.

Dr Paolo Marino will present novel data from a comprehensive systematic review on the association of violent events with cannabis use. This study aims to expand our understanding of the impact that cannabis use has on society beyond its association with risk of psychosis. Indeed, the combined pooled effect showed a doubling in the probability of being an offender in cannabis user from the general population and even greater among cannabis users with a psychiatric disorder. Cannabis use was also associated, to a lesser extent, with an increased probability of being a victim of violence.

Professor Cyril D'Souza will conclude with a unique longitudinal behavioural, cognitive and electro-physiological characterization of patients with FEP with exposure to cannabis compared to FEP with no cannabis exposure. These novel findings will contribute to understand the biological mechanism and changes that underlie the effect of cannabis use on risk of psychosis and beyond.

Thus, at a time when cannabis is becoming legal in many countries across the world, the work we propose to present can further support the importance of public education programs that inform about the wider impact of cannabis use at an individual and societal level.

44.1 THE COMBINED AND INDEPENDENT EFFECT OF SCHIZOPHRENIA GENES AND CANNABIS USE ON RISK FOR PSYCHOTIC DISORDER

Isabelle Austin-Zimmerman*[1], Beatrice Wu-Choi[2], Diego Quattrone[3], Alexander L Richards[4], Tom P Freeman[5], Giada Tripoli[6], Charlotte Gayer-Anderson[1], Victoria Rodriguez[1], Hannah E Jongsma[7], Laura Ferraro[8], Caterina La Cascia[8], Sarah Tosato[9], Illaria Tarricone[10], Celso Arango[11], Julio Bobes[12], Julian Sanjuán[13], Jose Luis Santos[14], Manuel Arrojo[15], Eva Velthorst[16], Miguel Bernardo[17], Cristina Marta Del-Ben[18], Paulo Rossi Menezes[18], Jean-Paul Selten[19], Peter B Jones[20], James Kirkbride[21], Bart PF Rutten[22], Andrea Tortelli[23], Pierre-Michel Llorca[24], Lieuwe de Haan[16], Jim van Os[25], Michael Lynskey[1], Craig Morgan[1], Evangelos Vassos[1], Michael O'Donovan[4], Cathryn Lewis[1], Pak Sham[26], Robin Murray[3], Marta Di Forti[3]

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Background: Polygenic risk scores (PRS) for schizophrenia seem to explain a small, but significant, proportion of the variance in cannabis use initiation and in cannabis use disorder (CUD). Thus far, Mendelian randomisation studies have failed to clarify the direction of causality between cannabis use and schizophrenia. We used data from the European Union Gene-Environment Interaction consortium (EUGEI) case-control study and from UK Biobank to investigate the independent and combined effect of heavy cannabis use and Schizophrenia Polygenic risk score on risk for psychotic disorder.

Methods: We generated PRS for schizophrenia in the EUGEI study and UK Bioban, using data from the most recent Psychiatric Genetics Consortium schizophrenia GWAS. Information on pattern of cannabis use was used to build a measure of "degree of exposure" to cannabis. Using R, we investigated if schizophrenia PRS predicted lifetime cannabis use or pattern of use, and the independent and combined effect of cannabis use and schizophrenia PRS on the risk of psychotic disorder. In addition, we tested the statistical interaction between cannabis use and schizophrenia PRS. All models were adjusted for age, sex, the first 10 principal components and tobacco smoking habits.

Results: In the EUGEI sample schizophrenia PRS did not predict cannabis initiation, how frequently controls or first episode psychosis patients used it, or the type of cannabis they used. The "measure of degree of exposure" and schizophrenia PRS showed independent effects from

each other on the odds ratio for psychotic disorder. The analyses in the UK Biobank sample are ongoing.
Conclusions: Our preliminary data from the EUGEI study suggest that schizophrenia PRS does not explain who is likely to try cannabis and their frequency of use, or the potency of the cannabis used. The analyses in UK Biobank will provide further evidence of the extent of the independent and combined effect that schizophrenia PRS and heavy cannabis use exert on the risk for psychotic disorder.

44.2 THINKING ABOUT CANNABIS IN THE DEVELOPMENTAL TRAJECTORIES OF YOUNG PEOPLE PREDISPOSED TO PSYCHOSIS

Laura Ferraro*[1], Evangelos Vassos[2], Diego Quattrone[3], Caterina La Cascia[4], Alastair Cardno[5], Giada Tripoli[6], Fabio Seminerio[1], Crocettarachele Sartorio[1], Lucia Sideli[1], Giovanna Marrazzo[1], Victoria Rodriguez[6], Simona Stilo[7], Ilaria Tarricone[8], Andrei Szoke[9], Miquel Bernardo[10], Pak Sham[11], James Kirkbride[12], Craig Morgan[13], Daniele La Barbera[1], Marta Di Forti[14], Robin Murray[15]

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Background: A variable cognitive impairment is present in patients with psychosis. To explain why cannabis use in psychotic subjects is related to better cognitive performance, we explored premorbid adjustment of patients at their first episode of psychosis (FEP) and their history of cannabis use. Among FEP from the GAP study (UK), cannabis users had a higher premorbid IQ than non-using, an association not witnessed among controls. Thus, cannabis represented a potent risk factor for FEP less neurodevelopmentally impaired. Following this hypothesis, more patients reflecting better cognitive characteristics should be present in FEP samples where cannabis is most used. This was the case comparing FEP recruited in the SGAP (Italy) whit the GAP study, where patients were more likely to have smoked high potency cannabis. The higher IQ of FEP from London than from Palermo was due to the subgroup of cannabis users. We hypothesized that a better premorbid adjustment allowed some patients to enter in contact with the substance, sharing it with friends. The findings of the EUGEI study indicated that FEP users had higher premorbid social adjustment (PSF) than nonusers, a difference not present in controls. The premorbid academic adjustment (PAF) was lower when the frequency of cannabis use increased. Occasional users had the highest IQ and nonusers had the lowest, while daily users were intermediate.
Why only a small proportion of people develop psychosis after using or abusing cannabis, despite a comparable premorbid adjustment than the others remains an intriguing question. Based on results from a previous study, we wanted to examine whether developmental trajectories and IQ can group FEP patients in clusters and compare them using PRSs for Schizophrenia (SCZ), Bipolar Disorder (BD), Major Depression (MD) and IQ.

Methods: A TwoStep Cluster Analysis clustered 802 FEP according to premorbid adjustment in childhood (<12 years) and puberty (change-scores ((12-16 years)-(<12 years)) for both PSF and PAF from the premorbid adjustment scale (PAS), and current IQ (WAIS). A multinomial

logistic regression tested between-groups PRSs differences among subjects with European ancestry. Age, sex, country, ten principal ancestry components, SZ, BD, MD, and IQ PRSs were all predictors, assuming 1263 not clustered population controls as the baseline category.
Results: We found four transdiagnostic clusters (BIC=2268.5): 1) High (n=205; 25.5%), with the highest IQ (M=106.1, 95% CI 104.3, 107.9) and PAF but low PSF. PAF was deteriorating while PSF was slightly improving from childhood to puberty. 2) Low (n=223; 27.8%), with the lowest IQ (M=73.9, 95% CI 72.2, 75.7), and PAF, but near-normal PSF. PAF improved, and PSF deteriorated a bit over time. 3) Intermediate (n=224; 27.9%), with intermediate IQ (M=80.8, 95% CI 79.1, 82.5) and low PAF and PSF, both improving. 4) Deteriorating (n=150, 18.7%), with intermediate IQ (M=80.6, 95% CI 78.5, 82.7) and PAF and PSF comparable to controls, then markedly deteriorating. PRSs explained 7.9% of the variance. Patients had higher SCZ PRS than controls ($F(4,1319)=20.4$, $p>0.001$), but deteriorating patients presented the lowest SCZ PRS among patients and no other PRSs differences with controls. Interestingly, they started using cannabis at the lowest age, and they had the highest likelihood of being daily users of high potency cannabis.
Conclusions: There was a discontinuity between cognitive impairment, premorbid deterioration and SCZ PRS. Among FEP, those with a deteriorating pattern had the lowest PRS but the early start of cannabis use and use of high potency strength. This finding challenges the unavoidable message of a "deterioration" preceding psychosis onset and informs prevention strategies, focusing on risk factors during the development, such as cannabis use.

44.3 EXPLORING ASSOCIATIONS BETWEEN CANNABIS USE AND BEING VICTIM OR PERPETRATOR OF VIOLENCE IN GENERAL AND PSYCHIATRIC POPULATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: There is a strong worldwide trend towards liberalising policy towards cannabis use and commercialising its sale. At time, in the US seventeen states, two territories, and the District of Columbia, have legalised marijuana for adult recreational use. According with the World Drug Report 2020, habitual cannabis users were estimated 192 million worldwide, making cannabis the most used substance. While well-established evidence indicated that prolonged heavy use can increase the likelihood of psychosis and related symptoms4, the question of whether the use of cannabis is associated with violence remains unsolved. Therefore, we conducted a comprehensive systematic review on the risk of violent events – both in victims and perpetrators – in lifetime cannabis users (in patients with psychosis and in healthy cannabis users), with the aim to elucidate whether and to which extent cannabis use is associated with violent events.
Methods: The PRISMA5 standards were applied and the review was successfully submitted and accepted at PROSPERO on March 2021 under the protocol registration number CRD42021240658. The main search was conducted in MEDLINE, EMBASE and PsycINFO, through Ovid provider for articles published from inception to May 2020. We searched Medical Subjects Headings (MeSH) and keywords related to: (1) violence; (2) cannabis use, using the Boolean operators. Studies were included it they satisfied the following criteria: (1) examined the relationship between cannabis use and subsequent exposure to violence either as a perpetrator or as victim of a violent act; (2) performed in humans; (3) published in English. Studies were excluded if they reported other substance use that might have influenced the relationship between cannabis and violence. We also excluded from quantitative analyses overlapping samples, prioritizing the more recent or larger sample study. We extracted the

following information from included studies: name of first author, year, and country of publication; study design, and name of cohort; total sample size; sociodemographic of the sample; population; cannabis use and outcome assessment; type of violence; counts of exposed and unexposed to cannabis among violent and non-violent groups. When this information was obtained, effect sizes in form of odds ratio (OR) were calculated. Where exposed/unexposed numbers were not reported and effect sizes were given (adjusted or unadjusted OR), these were extracted together with their 95% confidence intervals (CIs)

Results: From the 6186 studies identified in initial searches, 110 fulfilled inclusion criteria for the qualitative synthesis and 48 of those were included in the quantitative analysis. Reasons for the exclusion of 62 studies from the quantitative analysis included: (i) lack of data to calculate OR when these were not provided, (ii) duplication or overlap of samples; (iii) disparity of effect size provided which we were not able to combine with OR. Thirty-seven studies (70.6%) examined the outcome of being an offender, and 20 studies (39.2%) examined the association between cannabis use and being a victim. For most of the analyses, we observed high heterogeneity (ranging from 84.9 to 97.8). Main analyses were conducted on 48 studies showing associations between having used cannabis and being offender. The combined pooled effect after random-effect analyses showed a significant risk for being an offender (OR 2.09, 95%CI 1.85-2.36). When looking as to whether the risk to being offender differed based on having a Psychiatric condition or not, we saw that combined effects in this subgroup of population (OR 2.46, 95%CI 1.68-3.61) was higher than pooled effect in general population (OR 2.04, 95%CI 1.74-2.38). Source of information of reported violence caused as offender seem to be higher when the source was having a criminal conviction (OR 3.97, 95%CI 3.02-5.23) compared with self-reported violence (OR 1.70, 95%CI 1.70-2.20). The combined pooled effect after random-effect analyses also showed a significant risk for ending to be victim (OR 1.66, 95%CI 1.47-1.86).

Conclusions: Our data suggest that cannabis use increases the probability of perpetrating violent events both in the general population and in psychiatric patients but also of being a victim of violence. These finding have importance implications not only at an individual but also at a societal level and support the importance of prevention programs.

44.4 CHARACTERIZATION OF CANNABINOID RELATED FIRST EPISODE PSYCHOSIS (CFEP)

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Background: There is increasing recognition that the first episode of psychosis (FEP) can occur in the context of exposure to cannabis/cannabinoids. Cannabinoid-related FEP (CFEP) outlasts the period of acute intoxication and may require clinical intervention, including hospitalization. With the increasing liberalization of cannabis laws, greater availability of cannabis and cannabis products, greater availability of high potency cannabis and cannabis products, there is concern that the rates of psychosis are going to increase. Therefore, understanding the expression and course of psychosis related to cannabis exposure is becoming important. The goal of this study was to characterize the presentation and short-term course of hospitalized cases of Cannabinoid Related First Episode Psychosis (CFEP).

Methods: In this prospective study, hospitalized new cases of first episode psychosis occurring in the context of cannabis use (CFEP) were compared to controls with FEP unrelated to

cannabis. Urine toxicology, demographic information, personal and family history of mental illness and drug use, measures of psychosis (PANSS), depression (Calgary Depression Rating Scale), mania (Young Mania Rating Scale), and a number of cognitive measures (Cogstate battery) were assessed at admission and discharge.

Results: In this prospective study, 70 hospitalized new cases of CFEP with toxicological confirmation of cannabis exposure were compared to 60 FEP unrelated to cannabis. Despite both groups meeting the clinical threshold for hospitalization by a group of independent clinicians unaffiliated with the research team, relative to cannabis negative FEP, CFEP have significantly less positive ($p = 0.001$) and negative symptoms ($p < 0.0001$), but no difference in depression ($p = 0.16$) or mania ($p = 0.59$), or cognitive test performance ($p > 0.05$, on all domains) at admission. At discharge CFEP have significantly lower residual positive ($p = 0.002$) and negative symptoms and show greater improvement cognitive deficits specifically on domains of executive function ($p = 0.002$), memory (0.04) and social emotional cognition ($p = 0.02$) over the course of 4 weeks of hospitalization. Of note, after discharge several cases of CFEP relapsed after resuming cannabis use and needed to be re-hospitalized.

Conclusions: While both groups were significantly ill enough to warrant hospitalization, CFEP appear to have milder symptoms, and have a greater reduction in symptoms with treatment. Furthermore, that 6 cases of CFEP were re-hospitalized within ~1 year for psychosis after resuming cannabis use suggesting that CFEP may evolve into a recurrent psychotic disorder and suggests a role for cannabis in the expression of chronic recurrent psychotic disorders. Whether CEP and cannabis negative FEP differ in their longitudinal course and prognosis remains unclear. Lastly, whether there are any biomarkers distinguishing CFEP will require further study.

45. SCHIZOPHRENIA AND DAILY LIFE: WHAT CAN WE LEARN FROM RECENT ECOLOGICAL RESEARCH?

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National Center for Scientific Research

Overall Symposia Abstract: In the last decade the focus of clinical research on Schizophrenia Spectrum Disorders (SSD) has shifted from the study of symptom profiles and overall psychopathology to real-life functioning, in order to grasp a more valid and fine-grained understanding of patients' daily life, and of factors which impede or facilitate psychosocial adjustment and good quality of life. People with SSD, even in advanced stages of the disorder, require a detailed assessment of their functional characteristics. If data relevant to the individual characteristics in all real-life domains are available, then personalized and integrated management programs can be implemented, their impact can be constantly monitored, and changes to ongoing programs can be introduced to meet new or still unmet needs. To achieve this, recent studies on daily life in this clinical population have been based on prospective and real-time assessments, such as the Experience Sampling Method (ESM) approach and actigraphy: these approaches rely on the use of digital technologies. The increasing use of digital technologies to improve our understanding of patients' daily life is in line with precision and personalized medicine. An exponential increase in the use of wearable devices and apps allows continuous tracking of health parameters and related behaviours, generating 'Big Data' fundamental for informing disease prevention, precise diagnostics, and therapeutic strategies.

The ESM approach provides an ecologically valid time sampling of self-reports that allows a real time assessment of several domains, including space (where patients are during the daily hours), time (what patients do during the day), interpersonal relationships (with how many

people patients interact during the day) and emotions (how patients' mood change during the day). Furthermore, ESM gives instant estimates of current behaviour that are less vulnerable to recall biases. This approach might be particularly efficient in evaluating SSD patients given their cognitive deficits and inclination to biases. To assess instantaneous estimates of behaviour and motor activity, current practice adds real-time measurements taken from actigraphy to ESM data: actigraphy is a valid instrument for the assessment and monitoring of physical activity, sedentary behaviour, sleep and energy expenditure in patients with SSD. Lowered motor activity in patients with SSD is associated with greater severity of negative symptoms, while less structured physical activity is associated with greater severity of positive symptoms, worse cognitive functioning involving attention and processing speed, illness chronicity, higher antipsychotic dose, and poorer quality of life. In terms of illness trajectory, there is some evidence that lower physical activity is associated with chronicity of schizophrenia.

This symposium will present the results of 4 studies which have employed ESM and actigraphy to assess psychosocial functioning, psychopathology, mood and physical activity. Taken together, they offer a naturalistic, ecologically valid view of patients with SSD, and contribute to a more humanistic understanding of the daily life of patients with SSD in the new context of community-based models of care.

45.1 DAILY TIME USE, PHYSICAL ACTIVITY AND INTERPERSONAL RELATIONSHIPS IN PATIENTS WITH SCHIZOPHRENIA SPECTRUM DISORDERS (DIAPASON): AN ITALIAN MULTICENTRE STUDY

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Background: Many people with Schizophrenia Spectrum Disorders (SSD) spend most of their daily time being inactive, and this is related to the severity of negative symptoms and to high levels of sedentary behavior. In the DiAPAson project we aimed at (1) evaluating the daily time use among patients with SSD living in Residential Facilities (RFs) compared to outpatients with SSD and to the general population (Study 1), and (2) assessing daily activity patterns in residential patients, outpatients with SSD and healthy controls using real-time methodologies to examine the directional associations among motor activity, energy and mood (Study 2).

Methods: Study 1 includes 300 patients with SSD living in RFs and 300 outpatients; data obtained in these clinical populations with the Time Use Survey (TUS), a paper-and-pencil methodology, have been compared with normative data obtained by the National Institute of Statistics (ISTAT) in the Italian adult population (N=54,000). TUS has been done asking participants to retrospectively report in a daily diary time spent in different activities in a weekday (from Monday to Friday) and in a Sunday. In Study 2, the daily time use has been evaluated in 80 residential patients, 60 outpatients and 115 healthy controls with ESM installing a specific application on all smartphones: participants have completed a brief questionnaire about time use (e.g., paid work, leisure, resting/doing nothing), mood (i.e., rating of different adjectives on a scale from 0 to 100; e.g., "sad", "happy", etc.) and perceived energy (i.e., rating of different adjectives on a scale from 0 to 100; e.g., "active", "tired", etc.) 8 times

a day for an entire week, for a total of 56 prompts. In these three groups of subjects Physical Activity (PA), sleep patterns, and energy expenditure have been monitored through a multi-sensor device worn on the nondominant wrist, the Actigraph GT9X, during the same week. Actigraphy data has been extracted as activity Count Per Minute (CPM, as vector magnitude count). For the assessment of PA, the primary end-point is the comparison of total PA, intensity specific PA and sedentary time between residential patients, outpatients and controls; we also assess the associations between activity-derived measures (PA and sedentary time) and clinical markers. As secondary analysis, we report the proportion of subjects who reach 150 minutes of Moderate and Vigorous Physical Activity (MVPA) every week and the >7.5 h and 10 hours of sedentary time per day. We compute Non-Parametric Measures of Actigraphy Data (nparACT), which provide information about the Inter-daily stability, Intra-daily Variability and Relative Amplitude.
Results: In order to assess the influence of non-productive hours on symptoms severity we developed a hierarchical linear regression model, with psychiatric severity, as assessed with BPRS, as dependent variable, and non-productive hours as independent variable, controlling for the patients' setting. The number of non-productive hours significantly affected BPRS score. Both residential patients and outpatients spend more time in non-productive activities compared to healthy controls; residential patients and healthy controls spend also more time engaged with other people compared to outpatients. All variables related to PA assessment show an higher level of sedentary behaviour among patients compared to healthy controls on Sundays, while a different pattern emerges on working days.
Conclusions: Using mobile monitoring (actigraphy and ESM) and traditional clinical methods, it is possible to assess the highly dynamic interplay of multiple brain-body systems involved in the homeostatic regulation of human energy, mood and motor activity.

45.2 MOMENTARY SAD MOODS AND CONCURRENT PRODUCTIVE BEHAVIOR: A 30-DAY ECOLOGICAL MOMENTARY ASSESSMENT STUDY OF PEOPLE WITH SCHIZOPHRENIA AND BIPOLAR ILLNESS

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Background: Previous research using weekly sampling has suggested that persistent sad moods are associated with disability in bipolar illness. We examined the momentary quality of activities (productive, unproductive, and passive recreation) in a 30 day ecological momentary assessment study and related the level of sadness to the quality of activities.
Methods: Participants with bipolar illness (N=71) or schizophrenia (n=102) were sampled 3 times per day for 30 days. At each survey, participants were queried as to where they were, with whom, what they were doing, and as to their mood state. Activities were characterized according to predetermined criteria and related to momentary sadness rated on a 1 (not at all) to 7 (extremely sad) scale.
Results: A total of 11,608 surveys were collected. Participants with bipolar disorder reported greater sad moods and their mood state was more variable than participants with schizophrenia. For the participants with schizophrenia, the level of sadness did not differ across concurrent activities. For the participants with bipolar illness, sadness reported was associated with activities, with unproductive activities associated with the most sadness, followed by passive recreation, and productive activities associated with the least sadness ($p<.001$).
Conclusions: The current study expands upon studies examining the course of sad moods in people with bipolar illness to momentary assessments. Our results suggest that momentary

sadness correlates with the quality of concurrent activity. Although we cannot determine the causal direction, these findings support the idea that sadness predicts less productivity. In participants with schizophrenia, their sadness was less variable and the association of sadness and quality of activities was considerably smaller.

45.3 LONELINESS AND SOCIAL EXCLUSION BREED PARANOIA – AN EXPERIENCE SAMPLING INVESTIGATION ACROSS THE PSYCHOSIS CONTINUUM

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Background: The role of loneliness and feelings of social exclusion in the development of paranoia is largely unexplored and negative affect has been suggested to explain potential associations. Being socially included is one of the most cited desired outcomes of individuals experiencing psychosis and our aim was therefore to investigate feelings of loneliness and social exclusion, and their temporal relationship with paranoid symptoms in the course of everyday life.

Methods: The analysis sample consisted of 75 participants, including (N=29) individuals with a diagnosis of non-affective psychosis, (N=20) unaffected first-degree relatives, and (N=26) controls. Participants completed app-based experience sampling that captured the loneliness, feelings of social exclusion, paranoid thinking, and negative affect up to 10 times per day for 1 week, resulting in a maximum of 70 measurement points per person. Experience sampling items were rated on a seven-point Likert scale (ranging from 'not at all' to 'very'). Time-lagged experience sampling variables (within a 180 minute time frame) were created for loneliness, feelings of social exclusion, paranoid thinking, and negative affect to analyse their temporal relationships. The data were analysed using multilevel regression analyses.

Results: Patients were significantly lonelier than controls ($p<.001$), but patients and relatives and relatives and controls did not differ from each other (both $p>.05$). Patients also experienced greater paranoia than relatives ($p<.05$) and controls ($p<.01$), but controls and relatives did not differ from each other significantly ($p>.05$). The three groups did not differ in feelings of social exclusion or negative affect (all $p>.05$). Loneliness and feelings of social exclusion were significant and independent predictors of paranoid thinking over time and in all groups ($b=.05$, $p<.001$ and $b=.06$, $p<.01$, respectively). Negative affect significantly predicted paranoia ($b=.23$, $p<.001$) and partially mediated these associations. Over time, paranoia significantly predicted feelings of social exclusion, with stronger effects in controls than patients ($b=-.21$, $p<.05$), but paranoia did not predict loneliness ($b=.07$, $p=.21$). Over time, negative affect significantly predicted loneliness ($b=.19$, $p<.0001$), but not feelings of social exclusion.

Conclusions: This study contributes to a better understanding of the temporal associations of paranoia – where loneliness, feelings of social exclusion and negative affect are related, yet independent predictors of paranoid thinking over time. The findings suggest worsening mental health in all groups following loneliness and feelings of social exclusion and show that different aspects of mental health precede the distinct social emotions in time, thus warranting separate treatment foci.

45.4 NEGATIVE SYMPTOMS IN THE DAILY LIFE OF INDIVIDUALS WITH PSYCHOSIS

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Background: It remains poorly understood how negative symptoms are experienced in the daily lives of individuals with psychosis. In addition, it is relevant to investigate whether these real-life manifestations of negative symptoms reflect a genuine lack of capacity or interest, or rather be the result of limited opportunities. We aimed to first investigate whether altered affective experience, anhedonia, social anhedonia, and asociality were more pronounced in individuals with an at-risk mental state for psychosis (ARMS) and individuals with first-episode psychosis (FEP) than in controls. In addition, we investigated whether asociality reflected a diminished interest in social contact or rather a diminished opportunity for social interaction in the daily life of individuals with established psychosis.
Methods: We used the experience sampling methodology (ESM) to assess negative symptoms, as they occurred in the daily life of 51 individuals with FEP and 46 ARMS, compared with 53 controls. Furthermore, we used ESM to investigate asociality in a sample of 149 individuals with psychosis compared to 143 healthy controls, comparing affect and percentage of structured versus non-structured social activities.
Results: Multilevel linear regression analyses showed no overall evidence for a blunting of affective experience. There was some evidence for anhedonia in FEP but not in ARMS, as shown by a smaller increase of positive affect (BΔat-risk v. FEP = 0.08, p = 0.006) as the pleasantness of activities increased. Against our expectations, no evidence was found for greater social anhedonia in any group. FEP were more often alone (57%) than ARMS (38%) and controls (35%) but appraisals of the social situation did not point to asociality. Furthermore, in the sample of individuals with established psychosis, we found that patients spent significantly smaller proportion of their time in structured social context, but matched the controls in the time spent in unstructured social contexts, and endorsed intact hedonic experience of both social contexts. Moreover, employment and living situation predicted the proportion of time patients spent in structured and unstructured social contexts.
Conclusions: Overall, altered affective experience, anhedonia, social anhedonia and asociality seem to play less of a role in the daily life of individuals in the early stages of psychosis than previously assumed. With the experience of affect and pleasure in daily life being largely intact, changing social situations and appraisals thereof should be further investigated to prevent development or deterioration of negative symptoms. Furthermore, we found that negative symptoms in established psychosis may reflect changes in lifestyle more than changes in underlying capacity or interests.

46. NOVEL APPROACHES FOR DETECTING INDIVIDUALS WITH CLINICAL HIGH-RISK FOR PSYCHOSIS

Peter Uhlhaas

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Overall Symposia Abstract: The clinical high-risk (CHR-P) paradigm introduced more than 20 years ago has significantly advanced the understanding of emerging psychosis as well as provided a blueprint for pre-emptive psychiatry. Despite these facts, significant challenges in the field remain, one of which is that only a minority of patients who develop a first-episode of psychosis (FEP) are detected in specialised CHR-P clinics. This is because CHR-P criteria need to be established through semi-structured interviews administered by trained personnel in help-seeking populations. Accordingly, it is important to develop novel ways of identifying

individuals who are at risk of psychosis but who are currently not detected within established clinical pathways. In the proposed symposium, we provide an overview of recent findings regarding the relevance of CHR-P pathways before a FEP as well as novel approaches for the detection of CHR-P participants.

First, J. Shah (McGill University, Canada) will describe retrospective work in a catchment-based FEP population suggesting that only a minority of individuals seeking help for a FEP did not pass through an identifiable CHR-P phase. The distinction between these different psychopathologic pathways is important because the former (CHR-P) appears to have longer durations of untreated psychosis, poorer symptomatic and functional outcomes, and more emergency department visits and hospitalizations during the recommended two-years of FEP treatment.

Second, P. Uhlhaas (University of Glasgow/Charite, Berlin, UK/Germany) will introduce an online screening platform for the detection of individuals meeting CHR-criteria in the community. Participants were invited via email, flyers, and posters to visit a website and n = 3500 completed the 16-item version of the prodromal questionnaire (PQ-16) and 9-item questionnaire for basic symptoms. Overall, 180 CHR-participants and 25 cases of FEP were detected. Receiver operating characteristic curve analysis revealed good to moderate sensitivity and specificity for predicting CHR-P status as assessed through clinical interviews (CAARMs, SPI-A) from online results.

Third, S. Sullivan (University of Bristol, UK) will report on the development and validation of a risk prediction algorithm using linked primary care routine NHS consultation data. The risk prediction model development is based on 12 prodromal symptoms, age, gender and consultation frequency both overall and per symptom. Model development and internal validation will be carried out on a routine dataset of 300,000 primary care patients consulting for a non-psychotic mental health problem. External validation will be carried out in a separate UK primary care routine dataset.

P. Fusar-Poli (King's College, UK) will introduce an automated, transdiagnostic, and clinically-based individualised risk calculator that provides a powerful tool for supporting the early detection of CHR-individuals at scale by leveraging Electronic Health Records (EHRs). This risk calculator has been externally validated twice and is undergoing pilot testing for clinical implementation. Here, we present an approach for a prospective implementation of a real-time psychosis risk detection and alerting service in a real-world EHR system. This method leverages the CogStack platform which is an open-source, lightweight, and distributed information retrieval and text extraction system. This is the first ever study which has developed and implemented a similar detection and alerting system in clinical routine.

The findings and their implications will be synthesized and critically appraised by the discussant, Prof A. Yung (University of Melbourne).

46.1 SMOKE BEFORE FIRE: TREATMENT OUTCOMES IN FIRST EPISODE PSYCHOSIS PATIENTS WITH AND WITHOUT PRIOR SUB-THRESHOLD PSYCHOTIC SYMPTOMS

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[1]*McGill University*

Background: The CHR-P syndrome has attracted attention as a potentially important stage for prevention and early intervention based on an implicit assumption: that most or all patients with a FEP actually experienced an earlier CHR-P state. Examining this assumption in the context of FEP treatment outcomes will provide an important lens onto the potential utility of prevention and early intervention directed at the CHR-P stage.
Methods: Semistructured interviews of 351 patients and families with the Circumstances of Onset and Relapse Schedule were supplemented by chart reviews in a FEP sample in Montréal, Canada to document pre-onset sub-threshold psychotic symptoms and treatment delays. Individuals were assessed at baseline and then followed within the FEP service for up to 2 years in order to record a range of symptomatic, functional, and other outcomes.
Results: At least 50% of patients experienced at least one early sub-threshold psychotic symptom prior to their FEP. This group experienced a longer prodrome, duration of untreated psychosis and time from onset of psychosis to help-seeking compared to those without sub-threshold psychotic symptoms. At year 1, those with prior CHR-P syndromes experienced greater positive symptoms (SAPS group effect, $F=4.79$, $p=0.03$); with significant group-by-time interactions for negative symptoms (SANS, $F= 5.67$, $p=0.018$), global functioning (GAF, $F=7.96$, $p=0.005$), and social/occupational functioning (SOFAS, $F=4.392$, $p=0.037$). Over 2 years, a prior CHR-P syndrome predicted nonadherence (OR 1.71).
Conclusions: There are important differences between those with identifiable CHR-P syndromes before a FEP, across pathways to early intervention care and longitudinal treatment outcomes. This strengthens previous arguments regarding the relevance of the CHR-P state, but has additional implications for prevention and transdiagnostic early intervention efforts.

46.2 USING ONLINE SCREENING TO DETECT EMERGING PSYCHOSIS IN THE COMMUNITY

Peter Uhlhaas*[1]

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Background: The clinical high-risk (CHR-P) paradigm introduced more than 20 years ago has significantly advanced the understanding of emerging psychosis as well as provided a blueprint for pre-emptive psychiatry that could ultimately lead to the prevention of a first episode of psychosis (FEP). Despite these facts, significant challenges in the field remain, one of which is that only a minority patients who develop FEP are detected in specialised CHR-P clinics as they are currently constructed and located. Accordingly, it is important to develop novel ways of identifying individuals who are at risk of psychosis but who are currently not detected within established clinical pathways.
Methods: We implemented an online-screening tool which consists of a web-based questionnaire that utilizes the 16-item version of the Prodromal Questionnaire (PQ-16) and a 9-items of perceptual and cognitive aberrations for the assessment of basic symptoms. In line with this approach, participants were invited to the study website via email invitations, posters, and flyers . Cut-off criteria for further clinical assessments were 6 or more positively endorsed items on the PQ-16. For the perceptual and cognitive aberrations, a cut-off score of 3 or more positively endorsed items was selected.
Results: 3500 participants completed the questionnaire. Receiver operating characteristic curve analysis revealed good to moderate sensitivity and specificity for predicting symptoms consistent with a CHR-P status based on online results for both CAARMS and Schizophrenia

Proneness Instrument criteria (adult version) (sensitivity/specificity: PQ-16 = 82%/46%; perceptual and cognitive aberrations = 94%/12%) (81). To examine the possibility of improving the specificity of the online screening tool, we implemented a machine-learning approach that selected all 25 items from both the PQ-16 and the perceptual and cognitive aberrations in addition to demographical variables. Selection of a subset of 10 items from both PQ-16 and perceptual and cognitive aberrations that included familial risk lead to an improved specificity of 57% while only marginally affecting sensitivity (81%).
Conclusions: These data provide the first evidence for the feasibility of using a digital detection tool to identify emerging psychosis in the community. However, several refinements are needed to improve this approach, in particular in regard to the specificity/sensitivity of the screener.

46.3 ELECTRONIC HEALTH RECORD SCREENING FOR DETECTING YOUNG PEOPLE AT RISK OF PSYCHOSIS

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Background: Many individuals who will experience a first episode of psychosis (FEP) are not detected before occurrence, limiting the effect of preventive interventions. The combination of machine-learning methods and electronic health records (EHRs) could help address this gap.
Methods: This lecture will summarise recent advancements in the development and validation of precision medicine algorithms to screen Electronic Health Records and detect young individuals at risk of developing psychosis, with a particular focus on real-world implementation.
Results: Embedding precision medicine algorithms in Electronic Health Records has the potential to facilitate the detection of young people with emerging mental disorders at large scale, thus enhancing the benefits of preventive approaches to many young people.
Conclusions: Precision medicine algorithms that leverage information routinely collected as part of clinical practice can be implemented into Electronic Health Records. These approaches may deliver beneficial improvements for preventive psychiatry in young people.

46.4 ASSOCIATION OF PRIMARY CARE CONSULTATION PATTERNS WITH EARLY SIGNS AND SYMPTOMS OF PSYCHOSIS

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Background: Primary care is an important part of the care pathway for patients with psychosis; therefore, primary care physicians need to be able to accurately identify those at clinical high risk of psychosis. The difficulty of this task is increased because clinical high-risk symptoms are frequently nonspecific to psychosis. OBJECTIVE To determine whether the consultation patterns for a prespecified set of symptoms can be used to identify primary care patients who later developed a psychotic illness.

Methods: This nested case-control study used primary care consultation data collected from 530 primary care practices in 13 UK regions from January 1, 2000,through September 30, 2009. Participants included 11 690 adults with a diagnosis of psychosis and 81 793 control

participants who did not have a diagnosis of psychosis individually matched by age group, sex, and primary care practice. Data were analyzed from July 1, 2015, through June 2, 2017.
EXPOSURES Prespecified symptoms selected from literature included attention-deficit/hyperactivity disorder–like symptoms, bizarre behavior, blunted affect, problems associated with cannabis, depressive symptoms, role functioning problems, social isolation, symptoms of mania, obsessive-compulsive disorder–like symptoms, disordered personal hygiene, sleep disturbance, problems associated with cigarette smoking, and suicidal behavior (including self-harm). MAIN OUTCOMES AND MEASURES Case (diagnosis of psychosis) or control (no diagnosis of psychosis) status. Conditional logistic regression was used to investigate the association between symptoms and case-control status in the 5 years before diagnosis. Positive predictive values (PPVs) were calculated using the Bayes theorem for symptoms stratified by age group and sex. Repeated measures Poisson regression was used to investigate symptom consultation rate.

Results: Of the total sample of 93 483 participants, 57.4%were female and 40.0%were older than 60 years (mean [SD] age, 51.34 [21.75] years). Twelve symptoms were associated with a later psychotic diagnosis (all prespecified symptoms except disordered personal hygiene). The strongest association was with suicidal behavior (odds ratio [OR], 19.06; 95%CI, 16.55-21.95). Positive predictive values were heterogeneous across age and sex. The highest PPVs were for suicidal behavior (33.0%in men 24 years or younger [95%CI, 24.2%-43.2%] and 19.6%in women aged 25-34 years [95%CI, 13.7%-27.2%]). Pairs of symptoms were associated with an increase in PPV. Consultation rates were higher in cases and increased 3 months before diagnosis.
Conclusions: Most of the preselected nonspecific symptoms were associated
with a later psychotic diagnosis, particularly among young men consulting for suicidal behaviour, especially if consulting with increasing frequency. These symptoms should alert physicians to patients who may benefit from a further assessment of psychotic symptoms.

47. CHILDHOOD TRAUMA AND PSYCHOPATHOLOGICAL, COGNITIVE AND FUNCTIONAL OUTCOMES IN PSYCHOSIS, EXPLORING POTENTIAL MECHANISMS

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Overall Symposia Abstract: Childhood trauma (CT) experiences such as severe forms of abuse and neglect are associated with a psychotic disorder. However, the impact of CT does not stop at the level of the risk of developing the condition but is also associated with a variety of harmful clinical (depressive, negative, and positive symptoms of psychosis), neurocognitive and functional outcomes. However, the mechanism and moderating factors linking CT to such outcomes are poorly understood. Furthermore, although a variety of psychopathological mechanisms have been suggested as possible mediators between CT and psychosis (including dissociation, mood related symptoms of negative biases about the self and the world), little is known about potential nonclinical mediators, such a cannabis use, that can be targeted via therapeutic interventions, thus potentially reduce the harmful effects of CT.
In the current symposia novel data from large epidemiological studies and meta-analyses will be presented exploring the relationship between CT and a variety of symptoms dimensions in psychosis, cognitive deficits, and functional outcomes. In addition, new insights into how

cannabis use can mediate the effect of CT on psychosis will be presented. Possible mechanisms and potential therapeutic interventions will be discussed.

The first speaker will explore the interplay between CT and schizophrenia-polygenic risk on the psychopathological profile of people with a first-episode psychosis (FEP) from the EU-GEI study consisting of 384 patients.

The second speaker will present new meta-analytical data from 41 studies, comprised of 1,1403 people with psychosis demonstrating an association between CT and functional outcomes at different stages of the disease, and secondly, novel data on neurocognitive and social cognition as putative mediating factors between CT and poorer function over time.

The third speaker with further explore the question of the link between CT, examining the differential effect of childhood abuse or neglect, and educational attainment and Intellectual Quotient (IQ), in a sample of 829 patients with a first-episode of psychosis (FEP) and 1,283 community controls from 16 EU-GEI

The last speaker will talk about how cannabis use, in various forms and at different times, can mediate the link between various CT experiences and psychosis. This question will be addressed in a sample of 853 patients with a first-episode psychosis (FEP) and 1,174 controls as part of the EU-GEI study.

47.1 CHILDHOOD TRAUMA AND THE PSYCHOPATHOLOGICAL PROFILE IN FIRST-EPISODE PSYCHOSIS (EU-GEI): EXPLORING THE MODERATING ROLE OF POLYGENIC RISK SCORES

Monica Aas*[1], Luis Alameda[2], Marta Di Forti[3], Diego Quattrone[4], Evangelos Vassos[5], Paola Dazzan[6], Craig Morgan[7], Robin Murray[8]

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Background: Childhood trauma is a well-known risk factor for developing a more severe and complex form of psychosis. However, knowledge is scarce about how both childhood maltreatment and underlying genetic vulnerability contribute to the psychopathological profile of those with psychosis, which we investigate in this study.

Methods: We assigned a schizophrenia-polygenic risk score (SZ-PRS), calculated from the Psychiatric Genomics Consortium (PGC2) to all participants in a sample of 384 first-episode psychosis patients as part of the EU-GEI study. Symptom ratings were analyzed using multidimensional item response modelling in Mplus to estimate five theory-based models of psychosis. A history of childhood adversity was collected using the Childhood Trauma

Questionnaire (CTQ). Data were adjusted for site and 10 Principal Components. Moderation analyses were applied with bootstrapping for skewed data. SZ-PRS was added as the moderator in the analyses.
Results: Our preliminary analyses gave some evidence of SZ-PRS moderating the relationship between exposure to childhood emotional abuse and negative symptoms (ßCTQxPRS = -0.04, p=0.006). Conditional effects of the predictor at the values of the moderator showed that patients with low SZ-PRS had the lowest negative symptoms if they had not been exposed to trauma, but if their trauma scores were high their negative symptoms would be high. The opposite relationship was observed for the group with high SZ-PRS. Moreover, SZ-PRS significantly moderated the relationship between exposure to childhood emotional neglect and depressive symptoms (ßCTQxPRS = -0.02, p=0.042). Conditional effects of the predictor at the values of the moderator showed that patients with low SZ-PRS and intermediate SZ-PRS levels had low depressive symptoms if they had not been exposed to trauma, but if their trauma exposure were high their negative symptoms would also be high. For the group with high PRS, their depressive symptoms were the same independent of trauma exposure. Lastly, SZ-PRS significantly moderated the relationship between exposure to childhood sexual abuse and positive symptoms (ßCTQxPRS = -0.05, p=0.012), in the same direction as shown above with trauma being associated with higher positive symptoms in the group with low SZ-PRS but not in the group with high SZ-PRS.
Conclusions: These preliminary findings indicate that childhood trauma may be particularly associated with symptom severity in first-episode psychosis patients with low polygenic risk for schizophrenia.

47.2 ASSOCIATION BETWEEN CHILDHOOD TRAUMA AND FUNCTIONAL OUTCOMES IN PEOPLE WITH PSYCHOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: The impact of childhood trauma (CT) and its subtypes on functional outcomes in psychosis
has received considerable attention, however with evidence not yet reviewed quantitatively. The aim of this study was to systematically examine quantitatively the association between broadly defined childhood trauma (CT), abuse (sexual/physical/emotional), and neglect (physical/emotional) subtypes and various functional outcomes in people with a psychotic disorder including cross sectional and prospective cohort studies.

Methods: A search was conducted across EMBASE, MEDLINE, PsychINFO, and Cochrane Libraries using search terms related to psychosis population, CT, and functional outcomes (social, vocational and broadly defined general functioning. After reviewing for relevance, data were extracted, synthesized, and meta-analyzed.

Results: Forty-one papers were identified, including 1140 cases with psychosis. General adversity was negatively associated with general functioning (28 studies; r = -0.095; p = 0.001) with greater effects when data was prospective (11 studies; r = -0.176; p = p<0.001; neglect traumas was the only subtype of trauma showing a negative significant association with general functioning (physical neglect: 4 studies; r = -0.200; p = p<0.001; emotional neglect (4 studies; r = -0.260; p = p<0.001) although the low number of studies prevent drawing conclusions. Sensitivity analyses revealed that when excluding studies that used the overall GAF measure (including symptom severity) the magnitude of the effect was greater (19 studies; r = -0.125; p = 0.003). When heterogeneity was found, it tended to be explained by one specific study; meta-regression did not reveal major influence of various covariates. Meta-analyses on specific functional domains will be conducted soon.
Conclusions: This meta-analysis provides evidence for a negative association between trauma, broadly defined, and general functional levels in people with psychosis. Differences between those exposed and nonexposed seem to be more prominent later in the disease, when the pervasive effect of symptoms has decreased, or accordingly, when we specifically use instruments that exclude the influence of symptoms. More studies examining the impact of neglect may help confirming our preliminary evidence of a specific pervasive effect of this trauma type on functioning.

47.3 CHILDHOOD MALTREATMENT, EDUCATIONAL ATTAINMENT AND IQ: FINDINGS FROM A MULTICENTRIC CASE-CONTROL STUDY OF FIRST-EPISODE PSYCHOSIS (EU-GEI)

Lucia Sideli*[1], Adriano Schimmenti[2], Daniele La Barbera[3], Caterina La Cascia[4], Laura Ferraro[3], Monica Aas[5], Luis Alameda[6], Giulia Trotta[7], Helen Fisher[8], Vincenzo Caretti[1], Marta Di Forti[9], Craig Morgan[10], Robin Murray[10]

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Background: Accumulating evidence suggests that childhood maltreatment affects educational attainment and cognition. However, the association between childhood maltreatment and cognition seems weaker in people with psychosis than in controls. It is not clear if the relationship between childhood maltreatment, educational attainment, and Intelligence Quotient (IQ) is confounded by other risk factors, or by type of psychotic disorder. Furthermore, the differential effect of childhood abuse versus neglect has been poorly investigated.
Methods: 829 patients with a first episode of psychosis (FEP) and 1283 community controls from 16 EU-GEI sites were administered the MRC sociodemographic questionnaire, the Childhood Trauma Questionnaire, and an abbreviated version of the Wechsler Adult Intelligence Scale - III. Associations were adjusted for the potentially confounding effects of sociodemographic variables, education/ IQ, psychotic experiences, cannabis use, premorbid social functioning, and social disadvantage.

Results: In both the FEP and control group, childhood maltreatment was associated with lower educational attainment. The association between childhood maltreatment and IQ was robust to adjustment for confounders only among controls. Whereas childhood neglect was consistently associated with lower attainment and IQ in both groups, childhood abuse was associated with IQ only in controls. Among both patients with affective and non-affective psychoses, negative associations between childhood maltreatment and educational attainment were observed, but the crude association with IQ was only evident in affective psychoses.
Conclusions: Our findings underscore the role of childhood neglect in shaping the long-term academic outcomes and cognitive functioning of people with FEP as well as healthy controls.

47.4 CANNABIS USE AS A POTENTIAL MEDIATOR BETWEEN CHILDHOOD ADVERSITY AND PSYCHOSIS: RESULTS FROM THE EU-GEI STUDY

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Background: Childhood adversity and cannabis use are independent risk factors for psychosis, but whether cannabis use may be acting as mediator between adversity and psychosis has never been explored yet. Using data from the EU-GEI case-control study of First-Episode Psychosis (FEP), we examined whether cannabis use in adolescence mediates the relationship between childhood adversity and psychosis.
Methods: 853 First episode psychosis patients and 1,174 controls were recruited as part of the EU-GEI study. Detailed history of cannabis use was collected with the Cannabis Experience Questionnaire. The Childhood Experience of Care and Abuse was used to assess exposure to household discord, sexual, physical or emotional abuse and bullying at two moments: Early (between birth and age 12), and Late (between 12 -17 years). Following Baron and Kenny criteria, we analysed whether the association between childhood adversity and psychosis was mediated by (1) lifetime cannabis use, (2) cannabis potency, and (3) frequency of use in adolescence.
Results: The association between household discord and psychosis was partially mediated by lifetime use (indirect effect coef . 0.015, 19%), potency (indirect effect 0.011, 14%), and totally mediated by frequency of use in adolescence (indirect effect 0.019, 24%). Both sexual abuse (indirect effect coef. 0.012, 15%) and Late bullying (indirect effect coef. -0.016, -14%) relationships with psychosis were partially mediated by cannabis use in adolescence.
Conclusions: The mediational role of cannabis use was particularly robust for experiences of household discord relative to other types of trauma. Thus, children and adolescents exposed to particularly challenging environments in their household could benefit from psychosocial interventions aiming at preventing cannabis misuse.

48. NMDA RECEPTOR HYPOFUNCTION REVISITED: TRANSLATIONAL APPROACHES TOWARDS STRATIFICATION AND EARLY INTERVENTION IN PSYCHOSIS

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Overall Symposia Abstract: Pharmacologic, neurochemical and electrophysiological studies provide compelling evidence that hypofunction of N-methyl-D-aspartate-receptors (NMDARs) is a pathologic feature of schizophrenia (SZ). This symposium highlights novel aspects of the critical role of NMDAR hypofunction, which open ways to mechanism-based stratification and early intervention. A dozen SZ risk genes encode for proteins within 2 degrees of separation from NMDAR including serine racemase (SR), which synthesizes the NMDARs co-agonist D-serine. Joe Coyle will introduce the topic by featuring the reduction in NMDAR function in SR knock-out mice (Srr-/-). Serine racemase, encoded by Srr, synthesizes the co-agonist for forebrain NMDARs. Srr-/- exhibit a ~90% loss of brain D-serine and a marked reduction in NMDAR function resulting in impaired long-term potentiation. The Srr-/- present most of of the phenotypic characteristics of Sz including the structural pathology (i.e. reduced cortical volume, enlarged ventricles, reduced dendrites and spines), impairments in EEG abnormalities, and cognition; SZ-related positive (hyperactivity, increased striatal dopamine release) and negative symptoms (anhedonia, social deficits), many of these rescued by D-serine in adulthood. Consistent with 20 risk genes for SZ impacting glutamatergic neurotransmission, NMDAR hypofunction recapitulates SZ pathology. Patients with chronic treatment resistant SZ display lower scores in social functioning and cognition compared to responders, however this is unclear in the early phase of psychosis and the involvement of NMDAR. Sara Camporesi will present unique data concerning clinical profile, cognition and NMDAR Co-agonists pathways comparing patients responding to treatment (RESP) and treatment resistant patients (TRS), in early psychosis patients (EPP). TRS display lower cognitive scores and poorer functioning. Plasma levels of glutamate and D-serine pathways combined with brain glutamate levels suggest that the Serine Racemase and Serine Hydroxymethyltransferase metabolic pathways are key limiting factors in TRS and glutamate transport regulation underlies difference between RESP and TRS. NMDAR-antibody (NMDAR-Ab) mediated encephalitis also presents with neuropsychiatric features (among other neurological symptoms) reflecting the shared pathophysiology of NMDAR hypofunction with SZ. Antibodies bind to the external surface of the NMDAR causing NMDAR internalization. Other symptoms include movement disorders, seizures, sleep disorders, autonomic dysfunction and even death. Sukhvir Wright will discuss the clinical features, treatment and outcomes of NMDAR-Ab encephalitis relevant to neurology and psychiatry, as well as current research from disease models to receptor specific treatments. Toru Nishikawa will give insight in the regulation of the extracellular concentrations of D-serine, a coagonist for the GluN1/GluN2 typed NMDA receptor, by the calcium-permeable AMPA receptor, GABAA receptor and Asc-1 transporter in the rodent prefrontal cortex. He will highlight the role of these molecules in SZ pathophysiology and development of novel pharmacotherapy: (1) a selective antagonist of the AMPA receptor ameliorates abnormal behavior induced by phencyclidine, a model of SZ, and (2) expressional of mRNAs levels for GABAA receptor subunits and Asc-1 are altered in postmortem prefrontal cortex of SZ patients.

48.1 THE NMDA RECEPTOR HYPOFUNCTION: TRANSLATIONAL APPROACHES TO UNDERSTANDING SCHIZOPHRENIA

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Background: Genome-wide association studies (GWAS) have identified over 100 sites on the human genome conferring significant (5X10-8) risk for schizophrenia (SZ). Nearly two dozen are closely linked to the glutamate synapse, especially the NMDAR. We have genetically silenced the risk gene (Srr) encoding serine racemase, which synthesizes D-serine, a co-agonist at forebrain NMDARs to produce NMDAR hypofunction.
Methods: Srr-/- mice were generated as previously described (Basu et al., Mol Psychiatry 14: 719, 2009). Adult mice (3-5months) were used for all experiments Hippocampal slices were prepared with a vibratome, and intra-neuronal recordings were obtained as previously described (Balu et al., PNAS E2400, 2013). Golgi staining was performed with the FD Rapid Golgi Stain Kit. Immunocytochemical characterization of parvalbumin (PV) expressing neurons was performed as described by Steullet et al. (Mol Psychiatry 22: 936, 2017).Mice were subjected to trace fear conditioning adapted from Chowdry et al. (Behav Neurosci 19, 1396, 2005). Hedonic responses were quantified by intracranial self-stimulation according to Carlezon and Chartoff (Nat Prococ 2: 238, 2007). In vitro dialysis was performed in the ventral striatum to measure extracellular dopamine, glutamate and GABA (Addict Biol 24: 40, 2019).
Results: Srr-/- mice have <15% of normal brain levels of D-serine and~70% reductionin NMDAR function. The Srr-/- mice exhibit reduced cortical volume (-4%), enlarged ventricles (+20%), reduced pyramidal cell dendritic complexity and reduce spine density. Immunocytochemical studies of the cerebral cortex revealed down-regulation of PV expression in inter-neurons and reduced number of PV+-neurons. The Srr-/- mice exhibit persistent hyperactivity and a doubling of striatal dopamine release as assessed by in vivo dialysis. Finally, there was a >3-fold reduction in the response to cocaine, which failed to substitute for ICSS. Notably, many of the deficits could be reversed by treatment with doses of D-serine that restored the hippocampal levels of D-serine, which electrophysiologic studies indicate is taken up into the D-serine deficient neurons.
Conclusions: These studies indicate that silencing Srr, a risk gene for SZ, replicates the three domains of SZ as well its well established neuropathology. Positive symptoms were suggested by persistent hyperactivity, a rodent surrogate for psychosis and reinforced by the demonstration of a sustained increase in striatal dopamine release. Anhedonia, a negative symptom, was revealed wit a > 3-fold reduction in sensitivity to cocaine in an ICSS paradigm. Also, social interactions were impaired. Cognitive impairments were demonstrated in Srr-/- mice with the Morris Water Maze (probe task), sequential learning and trace fear conditioning.Equating mouse behavior with human psychiatric symptoms is tenuous, given the fact that SZ is a uniquely human condition. Nevertheless, the replication of the neuropathology of SZ in Srr-/- mice is much more compelling with cortical atrophy, reduced dendritic length and spine density in cortical pyramidal neurons, Down-regulation of PV+-GABAergic neurons, and reduced mTOR/BDNF signalling. Notably, NMDAR hypofunction disrupts the function of a circuit implicated in SZ that includes cortical glutamatergic and GABAergic and subcortical GABAergic neurons (Lisman et al., TINS 31 234, 2008).

48.2 NEUROCOGNITION, CLINICAL PROFILE AND NMDAR CO-AGONISTS PATHWAYS IN TREATMENT RESISTANT EARLY PSYCHOSIS PATIENTS

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

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Background: Patients with chronic treatment resistant schizophrenia (TRS) display lower scores in social functioning and cognition compared to patients responding to treatment (RESP), however little is known of early psychosis patients (EPP) with TRS. 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 hypothesized that: 1) poorer neurocognitive profiles, higher scores in positive and negative symptoms scale (PANSS) and lower global assessment of functioning (GAF) are early features of TRS; 2) NMDAR hypofunction could be an underlying mechanism of TRS. To test these hypotheses, we investigated in patients (TRS and RESP subgroups) and in their age and gender-matched controls subjects the clinical and neurocognitive profiles and we assessed the metabolic pathways of two main NMDAR agonists: glutamate and D-serine.
Methods: From a total of 621 EPP (31.24% women) aged 18 to 35, included in the Treatment and Intervention in early Psychosis Patients cohort in Lausanne, we identified 192 RESP and 33 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; 37.72% women) 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 (HPLC), Serine Racemase (SRR) and Serine Hydroxymethyltransferase (SHMT1) plasma levels (ELISA) and d) Glutamate pathway: glutamate and glutamine plasma and prefrontal cortex levels (MRS); EAAT3 (glutamate transporter) plasma levels.
Results: compared to treatment responder group, 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 treatment responder patients.
Conclusions: Taken together, our results highlight that TRS display lower cognitive scores and poorer functioning than RESP already in the early phases of psychosis. Moreover, our results suggest that SRR and SHMT1 metabolic pathways could be key limiting factors in TRS and that glutamate transport regulation underlies differences between RESP and TRS.

48.3 FROM SYMPTOMS TO SYNAPSE IN NMDAR-ANTIBODY MEDIATED NEUROLOGICAL DISEASE

Sukhvir Wright*[1]

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Background: The N-methyl-D-aspartic receptor (NMDAR) is an ionotropic glutamate receptor. NMDAR activation is required for long-term potentiation and long-term depression, processes thought to underlie learning and memory. The functional importance of NMDARs to cerebral processing and neural plasticity is best illustrated by the catastrophic neuro-immunological syndrome seen in NMDAR-Ab encephalitis patients when specific circulating antibodies bind to the extracellular membrane portion of the receptor, causing defects in normal synaptic function. The antibodies cause internalisation of the NMDARs leading to a state of NMDAR hypofunction. This leads to a myriad of neurological symptoms including neuropsychiatric features, movement disorders, seizures, sleep disorders, autonomic dysfunction and even death.
Methods: A combination of basic science (synaptic electrophysiology) and clinical studies will be presented to illustrate the effects of NMDAR-Antibody mediated neurological disease.
Results: The results of these studies will be discussed, including clinical features, treatment and outcomes of NMDAR-Ab encephalitis relevant to neurology and psychiatry, as well as current research from disease models to receptor specific treatments.
Conclusions: NMDAR-Abs disrupt normal brain function and are associated with a range of neurological symptoms. Increased understanding of the synaptic changes incurred when these specific human auto-antibodies bind to the NMDAR is an important first step towards development of receptor-specific treatments and potential improvement in patients' acute symptoms and long-term outcomes.

48.4 D-SERINE AND NMDA RECEPTOR IN THE PATHOPHYSIOLOGY AND TREATMENT OF SCHIZOPHRENIA

Toru Nishikawa*[1]

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Background: The schizophrenomimetic effects of antagonists and autoantibodies against the GluN1/GluN2 type NMDA glutamate receptor (NMDAR) indicate the putative NMDAR hypofunction in the pathophysiology of schizophrenia. Since D-serine has been shown to act as an endogenous coagonist for the NMDAR in the forebrain areas, the regulatory systems for the synaptic extracellular concentrations of D-serine may be a material target for the pathophysiological analyses and treatment development for schizophrenia.
Methods: An in vivo dialysis technique was used to monitor the extracellular concentrations of D-serine and other amino acids in freely moving mice and rats. The free amino acid enantiomers and non-chiral amino acids in the dialysate were simultaneously and quantitatively analyzed by using high-performance liquid chromatography (HPLC) and fluorometric detection. Expression of mRNAs of genes of Asc-1 and several GABAA receptor subunits in the postmortem brain tissues were quantitated by RT-PCR method. To examine the behavioral effects of each drug administration, the spontaneous vertical and horizontal movements including locomotor activities, rearing and head-moving were quantified by automatically counting the number of heat changes in the multiple zones of the test cage using the heat sensor with a Supermex instrument (Muromachi-kikai Co. Ltd., Tokyo, Japan).
Results: We have revealed by an in vivo dialysis technique that the calcium-permeable AMPA glutamate receptor (CP-AMPAR) and GABAA receptor exert a phasic reducing and tonic elevating control over the extracellular D-serine concentrations, respectively in the rodent medial frontal cortex. Moreover, the possible involvement of the Asc-1 neutral amino acid transporter in the prefrontal D-serine signal regulation is suggested by an increase in the extracellular D-seine levels after an Asc-1 inhibitor application. The selective CP-AMPAR antagonist, IEM 1460, given systemically has been observed to attenuate the NMDAR

antagonist phencyclidine-induced abnormal behavior in the mouse, which is a pharmacological animal model of positive, negative and cognitive symptoms of schizophrenia. In the postmortem prefrontal cortex of patients with schizophrenia, mRNA expression of the genes of Asc-1 and several GABAA receptor subunits has been found to be significantly increased and decreased, respectively.

Conclusions: The present data support the possibilities that inhibition of the CP-AMPAR might be a novel way to ameliorate both resistant negative and cognitive, and responsive positive symptoms of schizophrenia to antipsychotics and that maintenance of NMDAR activity by the extracellular D-serine signaling through Asc-1 and GABAA receptor could be impaired in schizophrenia.

O1. Oral Session: Cognition, Cannabis Use and Risk Genes

O1.1. PLACENTAL GENOMIC RISK FOR SCHIZOPHRENIA AND BIRTH ASPHYXIA ON BRAIN DEVELOPMENT

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Background: Birth asphyxia (ASPH) occurs when a newborn experiences a deficiency in brain oxygenation during or around the time of birth. ASPH reportedly increases the risk of developing neurodevelopmental disorders such as schizophrenia (SZ), autism spectrum disorder and attention deficit hyperactivity disorder, all of which have a higher incidence in males. A higher placental genomic risk for SZ was associated with smaller neonatal and adult intracranial volumes (ICV) of males in two different cohorts. The aim of this large-scale case-control study was to investigate whether placental genomic risk for SZ and a history of ASPH are associated with neonatal head circumference (nHC) and adult ICV using prospective data from the national Medical Birth Registry of Norway (MBRN) and magnetic resonance imaging (MRI).

Methods: Four hundred thirty-three patients with SZ (254, 59%, males; total mean age, SD: 27.10 years, 6.81) and 870 healthy controls (467, 54%, males; total mean age, SD: 31.18 years, 7.83) from the ongoing Thematically Organized Psychosis (TOP) project were linked to the MBRN. Summary statistics from the latest genome-wide association study (GWAS) in SZ were used to compute polygenic risk scores (PRS; GWAS $p < 5 \times 10–8$) on the 1303 participants. The fractionated PRS based on placental gene-expression loci (placental polygenic risk scores; PlacPRS) and the remaining GWAS loci (non-placental polygenic risk scores; NonPlacPRS) were calculated. We used multiple logistic regressions to test the interaction between PRS, PlacPRS or NonPlacPRS and ASPH on patient–control status. Associations between PlacPRS or NonPlacPRS and ASPH on nHC and adult ICV, measured with SAMSEG in FreeSurfer (v7.1.0), were assessed using multiple regressions. Sex-stratified analyses were performed.

Results: The prevalence of ASPH did not differ between groups ($\chi 2$ = 0.53, p = .466; 52 patients, 12%, and 117, 13%, controls). In the control group, significantly more males (74, 63%) had experienced ASPH ($\chi 2$ = 4.98, p = .026) than had females (43, 37%). A significant interaction between PlacPRS and ASPH on patient–control status (t = 2.10, p = .036) revealed that only among individuals with ASPH, a higher PlacPRS was associated with a higher likelihood of being a patient. We found a significant interaction between PlacPRS and ASPH on nHC (t = -2.14, p = .033) in the whole sample, so that lower nHC was associated with higher placental genomic risk for SZ in those with ASPH. This relationship was driven by males, particularly male controls with ASPH (t = -2.81, p = .008), and not females. Even though nHC and adult ICV correlated in each group (patients: t = 6.73, p = 3.9 x 10–14; control: t = 7.83, p = 4.1 x 10–10), a significant group x nHC interaction on adult ICV (t = 2.21, p = .028) showed that this relationship was stronger in patients. Additionally, we found a trend towards a negative association between PlacPRS and adult ICV (t = -1.97, p = .055) only in male controls with ASPH.
Discussion: An association between placental genomic risk for SZ and neonatal and adult head size in males with a history of ASPH could suggest that placental pathophysiology and ASPH play a role in affecting early trajectories of brain development, potentially linked with the higher vulnerability to SZ in males. This knowledge might lead to new strategies of treatment that prevent SZ development.

O1.2. SCHIZOPHRENIA RISK GENES CONVERGE INTO SHIFTING CO-EXPRESSION NETWORKS ACROSS BRAIN DEVELOPMENT, AGEING AND BRAIN REGIONS

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Background: Schizophrenia is thought to be a neurodevelopmental brain disorder with genetic risk being associated with shifting clinical phenomena across the lifespan. Because gene expression in the brain is coordinated and co-regulated across development, we investigated the convergence of schizophrenia risk genes in brain co-expression networks in postmortem human prefrontal cortex (DLPFC), hippocampus, caudate nucleus and in dentate gyrus granule cells, parsed by specific age periods.
Methods: Using 562 postmortem brains from neurotypical individuals, we identified 17 weighted gene co-expression networks across four brain regions and four lifespan stages (fetal to 5 years, 5-25 years, 25-50 years, over 50). We characterized co-expressed gene sets with hypergeometric and permutation enrichments tests, most notably regarding the overrepresentation of genes located within ± 500 kbp from the latest Psychiatric Genomic Consortium single-nucleotide polymorphisms (PGC3 SNPs; we refer to these genes as schizophrenia risk genes). We computed a continuous measure of the association with schizophrenia of each gene based on the GWAS statistic of the genetic variants in the gene proximity (H-MAGMA) to study via linear models how gene membership to a co-expression set predicted variation in schizophrenia association between genes.
Results: Schizophrenia risk genes were co-expressed with other genes and thus more likely to participate in a module, rather than be isolated, as evidenced by significant depletion of these

genes in the grey module of non-clustered genes. Competitive enrichment analysis showed that schizophrenia risk genes tend to cluster into specific modules, which in DLPFC and caudate were not enriched for other CNS disorders and trait genes. Cell specificity analysis highlighted that co-expression modules enriched for schizophrenia risk genes are predominantly neuronal across all brain regions considered. Parsing by age periods explained more variance in a score of gene importance for schizophrenia as measured by H-MAGMA (Vuong test for non-nested models z = 7.4, p-value = 9.1e-14) compared to lumping all age periods together in a single network. Perinatal (fetal to 5 years) and juvenile (5-25 years) networks showed greater maximum over-representation and greater variance relative to adult networks, hence suggesting that schizophrenia risk genes cluster best into co-expression networks in younger neurotypical brain tissue. Schizophrenia risk genes tend to continue to be clustered together from perinatal to juvenile life in DLPFC, but some of their co-expression partners change.
Discussion: The results support an early prefrontal involvement in the biology underlying schizophrenia, but data from all regions and age periods show that age-parsing explains more variance in schizophrenia risk compared to lumping all age periods together. Results suggest that schizophrenia risk genes continue to exert combined effects as part of their molecular environment changes across development, potentially underwriting its shifting clinical presentation.

O1.3. THE ASSOCIATION BETWEEN CANNABIS USE AND FACIAL EMOTION RECOGNITION IN SCHIZOPHRENIA, SIBLINGS, AND HEALTHY CONTROLS: RESULTS FROM THE EUGEI STUDY

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Background: Schizophrenia spectrum disorder is frequently accompanied by disturbances in social cognition. Cannabis represents one established environmental factor associated with the onset and progression of schizophrenia. The present study aimed to investigate the association of facial emotion recognition (FER) performance with patterns of cannabis use in patients with schizophrenia, siblings, and healthy controls.
Methods: Data were derived from the Workpackage 6 (WP6) of the European Network of National Networks studying Gene-Environment Interactions in Schizophrenia (EUGEI) and the Genetic Risk and Outcome for Psychosis (GROUP) studies, collected using uniform assessment schedules between 2010 and 2015 in the Netherlands, Turkey, Spain, and Serbia. FER performance was measured using the Degraded Facial Affect Recognition Task (DFAR). Linear regression models were applied to test the association of DFAR with lifetime regular cannabis use, current cannabis use, and age at first cannabis use (<16 or ≥16 years). All analyses were a priori adjusted for age, sex, country, and took into account of clustering of observations within families.
Results: 2039 patients with schizophrenia, 2141 siblings, and 2049 healthy controls were included in the analyses. Better FER performance as indicated by higher DFAR-total scores was associated with lifetime regular cannabis use in schizophrenia (B=1.36, 95% CI 0.02 to 2.69), siblings (B=2.17, 95% CI 0.79 to 3.56), and healthy controls (B=3.10, 95% CI 1.14 to 5.06). No associations were found between DFAR-total and current cannabis use. Patients with schizophrenia who started to use cannabis after the age of 16 showed better FER performance

than patients who started earlier (B=2.50, 95% CI 0.15 to 4.84) and non-users (B=3.72, 95% CI 1.96 to 5.49). Better FER performance was found also in siblings who started to use cannabis after the age of 16 compared to non-users (B=2.37, 95% CI 0.58 to 4.16), while healthy controls using cannabis performed better than non-users at DFAR-total regardless of the age at first use.
Discussion: Our findings suggest that lifetime regular cannabis use may be associated with better social cognition regardless of the psychosis risk, but that the social cognition might be moderated by age at first use of cannabis in people with higher genetic risk. Longitudinal studies may clarify whether there is a cause-and-effect relationship between cannabis use and social cognitive performance in psychotic and non-psychotic samples.

O1.4. MICROGLIAL-EXPRESSED GENETIC RISK VARIANTS, COGNITIVE FUNCTION AND BRAIN VOLUME IN PATIENTS WITH SCHIZOPHRENIA AND HEALTHY CONTROLS

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Background: Schizophrenia (SZ) is a complex heritable neuropsychiatric disorder, in which level of disability is strongly predicted by impairments in cognitive function. This variation in cognition has previously been associated with immune-relevant genetic loci, including genes of the complement system. In addition, microglia have also been associated with SZ pathophysiology and cognition; findings which have supported the growing evidence of immune involvement in variation in cognitive functioning and brain structure in patients with SZ. Given that microglia are the primary innate immune cells in the brain, with known roles in synaptic functioning, we sought to investigate the effects of a microglial genetic score on that of SZ risk, cognitive performance and brain structure in healthy participants and in patients with SZ.
Methods: To explore the impact of SZ risk alleles linked to microglia, we generated a microglial-based polygenic score (PGS) using recent GWAS summary data for SZ. We examined whether this microglial PGS explained variation in cognition in an Irish sample of SZ patients and controls (n = 1,234), and tested whether grey matter (GM) volume mediated this association. Three domains of cognitive functioning were assessed, including general cognitive ability, working memory and episodic memory. The strength of these microglial scores were then compared to that of neuronal and astroglial (i.e., other brain-relevant genes) PGSs, and MAGMA was used to test for enrichment of these gene-sets with SZ risk. Subsequently, results were examined in a large independent sample of UK Biobank participants (n =134,827). Throughout, analyses were corrected for age, sex and intracranial volume
Results: Increased microglial SZ-PGS was significantly associated with lower performance across several measures of cognitive functioning (R2 range= 0.8-1.8) in both samples; associations which were then found to be mediated via total GM volume in the UK Biobank (β = -0.004). The most markedly significant domain was found for episodic memory (β=-0.135, $p < 0.001$). In a post-hoc analysis, the association between the microglial PGS and episodic memory remained significant in cases (β=-0.096, p= 0.028) and trended toward significance in controls (β= -0.154, p= 0.057). No significant enrichment of association was observed between the microglial genes and SZ risk (β=-0.0087, p= 0.860), unlike neuronal genes which did show evidence of enrichment (β= 0.0285 p= 0.0002). Further, the difference in magnitude between the microglial, neuronal and astroglial SZ-PGSs across the various cognitive tests was not statistically significant.

Discussion: Results from our study provide novel evidence that increased microglial PGS is associated with decreased performance in both patients and healthy controls. We further highlight that variation in GM volume mediates the association between the microglial PGS and cognition, supporting evidence of immune processes being associated with variation in brain structure. We also highlight, both the non-illness specificity of the findings and the absence of microglial enrichment for SZ risk, and interpret this to reflect the relevance of microglial-expressed genetic variation is for neurodevelopmental processes related more generally to cognition. This is also consistent with the finding that the association between the microglial and neuronal PGSs did not differ significantly but rather demonstrated comparable associations across the various cognitive tests.

O1.5. BIDIRECTIONAL RELATIONSHIP BETWEEN CANNABIS USE, ANXIETY AND AFFECTIVE DYSREGULATION IN MEDIATION OF THE ASSOCIATION WITH PSYCHOSIS: FURTHER SUPPORT FOR AN AFFECTIVE PATHWAY TO PSYCHOSIS

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Background: Empirical evidence suggests that people use cannabis in order to reduce anxiety and affective-dysregulation, yet cannabis use also worsens psychosis and affective symptoms. Independently, anxiety and affective-dysregulation are also risk factors for psychosis. However, the temporal relationship between cannabis use, anxiety, and affective-dysregulation and psychosis are unclear. This may be informed by an examination of the mutually mediating roles of cannabis and affective-dysregulation in the emergence of psychosis.

Methods: Data were derived from four waves of the second longitudinal Netherlands Mental Health Survey and Incidence Study (NEMESIS-2). Mediation analysis was performed to examine (a) whether cannabis use mediates the relationship between preceding affective dysregulation (anxiety and depression) and later psychosis incidence; and (b) whether affective dysregulation mediates the relationship between cannabis use and later psychosis incidence, using KHB logit in STATA while adjusting for age, sex and education status.

Results: In mediation analysis, cannabis use was found to mediate the relationship between pre-existing anxiety, depression, and later psychosis incidence, but the indirect contribution of cannabis use was small (for anxiety: indirect effect due to cannabis use OR= 1.01; 95% CI 1.00-1.01, p=0.045; % of the total effect that is due to cannabis use =1.00%; for depression: indirect effect due to cannabis use OR= 1.01; 95% CI 1.00-1.02, p=0.045; % of the total effect that is due to cannabis use =1.4%). Interestingly, pre-existing anxiety and depression were found to mediate the relationship between cannabis use and later psychosis incidence to a greater degree (indirect effect due to anxiety OR= 1.10; 95% CI 0.99-1.21, p=0.065; % of the

total effect that is due to anxiety =17%; indirect effect due to depression OR= 1.23; 95% CI 1.11-1.37, p<0.001; % of the total effect that is due to depression =37%).
Discussion: This is the first longitudinal cohort study, to our knowledge, to examine the mediational relationship between cannabis use, anxiety, and mood-dysregulation in the emergence of psychosis. The results suggest the presence of a bidirectional relationship between cannabis use, anxiety, and mood-dysregulation in the emergence of psychosis. This may explain the seemingly anomalous finding of greater cannabis use, and greater anxiety/affective-dysregulation among people with psychosis.

O1.6. PATTERNS OF COGNITIVE VARIABILITY ACROSS MULTIPLE COGNITIVE FUNCTIONS IN SCHIZOPHRENIA SPECTRUM DISORDER COMPARED TO HEALTHY INDIVIDUALS

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Background: Cognitive heterogeneity is well documented in schizophrenia spectrum disorders (SZ) and is likely to represent different subtypes with different cognitive, clinical and symptom profiles. However, no previous study has investigated whether the observed heterogeneity differs from the normal variability-range within healthy controls. Thus, we have investigated whether heterogeneity is specific to SZ compared to HC and explored whether it is restricted to some cognitive functions or tests, to understand more about the underlying mechanisms.
Methods: Participants with SZ (n = 905) and healthy controls (n= 1170) were recruited as part of the Norwegian TOP study. All participants underwent cognitive assessment covering a wide range of cognitive functions encompassing premorbid and current intellectual functioning, mental and psychomotor processing speed, fine motor speed, verbal learning and memory, inhibition, semantic fluency and working memory. Additional clinical assessment of symptoms and functioning were obtained from patients. To investigate mean and variability differences, we used double generalized linear models (DGLM, Y ~ Age + Sex + Dx, ~ Age + Sex + Dx), where Y is the mean in the first GLM, and the variability of the first GLM is the responses in the second GLM. Correction for multiple testing was performed using the Bonferroni method ($\alpha = 0.005/44$ tests ~ $p < 0.000115$). In follow-up analyses, we tested whether symptom scores were associated with variability in cognitive performance.
Results: In addition to significant group-level mean differences on 96 % of the tested cognitive variables, we found increased variability in SZ compared to HC on 64 % of the tested variables. Increased variability was found on measures of intellectual functioning, verbal memory, fine-motor speed, mental processing speed, and inhibition. There were no variability differences in complex cognitive functions including semantic fluency, psychomotor processing speed, and working memory, and no function showed the opposite pattern of increased homogeneity in patients. Increased variability in SZ was associated with reduced global functioning and more negative and disorganized symptoms.
Discussion: Here we extend previous findings by verifying heterogeneity specific to SZ compared to HC in several measure with a common speeded component (fine-motor speed, mental processing speed, and inhibition), in verbal learning and memory, and in intellectual functioning. The considerable performance variability seems partly to be related to symptom

severity and global functioning and may represent different patient subtypes with specific cognitive challenges.
Measures of working memory, fluency, and psychomotor processing speed, that require rapid assembly and coordination of simultaneous processes, are similarly affected, and might reflect common disease mechanisms.

Cognitive heterogeneity represents a significant challenge both in schizophrenia research and in the clinic. These findings emphasize the importance of developing personalized treatment programs in mental health services.

O1.7. PENETRANCE AND PLEIOTROPY OF NEUROPSYCHIATRIC CNVS IN 660,000 US VETERANS

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Background: Rare, large copy number variants (CNVs) are causally associated with neurodevelopmental and neuropsychiatric disorders, and carriers of specific CNVs often have a typical, syndromic clinical presentation. However, there is growing recognition that many well-studied CNVs have variable penetrance and phenotypic expressivity.
Methods: The Million Veteran Program (MVP) Genomics Working Group CNV Sub-Committee utilized the MoChA software extension to bcftools (https://github.com/freeseek/mocha) to infer CNVs in 662,681 participants in MVP and Cooperative Studies Program (CSP) #572. We performed phenome-wide association studies (PheWAS) of 53 neuropsychiatrically relevant CNVs with 1,800 disease categories and 70 laboratory measurements, using Fisher's exact test and logistic or linear regression with standard covariates.
Results: PheWAS in 450,000 European American participants highlighted robust associations of 22q11.2 deletions with schizophrenia (OR=17, 95% CI:[5.33,46.65]; P<2e-7); 16p11.2 duplications with schizophrenia (OR=4.72, 95% CI:[3.14,6.84]; P<6e-15); 16p11.2 deletions with schizoid personality disorder (OR=7.1, 95% CI:[3.01,14.01]; P<4e-7); and 17q12 duplications with major depressive disorder (OR=2.02, 95% CI:[1.54,2.67]; P<5e-7). Associations between 16p11.2 deletions and tobacco-use disorder, and 16p13.11 deletions and mood disorders were directly replicated in >120,000 African American participants (P<0.05). We observed characteristic patterns of associations between 16p11.2 deletions and obesity (OR=4.44, 95% CI:[3.21,6.25]; P<2e-18), type 2 diabetes (OR=3.11, 95% CI:[2.35,4.13]; P<3e-15), and respiratory issues (OR=2.5, 95% CI:[1.85,3.42]; P<5e-9), with partial replication in African Americans (P<0.05). Increased risk of tinnitus among carriers of 22q11.2 microduplication carriers was evident in European (P<2e-6), African (P<0.03), and Hispanic American (P<0.03) veterans.
Discussion: The Million Veteran Program (MVP) Genomics Working Group CNV Sub-Committee is applying cutting-edge approaches to the detection and study of CNVs. Our

preliminary results confirm established phenotypic associations and highlight new pleiotropic relationships of well-studied CNV events. We are presently extending these analyses to the study of CNV burden and enhanced genetic risk prediction.

O2. Oral Session: Early Psychosis and Markers of Psychosis

O2.1. MULTIMODAL PREDICTION OF CONTINUED CANNABIS USE IN INDIVIDUALS WITH RECENT-ONSET PSYCHOSIS AND CLINICAL HIGH-RISK FOR PSYCHOSIS

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Background: Continued cannabis use (CCu) is one of the most important predictors for poor long-term outcomes in individuals with recent-onset psychosis (ROP) and individuals at clinical high-risk for psychosis (CHR). The vulnerability to CCu persists even after treatment to establish and maintain abstinence from cannabis use, and the response to abstinence interventions varies greatly between individuals. However, no generalisable model has hitherto been developed and tested for its ability to predict CCu among individuals with ROP or CHR. In the current study, we therefore aimed to investigate the power of an ensemble of clinical, cognitive, and structural magnetic resonance imaging (sMRI) variables to predict CCu in these vulnerable patient groups using machine learning.

Methods: Within the longitudinal multisite 'Personalized Prognostic Tools for Early Psychosis Management' study and the longitudinal Cannabis-induced psychosis study, we recruited N = 109 individuals with ROP and N = 73 individuals at CHR. All individuals were lifetime cannabis users at baseline. CCu was defined as any cannabis consumption between baseline and nine-months follow-up as assessed in structured interviews. Within a repeated nested cross-validation framework, we employed a linear support vector machine to investigate how structured clinical and cognitive assessments and sMRI contributed to the prediction of CCu in ROP individuals. We tested our predictions for generalizability to the cohort of CHR individuals.

Results: Data from clinical assessment alone predicted CCu with 73.3% Balanced Accuracy (BAC) ($p<.001$) in the ROP group, and 58.7% in CHR individuals, whereas CCu predictions based on cognition and sMRI were non-significant (all $p>.093$, cognition: BAC-ROP=47.4%, BAC-CHR=52.3%, sMRI: BAC-ROP=55.7%, BAC-CHR=54.6%). Adding sMRI or cognition to the clinical predictor via stacking did not significantly improve prediction accuracy, either in ROP or CHR groups (all $p>.065$). Lower functioning, specific patterns of substance use, i.e., lifetime diagnoses of cannabis dependency and number of other illicit substances consumed in life, urbanicity, and lack of adaptive coping strategies, all contributed reliably to the CCu clinical prediction.
Discussion: Our results suggest that it may be possible to identify individuals with ROP and CHR at higher risk for CCu based solely on clinical predictors. Lower functioning, substance use patterns, urbanicity and a lack of coping strategies might represent important factors for guiding preventative efforts. Importantly, our model needs further testing in larger, clinically diverse samples before its transfer into clinical practice. Overall, our findings might pave the way for tailored interventions for particularly vulnerable individuals to improve their clinical outcome.

O2.2. IMPACT OF COMORBID AFFECTIVE DISORDERS ON LONGITUDINAL CLINICAL OUTCOMES IN INDIVIDUALS AT CLINICAL HIGH RISK FOR PSYCHOSIS

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Background: Mood (41%) and anxiety disorders (15%) are reported as one of the most frequent co-occurring conditions in subjects at Clinical High Risk for Psychosis (CHR-P). These comorbid affective diagnoses tend to persist and are associated with increased experienced distress and a lower level of global and psychosocial functioning over time. Less is known about the impact of affective comorbidities on the prospective course of attenuated psychotic symptoms (APS). We aimed to examine distinct trajectories of APS severity over a two-year period in a CHR-P sample. We subsequently investigated the prognostic value of past, baseline or one-year comorbidity of anxiety or depression on these trajectories and the risk to transition to psychosis.
Methods: Latent class mixed model analysis (LCMM) were used to identify most likely APS trajectory class membership in 331 CHR-P subjects from the multicenter European Gene-Environment Interactions (EU-GEI) study assessed at baseline, 6, 12 and 24 months follow-up. The prognostic value of past, baseline and one-year DSM-IV depressive or anxiety disorders on trajectory class was investigated using logistic regression, controlling for confounders. Cox proportional hazard analyses investigated associations with transition risk.
Results: 46.8% of participants fulfilled criteria for a past depressive disorder; 33.2% at baseline and 15.1% at one-year follow-up. Any past, baseline or one-year anxiety disorder was diagnosed in 42.9%, 37.2% and 27.0%, respectively. Participants were classified into one of three latent APS trajectory classes: (i) persistently low, (ii) increasing and (iii) decreasing. Past depression was associated with a higher risk of belonging to the increasing trajectory class, compared to the persistently low (OR=3.149, [95%CI:1.298-7.642]) or decreasing class (OR=3.137,[1.165-8.450]). In contrast, past (OR=.443,[.179-1.094]) or current

(OR=.414,[.156-1.094]) anxiety disorders showed a trend-level association with a lower risk of belonging to the increasing class compared to the persistently low class. Past depression was significantly associated with a higher risk of transitioning to psychosis (HR=2.123,[1.178-3.828]).
Discussion: A past depressive episode might be a particularly relevant risk factor for an unfavorable course of APS in CHR-P individuals. Early affective disturbances may be used to advance detection, prognostic, and clinical strategies.

O2.3. NEARLY HALF OF INCIDENT PSYCHOTIC DISORDERS OVER SIX YEARS IS NOT ATTRIBUTABLE TO PRECEDING POSITIVE PSYCHOTIC EXPERIENCES: A PROSPECTIVE STUDY IN A REPRESENTATIVE GENERAL POPULATION

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Background: Growing evidence suggests that early intervention in psychosis is a promising paradigm shift. Its utility may be boosted through more comprehensive strategies for early detection in general populations. Robust evidence has linked baseline psychotic experiences (PEs) and general psychopathology, family history of mental disorders, and some environmental exposures (e.g. cannabis use) with increased risk for subsequent psychotic disorders (PDs). However, assessments of incidence of PDs attributable to these 'markers' in general populations is limited. By combining prevalence rates and relative risk, these assessments might indeed open a new era of community-based early detection in psychosis. The aim of this study is to estimate the population attributable fraction (PAF) of incident PDs for preceding PEs, mood episodes, general psychopathology, and family history of mental disorders/ cannabis use in a six years follow-up of a representative general population
Methods: A community-based sample, representative of the urban and rural population of a metropolitan city (n: 2185) was visited twice at their households (baseline and sixth year follow-up assessments). PEs, mood episodes, general psychopathology, cannabis and alcohol use was evaluated using Composite International Diagnostic Interview 1.2. PEs were categorized into clinical PEs (associated with distress or help-seeking or frequent) and subclinical PEs. Family history of mental disorders was assessed using questions derived from the Family Interview for Genetic Studies. Participants with probable PDs were re-interviewed with the SCID-I by team psychiatrists at both assessments. PAF analyses were performed adjusting for age, gender and education
Results: The incidence rate of PDs was 21.8 per 100,000 person-years. Of the PDs incidence in the general population, 62.2% (%95 CI: %32.0-78.9) was attributable to help seeking for any mental disorders at baseline. Only half of the PDs incidence was attributable to baseline PEs (PAF: 53.3; 95% CI: %22.8-71.4) at any severity (including clinical and subclinical PEs). Interestingly, PAFs of PDs incidence for baseline clinical PEs and baseline mood episodes were similar (PAFs respectively; 41.1, 95%CI: 17.5-58.6 and 39.3, 95%CI:12.1-58.1). Furthermore, the PAFs of PDs incidence for any family history of mental disorders (37.0, %95CI: 8.7- 56.5) and cannabis use (PAF: 26.6, %95 CI: %7.2-41.9) were also high.
Discussion: These results highlight the importance of different pathways through psychotic disorders outside the 'exacerbation of positive symptoms' pathway. Assessments of multiple dimensions of psychopathology next to subthreshold positive domain may be more effective for community-based achievements in early detection of PDs

O2.4. ACCELERATED CORTICAL THINNING PRECEDES CONVERSION TO PSYCHOSIS: THE NAPLS3 LONGITUDINAL STUDY OF YOUTH AT CLINICAL HIGH-RISK

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Background: Progressive gray matter loss has been demonstrated among clinical high-risk (CHR) individuals who convert to psychosis, but it is unknown whether these changes occur prior to psychosis onset. Identifying illness-related neurobiological mechanisms that occur prior to conversion are essential for targeted early intervention. The aim of this study was to determine if steeper cortical thinning is observable prior to psychosis onset among CHR individuals who ultimately convert (CHR-C), and to assess the shortest possible time interval in which rates of cortical thinning differ among CHR-C and CHR non-converters (CHR-NC).

Methods: Participants took part in the third wave of the North American Prodrome Longitudinal Study (NAPLS3), completing 1-5 clinical and structural MRI assessments at 0, 2, 4, 6, and 8 months (or at the time of conversion to psychosis). Healthy control (HC) and CHR participants who completed at least one structural magnetic resonance imaging (MRI) scan that met quality control standards were included in the present study. Initial vertex-level linear mixed effect (LME) analyses were conducted to identify brain regions in which the rate of cortical thinning differed by clinical group in models including age, age2, sex, and scanner as fixed effect covariates and a random subject-specific intercept. Regions with an area of at least 100 mm2 were retained as clusters for further analyses. Across all left hemisphere clusters (left ROI) and right hemisphere clusters (right ROI), relationships between clinical group and the percent change in cortical thickness between first and second scan (PCscan2) and between first and last scan (PCFinal) were assessed, after accounting for age, age2, sex, and scanner. Follow-up analyses were conducted to examine the effects of antipsychotic medications on all LME and percent change statistical tests. Receiver operating curve (ROC) analyses were conducted to see if the left ROI could discriminate CHR-NC from CHR-C at the individual subject level.

Results: 338 CHR-NC, 42 CHR-C, and 62 HC participants (age 19.3 +/- 4.2, 44.8% female, 52.5% racial/ethnic minority) completed at least one structural MRI that met quality control standards. Accelerated cortical thinning among CHR-C compared to CHR-NC and HC was observed in LME analyses in multiple regions of prefrontal, temporal, and parietal cortex. CHR-NC also exhibited accelerated cortical thinning compared to HC in several of these areas. Greater percent decrease in cortical thickness (PCscan2) was observed among CHR-C compared to other groups across 2.9 +/- 1.8 months, on average, in the left ROI. In both the left and right ROIs, greater cortical thinning was observed among CHR-C compared to other groups when assessing percent change between first and last scan, conducted 6.8 +/- 2.5 months apart (PCFinal). Antipsychotic medication exposure did not account for group differences in cortical thinning in LME or percent change analyses. ROC analyses discriminating CHR-C

from CHR-NC by PCscan2 in the left ROI, scanner, age, age2, and sex had an AUC of 0.74 (95% CI: [0.72, 0.85]), with model predictive power driven primarily by percent change in thickness.
Discussion: Accelerated cortical thinning precedes psychosis onset and differentiates CHR-C from CHR-NC and HC across less than three months, on average. Results indicate the importance of evaluating cortical thinning as a biomarker of conversion and encourages further research into mechanisms underlying cortical thinning among CHR individuals, which may provide novel treatment targets prior to psychosis onset.

O2.5. LONGITUDINAL MACRO- AND MICROSTRUCTURE CHANGES IN CORTICAL GRAY MATTER IN CLINICAL HIGH RISK FOR PSYCHOSIS

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Background: Recent anatomical MRI studies found a steep decrease in gray matter (GM) volume following the onset of psychosis. However, volumetric GM changes are thought to be rooted in microstructural changes, such as reduced spine density and dendritic arborization. Indeed, diffusion MRI (dMRI) studies identified an increase in free-water (FW) in GM following the onset of psychosis, implicating microstructural pathologies. However, FW in GM is dramatically affected by partial volume with cerebrospinal fluid (CSF), and thus it remains unclear if FW changes truly reflect microstructural changes, or if they indirectly reflect the same macrostructural changes that affect volumetric measures. Therefore, we aimed to study individuals at clinical high risk for psychosis (CHR) to investigate earlier manifestations of macro- and microstructure GM pathology as potential precursors for psychosis. To better dissociate macro- and microstructural effects, we investigate a novel analysis that eliminates CSF contribution from GM measures, to estimate interstitial free-water (iFW), and its relationship with macrostructural volumetric changes.
Methods: Longitudinal dMRI and anatomical MRI were acquired from 160 CHR and 96 matched healthy controls (HC) in a single site as part of the Shanghai at Risk for Psychosis (SHARP) study. Thirty-three CHR individuals developed psychosis (CHR-P), and 127 individuals did not (CHR-NP) within the timeframe of the study. FreeSurfer was used to parcellate the cortical GM into eight regions of interest (ROI) (orbitofrontal, OFC; lateral prefrontal, LPFC; medial prefrontal, MPFC; lateral temporal, LTC; medial temporal, MTC; somatormotor, SMC; parietal, PC; occipital cortex, OCC). FW maps were estimated from dMRI. Tissue segmentation (DD-seg) was performed directly on the dMRI to estimate CSF fraction, which was used to calculate iFW maps. Analyses of covariance of linear mixed effects models with random intercept and Tukey posthoc tests were used to statistically test for group effects, and for group by time interaction in iFW and volume of each cortical ROI, while controlling for age, sex, and intracranial volume.

Results: There were group differences in volume in two of eight cortical ROIs: LTC (P=0.001) and MTC (P=0.005), where CHR-P had significantly lower volume in both ROIs compared to HC, and CHR-NP had a significantly reduced volume only in the LTC compared to HC. All ROIs except the MTC showed significant group by time interaction, indicating faster longitudinal volume reduction in CHR-P compared to both HC and CHR-NP groups. Moreover, iFW in both CHR-NP and CHR-P was significantly higher than HC in four out of eight ROIs: MPFC (P=0.007), LTC (P=0.005), PC (P=0.004), and OCC (P=0.004). Group by time interactions indicated faster longitudinal iFW increase in CHR-P compared to both HC and CHR-NP group for LTC, MPFC, and SMC. For OCC and PC, CHR-P showed faster iFW increase than CHR-NP group. The CHR-P group showed significant negative correlations between rate of change in volume and iFW in all cortical ROIs (MPFC, P=0.031; LTC, P=0.019; MTC, P=0.031; SMC, P=0.001; PC, P=0.010; OCC, P=0.001), except LPFC. However, less ROIs showed significant negative correlation between iFW and volume in CHR-NP (LPFC, MPFC, LTC) and HC (OCC) than in CHR-P.
Discussion: We found both volumetric macrostructural and iFW microstructural GM changes in CHR at baseline, although there were more regions with iFW changes. In CHR-P, both volume and iFW show accelerated longitudinal changes, although more regions show accelerated volume changes. These results suggest that CHR-P iFW increases in GM precede accelerated volumetric changes. Changes over time were correlated in CHR-P, and less so in CHR-NP or HC, indicating this association is more evident in pathology.

O2.6. ALTERATIONS OF THE BASAL FOREBRAIN CHOLINERGIC NUCLEI ACROSS THE SCHIZOPHRENIA SPECTRUM

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Background: The cholinergic basal forebrain nuclei (BFCN) are the main source of cholinergic innervation in the cortex, and support several cognitive functions (e.g., attention). The BFCN can be divided into an anterior part projecting into the hippocampus/entorhinal cortex and a posterior part projecting into the neocortex. Mounting evidence indicates that cholinergic transmission is altered in schizophrenia and associated with distinct symptoms. Beyond alterations in cholinergic transmission, the BFCN themselves have lower volumes in schizophrenia and correlate with attentional difficulties. However, whether lower BFCN volumes reflect an aberrant neurodevelopmental process – i.e., changes are already present in the prodrome/first-episode psychosis - or a neurodegenerative one – i.e., changes are only present in later stages of the disorder – is unknown. To investigate this question, we analyzed gray matter (GM) integrity of the anterior and posterior BFCN across the schizophrenia spectrum.
Methods: We investigated GM integrity of cytoarchitectonically defined BFCN masks, reflecting the anterior and posterior BFCN, in 72 subjects at clinical high-risk for psychosis (CHR), 98 first-episode psychosis (FEP) (30 unmedicated and 68 medicated), 141 patients with schizophrenia (SCZ), and 169 healthy controls (HC) in a cross-sectional, multi-site (N=4) structural magnetic resonance imaging (MRI)–based volumetry study. Anterior and posterior

BFCN volumes were compared between groups with ANOVAs, and correlation analysis was used to evaluate relationships between volumes and antipsychotic medication, illness duration, positive, negative, and cognitive symptoms. Data were harmonized to allow for comparisons between distinct acquisition sites.

Results: An ANOVA demonstrated significant differences across the schizophrenia spectrum in the anterior BFCN ($F_{3,470}=4.94$, $p=0.002$). Posthoc comparisons revealed that SCZ had significantly lower volumes than all other groups, with no other differences between groups, or subgroups (i.e., medicated and nonmedicated FEP). Anterior BFCN volumes remained significantly lower in SCZ after controlling for global GM and medication. No significant correlations were found between lower anterior BFCN volumes and antipsychotic medication, positive, or negative symptoms in SCZ, but there was a significant correlation with attentional capacity, as measured by the continuous performance test ($r=0.27$, $p=0.03$).

Correspondingly, an ANOVA demonstrated significant differences in posterior BFCN volumes across the schizophrenia spectrum ($F_{3,470}=2.98$, $p=0.03$). Posthoc comparisons revealed that FEP had higher volumes than both HC ($p=0.02$) and SCZ ($p=0.005$), with no other significant differences between groups. Posterior BFCN volumes remained higher in FEP compared to HC ($p=0.01$), but not compared to SCZ ($p=0.08$) after controlling for global GM. Controlling for medication did not influence the main result. Subgroup analyses demonstrated that unmedicated FEP had higher posterior BFCN volumes than both HC ($p=0.001$) and medicated FEP ($p=0.005$). No significant correlations were found between higher posterior BFCN volumes and antipsychotic medication, positive, or negative symptoms in FEP, but there was a trend correlation with verbal fluency ($r=-0.29$, $p=0.08$).

Discussion: Anterior and posterior BFCN volumes are differentially affected across the schizophrenia spectrum. Early phases of psychosis are accompanied by higher volumes in the posterior BFCN, whereas later phases are accompanied by lower anterior BFCN volumes. Data suggest that both neurodevelopmental and neurodegenerative processes are relevant for altered BFCN in schizophrenia.

O2.7. ASSOCIATIONS BETWEEN MULTIPLE LEVELS OF SOCIALLY SUPPORTIVE ENVIRONMENT AND DISTRESSING PSYCHOSIS-LIKE EXPERIENCES

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Background: Negative social environment experiences during developmental years have been associated with psychosis risk. However, many gaps remain in a full understanding of the various levels of negative social experiences that may influence psychosis risk. Using an ecological systems framework, we analyzed Adolescent Brain Cognitive Development (ABCD) Study data to examine the associations between self-reported distressing psychosis-like experiences (PLEs) and five dimensions of social environment, specifically: 1) community cohesion; 2) low regional religious affiliation; 3) school environment; 4) family environment; and 5) number of close friends.

Methods: Our sample was derived from the ABCD 3.0 Data Release. Our subsample included n= 6,444 youth ages 9-10 from 21 different research sites. Distressing PLEs were youth-reported using the Prodromal Questionnaire-Brief Child Version. Community cohesion was measured using the caregiver-reported Community Cohesion scale. Regional religious

affiliation was calculated as the estimated proportion of individuals at the location of the youth's research site with the same religious affiliation as the youth (based on caregiver-reported youth religious affiliation). School environment was measured using the youth-reported School Environment subscale of the Community Risk and Protective Factors scale. Family environment was measured using the youth-rated Family Conflict subscale of the PhenX Family Environment Scale. Number of close friends was assessed as the number of youth-reported male and female close friends. Separate linear mixed models were used to examine the association between distressing PLEs and each of the five dimensions of social experience, adjusting for gender and age, with the 21 ABCD sites and family nested.
Results: Higher scores on community cohesion (β=-0.062; p<0.0001) significantly predicted lower distressing PLEs. Lower regional religious affiliation also predicted more distressing PLEs (β=-0.054; p<0.0001). A less positive school environment (β=-0.101; p<0.0001) and higher family conflict (β=0.120; p<0.0001) were also associated with higher levels of distressing PLEs. However, a lower number of youth-report close friends was associated with lower distressing PLEs (β=0.040; p<0.0001).
Discussion: The current study provides incremental steps towards a more comprehensive ecological model to understand the role of social environment in shaping risk for psychosis. Aspects of community, religion, school, and family environment all appear to increase likelihood of endorsing distressing PLE, which is consistent with current models of stress and isolation being associated with PLEs (e.g., social defeat; social deafferentation; minority stress theory). However, the finding that a lower number of close friendships is associated with lower PLEs is inconsistent with existing models. Limitations include a reliance on self-report and the mix of parents and youth-reported measures. Future directions may include more comprehensive assessments of both positive and negative aspects of social environments and qualitative approaches.

O3. Oral Session: Intervention in the Context of Global Public Health

O3.1. NEIGHBORHOOD POVERTY AND HIPPOCAMPAL VOLUME AMONG YOUTH AT CLINICAL HIGH RISK FOR PSYCHOSIS: THE MODERATING ROLE OF SOCIAL ENGAGEMENT

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Background: While hippocampal volume (HV) reduction has been shown in psychotic disorders, the relation of neighborhood poverty (NP) and HVs in clinical high risk for psychosis (CHR-P) individuals is unknown. In this study, we explore the associations between NP and HV, and whether social engagement (SE) moderated this relationship in CHR-P individuals.
Methods: Data were collected at baseline as part of the North American Prodrome Longitudinal Study Phase 2. All available addresses where participants resided at baseline were geographically coded to NP at the census tract level using the 5 Year Estimate American Community Survey. NP was defined as the percentage of residents whose income was below

the poverty level in the past year. SE was derived from sub-scale items of the Life Events Scale. Generalized linear mixed models tested associations between NP and HV. Models controlled for age, sex, race/ethnicity, family history of mental illnesses, household poverty, educational level, and life events stress. Moderating effects of age, sex, and SE were tested using interaction term of neighborhood poverty x social engagement.
Results: This study included 174 CHR-P individuals, aged 12 to 33 years. NP was associated with reductions in HV (unadjusted $\beta = -0.203$; 95% CI = -0.351 – -0.056; $p = 0.007$) even after controlling for seven covariates (adjusted $\beta = -0.196$; 95% CI = -0.342 – -0.050; $p = 0.009$). Interaction terms NP x age and NP x sex were not significantly associated with HV ($p>0.05$). Interaction term NP x SE was significantly associated with HV ($p <0.05$). Subgroup analyses show that among those with lower SE (n=77), NP was associated with reductions in HV (adjusted $\beta = -0.341$; 95% CI = -0.551 – -0.131; $p = 0.002$). However, among those with greater SE (n=97), NP was not significantly associated with HV (adjusted $\beta = -0.041$; 95% CI = -0.186 – -0.268; $p = 0.719$).
Discussion: In this study, NP is associated with HV above and beyond individual-level risk factors including household poverty among individuals at CHR-P. This association is moderated by SE. Among those with lower SE, NP was negatively associated with HV, while there was no significant association between NP and HV among CHR-P individuals with greater SE. These preliminary findings suggest that SE may buffer the negative relationship between NP and HV among CHR-P individuals, which has potential implications for early intervention.

O3.2. REAL-WORLD ANTIPSYCHOTIC TREATMENT TRAJECTORIES IN PEOPLE WITH FIRST EPISODE PSYCHOSIS (FEP): A LONGITUDINAL ANALYSIS OF ELECTRONIC HEALTH RECORD (EHR) DATA

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Background: Response and tolerability of antipsychotics vary between patients with FEP. Randomised controlled trials do not necessarily reflect prescribing practice in real-world clinical settings. Real-world data studies could help to better characterise which antipsychotics are prescribed as first and second-line treatment for FEP and how patients switch between different medications. We investigated antipsychotic treatment trajectories in FEP by analysing data from a large mental healthcare EHR dataset.
Methods: De-identified EHR data were obtained from the South London and Maudsley (SLaM) NHS Foundation Trust Biomedical Research Centre (BRC) Case Register. SLaM is a large secondary mental healthcare provider in South London (UK) and has one of the greatest rates of psychosis incidence worldwide. Data on start and stop dates of antipsychotics were obtained from 2,309 adults with FEP receiving care from early intervention services between 1st April 2008 and 31st March 2019 using the Clinical Interactive Record Search (CRIS) tool. All patients were followed up for a minimum of 24 months (mean duration 34.2 months). Data were assembled and visualised using R (networkD3 library).
Results: A total of 12 different antipsychotics were prescribed as first-line treatment. From 2008 to 2019, olanzapine was most frequently prescribed (1013 patients, 43.9%) for all years except 2010-2011. Risperidone (571 patients, 24.7%) and aripiprazole (460 patients, 19.9%) were the second and third most frequently prescribed antipsychotics, with aripiprazole overtaking risperidone for second place from 2014 onwards. 1589 patients (68.8%) switched

antipsychotic during follow-up. For patients who did not switch, 334 (42.2%) were prescribed olanzapine, 189 (26.2%) risperidone, 168 (23.3%) aripiprazole, 40 (5.6%) quetiapine and 20 (2.7%) amisulpride. The most common first treatment switch was from olanzapine to aripiprazole (17.9%). Within this group, 48.4% remained on aripiprazole, whilst 26.0% switched back to olanzapine. Olanzapine to risperidone was the second most frequent first treatment switch (7.9%), followed by risperidone to aripiprazole (7.0%). 1032 (44.7%) patients switched medication at least three times. A Sankey diagram illustrating the treatment pathway of oral antipsychotics (excluding clozapine) with more than 5 prescription instances is available at http://rpatel.co.uk/docs/SIRS2022Sankey.html.

Discussion: We present one of the largest real-world studies examining antipsychotic treatment trajectories in FEP. Most patients switched from their first-line antipsychotic medication. This may reflect poor efficacy or poor tolerability of first-line treatments. The most common medication switch was from olanzapine to aripiprazole, which may reflect patient and/or clinician-led decisions to initiate medications with different tolerability and side effect profiles. Future studies will investigate the clinical rationale for switching antipsychotics to better understand the correlates of treatment trajectory in real world clinical practice.

O3.3. A SIX-YEAR FOLLOW-UP STUDY IN A COMMUNITY-BASED POPULATION: IS NEIGHBOURHOOD-LEVEL SOCIAL CAPITAL ASSOCIATED WITH THE RISK OF EMERGENCE AND PERSISTENCE OF PSYCHOTIC EXPERIENCES AND TRANSITION TO PSYCHOTIC DISORDER?

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Background: Social capital is thought to represent an environmental influence impacting risk of psychotic disorder. This study aims to investigate the association between neighbourhood-level social capital and clinical transitions within the spectrum of psychosis.

Methods: 2175 participants, representative of a community-based population, were assessed twice (6-years apart) to determine their position within an extended psychosis spectrum: no symptoms, subclinical psychotic experiences (PE), clinical PE, psychotic disorder (PD). A variable representing change between baseline (T1) and follow-up (T2) assessment was constructed. Four dimensions of social capital (informal social control, social disorganisation, social cohesion and trust, cognitive social capital) were assessed at baseline in an independent sample, and the measures were aggregated to the neighbourhood level. Associations between the variable representing psychosis spectrum change from T1 to T2 and the social capital variables were investigated.

Results: Lower levels of neighbourhood-level social disorganization, meaning higher levels of social capital, reduced the risk of clinical PE onset (OR=0.300; z=-2.75; p=0.006), persistence of clinical PE (OR=0.314; z=-2.36; p=0.018) and also the transition to PD (OR=0.136; z=-2.12; p=0.034). The other social capital variables were not associated with changes from T1 to T2.

Discussion: Neighbourhood-level social disorganisation may impact the risk of psychosis expression. Whilst replication of this finding is required, it may point to level of social disorganisation as a public health target moderating population psychosis risk.

O3.4. REASONS FOR FIRST USING CANNABIS AND PATHWAYS TO PSYCHOSIS

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Background: Heavy cannabis use is associated with a 4-fold increase in the risk for psychosis. Both frequency and potency contribute to differences in the incidence of psychosis across Europe. However, sceptics argue that the association between cannabis use and psychotic disorders could be explained by other confounding factors, such as the possibility that subjects who start experiencing psychosis, use cannabis as a form of self-medication (reverse causality hypothesis). However, previous research has never taken into consideration reported Reasons for First Using Cannabis (RFUC). Therefore, we examined the hypothesis that different reported RFUC lead to psychosis through the indirect effect of heavy cannabis use.

Methods: We analysed data from the multicentric EUGEI First-Episode Psychosis (FEP) case-control study. Detailed data on patterns of cannabis use were collected using the Cannabis Experiences Questionnaire, including the RFUC ("to feel better", "because of friends using it", and "because of family members using it"). We examined differences in RFUC between cases and controls, and we estimated the temporal occurrence of reported RFUC, pattern of use, and psychosis-control status, using path analyses in Mplus. RFUC were the exogenous variables; case-control status, and frequency and potency of use of cannabis were the endogenous variables. We estimated an additional model with age at first use of cannabis as endogenous variable. We used fit indices – such as Comparative Fit Index (CFI) and Root Mean Square Error of Approximation (RMSEA) – to evaluate whether the hypothesised model fitted the model better than the null model.

Results: We studied 475 FEP patients and 508 population controls. More than 85% of controls compared to 75% of FEP started using cannabis because their friends were using it. Instead, 19.9% of cases started using cannabis to feel better compared to 5.8% of controls, reporting the 12.3% of cases and 6.6% of controls having started because family members were using it. The fit indices of the path analysis indicated that the model fitted the data well (CFI=0.977; RMSEA=0.04; 90% CI 0.01 – 0.06). We found a direct pathway from "to feel better" (β=0.21; 90% CI 0.16 – 0.27) to psychosis status. Frequency and potency had an indirect effect in the relationship of both "to feel better" (β=0.09; 90% CI 0.06 – 0.11) and "because of family members" (β=0.07; 90% CI 0.04 – 0.1) with case-control status. The second model showed that an earlier age at first use entirely explained the relationship of "Because of family members" and case-control status.

Discussion: These findings show that only a minority of patients with psychosis started using cannabis to "feel better", in contrast with the reverse causality hypothesis. They are more likely to develop psychosis compared to other RFUC; however, this is in part because they presented higher chances to smoke more frequently. In addition, they did not start earlier compared to those who initiated using cannabis due to any other reasons. Conversely, starting to use cannabis "because of family members" was associated with an earlier age at first use. Moreover, this suggests the need to tailor intervention strategies to support reduction or cessation of use, and to design better public health campaigns aiming to reach the individual in the context where first use is more likely to begin.

O3.5. THE IMPACT OF CANNABIS LEGALIZATION ON THE FREQUENCY AND HEALTH SERVICES USE FOR PSYCHOTIC DISORDERS: POPULATION-BASED EVIDENCE TO INFORM POLICY INITIATIVES

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Background: Background/Objectives: Cannabis has been implicated as a causal factor in the onset and persistence of psychotic disorders. Approximately 20% of psychotic disorders in the population may be attributable to daily use of cannabis, and 12% of cases may be attributable to high potency cannabis. A recent review on the association between cannabis use and psychotic disorders concluded that the evidence base is sufficiently robust to warrant a public health approach. Canada and other regions around the world have recently legalized the recreational use of cannabis, 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. We sought to (i) examine changes in the incidence and health service utilization for psychotic disorders pre- and post-legalization of cannabis, and (ii) conduct subgroup analyses by age group, sex, and other socio-demographic factors to identify population subgroups who may have been most impacted.
Methods: We used population-based health administrative data from the province of Ontario (Canada) over the period January 2014 to March 2020. We identified all new cases of psychotic disorder over this period, as well as all contacts with health services with a psychosis-related diagnostic code. We analyzed these data using an interrupted time-series design, which is a robust method for examining population-level effects of a policy in "real world" settings. Data on new cases of psychotic disorder and contacts with services over the pre-implementation period were used to establish an underlying trend, and then we used a similar series of repeated observations over the post-implementation period to evaluate whether the trend is "interrupted" (e.g. change in level or slope) at the point corresponding to cannabis legalization. Subgroup analyses by age, sex, migrant status, and neighbourhood-level marginalization were conducted.
Results: The data are currently being analyzed and results will be available in time for the conference.
Discussion: Our findings will inform cannabis-related policies and regulations, with an aim of mitigating harm. Rigorous evidence on the population mental health consequences of cannabis legalization is crucial for evaluating whether the public health benefits of cannabis legalization outweigh the notable harms.

O3.6. SCREENING FOR EARLY EMERGING MENTAL EXPERIENCES (SEE ME), A MODEL FOR EARLY DETECTION OF PSYCHOSIS IN U.S. PRIMARY CARE

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Background: Despite the prominent role primary care plays in the prevention of serious and chronic physical health conditions, its role in the early detection of and intervention in major mental health conditions has been peripheral, particularly in the U.S. Existing strategies, generally reliant on community education and help-seeking, continue to identify only a small fraction of people with psychotic disorders within the critical window associated with best outcomes. Given promising data from international efforts, it is time to strategize a more central role for primary care in U.S. early intervention efforts. Barriers related to the poor accuracy of

current screening tools, reimbursement of screening efforts, and training of primary care staff will need to be addressed.
Methods: Screening for Early Emerging Mental Experiences (SEE ME) is a two-step psychosis screening and triage model designed for use in U.S. primary care settings with integrated behavioral health specialists. Three small projects provide preliminary data on the design and feasibility of this model. The first project compared self-report endorsement of psychosis-risk-relevant experiences and distress in diverse samples of adolescent and young adult primary care patients who did and did not score in a clinical range on a depression screen. The second project collected program evaluation data on a pilot implementation of the SEE ME model in family medicine and pediatric clinics. The third project collected data on psychosis screening within the context of mental health consultations within an urban academic adolescent and young adult medicine clinic.
Results: Preliminary findings include: 1) The majority (89%), but not all, of self-reported distress related to psychosis-risk-relevant experiences was endorsed by adolescents and young adults with histories of mental health treatment and/or with positive depression screens; 2) It is feasible to train behavioral health clinicians imbedded in primary care settings to a) appropriately assess and triage patients referred for mental health treatment who also screen positive on a self-report psychosis risk screen (46% had a distress score ≥ 8 on the Prodromal Questionnaire -16), and b) facilitate specialized early psychosis program referrals (8 % of positive screens), extended assessment and engagement (25% of positive screens), consultation and symptom monitoring (25% of positive screens), and appropriate mental health treatment for individuals assessed to have low psychosis risk (33% of positive screens); and 3) SEE ME implementation was associated with an increase in direct referrals to coordinated specialty care (39% of referrals come from primary care). Additional findings on clinician training, screen and triage outcomes, and feasibility will be reported.
Discussion: SEE ME may provide a feasible model for improving early detection of psychosis in adolescents and young adults within integrated physical and mental healthcare in U.S. communities. Available data suggest that systematic inquiry into psychotic-spectrum experiences, when followed by clinical triage by trained and well-supervised behavioral health clinicians imbedded in primary care, can improve timely referral of young people with psychotic-spectrum experiences or at increased risk for imminent psychosis. Importantly, these data suggest that clinicians trained to conduct mental health triage can appropriately monitor or redirect individuals with subthreshold symptoms or "false positive" screens. Future work is needed to improve self-report psychosis screen accuracy in adolescents and young adults and to assure funding for screening time and clinician training and supervision.

O4. Oral Session: Frontiers of Functional Neuroanatomy and Electrophysiology in Psychosis Research

O4.1. AGE-RELATED FUNCTIONAL NETWORK CONNECTIVITY PATTERN CHANGES ARE ASSOCIATED WITH RISK FOR PSYCHOSIS

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Background: Psychosis onset typically occurs during adolescence or early adulthood, coinciding with a relatively late stage of brain maturation. Alterations in brain functional connectivity, or its network analog, functional network connectivity (FNC) accompany the emergence of psychotic symptoms, and are already present during earlier development associated with the genetic risk or onset of psychosis, and resembling FNC characteristic of older ages. We hypothesized deviations in FNC patterns in unaffected siblings of patients with schizophrenia (SIB) and individuals at clinical high risk (CHR) for psychosis compared to neurotypical FNC patterns, in the direction observed in older adults. We investigated age-related FNC patterns and estimated developmental FNC trajectories during resting state and task evoked fMRI. We compared SIB and CHR with neurotypical controls (NC) at the same developmental period to identify FNC potential changes characteristic of the risk to develop psychosis.

Methods: We analyzed resting state, working and episodic memory, and implicit emotion recognition fMRI data from three independent cohorts. The main cohort included 200 young NC adults (yNC, μ ± SD age = 22 ± 2, %m = 42), 247 older NC adults (oNC, μ ± SD age = 41 ± 7, %m = 47), 31 young adult SIB (ySIB, μ ± SD age = 21 ± 2, %m = 68), and 41 older SIB (oSIB, μ ± SD age = 42 ± 8, %m = 41). The second cohort included 356 yNC (μ ± SD age = 22 ± 2, %m = 39) and 127 oNC (μ ± SD age=38±7, %m = 62). The third cohort included 92 yNC (μ ± SD age = 22 ± 2, %m = 37), 33 oNC (μ ± SD age = 38 ± 7, %m = 63), and 38 young adult CHR (yCHR, μ ± SD age = 20 ± 3, %m = 47). FNC was calculated by NeuroMark, based on independent component (IC) analysis. The derived 53 individual IC time courses were correlated one another to obtain individual session specific FNC matrix. The effect of the age group (yNC vs oNC) was tested by linear mixed-effect regressions (dependent variable: IC pairs FC [Pearson's r]; fixed effects: group, session, group × session, sex; random effect: participants). The ySIB-yCHR vs yNC, ySIB-yCHR vs oNC, oSIB vs oNC, ySIB-yCHR vs oSIB differences on averaged FNC across sessions were tested by Wilcoxon rank-sum test (pFDR<0.05). The three cohorts were analyzed independently. We considered reproducible the IC pairs that differed between groups at pFDR<0.05 in all cohorts.

Results: Analyses in all cohorts reported a reproducible effect of age grouping in 17 IC pairs (pFDR<0.05), of which three showed a difference between both yNC and ySIB, and yNC and yCHR (pFDR<0.05). Both ySIB and yCHR showed increased FNC compared with yNC in a network including medial and dorsolateral prefrontal cortex (PFC) and sensory-motor cortex, and decreased FC among cerebellum, parietal, and primary visual cortices. FNC of ySIB/yCHR compared with oNC showed no significant differences (pFDR>0.05). oSIB differed both from oNC (pFDR=0.007), and ySIB (pFDR=0.01) only in the dorsolateral PFC-sensorimotor network in terms of hyperconnectivity, mirroring the ySIB FNC patterns.

Discussion: Both ySIB and yCHR FNC differed across multiple sessions compared to yNC at the same developmental period, while ySIB and yCHR showed no difference with the oNC, suggesting that the ySIB-yCHR mirrors FNC observed in the oNC over a decade older on average. oSIB are characterized by a possible stabilization of FNC across multiple sessions showing no differences compared with age-matched oNC in sensorimotor-dorsolateral PFC and parietal-visual-cerebellar networks. Sessions specific FNC is still to be explored. Our findings suggest early deviations from NC brain trajectories in young adults who may later

manifest a psychiatric disorder, whereas those who reached later life without psychiatric diagnoses no longer show anomalies except for the dorsolateral PFC-sensorimotor network.

O4.2. HIGHLY DISTINCT STATE-INDEPENDENT LOCAL FUNCTIONAL FINGERPRINTS PREDICT INTELLIGENCE IN HEALTH AND SCHIZOPHRENIA

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Background: Symptomatology, neurobiology, and prognosis are highly heterogeneous across individuals with schizophrenia (1). Therefore, the need for biomarkers to tailor treatment to the individual is increasingly urgent. These markers should be 1) accurate (i.e. stable), 2) independent of mental state, and 3) capture inter-individual differences. Previous studies have proposed the functional connectome (FC) (i.e. the synchrony between spatially distant regions) to be such a marker, calling it an FC "fingerprint" (2,3). However, its identification accuracy - i.e. the ability to use a subjects' FC to identify that same subject in a new database - drastically drops with mental state changes. Moreover, the stability of the FC is delayed (4) and decreased in individuals with schizophrenia (SZ) (5). Here, we hypothesize that spatially localized brain measures – as opposed to the global measure of synchrony between spatially distant regions – might be more state-independent, and, therefore, better suited to fulfill all three criteria for successful application as a biomarker for precision psychiatry.

Methods: fMRI-data of two resting state and seven task sessions of 399 healthy unrelated subjects of the Human Connectome Project (HCP) S1200 release were selected (195 females; males and females matched for age, education, race, and BMI). We investigated whether three local fingerprints satisfy the above-mentioned three criteria for biomarker discovery: regional homogeneity (ReHo) (6), amplitude of low-frequency fluctuations (ALFF) (7), and fractional ALFF (fALFF) (8) within predefined brain regions (9). Identification accuracies and prediction of intelligence with the stability of these local fingerprints were compared with the FC baseline (i.e. Pearson correlations between regional time courses). Next, we examined identification accuracies and the association with intelligence using fMRI-data of the 0- and 2-back tasks of the OpenNeuro.ds000115 dataset (21 SZ; 20 HC) (10).

Results: With the HCP-dataset, we found perfect identification accuracies (i.e. 100%) between resting-state sessions, and near-perfect identification accuracies across mental states (i.e. across resting state and tasks) when using ReHo (95-100%), followed by ALFF (84-100%), fALFF (71-100%), and FC (54-99%). Results were replicable across other parcellations (11–13), and resilient to confounding effects (sex, age, and total intracranial volume). The attention networks and Default Mode Network drove identification accuracy most. Stability of ReHo was predictive of crystallized intelligence ($r=0.2$, $p<0.001$), ALFF of both crystallized ($r=0.17$, $p<0.001$) and fluid intelligence ($r=0.18$, $p<0.001$), while fALFF and FC were not predictive. With the OpenNeuro.ds000115 dataset, identification accuracies for ReHo and ALFF were similar in SZ and HC (100%), while they were lower in SZ for fALFF (SZ: 65%; HC: 88%) and FC (SZ: 99%; HC: 100%). In SZ, higher stability of ReHo ($r=-0.50$, $p=0.03$), ALFF ($r=-0.65$, $p=0.002$) and FC ($r=-0.6$, $p = 0.005$) fingerprints were associated with lower WAIS Matrix Reasoning scores, while in HC higher ALFF stability was associated with higher WAIS Vocabulary scores ($r=0.47$, $p=0.04$).

Discussion: We show that local functional fingerprints, and especially ReHo, is 1) a highly accurate neural fingerprint, 2) more stable within an individual regardless of their mental state, and 3) captures specific inter-individual differences. Moreover, we show that ReHo is also stable in individuals with schizophrenia and that its (in)stability across mental states relates to

intelligence subtest scores. Altogether, our findings show the potential of the application of local functional fingerprints in precision psychiatry.

O4.3. CONNECTIVITY ALTERATIONS UNDERLYING MISMATCH NEGATIVITY RESPONSES IN CHILDREN AT FAMILIAL HIGH RISK FOR SCHIZOPHRENIA AND BIPOLAR DISORDER

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Background: Children born to parents with serious mental disorders are at familial high-risk (FHR) of developing a serious mental disorder themselves. In fact, it has been estimated that 15-40% of children at FHR will develop a psychotic disorder. It is robustly found that individuals with schizophrenia and bipolar disorder have reduced abilities to adapt to changes in the environment as shown by reduced auditory mismatch negativity (MMN) responses. This reduction is further seen in first episode psychosis and in first degree relatives, pointing towards MMN responses being an early marker of disease. Using computational models of effective connectivity between the brain areas underlying these MMN responses, previous studies have shown reduced connectivity between fronto-temporal areas in individuals with schizophrenia. Within the framework of predictive coding postulating that the brain constantly makes predictions of sensory input and comparing to actual sensory input, these reductions in connectivity means that individuals with psychosis have less ability to make predictions.
Methods: Here, we included 11-year-old children at FHR for schizophrenia (67), children at FHR for bipolar disorder (47) as well as matched population-based controls (59) as part of the Danish High Risk and Resilience study. Participants engaged in a classical auditory MMN paradigm with deviations in three different domains; frequency, duration and a combination of the two while we recorded their cortical responses using EEG. We use dynamic causal modelling (DCM) to infer on the effective connectivity of the brain areas underlying MMN responses. DCM can estimate directed connectivity between a priory defined brain areas and use biological plausible models for activity in each brain area. This is to date the largest study including children at FHR for schizophrenia and bipolar disorder with a narrow age range where the underlying connectivity for MMN is assessed.
Results: In the cortical MMN responses we found an interaction between group and deviant type, meaning that the different deviations are processed differently across groups. However, no overall main effect of group was present. Children at FHR showed reduced connectivity from right inferior frontal gyrus to superior temporal gyrus when compared to the population-based controls in the frequency MMN. For the duration and combined frequency and duration MMN we observed reduced connectivity from left primary auditory cortex to superior temporal gyrus. Critically, we observed a difference between the children at FHR for schizophrenia and at FHR for bipolar disorder in the intrinsic connection in right IFG underlying the duration MMN responses.

Discussion: Here, we provide first time evidence that connectivity underlying MMN responses in children at FHR for schizophrenia and bipolar disorder is altered. The connectivity pattern found in these children at FHR echo alterations in effective connectivity patterns that have been described in individuals with schizophrenia. This cross-sectional study will be complemented with a follow-up of these children at the age of 15. This longitudinal extension will enable us to clarify if these connectivity patterns are stable trait markers reflecting the risk of developing these disorders.

O4.4. THE ASSOCIATION BETWEEN N-METHYL-D-ASPARTATE RECEPTOR AVAILABILITY AND GLUTAMATE LEVELS: A MULTI-MODAL PET-MR BRAIN IMAGING STUDY IN FIRST EPISODE PSYCHOSIS AND HEALTHY CONTROLS

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Background: Evidence from post-mortem studies and in vivo imaging studies suggests there may be reduced N-Methyl-D-Aspartate Receptor (NMDAR) levels in the hippocampus in patients with schizophrenia. Other studies have reported increased glutamate in striatum in schizophrenia patients. It has been hypothesized that NMDAR hypofunction leads to the disinhibition of glutamatergic signaling, however, this has not been tested in vivo.
Methods: In this study we investigated the relationship between hippocampal NMDAR and striatal glutamate using simultaneous Positron Emission Tomography-Magnetic Resonance (PET-MR) imaging. We recruited 40 volunteers to this cross-sectional study; 21 patients with schizophrenia, all in their first episode of illness, and 19 healthy controls. We measured hippocampal NMDAR availability using the PET ligand [18F]GE179. This was indexed relative to whole brain as the distribution volume ratio (DVR). Striatal glutamatergic indices (glutamate and Glx) were acquired simultaneously, using combined PET-MR proton magnetic resonance spectroscopy (1H-MRS).
Results: A total of 33 individuals (15 healthy controls, 18 patients) were included in the analyses (mean [SD] age of controls, 27.31(4.68) years; mean [SD] age of patients, 24.75 (4.33), 27 male and 6 female). We found an inverse relationship between hippocampal NMDAR availability and striatal glutamate levels in people with first-episode psychosis (rho = -0.74, $p < 0.001$) but not in healthy controls (rho = -0.22, $p = 0.44$).
Discussion: This study suggests lower NMDAR availability in the hippocampus may drive increased striatal glutamate levels in patients with schizophrenia. Further work is required to determine whether these findings may yield new targets for drug development in schizophrenia.

O4.5. INTERFERENCE CONTROL AND RELATED BRAIN ACTIVITY IN HEALTHY CHILDREN AT FAMILIAL HIGH-RISK OF SCHIZOPHRENIA OR BIPOLAR DISORDER

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Background: Children of parents with schizophrenia (SZ) and bipolar disorder (BP) have a one-in-three risk of developing a psychotic or major mood disorder and a one-in-two risk of developing any mental disorder. They represent a familial high-risk (FHR) group in which endophenotypes of mental disorders can be studied prospectively. Impaired interference control (IFC) is part of the clinical presentation of SZ and BP and it can be captured by neurocognitive tasks like the Eriksen flanker task (EFT). Our group has previously shown that at an age of seven, children at FHR of SZ (FHR-SZ) show decreased interference control in the EFT compared to children at FHR of BP (FHR-BP) and children without FHR. The persistence of these impairments at a later developmental stage in childhood as well as the underlying neural activity are unexplored. Expanding our previous work, we applied the EFT in the same group of children at age 11 and use functional magnetic resonance imaging (fMRI) to map task-related changes in regional brain activity.

Methods: We included 40 children (50% female) with FHR-SZ, 32 children (41% female) with FHR-BP, and 75 (51% female) healthy control (HC) children. All children were free of any past or present Axis-1 disorders. We took this approach to investigate psychiatrically healthy, highly functioning children with FHR and possible resilience factors. IFC was assessed on congruent and incongruent trial conditions by accuracy rate, reaction time (RT), and reaction time variability (coefficient of variation; CV-RT). Task-related regional brain

activity was mapped with blood oxygen level dependent (BOLD) fMRI at 3 Tesla and analyzed using a general linear model, creating contrast images for successful IFC (incongruent trials minus congruent trials) at the group level.
Results: The three groups performed overall equally on the EFT in terms of accuracy and mean RT. However, RTs were overall more variable in FHR-BP and FHR-SZ, showing strong evidence for a difference in CV-RT among groups and anecdotal evidence against a group by condition interaction. Successful IFC led to a consistent activation of the IFC network, including the lateral occipital cortex, anterior intraparietal sulcus, premotor area, superior parietal lobule, Brodmann area (BA) 44, and BA 6. The magnitude of task related activation of these regions did not differ among groups. In a region-of-interest (ROI) analysis, Bayesian inference on the contrast estimates (derived from the eight IFC regions) revealed evidence against group effects and group by ROI interactions.
Discussion: We provide first-time evidence that 11-year-old children at FHR-SZ and FHR-BP express more inconsistent response timing during interference control. This abnormality was expressed despite of the fact that participants had no history of psychiatric illness, and thus, may reflect an endophenotypic trait marker of risk or contribute to resilience. The between-group differences in CVRT were not associated with differences in task-related brain activation during successful IFC. We are currently conducting follow-up analyses of the BOLD fMRI data to explore details of the relationship between inter-individual variations in task-related activity and variations in RTs. Longitudinal follow-up studies are needed to investigate the developmental trajectory.

O4.6. FKBP5 METHYLATION PATTERNS AND BRAIN STRUCTURAL CORRELATES IN SCHIZOPHRENIA

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Background: Schizophrenia (SZ) is a mental disorder that arises from subtle deviations in brain development and maturation due to genetic and environmental insults and their interplay. The FKBP5 gene is an important regulator of the stress hormone response that has been associated with SZ and also with the sensitivity to SZ environmental risk factors. Its methylation has been linked to dysregulation of the stress response system and also to morphological changes in brain regions after childhood trauma. Also, different methylation and expression levels of FKBP5 have been described in patients with SZ compared to controls. On the other hand, widespread cortical thinning has been observed in SZ. Some studies have investigated the impact of methylation levels variability at this gene on structural brain phenotypes in other psychiatric disorders, but none have examined differential effects between subjects diagnosed with SZ and controls.
Methods: Our objectives were: i) To test the impact of FKBP5 methylation levels (FKBP5met) on cortical measures, separately in SZ patients and healthy controls (HC). ii) To analyse whether the effect of FKBP5met on cortical measures differs between SZ patients and HC.

We conducted a neuroimaging-methylation study in a sample of 35 subjects diagnosed with SZ and 35 HC (matched by sex, age and estimated IQ). From MRI scans, we obtained surface area (SA) and cortical thickness (CT) for 34 cortical regions (FreeSurfer). Methylation levels were analysed in DNA extracted from mouth mucosa samples. Three CpG Islands (CGIs), including 153 CpG sites at the FKBP5 gene, were analysed using the Agena Bioscience EpiTYPER system. Linear regression analyses adjusted for sex, age, intracranial volume (and treatment for patients) were performed. P-values were corrected with the FDR method, and only those significant after correction have been considered.

Results: Regarding the first objective, our results showed a non-overlapping effect of methylation levels of distinct CpG sites on different cortical measures, both in SZ and HC. Specifically, within HC, a widespread effect of one CpG unit on the CT of the different regions of the right hemisphere stood out. In individuals diagnosed with SZ another CpG unit had a widespread bilateral impact on both CT and SA.
Concerning the second objective, several methylation x diagnosis interactions were revealed. One CpG site had a diagnosis-dependent bilateral effect on several parietal regions, as well as on several right frontal and right temporal areas. In relation to the surface area, several widespread interactions were observed, but they were not localised in a particular CpG unit or lobe

Discussion: Our results represent the first case-control approach to analyse the effect of FKBP5 methylation status on neuroanatomical measures and they indicate the impact of the methylation levels of this gene on the cortical structure both in SZ patients and HC. This effect can differ between SZ and health status, suggesting that epigenetic marks at this gene could be underlying, at least partially, the observed brain phenotypic differences in the disorder. Based on the well-described relationship of this gene with the stress response, these marks could be acting as a molecular bridge between early adversities altering neurodevelopment and altered phenotypes observed in adult patients.

O4.7. DYNAMIC CAUSAL MODELLING OF P300 AND P50 EEG PARADIGMS IN THE BSNIP DATASET

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Background: The P300 (auditory oddball) and P50 (‘sensory gating’) EEG paradigms show reliable and robust group differences between participants with a psychotic disorder diagnosis and control subjects. These paradigms are not well understood at the mechanistic level, however: only one (the P300) has previously been subject to biophysical modelling, and this was in a small sample (n=73 psychosis patients, relatives and controls). We used the BSNIP dataset and dynamic causal modelling (DCM) to investigate group differences in EEG responses in these paradigms in participants with a schizophrenia diagnosis (Scz, n=211) and controls (n=268).
Methods: The P300 and P50 paradigm data were preprocessed using an automated pipeline incorporating a machine learning-based artefact rejection algorithm (MARA). The grandaveraged data were source localised using SPM12; both paradigms yielded auditory, frontal and parietal sources. Model comparison was used to select the best configuration of these sources in each paradigm. They were then modelled with DCM, using a biophysical model that includes NMDA receptors on backward connections between cortical areas. Group

differences in the 'oddball' (deviant > standard) and 'novel' (S1 > S2) effects were assessed using Bayesian statistics.

Results: In the P50, the S1 > S2 effect was largely due to robust (>60%) increases in backward connectivity from medial frontal gyrus (MFG) to posterior cingulate cortex (PCC) and from PCC to auditory cortex (A1). Scz showed substantial (-23 to -40%) reductions in 3/4 of these backward connections ($p>0.99$): these were the largest effects in Scz.

In the P300, the deviant > standard effect was largely due to marked increases (37% and 105%) in bilateral forward connectivity between inferior frontal sulcus (IFS) and the superior parietal lobule (SPL), and similarly large increases in backward connectivity on the left side from SPL to IFS (110%) and IFS to A2 (125%; all $p>0.99$). Scz showed a loss of backward connectivity from bilateral SPL to IFS in the deviant > standard effect (-22% and -50%; both $p>0.99$). They also showed more inconsistent changes in forward connectivity between all nodes (reduced in 3/4, increased between L IFS and SPL, all $p>0.99$).

Discussion: In both P50 and P300 paradigms, Scz showed a consistent loss of backward connectivity that explained the classic reductions in 'oddball' and 'gating' effects. It is significant that backward connections are the only connections in the model that contain NMDA receptors: these P50 and P300 changes are therefore consistent with NMDA receptor hypofunction in schizophrenia.

O5. Oral Session: Integrative Approaches to Treatment and Intervention

O5.1. TESTING INTERNATIONAL TRANSPORTABILITY OF THE PSYMETRIC CARDIOMETABOLIC RISK PREDICTION ALGORITHM FOR YOUNG PEOPLE WITH PSYCHOSIS: INTERNATIONAL EXTERNAL VALIDATION AND REVISION IN TWO EUROPEAN NATIONS

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Background: Cardiometabolic dysfunction is detectable from the onset of psychosis in young people. Recently, the Psychosis Metabolic Risk Calculator (PsyMetRiC) was developed in the

UK, predicting six-year risk of metabolic syndrome in young people with psychosis. However, all risk prediction algorithms require international validation before they can be used in other countries. Here, we examined the international transportability of PsyMetRiC by performing an external validation in two distinct European samples. We also examined whether additional pre-defined variables improved the predictive performance of PsyMetRiC.
Methods: We used data from the PsyMetab (Lausanne, Switzerland) and PAFIP (Cantabria, Spain) cohorts, including participants (16-35y) without metabolic syndrome at baseline, who had 1-6y follow-up data. Missing data were addressed using multiple imputation. The PsyMetRiC algorithms were applied to the samples, and predictive performance was assessed primarily through discrimination (C-statistic) and calibration (calibration plots). Site-specific recalibration was considered where necessary. A model updating and revision analysis examined the predictive performance after adding polygenic risk scores, socio-economic status, and first-month weight and lipids changes (Switzerland only).
Results: We included 652 participants (58% male) from Switzerland and 466 (65% male) from Spain. The outcome prevalence in Switzerland and Spain was 18% and 14%, for a mean follow-up of 2.02 and 2.59 years respectively. Sociodemographic characteristics were similar to the original PsyMetRiC study in both samples. Both versions of PsyMetRiC validated well but performance was better with the full-model (Switzerland = full-model C=0.77, 95% CI 0.72-0.82, partial-model C=0.70, 95% CI 0.65-0.76; Spain = full model C=0.72, 95% CI 0.66-0.78; partial model C=0.66, 95% CI 0.66-0.73). Calibration plots showed a minor degree of miscalibration universally, which in all instances recovered fully after recalibration of the intercept term. Model updating analysis is being performed and will be presented at the congress.
Discussion: PsyMetRiC is likely to be internationally transportable, at least to some European nations. However, the full model should be used preferentially where possible. In future, PsyMetRiC could help clinicians across the world to identify patients at risk of developing cardiometabolic disorders, so interventions can be directed in an informed manner to reduce long-term morbidity and mortality.

O5.2. IN VIVO 7-TESLA NEUROIMAGING INVESTIGATION OF BRAIN IRON AND METABOLIC CHANGES IN CHRONIC SCHIZOPHRENIA

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Background: Brain iron is a central component in dopaminergic neurotransmission and oxidative stress, which are implicated as pathophysiological mechanisms in schizophrenia. It is not yet determined whether brain iron is also associated with the structural brain changes in schizophrenia. In this study we investigated iron in the subcortical structures of the dopaminergic fronto-striato-thalamic pathways and evaluated whether it is associated with indices of oxidative stress.
Methods: In 12 individuals with chronic schizophrenia and 14 healthy age-matched controls (CTRLs), we acquired 7-Tesla MRI whole brain quantitative susceptibility mapping (QSM) images, to assess brain iron content. Magnetic resonance spectroscopy (MRS) was also obtained in these subjects to evaluate metabolic changes associated with oxidative damage and anaerobic metabolism in a single voxel in the caudal anterior cingulate cortex (caCC). Structural covariance analysis was performed using regional QSM values of regions within the cortico-subcortical associative and limbic pathways.
Results: In individuals with schizophrenia, there was significantly higher iron content in bilateral putamen. Structural covariance analysis of QSM values within cortico-subcortical circuits revealed a significant correlation between putamen and rostral middle frontal cortex in healthy controls, while in schizophrenia, there was only a correlation between putamen and caudate nucleus within the associative network. In limbic pathways, while no correlation was found in controls, there were significant correlations between the substantia nigra and nucleus accumbens with caCC, as well as the hippocampus and amygdala. MRS in the caCC identified higher concentrations of phosphocreatine and lactate, which were positively correlated with QSM in structures associated with the caCC.
Discussion: This is the first in vivo study of brain iron in chronic schizophrenia. We report increased iron content in the putamen accompanied by a circuit-wide abnormality of iron regulation consistent with dopaminergic hyperactivity. The increased concentrations of lactate and phosphocreatine in the caCC are indicative of higher cortical anaerobic metabolism in schizophrenia.

O5.3. CONTINGENCY PLANNING AND RISK MITIGATION STRATEGIES FOR A SCHIZOPHRENIA RELAPSE PREVENTION TRIAL DURING THE COVID-19 PANDEMIC

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Background: The COVID-19 pandemic disrupted clinical trials that study potentially life-changing therapies. Investigators were required to rapidly adapt to guidance from health authorities to ensure that research could continue.
Methods: Risk mitigation strategies were developed to complete a randomized, double-blind, phase 3, schizophrenia relapse prevention study (RIsperidone Subcutaneous Extended-release [RISE] study; NCT03503318) while ensuring the safety of patients and investigators during a global pandemic.

Results: Several areas typical of normal trial conduct that could be impacted by the pandemic were identified. Due to the risk of COVID-19 transmission, study personnel were permitted to visit patients at their homes while following barrier precautions and regulatory procedures to remotely administer interventions, perform assessments, collect blood for safety and pharmacokinetic analyses, and monitor for adverse events; however, most patients were adherent with scheduled in-clinic visits. Remote site monitoring was also permitted. Safety and efficacy assessments were performed through video or telephone interviews when in-person assessments were not feasible. Study sites were also instructed to perform more frequent patient monitoring, if needed. Staff were trained to document protocol deviations and call attention to early terminations due to COVID-19 logistical reasons, such as missed administration of interventions. Overall, the COVID-19 pandemic had an impact on study participation for 24 (13%) patients in the TV-46000 once monthly (q1m) group, 21 (12%) patients in the TV 46000 once every 2 months (q2m) group, and 14 (8%) patients in the placebo group. Challenges emerged while implementing risk mitigation strategies, such as Bulgarian authorities preventing home visits and difficulties inherent in remote monitoring.
Discussion: Despite these obstacles, the implementation of these strategies facilitated the successful completion of the RISE study and may be applied in the future to reduce the patient burden of participating in clinical trials.

O5.4. OUTCOMES DURING AND AFTER EARLY INTERVENTION SERVICES FOR FIRST-EPISODE PSYCHOSIS: RESULTS OVER FIVE YEARS FROM THE RAISE-ETP TRIAL

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Background: Early intervention services (EIS) for first-episode psychosis (FEP) improves initial outcomes but long-term benefits are unclear. We compared quality of life, symptom severity and inpatient hospitalization days over 5 years with the EIS NAVIGATE versus standard care using data from the RAISE-ETP study. We also examined whether over a 5-year trajectory duration of untreated psychosis remained a significant moderator of differential QLS outcomes between NAVIGATE and standard care as was found in prior analyses covering the first 2 years of RAISE-ETP participation.
Methods: The site-randomized RAISE-ETP trial compared NAVIGATE (17 sites; 223 participants) and standard care (17 sites; 181 participants). Participants were 15-40 years old, had DSM-IV diagnoses of schizophrenia, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, or psychotic disorder not otherwise specified, had experienced only one psychotic episode and had taken antipsychotic medication for < six months. NAVIGATE-

randomized participants could receive NAVIGATE from their study entry date until the date when the last enrolled NAVIGATE participant completed 2 years of treatment after which NAVIGATE care ended. Outcome assessments occurred every 6 months for 5 years.
Results: Participants had a mean age of 23; most were male. Compared with standard care, NAVIGATE over 5 years was associated with a 13.14 (95%CI 6.92,19.37) unit Heinrichs-Carpenter Quality of Life (QLS) Scale and 7.73 (95%CI 2.98,12.47) unit Positive and Negative Syndrome Scale (PANSS) better improvement and 2.53 (95%CI 0.59,4.47) fewer inpatient days (all comparisons statistically significant). QLS and PANSS effect sizes were 0.856 and 0.70. NAVIGATE opportunity length (mean 33.8 (SD=5.1) months) was not associated (p=0.72) with QLS outcome. Duration of untreated psychosis moderator analyses did not find a significant association (p=0.32) of duration of untreated psychosis and differential NAVIGATE versus standard care QLS outcomes.
Discussion: RAISE-ETP provides evidence of long-term clinical benefits from NAVIGATE compared with standard care. Duration of untreated psychosis was a significant moderator of differential QLS outcomes over the first 2 years but not over a 5-year timeframe.

O5.5. ANTIPSYCHOTIC DOSES FOR RELAPSE PREVENTION IN FIRST-EPISODE SCHIZOPHRENIA IN FINLAND

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Background: The optimal antipsychotic dose for maintenance treatment of first-episode schizophrenia (FES) patients is unknown. We aimed to study the evolution of antipsychotic dose and risk of severe relapse indicated by psychiatric rehospitalization, associated with antipsychotic use and specific dose categories in a Finnish nationwide cohort of FES.
Methods: Persons with FES, diagnosed as inpatients aged ≤45 years were followed for 5 years of illness, or until ≤5 relapses. Dose was summed from all concomitant antipsychotics. Antipsychotic effectiveness for preventing re-hospitalization was studied using within-individual analyses to minimize selection bias, stratifying time to before and after the second relapse.
Results: Of 5367 patients (64.2%, N=3444 men, mean age 29.5, SD 7.8), 3058 (57%) had rehospitalizations. In those, the mean antipsychotic dose increased gradually after each new relapse from 1.22 (95%CI=1.18-1.26) defined daily doses (DDDs)/day before the 1st relapse to 1.56 (95%CI=1.48-1.64) DDDs before the 5th relapse. Adjusted hazard ratio (aHR) for rehospitalization with antipsychotic use versus non-use increased from 0.42 (95%CI=0.35-0.51) prior to the second relapse to 0.78 (95%CI=0.62-0.99) after the second relapse (p<0.001), indicating markedly decreased effectiveness. Analyzing specific dose categories revealed a U-shaped curve, showing the lowest rehospitalization risk during use of standard dose (0.9-1.1 DDDs/day) prior to but not after the second relapse. Low (<0.6 DDDs/day) dose was associated with substantially higher rehospitalization risk (aHR=1.54, 95%CI=1.06-2.24) versus standard dose before the second relapse, but not after the second relapse (aHR=1.11, 95%CI=0.76-1.62), owing to diluted effectiveness of all doses after the second relapse.
Discussion: Prevention of the second relapse is critical, and all patients should receive sufficient antipsychotic doses and enhanced relapse prevention efforts after their first relapse.

O5.6. UPREGULATION OF COMPLEMENT AND COAGULATION PROTEINS AT BASELINE IS ASSOCIATED WITH EARLY RESPONSE TO AMISULPRIDE IN FIRST EPISODE PSYCHOSIS - FINDINGS FROM THE OPTIMISE TRIAL

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Background: The Optimization of Treatment and Management of Schizophrenia in Europe (OPTiMiSE) trial is a multi-centre, multi-phase, double blind clinical trial. 500 first episode psychosis patients were recruited and treated for 4 weeks with amisulpride (Phase I), followed by a 6 weeks of double blind randomized controlled trial comparing continuation of amisulpride versus switching to olanzapine (Phase II) and ultimately 12 weeks of clozapine in non-remitters (Phase III). This study aims to investigate the relationship of baseline plasma complement and coagulation pathway proteins with symptomatic remission to the antipsychotic amisulpride in FEP to identify potential plasma theranostic markers for treatment response in first episode psychosis (FEP).

Methods: Baseline plasma samples of participants who had completed the clinical trial were considered for the analysis. Plasma levels of complement and coagulation proteins were measured using two different proteomic approaches; data dependent acquisition (DDA) and data independent acquisition (DIA). The primary outcome was to evaluate the associations between baseline plasma protein levels and the remission status at 4 weeks and 74 weeks using a logistic regression model. In addition, associations of baseline protein levels with change in total Positive and Negative Symptom (PANSS) scores, Calgary Depression Scale for Schizophrenia (CDSS) and Personal and Social Performance (PSP) scores after 4 weeks (Phase I) were evaluated using linear regression models. Finally, we evaluated the role of baseline complement activation marker C5b-9 with the change in psychotic symptoms and validated a selection of key proteomic findings using immune-assays.

Results: Complement factor C4A (measured by DIA) was associated with remission status following 4 weeks of amisulpride treatment (Odds ratio= 1.60, FDR adjusted p value= 0.046). In a linear regression model, increased expression of complement and coagulation pathway proteins at baseline strongly associated with reduction of psychotic symptoms (PANSS score) and improvement of functional symptoms (PSP score) at 4 weeks follow-up. Meanwhile the marker of complement activation (C5b-9) was significantly decreased in participants with good clinical outcome. Independent validation using ELISA confirmed the association of C4A and C1R with remission and psychotic symptom reduction, respectively.

Discussion: This study provides novel insights for a therapeutic role of the complement and coagulation cascades on response to antipsychotics medication in FEP. Our results demonstrate that FEP patients with higher complement and coagulation pathway proteins and higher complement activation marker (C5b-9) at baseline are associated with good and poor clinical response respectively in terms of psychotic and functional symptoms after 4 weeks of treatment with amisulpride in FEP.

O5.7. THE ASSOCIATION BETWEEN PREFRONTAL GABA LEVELS AND STRIATAL PERFUSION IN ANTIPSYCHOTIC-NAïVE PSYCHOSIS PATIENTS CHANGES AFTER LONG-TERM TREATMENT

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Background: Insufficient function of prefrontal GABAergic interneurons causes striatal dysregulation in animal models of psychosis. In support, prefrontal GABA levels are reduced in antipsychotic-naïve patients with psychosis, but the prefrontal GABAergic regulation of striatum as well as the effect of long-term treatment has not been investigated in this patient group. Moreover, GABAergic function and striatal dopaminergic activity are influenced by sex hormones in animal models and may differ between male and female patients.
To address these questions, we assessed prefrontal GABA levels as a marker of GABAergic tone and striatal perfusion as a marker of striatal neuronal activity in antipsychotic-naïve patients with psychosis before and after two years treatment.

Methods: We recruited 46 patients aged 22.7 ± 5.5 years (61% females) and 48 matched healthy controls (HC) aged 22.5 ± 4.5 years (60% females) at baseline and followed 28 patients and 44 HCs up after two years. Magnetic resonance spectroscopy was used to assess GABA levels in a 3*3*3cm3 voxel placed in dorsal anterior cingulate cortex with the MEGA-PRESS sequence and striatal perfusion was assessed with the pseudo-Continuous Arterial Spin Labelling sequence on a 3T scanner. The Gannet software assessed prefrontal GABA levels and the FSL software package quantified striatal perfusion in mL/100g/min.
General linear and linear mixed models were used to evaluate baseline differences and trajectories of GABA levels and striatal perfusion as well as sex differences. Analyses were corrected for age and sex, and analyses of striatal perfusion were also corrected for global perfusion.

Results: Prefrontal GABA levels were lower in patients at baseline (patients: 2.66 ± 0.38; HCs: 2.71 ± 0.28; p=0.03) but normalized after two years treatment. Striatal perfusion did not differ between patients and HCs at baseline or after two years. At baseline, prefrontal GABA levels were negatively associated with striatal perfusion in both antipsychotic-naïve patients and HCs (b=-4.9, p=0.001), but not after two years.
Analyses of the sexes separately revealed lower prefrontal GABA levels at baseline in male patients (patients: 2.54 ± 0.39; HCs: 2.38 ± 0.34; p=0.021) and higher striatal perfusion (patients: 41.4 ± 9.9, HCs: 40.6 ± 6.6, p=0.04), but no group differences after two years. In females, there were no group differences. Prefrontal GABA levels were negatively associated with striatal perfusion at baseline in both females and males (females: b=-4.9, p=0.018; males: b=-6.2, p=0.015). After two years, prefrontal GABA levels were positively associated with striatal perfusion in males (B=5.7, p=0.04), but the association in females was not significant.

Discussion: Antipsychotic-naïve male patients display lower prefrontal GABA levels and higher striatal perfusion, but this is not found in female patients. The association between prefrontal GABA levels and striatal perfusion is altered in patients and HCs during the first two years, and in males it is changed from a negative to a positive association. The findings

underline the importance of both illness stage and sex in the neurobiology underlying psychosis and point toward differentiated treatment strategies.

O6. Oral Session: Course of Illness and Outcome

O6.1. KNOWLEDGE, ATTITUDES, AND BEHAVIOURS TOWARDS SCHIZOPHRENIA, BIPOLAR DISORDER, AND AUTISM IN IRELAND: A PILOT STUDY

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Background: Stigma is defined as interrelated problems of knowledge (ignorance), attitudes (prejudice), and behaviors (discrimination). Stigmatization of individuals with mental disorders is a worldwide problem, impacting employment and accommodation opportunities, access to mental and physical health care, reduced life expectancy and quality of life. Negative outcomes of stigma are particularly harmful for young people and create barriers to help seeking behavior. Ireland has the youngest population in Europe, with one-third of the population under 25 years of age. Mental health de-stigmatization campaigns have recently been shown to be effective in Ireland. However, there is growing evidence that the reduction in stigmatization is not felt equally across all mental disorders; that while the type of illness people feel able to identify with (such as depression and anxiety) is experiencing more compassion and understanding than ever before, stigma associated with chronic mental disorders such as psychosis may be increasing. This study aims to explore public perceptions and quantify stigma for two chronic psychotic mental disorders: schizophrenia and bipolar disorders in Ireland. As a comparison, the non-psychotic, chronic developmental disorder of autism will be assessed.

Methods: In a correlational, cross-sectional design, 307 adults in Ireland over the age of 18 completed a questionnaire over Google Forms examining knowledge, attitudes, and behaviors towards 1) mental health in general and 2) schizophrenia, bipolar disorder, and autism in particular. Responses to questions specifically relating to each diagnosis were compared using trimmed mean ANOVA to examine whether responses differed depending on diagnosis.

Results: ANOVA and post-hoc tests revealed significant differences in knowledge, attitudes, and behaviours towards each of schizophrenia, bipolar disorder, and autism ($p < 0.005$), and reported attitudes and behaviours towards schizophrenia were more negative than either bipolar disorder or autism. Linear mixed model analysis showed that knowledge was a strong predictor of behavior. A majority of participants (54.8%) felt not informed enough about mental health by the media and a majority believe mental health should be a research priority.

Discussion: Given that 1) patients with schizophrenia experience greater levels of stigmatisation than either bipolar disorder or autism, and 2) most participants report not being informed enough about mental health by the media, we suggest that future policy and anti-stigma campaigns focus on improving public knowledge about schizophrenia to reduce stigma. Increasing knowledge base is particularly important in light of the finding that knowledge is a strong predictor of behavior. As such, appropriate campaigns may serve to reduce both stigma and discrimination.

O6.2. POSITIVE AND NEGATIVE SYMPTOMS IN SCHIZOPHRENIA: A NATURAL LANGUAGE PROCESSING STUDY OF REAL-WORLD ELECTRONIC HEALTH RECORD DATA

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Background: Schizophrenia is a complex and heterogeneous mental disorder and response to treatment varies depending on the nature of presenting symptoms. Electronic health records (EHRs) contain detailed information on the presenting symptoms of mental disorders. Natural language processing (NLP) can automatically extract symptom data from free text EHR documents. We applied NLP to EHR data to identify the presence of positive and negative symptoms in people with schizophrenia and assessed their associations with clinical severity measured using the Clinical Global Impression – Severity Scale (CGI-S) and with psychiatric hospitalization.

Methods: Data were obtained from 4,440 patients using Holmusk's NeuroBlu™ platform, a Trusted Research Environment that supports the assembly and analysis of data from the MindLinc EHR system. MindLinc includes structured data from over 560,000 patients receiving care from 25 U.S. mental healthcare providers, including sociodemographics, psychiatric diagnoses, prescribed medications, CGI-S and psychiatric hospitalization, as well as NLP-derived data on symptoms documented during the Mental State Examination (MSE). The index date was defined as the date of the first recorded clinical event in the EHR. Data on 14 positive symptoms and 15 negative symptoms recorded within three months of the index date were included in the study. The associations of number of recorded positive and negative symptoms with CGI-S at index date and number of days spent in a psychiatric hospital within 12 months of the index date were analyzed using multiple linear regression with age, gender, race, and marital status as covariates.

Results: The mean age of patients was 39.4 years (standard deviation: 15.3), 2795 (63.0%) were male, 2,600 (58.6%) were from a minority ethnic background, and 3,025 (68.1%) were single. The most frequently documented positive symptoms were paranoid thoughts/delusions (39.8%), auditory hallucinations (36.5%) and non-specific delusions (29.0%). The most frequently documented negative symptoms were blunted or restricted affect (50.4%), issues with grooming/hygiene (28.7%) and issues with eye contact (13.4%). 2948 (66.4%) patients had at least one and 2060 (46.4%) at least two positive symptoms. 3004 (67.7%) had at least one, and 1790 (40.3%) had at least two negative symptoms documented. Positive symptoms (β coefficient: 0.15, 95% CI 0.13 to 0.18, $p<0.001$) and negative symptoms (β coefficient: 0.11, 95% CI 0.09 to 0.14, $p<0.001$) were associated with greater CGI-S at index date. Positive symptoms (β coefficient: 2.74, 95% CI 2.31 to 3.18, $p<0.001$) and negative symptoms (β coefficient: 3.13, 95% CI 2.70 to 3.57, $p<0.001$) were associated with a greater number of inpatient days within 12 months of the index date.

Discussion: A greater number of recorded positive or negative symptoms was associated with greater illness severity at the first clinical visit and time spent in a psychiatric hospital. NLP is an effective method to estimate positive and negative symptom burden in EHR data and could be used to identify individuals who may benefit from specific treatments for predominantly positive or negative symptoms.

O6.3. LONG TERM EFFECTS OF CLOZAPINE AND OXYTOCIN ON FUNCTIONAL RECOVERY IN SOBRIETY MAINTENANCE IN TREATMENT RESISTANT SCHIZOPHRENIA

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Background: Successful long term treatment of schizophrenia and schizoaffective disorders (SSD) remains a central problem in clinical psychiatry. Development of effective interventions to mitigate the long term morbidity and mortality of SSD is critical, and likely to involve complex and costly combinations of treatment modalities. In recent years, substance use, both before and after diagnosis, has made successful treatment even more difficult. Substance use is a likely factor in the increase in incidence and severity of illness recognized in the last decades. Our program treats young SSD patients who have failed multiple interventions. Many began using cannabis, alcohol, and other drugs at an early age and have proven particularly resistant to conventional interventions. Given their severity of illness and treatment failures a large percentage of them were treated by us with clozapine which improved their clinical status, reflected in significant changes in PANSS scores. However, many still exhibited marked functional impairment. In an effort to improve long term outcomes we added sublingual oxytocin (OXT/SL) to their treatment, and noted a further decrease in PANSS scores. When followed over several years on this medication regimen, patients often were able to complete and extend their education, maintain employment, and reintegrate into their family and community lives.

Methods: Our program at Silver Hill Hospital accepts young adults who have been diagnosed with SSD and failed to reach functional recovery despite multiple hospitalizations and medication trials. These patients lived on campus, in a large residence with a committed staff and a highly organized treatment program. Simultaneously, multiple medication trials were initiated while medical and neurological investigations continued. Thirty patients (22 male, 8 female) admitted for 6 to 18 weeks, were then followed continually for up to five years, and improved when treated with Clozapine. OXT administered sublingually was added to their medication regime with gratifying results. We conducted a retrospective chart review of these patients who continued to be treated by our team members and were followed closely after leaving our Residential Program.

Results: All patients entered the program on antipsychotic and other medications and were still quite impaired with PANSS scores ranging from 76-130. They were cross tapered to Clozapine and showed improvement with PANSS scores decreasing 33 %. Although less overtly psychotic, the persistence of negative symptoms prevented return to more productive endeavors. When CLZ improvement had plateaued after months of treatment, OXT/SL was added and PANSS scores further decreased by 26%. More impressive than this improvement in rating scales however, was their change in life course. Of the 30 patients, 24 of whom had been serious and early substance users (mostly cannabis and alcohol) only one relapse was recorded. 90% were able to return to school, work, and have engaging social and family lives. In particular, three of the group are in graduate social work or psychotherapy programs, three work in real estate, one is working at a high level computer security job and another works on Wall Street. All families report great and sustained improvement in overall functioning. We will present a more detailed subset of these patients with a focus on family relations, repeat PANSS scores and work/school success. We will also review data on long term difficulties

these patients face, including dating, socializing, adjustment to COVID crisis and other problems.

Discussion: This subset of patients suffering from treatment resistant SSD was cared for in a comprehensive program of biological, psychological, and social Interventions. They responded partially to CLZ, along with individual family and social intervention groups. They lived and cohabitated together with dedicated staff. However, the addition of OXT/SL to the treatment regime was followed by remarkable and persistent improvement, not only in rating scales but also in the ability to complete college and work in many cases. These patients were privileged financially and socially and therefore able to access a very intensive long term program for which we could not have a control group. Still these positive results strike us to be worthy of reporting. We are intrigued by the role of sobriety and improved social relationships seen in these patients over several years when compared to our usual experience. CLZ alone has been documented to facilitate sobriety, as well as contain impulsivity. OXT seems to improve social ability in some settings and we see real decreases in social anxiety in our patients. There are also reports of improvement in substance abuse patients with the use of OXT. It is possible that we are observing a virtuous cycle of improvement due to this complex array of treatments impacting multiple pathological processes in our SSD patients. The overlap of OXT and dopamine receptors in brain regions may be critical in the understanding of how addiction, psychosis and cognitive processes have all improved with this medication regimen. Our clinical findings hopefully will facilitate development of treatment protocols that can be extended to less affluent patient groups.

O6.4. SCHIZOPHRENIA IN THE COVID-19 ERA: MORBIDITY, MORTALITY AND VACCINATION TRENDS IN ISRAEL

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Background: The COVID-19 pandemic has created healthcare challenges worldwide, nonetheless, these challenges are amplified among individuals with severe mental illnesses. In a series of matched controlled cohort studies, we assessed the effect of the COVID-19 pandemic on morbidity and mortality, utilization of vaccinations, and post-vaccination trends among individuals with schizophrenia.

Methods: Schizophrenia patients and age-and-sex matched controls (total n=51,078) were assessed for COVID-19 infections, hospitalizations, mortality, and vaccination coverage. Univariate and multivariate logistic regression models were conducted to assess the odds for differential patterns of COVID-19-related factors across the two groups. Cox proportional hazard regression models and Kaplan-Meier analyses were conducted to assess longitudinal trends. Demographic and clinical factors served as covariates to control for potential confounding factors.

Results: Individuals with schizophrenia were less likely to test positive for COVID-19, but were twice as likely to be hospitalized for COVID-19, and three times more likely to experience COVID-19 mortality (OR 3.27 95%CI 1.39-7.68, p<.0001). Vaccination rates were lower among the schizophrenia group, even when assessed in the age groups of initial prioritization (60+). Hospitalization and mortality disparities remained higher among people with schizophrenia who had not been vaccinated in comparison to controls, but substantially declined in fully vaccinated groups.

Discussion: Schizophrenia patients are at higher risk for significant COVID-19 morbidity, nonetheless, are less likely to be vaccinated. These results should alert public health policy entities to focus efforts on easier access to COVID-19 prevention efforts for individuals with schizophrenia.

O6.5. CAUSE OF DEATH IN SCHIZOPHRENIA SPECTRUM DISORDER, INFLUENCE OF GENDER AND DIAGNOSIS

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Background: Patients with schizophrenia spectrum syndromes have a reduced life-time expectancy up to 20 years compared to the community. The situation does not differ between countries where similar studies has been performed. Although this is a well-known phenomenon, and so for a long time, little are done to improve the conditions. The Clinical Long-term Investigation of Psychosis in Sweden, CLIPS, follow patients over a period of 20 years. The major purpose is to identify risk-pattern for poor prognosis and early death, early in the illness. Of 509 included patients 170 has died. The average length of life was 65 year. This presentation aim is to present cause of death, differences in gender, age and type of psychiatric disorder, delusional disorder, schizophrenia, and schizoaffective disorder
Methods: Data are collected and analyzed from the CLIPS and the National Cause of Death Register.
Results: Females have a longer average life-length, 67.5 years vs 62.5 for males, p=0.003. Patients with delusional disorder live longer, 71.1 years, compared to schizophrenia 64.0 and schizoaffective disorder 61.9 years, p-values respectively 0.05 and 0.001. No difference was found between schizophrenia and schizoaffective disorder. 5 patients, 2.9 percent, had committed suicide compared to the Swedish average of 0.9 percent over a five-year period. Heart conditions was the most prominent cause of death, 38.8 percent, followed by cancer 15.9 and lung disease 11.2 percent. No difference was to be found between females and males. Of the population 44.9 was regular smokers at time of baseline, three times higher than the average use in Sweden. No gender difference was present.
Discussion: There are differences between gender and type of diagnose within the schizophrenia spectrum disorder. Independent of the findings, the average length of life compared to the Swedish population is of up 20 years shorter. The frequency of suicide was low compared earlier reported. There was no statistical difference in age according to type of somatic illness, 63.6 to 66.9 years of age. This compared to the average age for suicide, 51.4, and trauma, 57.5 years of age.

O6.6. ADVERSE SARS-COV-2 ASSOCIATED OUTCOMES AMONG PEOPLE EXPERIENCING HOMELESSNESS, SUPPORTED PSYCHIATRIC HOUSING, AND MENTAL DISORDERS: A POPULATION-BASED COHORT STUDY AMONG 4.4 MILLION PEOPLE

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Background: Marginalised or deprived groups may be at high risk of a serious COVID-19 outcome. We examined adverse outcomes associated with SARS-CoV-2 infection among vulnerable segments of society.
Methods: Using health and administrative registers, we performed a population-based cohort study of 4.38 million Danes, 27 February 2020¬ to 6 April 2021. For this presentation our main predictors were experiences of 1) homelessness, 2) supported psychiatric housing, and 3) mental disorder. COVID-19-related outcomes were: 1) hospitalisation, 2) intensive care, 3) 30-day mortality, and 4) overall mortality. PCR-confirmed SARS-CoV-2 infection and PCR-testing were also studied. Vulnerable groups were compared with the general population (using adjusted incidence and mortality rate ratios: IRRs, MRRs).
Results: Among individuals with a positive PCR-test experiencing homelessness and supported psychiatric housing, 8.6% (95% CI 6.9-10.4) and 11% (7.8-14.7), respectively, were admitted to hospital within two weeks and 1.8% (1.1-2.7) and 2.9% (1.4-5.1), respectively, had died within 30 days. The probability of hospitalisation was higher for all predictors compared with the general population (p=<0.0001). After adjustments, vulnerable housing situations, i.e. homelessness and supported psychiatric housing, increased the risk of adverse outcomes; highest 30-day MRR after COVID-19 was for homelessness (3.2, 95% CI 2.0-5.1) and supported psychiatric housing: (2.7, 1.4-5.2). Overall mortality during the study period was increased for all predictors and highest for homelessness combined with a PCR-confirmed SARS-CoV-2 infection (MRR 22.1, 15.2-32.2).
Discussion: This study highlights that pandemic preparedness should address inequalities in health, including infection prevention and vaccination of vulnerable groups. Higher awareness of people in vulnerable living situations is needed.

O6.7. CLIENT, FAMILY, AND PROVIDER EXPERIENCES OF VIRTUAL DELIVERY OF EARLY PSYCHOSIS INTERVENTION: RESULTS FROM A MIXED-METHODS EVALUATION

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Background: Early psychosis intervention (EPI) services are the standard of care for young people experiencing psychosis. The COVID-19 pandemic required programs to rapidly transition to delivering services virtually; however, there was little evidence at the time on telemental health care for people with psychosis to guide service delivery. We sought to understand client, family and provider perspectives on virtual delivery of EPI services using a mixed-methods convergent design.
Methods: The Centre for Addiction and Mental Health (CAMH) is home to Canada's largest EPI program, serving youth aged 16-29 and their families using the NAVIGATE model of coordinated specialty care. From April-September 2021, CAMH invited clients and family members receiving services to complete the Virtual Client Experience Survey (VCES) on

individual and group appointments. Items addressed the format of delivery, ease of use, beliefs about the effectiveness of virtual care, and satisfaction with care on a 4-point likert scale from strongly disagree to strongly agree. From June-September 2021, CAMH invited clinicians to complete the Virtual Provider Experience Survey (VPES). Items addressed beliefs about the effectiveness of virtual care and the quality of care they provide, and the future role of virtual care on a 4-point likert scale from strongly disagree to strongly agree. Surveys were sent using REDCap. We calculated descriptive statistics for EPI program respondents, identifying the proportion who agreed or strongly agreed with each item. We conducted individual interviews with 6 clients and 5 family members and a focus group with 6 EPI clinicians on their experiences with virtual care. The interview guide prompted participants to elaborate on items from the VCES and VPES respectively. We analyzed the transcripts using thematic content analysis.

Results: Sixty-nine EPI clients and family members completed the VCES for individual appointments; the vast majority (66/69; 95.7%) had received their care by video conference. After "not applicable" and "prefer not to answer" responses were removed, 95.6% (65/68) endorsed ease of use, 78.5% (51/65) endorsed that virtual care is just as effective as in-person care, and 97.0% (65/67) were satisfied with their virtual care. Twenty-one participants completed the VCES for group appointments; the vast majority were family members. Regarding group virtual care, 95.0% (19/20) endorsed ease of use, 61.9% (13/21) believed virtual groups are just as effective as in-person groups, and 100% (20/20) were satisfied with their virtual group. In individual interviews, clients and families were highly satisfied with virtual care and appreciated its convenience, but cited specific situations that should warrant in-person appointments, e.g., initial consultation and emergent crises. Among EPI providers, 93.8% (15/16) endorsed receiving proper training to provide virtual care, 62.5% (10/16) endorsed that virtual care is just as effective as in-person care, 93.8% (15/16) endorsed being able to provide high-quality virtual care, and 100% (16/16) thought the organization should continue to make virtual care available in the future. In the focus group, providers confirmed a positive experience with virtual care but noted gaps in assessing mental status and physical changes.

Discussion: With respect to virtual EPI services, among clients, families and providers, perceived ease of use and overall satisfaction were very high, and most endorsed that virtual services were just as effective as in person care, with some notable caveats. These findings may help inform virtual delivery of EPI services beyond the pandemic.

O6.8. DETECTING SUBTLE MOVEMENT DIFFERENCES IN PSYCHOSIS: GAIT ANALYSIS WITH THE LABAN MOVEMENT ANALYSIS

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Background: Worldwide roughly 1% of the population is daily suffering from the effects of a psychotic disorder in even the simplest of everyday tasks. Movement

disorders are often diagnosed but standard instruments are not able to detect subtle movement characteristics in, for example, posture and connectivity between body parts. Therefore, this study aims to investigate movement profiles with the Laban Movement Analysis. The present study firstly aims to reliably identify these movement characteristics within the Body-, Effort-, Shape-, and Space categories of the Laban/Bartenieff Movement Analysis. Secondly, this study aims to profile full body movement in psychotic patients.

Methods: Fifteen patients with psychosis and sixteen healthy controls were recorded on film while walking over a ten-meter line for six minutes. The recordings were analysed using a scoring sheet consisting of the following three items; 1). movement initiation; 2.) movement sequencing during locomotion applying Effort dynamics and Shape qualities; and, as a result, 3.) connectivity between body parts and compared to body halves. Afterwards the observations were repeated by a qualified independent rater.
Results: First, in movement initiation a significant distinction was found, i.e., 66,7% of the patients-initiated movement with their upper body, compared to 25,0% of the control group ($p<0.05$, $\varkappa=0,15$). Second, a recurring pattern of Effort dynamics and Shape qualities was found during locomotion in patients, and this manifested mainly in the upper body compared to the healthy controls (Space direction: 46,7% versus 87,5%; Lateral direction: 60,0% versus 12,5%; Sagittal direction: 80,0% versus 50,0%). Third, of the patients with psychosis, 93,3% exhibited disconnected movement patterns compared to 18,8% of healthy controls ($p<0,0001$, $\varkappa=0,60$). More specifically, the connectivity between the upper- and lower body halves was most deviating among patients.
Discussion: The results indicate that a valid registration of movement with the Laban/Bartenieff Movement Analysis is feasible in psychotic patients. The study further suggests that patients with a psychotic disorder may have disconnected movement profiles, driven by polarity in characteristics between the upper- and lower body half.

O7. Oral Session: Neurobiological Underpinnings of Symptom Expression

O7.1. CHARACTERIZING SPEECH HETEROGENEITY IN SCHIZOPHRENIA-SPECTRUM DISORDERS

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Background: Schizophrenia-spectrum disorders (SSD) are highly heterogeneous in risk factors, symptom characteristics and disease course outcome. Although speech anomalies have long been recognized as core symptom of SSD, speech markers are an unexplored source of symptom heterogeneity that may be informative in recognizing relevant subtypes. This study investigates speech heterogeneity and its relation to clinical characteristics in a large sample of patients with SSD and healthy controls.
Methods: Speech samples were obtained from 142 patients with SSD and 147 healthy controls by means of open-ended interviews. Speech was analyzed using standardized open source acoustic speech software. Hierarchical clustering was conducted using acoustic speech markers. Symptom severity was rated with the positive and negative syndrome scale (PANSS) and cognition was assessed with the brief assessment of cognition for schizophrenia (BACS).
Results: Three speech clusters could be distinguished in the patient group that differed regarding speech properties, independent of medication use. One cluster was characterized by mild speech disturbances, while two severely impaired clusters were recognized (fragmented

speakers and prolonged pausers). Both clusters with severely impaired speech have more severe cognitive dysfunction than the mildly impaired speakers. Prolonged pausers specifically have difficulties with memory-related tasks. Prolonged pausing, as opposed to fragmented speaking, relates to chronic active psychosis and refractory psychotic symptoms.
Discussion: Based on speech clustering, subtypes of patients emerged with distinct disease trajectories, symptomatology and cognitive functioning. The identification of clinically relevant subgroups within SSD may help to characterize distinct profiles and benefit the tailoring of early intervention and improvement of long-term functional outcome.

O7.2. THE EFFECT OF A SELECTIVE DOPAMINE D2/D3 ANTAGONIST ON BRAIN GLUTAMATE LEVELS: A LONGITUDINAL 1H-MRS STUDY IN HEALTHY VOLUNTEERS

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Background: Preclinical and clinical studies have suggested that antipsychotics can modulate brain glutamatergic neurotransmission. However, studies carried out in patient populations are confounded by the effects of the illness, environmental factors, and substance misuse. Thus, the effect of antipsychotic treatment on glutamate levels in vivo remains unclear. To address this, we investigated the effect of repeated exposure to amisulpride, a selective D2/D3 antagonist, on glutamate levels in healthy controls using magnetic resonance spectroscopy (1H-MRS). We hypothesised that sub-chronic administration of amisulpride would decrease metabolite levels across regions of interest relevant to the pathophysiology of psychotic disorders.
Methods: A double-blind, placebo-controlled, within-subject, crossover study design was used. Twenty-four healthy individuals received amisulpride and placebo for a period of 7 days each, in randomised order. Following the first week of drug administration, subjects entered a washout period of at least 10 days (>5 half-lives) before the second week of the study to minimize carry-over effects. 1H-MRS was used to measure glutamate, glutamine, Glx (the combined signal of glutamate and glutamine) and n-acetylaspartate (NAA) levels in three a priori hypothesised brain regions: the anterior cingulate cortex (ACC), striatum, and the thalamus. Measurements were carried out at three different time points: baseline, after 1 week of amisulpride and after 1 week of placebo.
Results: We found a significant association between amisulpride administration and an increase in glutamate levels in the thalamus corrected for voxel cerebrospinal fluid content (CSF) ($z = 2.02$ [95% CI 0.01 to 0.75]; $p = 0.043$) compared to placebo. We did not observe any association between amisulpride administration compared to placebo and changes in other metabolites of interest in the ACC and striatum.
Discussion: To our knowledge, this is the first study to examine the effects of sub-chronic administration of amisulpride in healthy subjects. We found that amisulpride treatment resulted in an increase in glutamate levels in the thalamus independently from the pathophysiology of psychosis. We found no evidence of impact of amisulpride treatment on metabolites in the ACC and striatum. Although previous studies in patients have shown a reduction in glutamate levels after antipsychotic treatment, and contrary to our hypothesis, we showed antipsychotic treatment increased glutamate levels. This is in line with findings from preclinical studies

where studies have demonstrated that in mice, repeated, but not acute, antipsychotic treatment increased VGLUT2 mRNA selectively in the thalamus. This suggests that thalamic glutamate levels may be part of a network modulated by selective D2/D3 antagonism, but there is no major effect of selective D2/D3 antagonism on glutamatergic markers in the ACC and the striatum.

O7.3. DIFFERENTIAL DEFICITS IN SOCIAL VERSUS MONETARY REWARD LEARNING IN SCHIZOPHRENIA: ASSOCIATIONS WITH FACIAL EMOTION PERCEPTION

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Background: Individuals with schizophrenia (SZ) tend to have small social networks and high levels of loneliness, which are associated with poor functional outcome. Difficulty learning from social feedback could impair the formation of social relationships in this population and could stem from a difficulty in social cue perception and/or from decreased valuation of social rewards. Although there is substantial research on monetary reward learning in SZ, research on social reward learning in this population is quite limited and mixed. As such, it remains unclear whether individuals with SZ have more difficulty learning from social rewards than they do from monetary rewards. The mixed findings on this topic also highlight the need to explore whether certain features of SZ are differentially related to social versus monetary reward learning deficits or to learning from positive versus negative feedback.

Methods: Thirty-one individuals with SZ and 32 healthy controls (HC) participated in a probabilistic reward learning paradigm that involved both monetary (gain vs. loss of money) and social (smiling vs. angry faces) reward learning. Repeated measures ANOVAS were used to examine between-group reward learning differences based on task (social vs. monetary), valence (positive vs. negative feedback), and block (early vs. later trials). For SZ, additional correlational analyses were conducted to examine whether performance in monetary positive, monetary negative, social positive, and social negative reward learning conditions were differentially associated with facial emotion perception measures.

Results: SZ exhibited decreased reinforcement learning compared to HC on both social ($F(1,61)= 15.23$, $p < .001$) and monetary $F(1,61) = 5.34$, $p = .024$) tasks. However, a group X task interaction ($F(1,61) = 5.76$, $p = 0.019$) demonstrated that SZ performed significantly more poorly on social than monetary reward learning ($F(1,61) = 14.56$, $p = <.001$), while HC performed equally well on both learning types ($F(1,61) = 0.21$, $p = 0.65$). In addition, the group difference in reward learning was larger for social than monetary tasks (Cohen's D of 1.02 vs. 0.65). SZ also performed more poorly on facial emotion recognition tasks, both overall (ER40; $t(1, 57) = 3.14$, $p = 0.003$), and for the faces specific to the reward learning paradigm (EmoDiscrim; $t(1, 61) = 4.90$, $p < 0.001$), although both groups performed quite well on these tasks overall. These group differences in emotion perception related to reward learning findings such that controlling for either ER40 or EmoDiscrim in our repeated measures ANOVA eliminated the observed group X task interaction. On the other hand, there were no group differences between SZ and HC in the pleasantness with which they rated either the happy (EmoHappy) or angry (EmoAngry) faces in the reward learning task. Further, controlling for either of these pleasantness ratings did not eliminate the presence of the group X task interaction for reward learning. Facial emotion recognition in SZ was negatively associated with social reward learning from positive (ER40: $r = 0.57$, $p = 0.002$) and negative (ER40: $r = 0.37$, $p = 0.052$, EmoDiscrm: $r = 0.46$, $p = 0.010$) feedback.

Discussion: These results suggest that although SZ demonstrate deficits in both social and monetary reward learning, they may be more impaired in their ability to learn from social than from monetary feedback. Critically, this differential impairment in learning from social rewards may stem from difficulty identifying the cues presented in social facial expressions rather than from decreased valuation of social rewards. Still, decreased facial expression detection may contribute to reduced valuation of social rewards.

O7.4. VOLATILITY OF SUBLIMINAL HAPTIC FEEDBACK ALTERS THE FEELING OF CONTROL IN SCHIZOPHRENIA

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Background: It has been proposed that agency disorders found in schizophrenia rely on aberrant processing of prediction error. Overreactivity to nonpertinent prediction errors may lead to the attribution of one's own actions to an external source. When applied to perception, this could explain hallucinations. However, experiments in motor control or perception have mainly suggested deficient prediction errors.
Methods: Using a novel approach based on the manipulation of temporal delays, 23 patients with schizophrenia, 18 patients with bipolar disorder, and 22 healthy participants performed a pointing task with a haptic device that provided haptic feedback without or with delays, which were processed consciously (65 ms) or unconsciously (15 ms). The processing of prediction errors was measured via the adaptation of the hand trajectory, that is, the deceleration in anticipation of the surface, and its modulation as a function of recent history (stable or unstable sensory feedback). Agency was evaluated by measuring the participants' feeling of controlling the device.
Results: Only patients with schizophrenia reported a decrease in the feeling of control following subliminally delayed haptic feedback and adapted deceleration durations following subliminally delayed haptic feedback. This effect was correlated with positive symptoms. The overreactivity to subliminal delays was present only when delays occurred repeatedly in an unpredictable way, that is, with a volatile distribution.
Discussion: Our novel paradigm shows results consistent with the hypothesis that patients overreact to negligible prediction errors regarding the timing of occurrence of haptic feedbacks, especially in a context of volatile feedback. The results suggest that small temporal uncertainties that should be held as negligible, trigger an aberrant overreactivity which could account for hallucinations and alterations of the patients' conscious feeling of control.

O7.5. LONGITUDINAL ILLNESS- AND MEDICATION-RELATED BRAIN VOLUME CHANGES IN PSYCHOSIS ARE SHAPED BY CONNECTOME ARCHITECTURE

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Background: Distributed grey matter brain regions are connected by a complex structural network of white matter fibres, which are responsible for the propagation of action potentials and the transport of neurochemicals, proteins, and other molecules. In neurodegenerative disease, these connections constrain the way in which grey matter volume loss progresses. Here, we investigated whether connectome architecture also shapes the spatial patenting of longitudinal grey matter volume changes attributable to illness and/or antipsychotic medication in first episode psychosis (FEP).
Methods: We conducted a triple-blind randomised placebo-control trial where 62 young people with first episode psychosis received either an atypical antipsychotic or placebo over 6 months. A healthy control group was also recruited. Anatomical MRI scans were acquired at baseline, 3-months and 12-months. Deformation-based morphometry was used to estimate gray matter volume changes over time. Structural brain connectivity patterns were derived from the healthy control group using diffusion weighted imaging. We tested the hypothesis that grey matter volume changes in any given brain region could be predicted by changes in areas to which it is structurally connected.
Results: At baseline, we found that regional illness-related volume differences were strongly correlated with volume differences in structurally connected neighbouring brain regions ($r = .608$; $p < 0.001$). We also found a strong correlation between longitudinal regional illness-related change ($r = .613$; $p < 0.001$) and medication-related volume change ($r = .591$; $p < 0.001$) with volumetric changes in structurally connected areas. No such associations were found for functionally connected regions (all $r < 0.391$).
Discussion: Psychosis- and antipsychotic-related grey matter volume changes are strongly shaped by structural brain connections. This result is consistent with findings in other neurological disorders and implies that structural brain connections may act as a conduit for the spread of pathological processes causing brain dysfunction in FEP.

O7.6. INTERLEUKIN-18 SIGNALING SYSTEM LINKS TO AGITATION IN SEVERE MENTAL DISORDERS

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Background: Agitation is a challenging clinical feature in severe mental disorders, but its biological correlates are largely unknown. Inflammasome-related abnormalities have been linked to severe mental disorders and implicated in animal models of agitation. We investigated if levels of circulating inflammasome-related immune markers were associated with agitation in severe mental disorders.
Methods: Individuals with a psychotic or affective disorder (N=660) underwent blood sampling and clinical characterization. Plasma levels of interleukin (IL)-18, IL-18 binding protein (IL-18BP), IL-18 receptor 1 (IL-18R1), IL-18 receptor accessory protein (IL-18RAP), and IL-1 receptor antagonist (IL-1RA) were measured. Agitation levels were estimated with the Positive and Negative Syndrome Scale Excited Component. Multiple linear- and logistic regression were used to investigate the associations between agitation and the immune markers,

while controlling for confounders. The influence of psychotic and affective symptoms was assessed in follow-up analyses.
Results: Agitation was positively associated with IL-18BP (β=0.13, t=3.41, p=0.0007) after controlling for multiple confounders, including BMI, smoking, medication, and substance use. Adjustment for psychotic, manic, and depressive symptoms did not affect the results. There were no significant associations between agitation and the other investigated immune markers (IL-1RA (β=0.06, t=1.27, p=0.20), IL-18 (β=0.05, t=1.25, p=0.21), IL-18R1 (β=0.04, t=1.01, p=0.31), IL-18RAP (odds ratio=0.96, p=0.30)). In a subsample (N=463), we also adjusted for cortisol levels, which yielded unaltered results.
Discussion: Our findings add to the accumulating evidence of immune system disturbances in severe mental disorders and suggest the IL-18 system as a part of the biological correlate of agitation independent of affective and psychotic symptoms.

O7.7. RESTING-STATE CEREBRAL BLOOD FLOW IN THE MOTOR SYSTEM IS LINKED TO THE SEVERITY OF MOTOR SLOWING IN SCHIZOPHRENIA

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Background: Psychomotor slowing (PS), which affects up to 30 to 50% of patients with schizophrenia is characterized by reduced levels of spontaneous motor activity, as well as slowing of gait and fine motor dexterity. PS predicts poor clinical outcomes for the patients. Recently, MRI studies have suggested aberrant functional and structural connectivity in schizophrenia patients with PS especially in the basal ganglia and the motor/premotor cortex. We used Arterial spin labeling imaging (ASL) perfusion MRI to assess the difference in resting-state cerebral blood flow (CBF) between schizophrenia patients with and without psychomotor slowing and healthy controls. We also aimed to correlate CBF with the severity of psychomotor slowing in patients. We hypothesized differential CBF levels in the motor system depending on the presence or absence of PS. We also hypothesized that the severity of PS would be linked to an abnormal increase of the CBF in several areas of the motor system, including basal ganglia, parietal cortex, and motor/premotor cortex.
Methods: In total, we recruited 112 participants (37 healthy controls (age: 37 ± 12, gender: 17 M), 56 schizophrenia patients with PS (age: 35 ± 12, gender: 29 M), and 19 schizophrenia patients without PS (age: 36 ± 13, gender: 10 M)) who underwent perfusion MRI during which we acquired ASL. PS was assessed using the Salpêtrière Retardation Rating Scale (SRRS). Patients who reached an SRRS score higher than 15 were classified as having PS. First, we assessed differences between the 3 groups in whole brain quantitative resting CBF controlling for age. Then, in patients with PS, we explored the association between the severity of PS (using only the pure motor items of the SRRS) and the whole-brain resting CBF by controlling for age and current medication.
Results: A one-way ANCOVA comparing the 3 groups identified significant CBF differences in cerebellum and basal ganglia ($F(2,108)=5.57$, cluster-level correction =159, $qFDR < 0.05$). The post-hoc t-test showed a hyperperfusion in the cerebellum, basal ganglia and cingulate cortex in schizophrenia patients (with and without PS) compared to healthy controls

(t(1,108)=2.62, cluster-level correction = 189, qFDR < 0.05). However, hyperperfusion was specific to PS only in the basal ganglia and in the cerebellum (t(1,108)=2.62, cluster-level correction = 670, qFDR < 0.05). Increased severity of PS was associated with higher CBF in a widespread network (Multiple regression, t(1,52) = 2.62, cluster-level correction = 229, qFDR < 0.05) including the motor, parietal, prefrontal, and temporal cortices as well as the basal ganglia (i.e. striatum and putamen) and hippocampus.
Discussion: These results corroborate previous findings suggesting that schizophrenia patients presented alterations of the resting cerebral blood flow that are specific to psychomotor slowing. Moreover, in line with our hypothesis, the severity of psychomotor slowing seems to be associated with increased blood flow within not only the motor network but also secondary in the prefrontal cortex and limbic system, suggesting add-on emotional processes when patients suffer from severe motor inhibition. Future studies will have to determine, whether the CBF alterations in the motor system represent a trait or a state marker of PS.

O8. Oral Session: Brain and Behaviour in Psychosis

O8.1. BEYOND REWARD-SEEKING BEHAVIOR: MODELING THE EXPLORE/EXPLOIT TRADE-OFF IN PSYCHOSIS

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Background: Prior evidence indicates that negative symptom severity and cognitive deficits, in people with schizophrenia (PSZ), relate to measures of reward-seeking behavior and uncertainty-driven exploration. Here, we focus on a particular type of decision, known as the "explore-exploit" dilemma, in which people must choose between exploiting options that yield relatively known rewards versus exploring more ambiguous options of uncertain reward probability or magnitude. Previous work has shown that healthy people use two distinct strategies to decide when to explore: directed exploration involves choosing options that would reduce uncertainty about the reward values (information seeking), whereas random exploration (exploring by chance) describes behavioral variability that is not goal-directed. Our goal was to determine whether schizophrenia is associated with reduced goal-directed exploration and/or increased random exploration, as well as the clinical and cognitive correlates of each behavior. Finally, based on evidence that uncertainty-driven exploration relies on rostrolateral prefrontal cortex (rlPFC), we performed an fMRI study to investigate whether deficits in goal-directed exploration could be definitively linked to rlPFC dysfunction.
Methods: In one study, we administered a recently-developed gambling task designed to quantify both directed and random exploration to 108 patients with schizophrenia (PSZ) and 33 healthy volunteers (HVs). In a second study, we used a Temporal Utility Integration decision-making task, together with using fMRI, to investigate the extent to which behavioral and neural measures of exploration and exploitation track measures of symptom severity and intellectual function in 29 PSZ and 36 healthy volunteers. Computational analyses were applied to estimate parameters corresponding to learning rates for both positive and negative reward prediction errors (RPEs) and the degree to which participates used representations of relative uncertainty to adjust response times, as well as generate trial-wise estimates of expected value, certainty, and RPEs (used to model fMRI data).

Results: In the first study, we found that PSZ show reduced directed exploration, relative to HVs, but no difference in random exploration. Moreover, we identified a specific subset of PSZ, comprising 21% of patients, who exhibit a form of "extreme ambiguity aversion" in which they almost never choose more informative options, even when they are clearly of higher value. Furthermore, in PSZ, deficits in directed exploration were related to measures of intellectual function, whereas random exploration was related to positive symptoms. In the second study, we observed close correspondences among behavioral, modeling, and neural measures of RPE-driven learning. Furthermore, we found that relative uncertainty contributed to adjustments in responding, and that neural activity in rlPFC distinguished healthy volunteers who used uncertainty in adjusting their response times from those who did not. As with the first study, we observed effects of cognitive capacity on behavioral and neural measures of the tendency to engage in uncertainty-driven exploration.
Discussion: Taken together, our results provide further evidence both attenuated reward-seeking behavior and a reduced tendency to explore reward contingencies based on uncertainty relate to measures of symptoms and intellectual function in PSZ. Furthermore, our results suggest that schizophrenia has differential effects on directed and random exploration and that investigating the explore-exploit dilemma in psychosis patients may reveal subgroups of patients with qualitatively different patterns of exploration. These results have implications for treatment in that they focus attention on information-seeking as a form of goal-directed behavior, as well as relationships between motivation and cold cognition, suggesting that treatments for negative symptoms can and should improve goal-directed exploration. They also indicate that common processes may underlie random explorations and positive symptoms.

O8.2. INCREASED BELIEF INSTABILITY IN PSYCHOTIC DISORDERS PREDICTS TREATMENT RESPONSE TO METACOGNITIVE TRAINING

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Background: In a complex world, gathering information and adjusting our beliefs about the world is of paramount importance. The literature suggests that patients with psychotic disorders display a tendency to draw early conclusions based on limited evidence, referred to as the jumping-to-conclusions bias. Yet, few studies have examined the computational mechanisms underlying this and related belief-updating biases. Here, we employ a computational approach to understand the relationship between psychotic disorders, jumping-to-conclusions, and current delusions. The objective of this study was to dissect this relationship based on the computational mechanisms underlying belief updating in an information sampling task.
Methods: We employed the Hierarchical Gaussian Filter to model probabilistic reasoning of 261 patients with psychotic disorders and 56 healthy controls during the fish task and proposed two different computational mechanisms: Standard Bayesian belief updating (M1) and Belief updating subject to belief instability (M2). To arbitrate between these hypotheses, we compared models with random-effects Bayesian model selection and report protected exceedance probabilities φ and relative model frequencies f. Subsequently, we examined the clinical utility of this computational approach, by testing, whether computational parameters, obtained from fitting the model to each individual's behavior, could predict treatment response to an

intervention that specifically targets reasoning biases (Metacognitive Training) using machine learning.
Results: We observed differences in probabilistic reasoning between patients with psychotic disorders and healthy controls ($F=4.420$, $p<0.001$), participants with and without jumping-to-conclusions bias ($F=11.598$, $p<0.001$), but not between patients with and without current delusions ($F=0.712$, $p=0.698$). Bayesian model selection strongly suggested that Belief updating subject to belief instability (M2) was the most likely mechanism explaining participants' behavior in our study ($\varphi=1.00$, $f=0.99$). This result replicates previous findings from Adams et al. (2018) in a larger and more heterogenous patient population. Furthermore, we found increased belief instability in patients with psychotic disorders ($\eta^2=0.033$, $p=0.005$). A propensity to jump to conclusions was associated with both, increased belief instability ($\eta^2=0.038$, $p=0.002$) and increased prior uncertainty ($\eta^2=0.021$, $p<0.050$ ($p=0.0499$)). Both, behavioral and computational results held in a sub-sample matched for IQ. Lastly, we found that the four computational parameters of the winning model, but not raw behavioral data or the available clinical data, predicted treatment response to Metacognitive Training at the individual level.
Discussion: Our results point towards increased belief instability as a key computational mechanism underlying probabilistic reasoning in psychotic disorders. Belief instability predicted treatment response to Metacognitive Training at the individual level providing a proof-of-concept that this computational mechanism may be useful to help identify suitable treatments for individual patients with psychotic disorders.

O8.3. NETWORK MODELLING OF SCHIZOPHRENIA AND MAJOR PSYCHIATRIC DISORDERS

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Background: Large-scale studies have confirmed cortical thickness and subcortical volume alterations in patients with Schizophrenia (SCZ). The organization of the brain as a network introduces the possibility that local pathological perturbations may affect synaptically-connected neuronal populations, and manifest as a diverse set of cognitive and affective symptoms, with recent studies suggesting a link between disease effects in SCZ and brain network architecture, which, if confirmed, could further elucidate the pathophysiological mechanisms of the disease. In our cross-sectional mega-analysis, we tested the hypothesis that cortical and subcortical connectivity architecture is linked to structural brain abnormalities, through the lens of nodal interconnectedness in SCZ. We tested if, and to what extent, clinical characteristics mediate such a link. Using ENIGMA meta-analytic findings, we then replicated our findings for SCZ and extended the analysis to other major psychiatric disorders.

Methods: Structural imaging data from 2,867 adults with SCZ and 2,439 healthy controls from 26 international sites of the ENIGMA SCZ Working Group were contrasted and related to normative connectivity information from 207 individuals of the Human Connectome Project. We tested two network-based nodal susceptibility models, controlling for spatial autocorrelation: (1) nodal stress models, correlating brain region centrality with the degree of morphological abnormality; (2) epicenter models, relating nodal connectivity profiles to the spatial distribution of morphological abnormalities. We leveraged data from the latest ENIGMA meta-analyses to perform a within-disorder robustness analysis of our models for SCZ and a cross-disorder comparison with Bipolar Disorder (BIP) and Major Depressive Disorder (MDD). Finally, we examined effects of individual patient clinical variables on the substrates of network pathology for SCZ.

Results: We found an increased susceptibility of cortico-cortical hub regions to morphological abnormality in SCZ ($R_{func}=0.58$, $p < 0.0001$, $R_{struc}= 0.32$, $p = 0.01$) . Our cross-disorder comparison, indicated that the correlation between cortical region centrality and cortical deformation could be observed, although with a smaller magnitude, in BIP, ($R_{func} = 0.32$, $p = 0.04$, $R_{struc} = 0.35$, $p= 0.01$) but not in MDD ($R_{func} =-0.31$, $p = 0.14$, $R_{struc} = 0.065$, $p = 0.6$). Our analysis could identify the frontal gyrus and temporoparalimbic regions, as well as the amygdala as the most probable disease epicenters of schizophrenia, with the entorhinal cortex emerging as a unique SCZ--specific epicenter and with a substantial epicenter overlap emerging from our cross-disorder comparison with BIP. Finally, our results showed that the epicenter maps of individuals low in positive symptoms, or receiving lower medication doses were most likely to deviate from the disease-specific epicenter pattern, whereas individuals' duration of illness and negative symptomatology had a lesser effect on the epicenter map.

Discussion: Leveraging the largest multisite neuroimaging dataset to date, our findings provide significantevidence that brain network architecture is intricately linked to morphological abnormalities in SCZ, with nodal centrality emerging as a fundamental component of this

relationship. We extend prior research by identifying robust unique epicenters of SCZ, exploring the effect of individual patient clinical variables on these and revealing the overlapping and disjoint epicenters compared to other major psychiatric disorders.

O8.4. BRAIN-INFLAMMATION SIGNATURES IN RECENT ONSET MENTAL HEALTH DISORDERS: A HIGH DIMENSIONAL DATA DRIVEN APPROACH

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Background: Identification of immune-relevant brain signatures in psychiatric disorders could enable early recognition and intervention, elucidate mechanistic pathways and aid the development of novel therapeutics. Previous research has been limited by univariate analysis, while being challenged by an apparently high degree of disease complexity, yielding mixed and difficult to interpret results. To address these challenges, we present an unsupervised machine learning approach to characterize the multifaceted relationship of brain structure and peripheral inflammation markers in a large, transdiagnostic context.

Methods: From the multicenter European PRONIA cohort, we acquired data from 678 female and male individuals comprising young, minimally medicated patients with clinical high-risk (CHR) states for psychosis, recent-onset depression (ROD) or psychosis (ROP), and healthy volunteers. We employed multivariate Sparse Partial Least Squares Analysis to detect parsimonious associations between peripheral cytokines and acute phase proteins (Interleukin (IL) 1B, IL1ra, IL2, IL4 and IL6, IFN-y, TNF-alpha, CRP, S100B, TGF, BDNF) and grey matter volume (GMV).

Results: Beyond age and gender effects, we discovered a brain-inflammation signature separating

ROP from CHR individuals, in which ROP individuals were identified via higher GMV in visual and dorsal attention networks as well as lower GMV in control, salience and ventral attention networks. This neuroanatomic pattern corresponded to a distinct inflammation pattern of increased IL-6 and TNF-alpha as well as decreased CRP.

Discussion: Distinct brain-inflammation signatures indicate disease progression between CHR states and full-blown psychosis. They further highlight the potential of machine learning to generate blood- and brain-based biomarkers for disease staging in the psychosis spectrum.

O8.5. A LONGITUDINAL NORMATIVE MODELLING APPROACH TO ASSESS HETEROGENEITY OF CORTICAL THICKNESS CHANGES IN CHRONIC SCHIZOPHRENIA

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Background: Longitudinal studies of structural brain changes in individuals with psychotic disorders have shown mixed results. One reason for the inconsistent findings may be the focus on group-average neurodevelopmental trajectories in the presence of large structural brain heterogeneity. Normative modelling is a recently developed machine learning method to assess and leverage structural brain heterogeneity at the individual level in a cross-sectional framework. To the best of our knowledge, no normative modelling using longitudinal data has been implemented. The current study aimed to develop a normative modelling method for parsing heterogeneity of longitudinal structural brain changes and apply it to a sample of healthy individuals and those with chronic schizophrenia to quantify individual deviation from the normative model.

Methods: A total of 1075 structural MRI brain scans from 168 patients with chronic schizophrenia and 293 healthy participants were available in this accelerated cohorts design longitudinal study. At least two scans were available for each participant, with a mean interscan interval of 3.78 years. Structural images were processed with Freesurfer to generate regional (68 regions) average cortical thickness values for each participant. For the normative model, a cross-sectional simple linear regression model was compared against a longitudinal linear mixed-effects (LME) model to find the best model. Both models were trained with 10-fold cross-validation using data from the healthy participants. The mean squared error (MSE) and mean absolute error (MAE) was calculated for both models and used to select the best model which was considered the normative model. Cortical thickness values of all participants (i.e. training and test set) were then predicted at the population level or at the subject level using so-called dynamic predictions, which enable estimation of the random effect for unseen data. Thereafter, a Z-value for each participant-per-region was calculated by subtracting the predicted value from the normative model from the observed value and dividing it by the residual standard deviation. The Z-value indicates the participant's deviance (which can be supra or infra) from the normative model for a given region.

Results: Across all 68 cortical regions, the LME model using dynamic predictions had the lowest MSE and MAE. Applying this modelling approach showed that no more than 45% of the patients deviated significantly from the normative model at each timepoint for at least one cortical region, while it was less than 23% in the case of the healthy controls. Supra-normal deviations ($Z>1.96$) were most commonly located in the lateral occipital region of the left hemisphere, although this was only observed in 3-4% of patients. Infra-normal deviations ($Z<1.96$) were more present at the third follow-up scan, in the pars opercularis region of the left hemisphere, with a frequency of 10% of the patients. The proportion of patients with at least one specific region being deviant increased with time (scan 1: 6.5% lateral occipital, scan 2: 7.1% rostral middle frontal, scan 3: 10.2% pars opercularis; all in the left hemisphere).

Discussion: In this study, we developed a normative modelling approach for assessing individual longitudinal structural brain heterogeneity in regional cortical thickness. In line with previous cross-sectional findings, we found that only a small proportion of patients deviated significantly from the norm. Infra-normal deviations in patients-per-regions increased in proportion at scans 2 and 3 suggesting progression of cortical thickness loss in a subgroup of patients. This modelling approach may lead to the detection of more homogeneous patient subgroups using regional patterns of cortical thickness changes.

O8.6. COGNITIVE CONTROL CHANGES DURING DISEASE PROGRESSION IN PSYCHOSIS

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Background: Cognitive control (CC) is the ability to focus attention and to execute the mental processes required for the task, including suppression of distractors. Deficits in CC can lead to inadequate filtering and integration of information. Such deficits in cognitive control are found along the psychosis continuum and are associated with symptoms of disorganization and poor functioning. Cognitive control has long been the target of cognitive remediation therapies to improve the quality of life and functioning of patients. However, daily life situations often require different levels of CC, from basic reward learning through to more complex social interactions. To gain insight into this gradation of cognitive control, we administered tasks with varied demand on CC to first episode (FEP) and chronic psychosis patients, investigating the variation in CC over illness stages. Furthermore, we identified the behavioural, neural and illness-related factors underpinning the most complex CC behaviour.
Methods: Forty-one chronic patients, 99 FEP and 39 healthy controls performed the interactive trust game during fMRI scanning. They also completed a reward learning and Stroop task – representing a lower demand version of CC tasks. Symptoms were assessed with the PANSS. First, correlational behavioural analyses were performed and region of interest neural analyses. Finally, all parameters were included in a machine learning model, to investigate the prediction of performance in the higher order CC task (trust game).
Results: Task performance at the lower levels of CC (Stroop and reward learning) was similarly impaired in both patient groups. This pattern was also reflected in the highest level of CC (trust) , however, learning over trials in the trust game did not differ significantly between groups. Negative symptoms and IQ impacted on task performance at all levels. The Stroop performance was unrelated to the other levels of CC performance. The number of correct choices in the reward task was associated with mean investment in the trust game. During investment (CC) in the trust game, patients showed generally attenuated neural activation compared to controls. During reward processing, FEP activated the ventral tegmental area (VTA) more than chronic patients and controls. The full model showed that faces task behaviour and neural activation of the caudate and orbitofrontal cortex were predicting learning in the trust game.
Discussion: Behavioural results show that patients both in early and late stages of psychosis performed worse than healthy controls on all three levels of complexity of cognitive control. The Stroop task was able to differentiate between patients and controls, but was not specific for illness phases, suggesting a marker for psychosis vulnerability. At the second level, patients

with FEP performed poorly when cognitive control involved explicit emotion related reward learning, suggesting that FEP exert greater CC in suppressing emotional information. At the neural level, reduced task related activation is common in psychosis. Increased VTA activation in FEP suggests an enhanced response or overcompensation in the regulation of emotions and learning effort, since behavioural outcomes are similar to controls. Complex CC behaviour, as measured with the trust game, can be predicted by faces task performance and neural activity associated with cognitive control and reward processing. Targeting these processes may increase functional outcome in psychosis.

O8.7. THE PSYCHOSIS PROGNOSIS PREDICTOR PROJECT: A COLLABORATION BETWEEN RESEARCHERS, CLINICIANS AND PEOPLE WITH LIVED EXPERIENCE

Hugo Schnack*[1], Violet van Dee[1], Daniël van Opstal[1], Seyed Mostafa Kia[1], Russel Cummins[2], Carola van Alphen[3], Danelle Zuidema[1], Karin Hagoort[1], Inge Winter-van Rossum[1], René Kahn[4], Richard Bruggeman[5], Wilma Swildens[2], Wiepke Cahn[1]

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Background: Clinical prediction models of outcome for patients with a psychotic disorder do not exist at present. However, since there is abundant evidence of factors influencing outcome, it should be possible to realize our main goal: To develop a prediction model for recovery for the individual patient that also indicates how certain modifiable factors can change the outcome in a favorable way. What is meant by 'favorable', is part of the project: Patients, their loved ones and health-care professionals together will define outcome variables that are important to them.
Methods: The Psychosis Prognosis Predictor project includes: (i) questionnaires and a discussion panel of people with lived experience to identify relevant predictors and outcomes; (ii) a systematic literature review and meta-analysis to obtain quantitative information about the relationship between (these) predictors and outcomes; (iii) large longitudinal multisite datasets with individual patient data to train outcome prediction models using machine learning algorithms; (iv) the integration of these three subprojects to create a tool that will be tested in a pilot with new patients and that can be used in the clinic to predict prognosis and the effect of (modifiable) predictors on prognosis.
Results: (i) A panel of 8 people with lived experience met 7 times. One of the results of these meetings was the identification of personal recovery as outcome that matters most to the panel members. (ii) The literature search yielded 558 studies that reported on 1463 outcomes. Better baseline functioning and shorter duration of untreated illness were among the positive predictors of good outcome. (iii) The first LSTM deep learning models show promising results with up to 76% prediction accuracy. Detailed results from subprojects (ii) and (iii) are discussed in other contributions to this conference. Currently, we are working on improving the prediction models and integrating the results from the different subprojects.
Discussion: We have identified important outcomes and predictors. The first prognosis prediction models provide reasonable predictive accuracy. The chosen algorithm not only provides a prediction, but also its uncertainty and the effect of changing a modifiable (lifestyle) factor on it. Insight in how changing (lifestyle) factors may improve a patient's personalized outcome will increase the patient's opportunities for self-management, enable tailored

interventions, reduce societal costs and improve the lives of those affected by this severe illness.

O9. Oral Session: Diagnostic and Treatment Aspects of Illness

O9.1. FOLLOWING BREADCRUMBS TO WIN THE RACE: RETROSPECTIVE EXAMINATION OF PRECURSOR SYMPTOMS IN FIRST-EPISODE PSYCHOSIS

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Background: Symptoms preceding the onset of psychosis offer critical data for tailoring early interventions. Yet we know little about the diverse trajectories of these precursor symptoms over time, and their relationship with the speed at which psychosis develops. This presentation examines how precursor symptoms to psychosis aggregate over time, and associations between the first precursor symptom and the rapidity of deterioration en route to psychosis.
Methods: Individuals with first-episode psychosis were systematically recruited from PEPP-Montreal, a specialized catchment-based early intervention service. Aided by available health and social records, we interviewed participants and their families to retrospectively capture and situate in time the symptoms that preceded psychosis. We first calculated the prevalence of precursor symptoms and their most common combinations. Then, using negative binomial regression, we compared incidence rates of precursor symptoms according to the content and age at onset of the first precursor symptom ever experienced. In Cox proportional hazards models, we compared speeds of progression to psychosis according to the first precursor symptom. We built online interactive data visualisations to disseminate our findings.
Results: Of 390 participants, 266 (68.2%) were male. Median age at psychosis onset was 22.1 years (interquartile range=6.6). Of 27 predefined precursor symptoms, the most common was depression (prevalence=74%). The most common pair was depression-anxiety (56%), and the most common trio was depression–anxiety–social withdrawal (38%). Suspiciousness was the most common subthreshold psychotic symptom (48%). After Bonferroni corrections, first symptoms of suspiciousness and self-harm were significantly associated with distinct symptom trajectories. Individuals with a first symptom of suspiciousness developed additional precursor symptoms (incidence rate ratio [IRR]=3.20; 95% CI: 1.55, 7.28) and converted to psychosis (hazard ratio=2.37; 95% CI: 1.38, 4.08) more rapidly compared to individuals with other first symptoms. In contrast, a first symptom of self-harm was associated with lower incidence rate of additional symptoms (IRR=0.06; 95% CI: 0.01, 0.73). For many first precursor symptoms, age at onset moderated their associations with subsequent symptom trajectories. For example, odd/bizarre ideas, suspiciousness, and impaired role functioning were associated with higher symptom incidence rates compared to other symptoms, but only below a certain age (≤10, ≤19 and ≤14 years respectively). There were also asymmetric associations within pairs of symptoms: after a first symptom of suspiciousness compared to other first symptoms, there was a greater risk of subsequent anxiety (IRR=3.69; 95% CI: 2.30, 5.67), whereas after a first symptom of anxiety, there was no significant difference in the risk of subsequent suspiciousness (IRR=1.15; 95% CI: 0.75, 1.72).
Discussion: Our study demonstrates diverse and complex patterning of symptoms prior to a first episode of psychosis. Strategies aimed at predicting individuals' risk of psychosis must consider the high prevalence of affective precursor symptoms, which tend to cluster together. Further, the content and age at onset of the first precursor symptom may help anticipate time windows for early intervention; as such, early onset of suspiciousness stands out as a marker

of rapid symptom accumulation and conversion to psychosis. In the race against time to anticipate a person's psychosis risk, clinicians and researchers should not overlook these potential breadcrumbs of illness trajectories.

O9.2. A RISK PREDICTION ALGORITHM FOR TREATMENT RESISTANT SCHIZOPHRENIA IN PEOPLE WITH FIRST-EPISODE PSYCHOSIS

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Background: 23% of people who experience a first episode of psychosis (FEP) will develop treatment resistant schizophrenia (TRS), but there are no established methods to accurately predict who will develop TRS. Commonly recorded inflammatory and metabolic biomarkers are longitudinally associated with TRS, but have been mostly excluded from predictive algorithms. We aimed to examine the predictive potential for TRS of commonly recorded sociodemographic, lifestyle and blood biomarkers at FEP onset.
Methods: We developed two risk prediction algorithms to predict up to 8-year risk of TRS from FEP using commonly recorded information.

We developed the risk calculator using two alternative model selection methods:

1. A forced-entry model including all sociodemographic and three biological predictors (one lipid, one inflammatory and one liver marker), based on a balance of clinical knowledge, past research, and likely clinical usefulness (see section on predictor variable selection above).

2. A least absolute shrinkage and selection operator (LASSO) based selection algorithm, following predictor scaling and centering, including all 11 sociodemographic, lifestyle and biological predictors we had pre-selected.

Both methods involved pre-selection of variables, after ruling out predictor multi-collinearity to minimise risk of overfitting, as is recommended for smaller datasets.

Using the forced-entry method, we included age, sex, ethnicity, triglycerides, alkaline phosphatase levels and lymphocyte counts. We also produced a least-absolute shrinkage and selection operator (LASSO) based model, including the above plus neutrophil count, smoking status, body mass index and random glucose levels.

The models were developed using data from two UK psychosis early intervention services (EIS) and externally validated in another UK EIS. Algorithm performance was assessed via discrimination and calibration.

Additionally, where performance at external validation differed from internal validation performance, we considered two recalibration approaches. First, we considered logistic recalibration. This method is used in cases where the coefficients of the original model may have been over-fitted thus affecting calibration performance. Logistic recalibration assumes similar relative effects of the predictors but allows for a larger or smaller absolute effect of the predictors. To perform logistic recalibration, we fitted a model with the linear predictor of the original model as a single predictor in the external validation sample. The model was then updated by multiplying the linear predictor by the coefficient and adding the estimated

intercept; the individual risks were then recalculated and predictive performance re-assessed using the methods described above.

Second, where there was evidence of a clear difference in the association of a predictor with TRS between the development and validation samples, we considered logistic recalibration plus revising a single predictor in the model. We limited this model revision approach to a maximum of one model predictor to preserve as much of the character of an external validation analysis as possible, though we note that all recalibrated/revised models will require a further external validation in an additional unseen sample.

Results: We trained the models in 785 patients, and externally validated them in 1,110 patients. Both models discriminated TRS well at internal validation (forced-entry: C 0.70; 95%CI 0.63,0.76; LASSO: 0.69; 95%CI 0.63,0.77).
At external validation, discrimination performance reduced (forced-entry: 0.63; 0.58,0.69; LASSO: 0.64; 0.58,0.69); the calibration plot for the forced-entry model showed excellent agreement between observed and expected risk, while that for the LASSO model showed evidence of mild overprediction of risk at higher predicted probabilities and of slight underprediction for very low risk.

Logistic recalibration and re-estimation of the lymphocyte count coefficient for the forced-entry model helped to preserve performance, with a C statistic of 0.67 (95% confidence interval (CI): 0.62-0.73). Calibration plots for both recalibrated models showed excellent agreement between observed and expected risk.

Discussion: In conclusion, this work is based on three large samples of FEP patients, totalling 1,895 people, from three separate EIS in England, with a follow-up of up to 8.5 years (mean of ~4 years). We show that commonly recorded demographics and biomarkers taken at FEP onset can explain part (57% in internal validation) of the variance of a long-term psychiatric clinical phenotype such as TRS, and they are readily available and objectively measured in most FEP settings.
We argue that, subject to further prospective validation, our developed models show the potential for simple clinical and routinely collected blood-based biomarkers to inform predictive models for TRS, which could be transformative in improving the early recognition and interventions for this disabling condition.

O9.3. CHANGES IN PERIPHERAL BLOOD COMPOUNDS FOLLOWING PSYCHOPHARMACOLOGICAL TREATMENT IN DRUG-NAïVE FIRST-EPISODE PATIENTS WITH EITHER SCHIZOPHRENIA OR MAJOR DEPRESSIVE DISORDER: A META-ANALYSIS

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Background: This meta-analysis on peripheral blood compounds in drug-naïve first-episode patients with either schizophrenia or major depressive disorder (MDD) examined which compounds change following psychopharmacological treatment.
Methods: The Embase, PubMed and PsycINFO databases were systematically searched for longitudinal studies reporting measurements of blood compounds in drug-naïve first-episode schizophrenia or MDD.

Results: For this random-effects meta-analysis, we retrieved a total of 31 studies comprising 1818 schizophrenia patients, and 14 studies comprising 469 MDD patients. Brain-derived neurotrophic factor (BDNF) increased following treatment in schizophrenia (Hedges' g (g): 0.55; 95% confidence interval (CI) 0.39–0.70; $p < 0.001$) and MDD (g: 0.51; CI 0.06–0.96; $p = 0.027$). Interleukin (IL)-6 levels decreased in schizophrenia (g: −0.48; CI −0.85 to −0.11; $p = 0.011$), and for MDD a trend of decreased IL-6 levels was observed (g: −0.39; CI −0.87 to 0.09; $p = 0.115$). Tumor necrosis factor alpha (TNFα) also decreased in schizophrenia (g: −0.34; CI −0.68 to −0.01; $p = 0.047$) and in MDD (g: −1.02; CI −1.79 to −0.25; $p = 0.009$). Fasting glucose levels increased only in schizophrenia (g: 0.26; CI 0.07–0.44; $p = 0.007$), but not in MDD. No changes were found for C-reactive protein, IL-1β, IL-2 and IL-4.
Discussion: Psychopharmacological treatment has modulating effects on BDNF and TNFα in drug-naïve first-episode patients with either schizophrenia or MDD. These findings support efforts for further research into transdiagnostic preventive strategies and augmentation therapy for those with immune dysfunctions.
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a meta-analysis. Psychological medicine. 2021 Mar;51(4):538-549]

O9.4. POSSIBLE PUTATIVE MECHANISMS INVOLVED IN THE ANTIPSYCHOTIC-LIKE EFFECT OF THE ESSENTIAL β-AMINO ACID, TAURINE IN KETAMINE-INDUCED EXPERIMENTAL PSYCHOSIS IN MICE

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Background: Neurochemical disorganizations, neurotrophic impairment, neuroimmune and oxidative/nitrergic alterations are some key neuropathological features sheared by schizophrenia disease. They are often derived from complex epigenetic biological processes that alter normal behavior and induce altered perception to reality. The current pharmacotherapies for schizophrenia efficiently treat the positive symptoms and its recurrence; however, the negative and cognitive symptoms of the disease remains poorly treated with extrapyramidal and metabolic side effects as some of their setbacks. Taurine is a naturally occurring essential β-amino acid that has been reported to elicit antipsychotic property in first episode psychosis in clinical setting without preclinical evidence. Here, we aimed to investigate the effects of taurine in prevention and reversal of ketamine-induced schizophrenia-like behavior, and associated putative neurobiological mechanisms underlying its effect.
Methods: Swiss mice were allotted into three separate cohorts of experiments (n = 7): drug alone, preventive and reversal studies. Each study consisted of saline (10 mL/kg/p.o./day),

taurine (50 and 100 mg/kg/p.o./day) and risperidone (0.5 mg/kg/p.o./day) alone for 14 days or a preventive protocol requiring these drugs for 14 days prior to ketamine (20 mg/kg/i.p./day) injections between days 8-14 respectively. However, in the reversal approach, ketamine was given for 14 days prior to taurine and risperidone administration from the 8-14 days. Behavioral hyperactivity (open-field test), social (social-interaction test) and cognitive (Y-maze test) impairments, as well as cataleptogenic and obesogenic potentials of taurine were measured. Brain concentrations of neurotransmitters and their biomarkers [dopamine, serotonin, glutamic-acid decarboxylase (GAD), acetylcholinesterase], pro-inflammatory cytokines (TNF-α, IL-6), oxidative/nitrergic (glutathione, malondialdehyde, nitrite), and brain-derived neurotrophic factor (BDNF) were determined in the striatal-prefrontal-cortal-hippocampal parts.

Results: Taurine prevents and reverses ketamine-induced schizophrenia-like behavior i.e., hyperlocomotion, social and memory deficits. Compared to risperidone, taurine showed no cataleptic potential and less weight gain change. Taurine efficiently protected against and reversed ketamine-induced dopamine deregulation, serotonin increments, and GAD and BDNF depletions in the striatum, prefrontal cortex and hippocampus. The increase release of TNF-α, IL-6 and increased acetylcholinesterase activity were attenuated by taurine in both studies. Moreover, ketamine treatment induced markedly reduced glutathione concentration with significant increase in malondialdehyde and nitrite contents in the striatum, prefrontal-cortex and hippocampus, which were significantly prevented and reversed by taurine in the striatum, prefrontal cortex and hippocampus. Of note, taurine alone enhanced antioxidant activity differentially in the brain but reduced acetylcholinesterase in the prefrontal-cortex relative to saline.

Discussion: Altogether, we thus conclude that taurine insulates against ketamine-induced schizophrenia-like behavior via attenuation of neurochemical imbalance, enhancement of BDNF effects, suppression oxidative/nitrergic and neuroimmune alterations in mice brains. To the best of our knowledge, this is first pre-clinical study that provides evidence for its benefit of taurine in first-episode psychotic patients.

O9.5. USE AND DISCONTINUATION OF ANTIPSYCHOTICS IN PATIENTS WITH FIRST-EPISODE SCHIZOPHRENIA TWO TO FIVE YEARS AFTER DIAGNOSIS - A DANISH REGISTERBASED NATIONWIDE STUDY

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Background: Patients with schizophrenia who discontinue antipsychotic medication may have higher risk of relapse, admission to psychiatric hospital and death. This study investigated antipsychotic use and discontinuation in patients with first-episode schizophrenia and the following outcomes of cohabitation with a partner, living with children, employment, hospital admission and death.

Methods: Nationwide registers were used to establish a cohort of patients with schizophrenia. They were included at time of diagnosis from 1995 to 2013. Exposure was redemption of

prescribed antipsychotic medication in therapeutic dosages during year two to five and calculated using DDD. Outcomes were measured year five to six.
Results: Among 23.268 patients diagnosed with schizophrenia almost one tenth took antipsychotics continuously two to five years after diagnosis, almost two fifths took no antipsychotics, four percent sustained discontinuation and almost half discontinued but resumed treatment with antipsychotics. At follow-up six years after diagnosis living with children or having employment was significantly higher in patients with sustained discontinuation, non-sustained discontinuation and no treatment with antipsychotics compared to patients with continuous use. Patients with non-sustained discontinuation had more and longer admissions to psychiatric hospital compared to continuous users during five to six years after diagnosis. Mortality during year five to six after diagnosis did not differ between groups.
Discussion: There are limitations in the study due to information on use of antipsychotics are based on register data, potentially leading to misclassification bias. Furthermore, individuals excluded during year two to five were potentially more ill and therefore underrepresented. The strengths are good quality and completeness of data from the Danish registers and the large study cohort. This study shows that most patients with first-episode schizophrenia discontinue or take no antipsychotic medication two to five years after diagnosis, which in new guidelines for treatment of schizophrenia is non-advisable. Sustained and non-sustained discontinuers and none-users of antipsychotics had higher odds of being employed or living with children compared to continuous users. Non-sustained discontinuers had higher risk of admissions and more outpatient visits compared to continuous users. Mortality did not differ between groups, but analyses were limited by the small number of events.

O9.6. CLOZAPINE RECHALLENGE OR CONTINUATION DESPITE NEUTROPENIA, AN EXTENDED FOLLOW-UP OF A CONSECUTIVE QUEBEC CASE SERIES

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Background: Clozapine (CLZ) is the most efficacious antipsychotic for treatment-resistant schizophrenia. However, CLZ induced neutropenia warrants treatment discontinuation, hindering recovery. Several case reports describe CLZ rechallenge or continuation despite neutropenia, although many are subject to selective reporting with incomplete information and short follow-up periods. Thus, consecutive case series, devoid of such bias, with long-term comprehensive follow-up are needed to better assess this practice.
Methods: This consecutive case series describes the evolution of every patient in the Québec City catchment area in whom CLZ was either reintroduced after neutropenia during a previous CLZ trial or was maintained despite a first neutropenia between January 1, 2000, and October 22, 2017. Patients were identified through CLZ's national hematological monitoring database and their medical records. The likelihood of CLZ being the cause of neutropenia was systematically assessed using the Naranjo Adverse Drug Reaction Probability Scale.
Results: Twenty-three patients were identified, 8 patients continued CLZ despite neutropenia ("continuers"), while 15 discontinued CLZ ("discontinuers") and attempted rechallenge. Among the latter, 4 patients were successfully rechallenged following agranulocytosis without

the use of granulocyte colony-stimulating factors, which is the largest published consecutively. Using the Naranjo Scale, the neutropenia episode was determined definitively caused by CLZ in 2 cases, probably in 3, and possibly in the other 18. Median neutropenia duration was 5 days for discontinuers and 1 day for continuers. Median nadir of absolute neutrophil count (ANC) was 800/μL and 1200/μL for the discontinuers and continuers respectively. Six patients discontinued CLZ due to a mild neutropenia (ANC between 1000-1500/μL) lasting 3 median days. A total of 6 patients experienced further neutropenia episodes, namely 3/15 (20%) and 3/8 (37.5%) for CLZ discontinuers and continuers respectively after median follow-up of 4.8 years. At the end of follow-up, 16 patients were still on CLZ, no deaths occurred and only 3 cases terminated CLZ due to a hematological event (i.e., 1/8 continuers and 2/15 discontinuers). Every patient who had a neutropenia recurrence also had a possible alternative explanation for neutropenia other than CLZ. It is noteworthy that all 4 patients who underwent a rechallenge following agranulocytosis did not experience further neutropenia. Among them, while the one with the most severe agranulocytosis in terms of duration (12 days) had a concomitant pneumonia, the 3 others did not have any distinctive alternative explanation for their neutropenia.
Discussion: The absence of differences in rates of CLZ cessation due to a hematological event between continuers and discontinuers at follow-up suggests that CLZ continuation, with the agreement of a consulting hematologist, if the neutropenia is of mild severity, may be considered to avoid the major consequences of CLZ cessation. The strategy of CLZ continuation was also recently suggested in a study by Tirupati and Gordon. The successfulness of the 4 cases rechallenged after agranulocytosis is surprising as only 3/17 such published cases in a recent review by Manu et al. had been successful. As an alternative cause for the agranulocytosis was found in only 1/4 cases, our success rate is unlikely to result from the fact that the agranulocytosis was not related to CLZ. This raises the possibility that such a practice may be less perilous than first thought. In conclusion, this case series further support that CLZ rechallenge or continuation may be possible following neutropenia regardless of its severity after a thorough risk/benefit assessment.

O10. Oral Session: Cognition, Connectivity and Neuroinflammation

O10.1. FUNCTIONAL DYSCONNECTIVITY IN VENTRAL STRIATOCORTICAL SYSTEMS IN 22Q11.2 DELETION SYNDROME

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Background: 22q11.2 deletion syndrome (22q11.2DS) is a genetic neuro-developmental disorder that represents one of the greatest known risk factors for psychosis, with 30 to 40% of patients developing schizophrenia.
Studies in psychotic subjects without this genetic deletion have identified a dopaminergic dysfunction in striatal regions, and dysconnectivity of striatocortical systems, as an important mechanism in the emergence of psychosis. Two striatocortical circuits have been proposed to be relevant for psychosis: the ventral and dorsal systems. The ventral system connects the nucleus accumbens and ventral striatum with limbic regions. The dorsal system links regions of dorsolateral prefrontal cortex and dorsal caudate/putamen, and it is involved in cognitive and associative functions. Previous studies in psychosis have proposed a dorsal to ventral gradient of hypoconnectivity to hyperconnectivity.

Dysconnectivity of both dorsal and ventral striatocortical circuits have also been proposed to represent a candidate risk phenotype. Functional decoupling of dorsal frontostriatal systems has been associated with genetic risk for psychosis (it has been described in first-degree relatives of psychotic patients and in subjects at ultra-high risk for psychosis). On the other hand, alterations in the ventral system have been described for first-degree relatives but not for ultra-high risk subjects.

Exploring striatocortical connectivity in patients with 22q11.2DS may help in further shedding light on the neural mechanisms underlying genetic vulnerability to psychosis.

Methods: We used resting-state functional MRI to examine striatocortical functional connectivity. We performed a 2x2 factorial design including 125 subjects (55 healthy controls, 28 22q11.2DS patients without a history of psychosis, 10 22q11.2DS patients with a history of psychosis, and 32 subjects with a history of psychosis without the deletion). This design allowed us to identify network effects related to the deletion (as a genetic vulnerability), to the presence of psychosis, and to their interaction.
All of our subjects were locally recruited in Chile. For subjects with a history of psychosis, current psychotic symptoms were measured using Positive and Negative Syndrome Scale (PANSS). In all participants, comorbid affective symptoms were measured and IQ was assessed using WAIS-IV test.

In a first-level statistical analysis, a GLM containing time series for six striatal seeds (three ventral and three dorsal) was used to model BOLD signals from gray matter voxels (including all cortical regions and the thalamus). In a second-level analysis, t-maps from the first-level were used to generate group-wise functional connectivity maps for each seed. Group effects were estimated using a 2×2 factorial ANOVA model with categorical variables 'psychosis' and '22q11.2DS (deletion)'. Separate models were used for each seed, and nuisance covariates were included: age, age squared, sex, IQ, and mean framewise displacement (fd) as a measure of in-scanner motion.

Results: Our findings in psychosis partially support the proposed dorsal to ventral gradient of hypoconnectivity to hyperconnectivity. We found reduced functional connectivity from one dorsal seed to somatomotor regions. From ventral seeds, we found both hypoconnectivity (with areas including prefrontal cortex, ACC, temporoparietal cortex and also occipital cortex) and hyperconnectivity (dorsal and dorsomedial prefrontal cortex).
22q11.2DS was associated with changes in the ventral striatocortical system (decreased functional connectivity between one seed and frontal, occipital and temporoparietal cortical

regions; and increased functional connectivity between another seed and somatomotor regions), with no significant differences identified in the dorsal system.

Our interaction analyses show that there are differences in the expression of psychosis in patients with and without 22q11.2DS, with lower presence of hypoconnectivity in the dorsal striatum in psychosis in the 22q11.2DS as well as increased hyperconnectivity in the ventral striatum.

Discussion: Our main finding was a dysfunction of the ventral striatocortical system related to the 22q11.2 deletion, which may reflect a marker of illness risk. Contrary to findings reported for other populations with genetic risk of developing psychosis (first-degree relatives and subjects in ultra-high risk for psychosis), we did not find significant differences in dorsal striatocortical systems in patients with 22q11.2DS.

Dorsal changes were only present in subjects with a known history of psychosis, which accompanied ventral system dysconnectivity in this group. Even when our findings partially support the proposed dorsal to ventral gradient of hypoconnectivity to hyperconnectivity, striatal dysconnectivity in psychosis seems to be more complex than the gradient would suggest. Moreover, our interaction analysis shows that there are differences in the expression of psychosis in patients with and without 22q11.2DS.

Our results point towards a dysfunction of ventral striatocortical networks in people at high genetic risk for psychosis, along with a more global dysfunction in striatocortical systems in people experiencing psychosis.

O10.2. VARIABILITY AND MAGNITUDE OF BRAIN GLUTAMATE LEVELS IN SCHIZOPHRENIA: A META AND MEGA-ANALYSIS

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Background: Studies report both increased and reduced levels of brain glutamate in schizophrenia relative to healthy volunteers, and it has been proposed that glutamate subtypes in schizophrenia may exist in relation to treatment response. To address this, we examine whether patients exhibit greater variability in glutamate measures compared to healthy volunteers and conduct an updated meta-analysis of glutamate differences.

Methods: MEDLINE and EMBASE databases were searched from inception to October 14, 2021 for proton magnetic resonance spectroscopy (1H-MRS) studies reporting glutamate, glutamine or Glx values in schizophrenia patients in comparison to healthy volunteers. We requested individual patient data from authors as part of a previous mega-analysis.

Outcomes were (1) variability of glutamate measures in patients relative to controls, indexed by coefficient of variation ratio (CVR); (2) mean differences quantified using Hedges g; (3) modal distribution of individual-level glutamate data using Hartigan's unimodality dip test. 116 studies reporting on 7,844 patients and 7,305 healthy volunteers were included. Analyses were carried out in R using the "metafor" package and "weights" package.

Results: 116 studies reporting on 7,844 patients and 7,305 healthy volunteers were included. Compared with healthy volunteers, patients demonstrated greater variability in glutamatergic metabolites in the medial frontal cortex (glutamate: CVR=0.15, p<0.001; glutamine: CVR=0.16, p=0.003; Glx: CVR=0.11, p=0.003), dorsolateral prefrontal cortex (glutamine: CVR=0.14, p=0.05; Glx: CVR=0.25, p<0.001) and thalamus (glutamate: CVR=0.16, p=0.008; Glx: CVR=0.19, p=0.008). Glutamatergic metabolite variability did not differ in the frontal white matter, basal ganglia and temporal lobe. Greater variability remained when analyses were restricted to antipsychotic naïve patients. Meta-regressions found greater variability in the MFC (glutamine: z=0.01, p=0.003), temporal lobe (glutamate: z=-0.03, p=0.01) and basal ganglia (glutamate: z=-0.03, p=0.003 and z=0.007, p=0.02) in younger, more symptomatic patients. Meta-analysis of mean differences found reduced glutamate levels in the medial frontal cortex (g=-0.18, p=0.02), and increased glutamine levels in the thalamus (g=0.53, p<0.001) and Glx in the basal ganglia in patients relative to healthy volunteers (g=0.28, p<0.001).
Discussion: The finding of greater variability in patients in the MFC, DLPFC and thalamus are consistent with the hypothesis of glutamate subtypes in schizophrenia. Future research focused on these brain regions may identify glutamate biomarkers to inform personalised medicine approaches to treatment.

O10.3. MULTIVARIATE RELATIONSHIPS BETWEEN COGNITIVE PERFORMANCE AND PERIPHERAL INFLAMMATORY MARKERS IN PSYCHOTIC DISORDERS

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Background: Accumulating evidence suggests that immune-inflammatory processes are involved in the pathophysiology of psychotic disorders such as schizophrenia (SZ) and bipolar disorder (BD). Elevated levels of peripheral inflammatory markers have been associated with cognitive dysfunction, a core feature of these disorders. However, previous studies have been limited in their selection of inflammatory markers and cognitive tests. Further, it is unclear whether individual or a combination of markers are involved. This study aimed to derive subgroups of a wide range of peripheral inflammatory markers using unsupervised independent component analysis (ICA) and investigate its relationships across several cognitive domains.
Methods: A large patient sample (n = 779, including SZ = 376, BD = 293, other psychotic disorders = 110) and healthy controls (n = 814) underwent cognitive assessment and blood

sampling. Ten cognitive variables: intellectual functioning, verbal learning, verbal memory, attention, attentional control, processing speed, fluency, fine-motor speed, mental processing speed, working memory, and a cognitive composite score were included. Twenty-five systemic markers reflecting relevant inflammatory pathways involved in neuroinflammation including factors involved chemotaxis of immune cells to neuronal tissues, BBB integrity markers and cell adhesion molecules involved in migration of immune cells and innate immune activation were analysed: SerpinA3, A2M, BAFF, April, S100B, GFAP, NSE/ENO2, GROα, SDF1α, Eotaxin, Rantes, MADCAM, JAMA, NCAD, ICAM1, VCAM1, PSEL, IL-18, IL-18Bp, IL-18R1, IL18Rap, HNP13, BD1 and BD2. Using independent component analysis (ICA) we reduced 25 peripheral inflammatory markers to five statistically independent subgroups of markers. The ICs subgroups were made up of markers reflecting neuroinflammation (IC1), microglia/astrocyte activation (IC2), cerebral ischemia (IC3), BBB inflammation (IC4) and leukocyte-BBB interactions (IC5).
Results: The patient sample differed significantly from healthy controls on all the cognitive variables, and on 52% of the inflammatory markers. Preliminary results indicate significant differences in IC loading scores across all but one IC between the patient sample and healthy controls. We identified significant correlations between two of the IC subgroups of markers (BBB-inflammation and leukocyte-BBB interactions) with several cognitive domains (processing speed, verbal memory, fine motor speed and cognitive composite score), with the strongest correlations in the patient sample.
Discussion: These preliminary findings suggest that markers involved in BBB migration may link systemic inflammation and cognitive performance in psychotic disorders. A combination of inflammatory markers may improve our ability to predict cognitive dysfunction in patients with psychotic disorders.

O10.4. CENTRAL OXIDATIVE STRESS AND FUNCTIONAL OUTCOMES IN FIRST EPISODE PSYCHOSIS: A 7-TESLA MAGNETIC RESONANCE SPECTROSCOPY STUDY

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Background: Following the first episode of psychosis, some patients develop poor social and occupational outcomes, while others display a pattern of preserved functioning. Some important functional outcomes include being enrolled in education, maintaining employment long-term, or participating in training for future careers, otherwise known as NEET status. Evidence from preclinical, genetic and biochemical studies suggest a role for high oxidative stress in poor functional outcomes among patients. The measurement of intracortical glutathione (GSH) using magnetic resonance spectroscopy (MRS) provides an opportunity to investigate the relationship between central antioxidant tone and functional outcomes at the time of first episode psychosis (FEP). Importantly, an increase in GSH is hypothesized to be a protective response to high oxidative stress. A body of epidemiological studies indicates better functional outcomes in patients at early stages of schizophrenia compared to patients at a chronic, established phase of illness. Additionally, studies have begun to show a relationship between higher GSH and better functional outcomes in FEP patients, however, there needs to be more research to investigate if this link persists in a larger sample of FEP patients.
Methods: We scanned 57 patients with FEP and 30 matched healthy controls and estimated GSH resonance using 7-Tesla MRS. We minimized the confounding effects of illness chronicity, long-term treatment exposure and metabolic complications by recruiting patients

with <2 weeks of lifetime antipsychotic exposure on average and followed up this cohort for the next 1 year to determine functional outcomes. Functional outcomes were measured by determining if the patient was engaged in employment, education or training for employment at their follow-up, and with the Social and Occupational Functioning Assessment Scale (SOFAS) at follow up as well.
Results: Patients with FEP who achieved employment/education or training status (EET) in the first year, had higher GSH at the baseline than healthy controls. SOFAS scores were also significantly higher in patients with higher GSH levels at the outset, after adjusting for various confounds including baseline SOFAS. Patients who were not in employment, education or training (NEET) did not differ from healthy subjects in their GSH levels.
Discussion: Our observations support a key role for the central antioxidant tone in the functional outcomes of early psychosis. These results indicate a possible biomarker for determining which FEP patients will have better functional outcomes later on, and which may require more chronic treatment. Additionally, these results may aid future researchers to develop new treatments for people with psychosis.

O10.5. EFFECTS OF TESTOSTERONE, ESTROGEN AND PROLACTIN SERUM LEVELS ON COGNITIVE FUNCTION AND SYMPTOM SEVERITY IN MEN AND WOMEN WITH SCHIZOPHRENIA-SPECTRUM DISORDERS

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Background: The onset and course of schizophrenia-spectrum disorders (SSD) show clear differences between men and women. Gonadal hormones play a determining role in the expression of sex characteristics and are known to be involved in the pathophysiology of SSD. Extensive research provides evidence for the protective role of estrogen in women with SSD. However, the underlying biological mechanisms of this effect remain unclear. Furthermore, the exact role of testosterone and estrogen in men with SSD remains equivocal, as previous studies reported conflicting findings (van Rijn et al., 2011; Markham 2012; Moore et al., 2013). Gonadal axis dysfunction appears to be widespread in both sexes, as gonadal deficiencies are closely associated with medication-induced increased prolactin levels in SSD. The relationship between prolactin and gonadal hormone deficiencies is however poorly understood. Unravelling the underlying mechanisms behind these disturbances would contribute to a better evaluation of potential undesired effects of current treatments. This study aims to contribute to an overarching understanding of the mechanisms behind the gonadal axis disturbances in men and women with SSD, by relating prolactin, testosterone and estrogen serum levels to symptom severity and cognitive function.
Methods: Serum hormone levels (estrogen and prolactin in women, estrogen, prolactin and testosterone in men), cognitive function and symptoms were assessed in 203 adults with SSD (135 males, 68 females). Cognitive function was based on four domains: verbal memory (VM), working memory (WM), processing speed (PS) and verbal fluency (VF) and was measured using a combination of the Wechsler Adult Intelligence Scale-3rd edition (WAIS-III), the Wechsler Test of Adult Reading (WTAR) and the Brief Assessment of Cognition in Schizophrenia (BACS). Symptom severity was assessed using positive, negative, cognitive, excitement/hostility and depression/anxiety symptom subscale scores according to the Positive and Negative Symptom Scale (PANSS) 5-factormodel (Citrome et al., 2011). Separate simple linear backward regression models were constructed to assess the extent to which gonadal hormone levels predict cognitive function and symptomatology in men and women with SSD.

Results: As expected, a significant difference in estrogen ($t(195) = -4.65$, $p < 0.0001$) and prolactin ($t(195) = -4.31$, $p < 0.0001$) levels was found between the sexes. Furthermore, PANSS subscale scores differed significantly between groups, as men showed more severe negative scores ($t(201) = 2.76$, $p = 0.006$), while women showed significantly higher depression/anxiety scores ($t(201) = -2.40$, $p = 0.02$).
In men, estrogen and testosterone levels were significantly correlated ($r = 0.17$, $p = 0.05$). Estrogen and prolactin levels were not significantly correlated in women ($p > 0.1$). Testosterone levels significantly predicted performance on VM ($\beta = 0.18$, $p = 0.04$), WM ($\beta = 0.20$, $p = 0.02$) and VF ($\beta = 0.29$, $p = 0.001$) in men. Furthermore, estrogen levels were significantly negatively associated with PS ($\beta = -0.23$, $p = 0.01$) and VF ($\beta = -0.21$, $p = 0.02$) in men. A significant negative effect of prolactin on PS was found in women ($\beta = -0.26$, $p = 0.033$). Testosterone levels were a significant negative predictor and estrogen levels a significant positive predictor for cognitive, negative and overall PANSS scores in men. Neither estrogen nor prolactin levels significantly predict symptomatology in women.

Discussion: The results suggest that circulating gonadal hormones are associated with cognitive deficits and symptomatology in both men and women with SSD. These findings stress the importance of considering gonadal hormones and prolactin in the pathophysiology of SSD.

O11. Oral Session: Caregiver Experience, Social Impairments and Outcomes in Psychosis

O11.1. EXPERIENCES OF HELPLESSNESS AND FEAR AMONG CAREGIVERS DIAGNOSED WITH SEVERE MENTAL ILLNESS AND CO-CAREGIVERS: THE DANISH HIGH RISK AND RESILIENCE STUDY – VIA 7

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Background: This study explores experiences of helplessness, fear, and role-reversal (disorganized caregiving representations) in the caregiver-child relationship among caregivers of children who have a familial predisposition of schizophrenia spectrum psychosis (SZ) or bipolar disorder (BP). The aim is to explore whether these children are at increased risk of being exposed to disorganized caregiving and whether experiences of helplessness, fear and role-reversal are associated with the caregivers' and children's level of functioning as well as children's internalizing and externalizing behavior problems.

Methods: We used the Danish nationwide registers to retrieve a cohort of 522 seven-year-old children of parents diagnosed with SZ (N=202), BP (N=120) or population-based controls (PBC; N=200). Experiences of helplessness, fear and role-reversal was assessed with the Caregiving Helplessness Questionnaire (CHQ; George and Solomon, 2011). For each child, the main informant was identified as the primary caregiver of the child and were asked to complete the CHQ. A total of 479 (91.7 %) primary caregivers provided data on the CHQ.
Level of functioning of the child was evaluated using the Children's Global Assessment Scale and the Personal and Social Performance Scale for the adults, while the dimensional psychopathology was measured with the Child Behavior Checklist (CBCL).

Pairwise comparisons were used to examine differences in experiences of helplessness, fear and role-reversal in the caregiver-child relationship between caregivers diagnosed with either SZ or BP, co-caregivers of child with a parent with either SZ (SZ co-caregiver) or BP (BP co-caregiver) and PBC.

Results: The result showed a significant difference on experiences of helplessness, denoting caregivers with SZ, caregivers with BP and SZ- and BP co-caregivers significantly higher scores on experiences of helplessness in the child-caregiver relationship compared to PBC. Further, caregivers diagnosed with BP had significantly higher scores on helplessness compared to caregivers diagnosed with SZ and BP co-caregivers. The pairwise comparisons on experiences of fear revealed that caregivers diagnosed with BP and SZ co-caregivers had significantly higher scores compared to PBCs.
Experiences of role-reversal did not differ across the groups.

Higher scores on helplessness and fear were associated with lower levels of functioning among caregivers and children and associated with children having externalizing and internalizing behavior problems.

Discussion: This is the first time that a familial high-risk cohort is studied by using the CHQ to assess disorganized caregiving representations including both caregivers with SZ or BP and co-caregivers. It seems understandable, that suffering from a severe mental illness may lead to elevated feelings of being overwhelmed in the caregiving role due to symptoms, medication side effects, and executive problems. The additional information on co-caregivers may further elucidate whether children at familial high-risk of SZ or BP experience disorganized caregiving not only from the caregiver burdened by SZ or BP but possibly also from the co-caregiver and therefore may be double exposed. The SZ co-caregivers report higher scores on experiences of

helplessness and fear compared to PBC, and BP co-caregivers report higher scores on experiences of helplessness compared to PBC. This may imply, that in a family with a parent suffering from SZ or BP, all family members can be influenced by the consequences of the mental disorder. Another point to consider in this aspect is assortative mating.
Supporting caregiving in families with SZ and BP may be a step forward.

O11.2. THE SCHOOL OF HARD TALKS: PILOT CLINICAL TRIAL OF A GROUP INTERVENTION FOR PARENTS OF TRANSITION AGE YOUTH

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Background: Adolescence and young adulthood represent a critical window for early intervention with youth experiencing the onset of mental health and substance use challenges (McGorry and Mei, 2018; Oscar, 2016). A large body of evidence demonstrates the importance of the family environment in the developmental trajectory of youth mental illness (Izon et al., 2021; Griffith et al., 2019; Roy et al., 2018; Caspi et al., 2004). Environments characterized by high stress, conflict, and criticism are likely to have a negative influence on youth mental health outcomes (Peris and Miklowitz, 2015; Izon et al., 2018; Schlosser et al., 2010; Luebbe and Bell, 2014). Therefore, there is a critical need to develop and implement interventions that address conflict and criticism at the family level across a wide range of diagnoses. Caregiver communication skills training represents a potential model for influencing the outcomes of youth struggling with emerging mental health and substance use difficulties. The aim of the current study is to describe the development of a telehealth group parent training intervention based on motivational interviewing communication skills and to report the results of a pilot feasibility-effectiveness study that took place in 2020-2021.
Methods: Authors created "The School of Hard Talks," an eight-hour group curriculum that focused on basic motivational interviewing concepts and skills. The intervention was adapted to telehealth due to COVID-19 restrictions. Caregivers of youth ages 14-24 with a wide range of psychiatric diagnoses were invited to participate in this pilot trial. Participants were assessed at three time points: time of study enrollment, post-intervention, and 12 weeks later. Outcomes of interest were caregivers' MI skill proficiency (assessed via direct observation) as well as caregivers' stress, confidence, expressed emotion, and perceptions of family conflict (assessed via validated self-report scales; respectively, the Perceived Stress Scale, Parenting Self-Agency Measure, Family Questionnaire, and Conflict Behavior Questionnaire). A repeated measures ANOVA was used to test difference over time in these four domains. Greenhouse-Geisser corrections were used as needed for violations of sphericity assumptions.
Results: Sixty-two participants enrolled in the study over the course of nine months (April-December 2020). Overall, 80% of participants who enrolled attended at least five hours of group training and 59% attended all eight hours. Participants cited a range of concerns about their children's behavior and mental health. The top behavioral concerns were defying rules (64%), substance use (41%), and difficulty with schoolwork (38%). Regarding psychiatric diagnosis, 20% reported that their child had no diagnosis and 80% reported one or more diagnoses. Diagnoses included anxiety disorders (49%), uni- and bi-polar mood disorders (47%), ADHD (33%), and post-traumatic stress disorder (10%). Nearly half (43%) reported that their child had at least one prior overnight admission to a psychiatric unit for treatment,

and nearly all (97%) reported that their child had received some form of therapy for mental health concerns.
Forty participants had complete data across the three measurement points (pre-training, post-training, and 12-week follow-up). A repeated measures ANOVA indicated significant and large effects on all four outcomes of interest (stress: $F [2,78] = 13.15$, $p<.001$; confidence: $F [2,62] = 10.70$, $p<.001$; expressed emotion: $F [2,64] = 20.09$; $p<.001$; and conflict: $F [2,78] = 13.20$, $p<.001$). Participants' scores on the Perceived Stress Scale, Parenting Self-Agency Measure, and Family Questionnaire changed substantially between pre- and post-intervention assessments, and then stabilized during the following 12 weeks. Conflict Behavioral Questionnaire scores showed a different pattern, with changes occurring both between pre-post assessments and continuing to improve in the following 12 weeks.

Discussion: Caregivers of transition age youth are an underserved constituency in the mental health care system. The "School of Hard Talks" intervention was well-received and feasible, and participants reported that they found it enjoyable and helpful. We observed large and significant differences on outcomes of interest from pre- and post- intervention, with little to no "rebound" 12 weeks later. Without a control condition for comparison, we cannot confidently attribute these changes to the intervention. Further testing with a control comparator is needed. It is worth noting that the intervention was well received by caregivers of a diagnostically heterogeneous group, suggesting that such a model could serve both a prevention and early intervention goal for youth in pluripotent stages of psychopathology development.

O11.3. DO THE COMPONENTS USED TO MAKE RISK FOR PSYCHOSIS RATINGS TRULY REPRESENT ONE CONSTRUCT?

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Background: Psychosis risk inventories, such as the Structured Interview for Psychosis-Risk Syndromes (SIPS), utilize several components of each symptom in order to coalesce the information into a single symptom severity rating. These components include frequency, duration, conviction in the moment (belief in the symptom while it is occurring), retrospective insight (understanding an experience is a symptom at the time of interview), distress, effect on social functioning, and effect on role functioning. While combining these components into one rating is concise and a fair proxy for risk, this method may be ignoring important information about how individuals differ and masking details that might be related to the greater clinical picture. It is therefore imperative to understand and interpret these separable components in order to determine if the way we have traditionally conceptualized rating high risk symptoms is adequate. For this purpose, the SIPS Score Separable Components (SSSC) scale was created to go along with the SIPS psychosis (P) items to break down each item into the seven components identified above. Using the SSSC, we aim to understand the latent structure of these components. We hypothesize that timing, conviction, and functioning will be separable constructs. Further, we aim to understand how the identified constructs relate to cognition, functioning, symptoms, and risk for conversion.
Methods: 68 individuals at clinical high risk for psychosis had reasonably complete data on the SSSC. We used exploratory factor analysis (EFA) to dissect the latent structure of the SSSC. Parallel analysis and observation of the scree plot were used to determine the number of factors. Several factoring methods and rotations were examined for fit. Ultimately, maximum likelihood was chosen as the factoring method and oblimin rotation was used.

Follow-up analyses with cognition, functioning, symptoms, and risk were done using linear multiple regressions with the identified factor scores as predictors.
Results: Parallel analysis indicated that 3 factors best fit for our data. EFA revealed that the SSSC did indeed have 3 interpretable factors with appropriate fit (rmsr = 0.024, TLI = 0.909, fit = 0.921): conviction, functioning, and timing. The conviction factor consisted of in the moment conviction (loading = 0.93, com = 1.0) and retrospective insight (loading = 0.90, com = 1.0). The functioning factor included distress (loading = 0.54, com = 1.2), social functioning (loading = 0.78, com = 1.2), and role functioning (loading = 0.81, com = 1.1). The timing factor included frequency (loading = 0.48, com = 1.3) and duration (loading = 0.82, com = 1.0). The conviction factor was positively related to the prodromal questionnaire and negatively related to the n-back and negative symptoms. The functioning factor was positively related to SHARP risk score and negative symptoms and negatively related to current GAF and GAF from one year ago. The timing factor was positively related to WASI vocabulary and n-back performance. Further, there are revealing interaction effects among the factors that facilitate the interpretation of these findings.
Discussion: By pairing down each symptom to a single rating, as is done in the SIPS, important information is lost about the symptom. This information reveals important relationships with cognition, functioning, symptoms, and risk. For example, as individuals have less conviction about (more insight into) their symptoms, they have increasing negative symptoms; this relationship becomes increasingly true as symptoms cause greater impairment in functioning. Therefore, we suggest utilizing the SSSC in future research using the SIPS.

O11.4. THE DEVELOPMENT IN EXECUTIVE FUNCTIONS IN CHILDREN AT FAMILIAL HIGH RISK OF SCHIZOPHRENIA OR BIPOLAR DISORDER FROM AGE 7 TO AGE 11 - THE DANISH HIGH RISK AND RESILIENCE STUDY

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Background: Executive functions (EF) deficits are well-documented in individuals with schizophrenia, and to a lesser degree in individuals with bipolar disorder. Similar deficits, though less pronounced, can be seen in children at familial high risk of schizophrenia (FHR-SZ) and in children at familial high risk of bipolar disorder (FHR-BP). Previous studies of individuals at familial high risk have mainly relied on a performance-based assessment of EF using neuropsychological tests. However, rating-based assessment of EF provides an important perspective into the experience of EF deficits in everyday life. The aim of this study was to investigate the development in EF from age 7 to age 11, in children at FHR-SZ, FHR-BP and population-based controls (PBC) using a multi-informant rating scale.

Methods: This study was part of the Danish High Risk and Resilience Study. A total of 519 children (FHR-SZ, n=201; FHR-BP, n=119; PBC, n=199) participated at age 7, at age 11 or at both time points. Caregivers and teachers completed the Behavior Rating Inventory of Executive Functions (BRIEF), a well-validated questionnaire measuring EF behavior, where scores are organized into nine subscales representing specific EF subdomains, three indices and one global score. Multilevel mixed-effects linear regression models were conducted to investigate the developmental patterns of EF from age 7 to age 11, as well as potential EF deficits at age 11.

Results: The development in EF from age 7 to age 11, did not differ between groups. At age 11, caregivers and teachers rated children at FHR-SZ as having more EF deficits than PBC on all BRIEF scales except one (the subdomain Organization of materials as rated by caregivers). A higher proportion of children at FHR-SZ had scores above the clinical cut-off on the General executive composite (GEC) and all BRIEF indices compared to PBC. According to the caregivers, children at FHR-BP had significantly more EF deficits than PBC on the GEC, Behavioral regulation index, Emotional regulation index, and four subdomains. According to the teachers, children at FHR-BP only had deficits on one subdomain (Initiate). Likewise, caregivers rated a significantly higher proportion of children at FHR-BP above the clinical cut-off on the GEC and Metacognition index, compared to PBC. There were no significant differences on cut-off scores between children at FHR-BP and PBC according to teachers.

Discussion: Children at FHR-SZ, FHR-BP, and PBC followed the same developmental pattern in EF from age 7 to age 11, which supports uniform developmental patterns of EF in this specific stage of development. According to caregivers and teachers, children at FHR-SZ show EF impairments in everyday life. Children at FHR-BP display EF impairments at age 11 in their home and extracurricular settings rated by their caregivers, but not when rated by their teachers in a school setting. The distribution of scores above the clinical cut-off across groups underline the clinical significance of the EF deficits found in this study, but also reveal that a considerable proportion of children at familial high risk do not have EF deficits that are

clinically significant. These findings imply the need to identify children at high risk who would benefit from targeted intervention. Furthermore, this study highlights the relevance of including multiple informants, and rating-based measures in the assessment of EF in children at familial high risk.

O11.5. CLINICAL AND FUNCTIONAL OUTCOMES AT 7-YEAR FOLLOW-UP OF CHILDREN PRESENTING MULTIPLE ANTECEDENTS OF SCHIZOPHRENIA AT AGE 9-12 YEARS

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Background: Efforts to detect individuals with increased vulnerability for psychosis have focused on help-seeking individuals who fulfil clinical high-risk (CHR) criteria, approximately 20% of whom go on to develop full psychosis. However, at the point of detection, this population is already characterised by significant functional disability and high levels of psychiatric comorbidity, with only a third experiencing symptom remission. These findings indicate the need for alternative earlier detection methods, which are not restricted to those seeking help from clinical services. To this end, the London Child Health and Development Study (CHADS) was established in 2004 to pilot a novel school-screening procedure to identify children presenting multiple antecedents of schizophrenia at age 9-12 years. This study examines clinical and functional outcomes measured at age 17-21 years.

Methods: From questionnaire-based screening of ~8,000 school children aged 9-12 years and ~1,500 of their caregivers in Greater London, UK, we recruited a subset of children who were assessed biennially throughout adolescence (N=112: 52% male, 51% white ethnicity). This intensively-studied sample included children presenting a triad of replicated antecedents of schizophrenia (ASz: n=35), family history of schizophrenia (FHx: n=26), or both risk factors (ASz+FHx: n=6), as well as typically-developing children with neither risk presentation (TD: n=45). Clinical and functional outcomes at age 17-21 years were assessed using the Prodromal Questionnaire (PQ), Social and Occupational Functioning Scale (SOFAS), and the Comprehensive Assessment of At-Risk Mental States (CAARMS). Linear and logistic regression analyses, adjusted for age at follow-up, sex, and ethnicity, were used to examine associations between risk status at initial screening (with those presenting ASz+FHx included with the ASz group) and these outcomes.

Results: In total, 93 participants (87%) were followed-up at age 17-21 years, on average 7.2 years after screening. Loss-to-follow-up was not associated with group status at recruitment. Compared to the TD group, those who presented ASz had higher total PQ scores (β = 12.55, 95% CI: 5.81, 19.28), were more likely to meet PQ 'probable prodrome' criteria (OR = 4.50, 95% CI: 1.22, 16.65), and had lower SOFAS scores (β = -11.90, 95% CI: -17.68, -6.13). The FHx group were intermediate to the ASz and TD group on these outcome measures, but were not significantly different to the latter group in any analysis ($p>0.05$ for all). Only 7 individuals met CHR or psychosis criteria as determined via the CAARMS (ASz=2; FHx=2, TD=3); therefore, regression analyses were not performed for this outcome.

Discussion: We have piloted a novel, community-screening procedure to identify children who present with a triad of replicated antecedents of schizophrenia. Follow-up of this unique cohort indicates that ASz status at age 9-12 years confers increased risk for poorer clinical and functional outcomes in early adulthood. Such findings are consistent with the results of our interim analyses, in which children presenting ASz were found to show several neurobiological and cognitive features that also characterise adults with established psychosis. The preliminary

findings derived from this pilot study suggest there may be utility in using community-screening methods during middle childhood to identify non-help-seeking youth at elevated risk for psychosis.

O11.6. SOCIAL IMPAIRMENTS IN CHILDREN AT FAMILIAL HIGH-RISK OF SCHIZOPHRENIA OR BIPOLAR DISORDER – A FOUR-YEAR FOLLOW-UP STUDY

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Background: Schizophrenia and bipolar disorder are severe mental disorders with a high heritability rate and partly shared genetic susceptibility. Social impairments are well established in both disorders and may serve as vulnerability markers, as abnormal development

has been suggested to emerge already in childhood and adolescence before illness onset. Moreover, previous research has demonstrated that adult first-degree relatives of individuals with schizophrenia or bipolar disorder display social impairments at an intermediate level between patients and healthy controls. Studies of social impairments in children with a genetic liability for schizophrenia or bipolar disorder is sparse, and results are inconclusive. Importantly, existing studies are cross-sectional and includes children with wide age ranges. Investigation of the development of social abilities in children with a genetic risk of severe mental illness is urgent as such research is an effective way of studying potential vulnerability markers. Further, detection of specific social impairments has both functional and clinical importance as they may facilitate early detection. On this basis, we aimed to examine social responsiveness and theory of mind (ToM) in children born to parents with schizophrenia (FHR-SZ) or bipolar disorder (FHR-BP) using a longitudinal research design.
Methods: This study is part of The Danish High Risk and Resilience Study, which is a nationwide cohort study of children at FHR-SZ or FHR-BP and population-based controls (PBC). All children had the same age at both assessments (age 7 at baseline and age 11 at follow-up). Social responsiveness was measured with the Social Responsiveness Scale (SRS-2), completed by teachers and primary caregivers. ToM was measured using The Animated Triangles Task (ATT), which is a more advanced task suggested to be a relatively pure measure of ToM not influenced by other demands. A total of 520 children (FHR-SZ, n = 201; FHR-BP, n = 119; PBC, n = 200) participated in at least one of the measures at some or both assessments. The retention rate from age 7 to 11 was 89 %.
Results: No time by group interactions were observed. However, children at FHR-SZ had higher SRS-2 scores compared to PBC regardless of the informant, and a higher proportion of children at FHR-SZ were rated at a clinically significant level. Compared to PBC, children at FHR-BP were rated higher on SRS-2 by primary caregivers at age 11. Additionally, a higher proportion of children at FHR-BP were rated at a clinically significant level by teachers at baseline. The three groups did not differ in their ToM abilities. However, children rated at a clinically significant level on SRS-2 exhibited ToM deficits compared to children not rated at a clinically significant level.
Discussion: Social responsiveness and ToM do not develop differently in children at FHR-SZ, FHR-BP and PBC from age 7 to 11. However, impairments in social responsiveness may constitute a vulnerability marker especially in children at FHR-SZ, but also FHR-BP. The social responsiveness impairments in children at FHR-SZ remain stable from age 7 to 11 and are thereby detectable already at an early age. Contrary, children at FHR-SZ or FHR-BP do not seem to have impaired ToM at this stage, but ToM impairment may emerge later as adolescence is a crucial period for the development of more complex ToM components, like those captured by ATT. Thereby, more follow-up studies are needed. Additionally, ATT may primarily be a suitable task for detection of severe ToM deficits like those observed in children rated at a clinically significant level on SRS-2, but not subtle ToM deficits as one would expect to see in children at FHR-SZ or FHR-BP.

O11.7. UNDERSTANDING PSYCHOTIC EXPERIENCES IN PEOPLE WITH BODY DYSMORPHIC DISORDER (BDD)

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Background: Body dysmorphic disorder (BDD) is a severe mental illness characterised by a preoccupation with a perceived flaw in appearance, along with repetitive behaviours and/or mental acts that occur in response to the preoccupation. Referential delusions (people take

special notice of me owing to how I look) are frequently noted in BDD. In DSM-5, there is an optional specifier "with absent insight/delusional beliefs" for patients who hold high conviction that their BDD beliefs are accurate and aligned with reality. This marks a key departure from past editions of the DSM (that is, from DSM-III-R onwards), where non-delusional and delusional variants of BDD were alleged to exist, with the latter double-coded as a delusional disorder, somatic subtype. However, there are only a handful of empirical studies which have examined the presence of delusions and insight in BDD; and no work to date to have explored the existence of hallucinations. Thus, further work is needed in BDD to characterise the psychotic symptoms of the disorder, especially to understand the possible differences or similarities that may exist with schizophrenia.

Methods: Data from three clinical and one neuroimaging study will be presented, examining: a) delusions and insight in BDD using Peters Delusion Inventory (PDI) and the Brown Assessment of Beliefs (BABS), respectively; b) differences in the presentation of psychotic symptoms between BDD and schizophrenia using the Questionnaire for Psychotic Experiences (QPE), and c) an examination of underlying neural networks using resting state data.

Results: The data from the PDI and BABS established that the majority of individuals with BDD hold substantial delusional beliefs, which are a) not restricted to referential delusions in terms of delusional themes, and typically include appearance-based (somatic) delusions, and b) the vast majority (>89%) of BDD patients are classified as having absent insight. Further, an extensive examination of hallucinatory experiences using the QPE in BDD has demonstrated that only somatic hallucinations are endorsed more frequently and qualitatively different from healthy controls (there were no differences for auditory, visual, olfactory, gustatory or multimodal hallucinations). With these somatic experiences akin to those present in schizophrenia.

Of note, a recent investigation of the functional connectivity of resting-state intrinsic connectivity networks in BDD as compared to healthy controls indicated abnormally heightened connectivity of somatic and visual processing regions with broader brain networks in BDD, which may relate to disturbed body image and an increased body focus in basic self-referential processing.

Discussion: This is the first study to have reported on hallucinatory experiences in BDD. In conclusion, this work suggests considerable similarities between BDD and schizophrenia in the somatosensory domain when examining psychotic symptoms.

O11.8. EXPLORING LINKS BETWEEN PSYCHOSIS SPECTRUM EXPERIENCES AND SUICIDAL THOUGHTS AND BEHAVIORS: QUANTITATIVE PATTERNS AND QUALITATIVE THEMES FROM AN ADOLESCENT INPATIENT SETTING

Elizabeth Thompson*[1], Shirley Yen[1], Margaret Nail[2], Anthony Spirito[1], Jennifer Wolff[1]

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Background: Individuals with psychosis-spectrum disorders have a markedly elevated risk for suicide in the early stage of illness. Suicide risk may be particularly high for individuals with psychosis under the age of 18, with untreated symptoms, and within the first year of psychosis onset. These factors indicate that understanding early signs of psychosis may be critical for reducing suicide risk. There is a dearth of research exploring the relation between suicidal thoughts and behaviors (STB) and emerging psychosis-spectrum experiences among teens in an acute psychiatric setting, where STB are prevalent, proximal, and severe.

Methods: Adolescents admitted to a psychiatric inpatient unit completed a brief assessment battery at intake. The Suicidal Ideation Questionnaire-Jr (SIQ-Jr) assessed suicidal ideation

(SI); scores > 30 indicate clinically significant SI. A series of questions probed suicide attempts (yes/no), ever and in the past year and past month. A brief diagnostic interview (MINI-KID) was used to screen for mental health diagnoses, and the psychosis module assessed current symptoms of psychosis. A follow-up qualitative interview was completed with a subsample of youth with psychosis-spectrum disorders, to explore the intersection of psychosis symptoms and STB.

Results: A total of 420 adolescents completed the intake battery. The mean age was 15.18 (SD = 1.72), and 68.1% were female at birth. The racial and ethnic breakdown was as follows: 56.2% white, 29.5% multiracial, 10.7% Black, 8.5% other races, and 28.3% Hispanic/Latino. In the full sample, 35.2% (148) met criteria for a psychosis-spectrum disorder. The mean SIQ score was 41.02 (SD = 1.72), with 61.5% (233/379) scoring above the clinical cutoff. A lifetime suicide attempt was reported by 57.6% (242/383) of the sample, 46.2% (194/383) had a past year attempt, and 28.6% (120/383) had a past month attempt. Correlations indicate that current psychotic disorder was positively associated with SIQ (rpb = .32), lifetime attempt (phi = .17), past year attempt (phi = .14), and past month attempt (phi = .11). Delusions were more strongly correlated with SIQ (rpb = .73) and attempt variables (phi = .23, .21, .14, respectively) compared to hallucinations. Individuals with psychotic disorders, compared to those without, were more likely to have lifetime (74.4% vs. 57.2%; X2 = 11.09), past year (60.2% vs. 45.5%; X2 = 7.35), and past month attempts (38.3% vs. 27.6%; X2 = 4.66). Patterns indicate that overall, the presence of delusional thoughts conveyed particular risk for suicide attempts, as all effects were greater for parallel analyses including delusions versus hallucinations.

Discussion: Results indicate that among psychiatrically hospitalized adolescents, psychotic symptoms are associated with increased suicidal ideation and suicide attempts. Given results from this quantitative analysis, further investigation into links between psychotic experiences and STB among high-risk adolescents is warranted. To this end, we conducted in-depth qualitative interviews with a subsample of 15 youth meeting criteria for psychosis-spectrum disorders. Preliminary themes indicate that for these youth, suicidal behaviors are linked to a need to escape their psychotic experiences or silence voices, a compulsion to act on command hallucinations, a desire to fulfill a greater purpose beyond this life, or due to a belief that one is invincible or unable to die. These findings indicate that youth with emerging psychosis may provide important perspective on how to tailor interventions for unsafe, psychosis-driven thoughts and behaviors. Qualitative themes will be presented and future directions, including implications for safety planning, will be discussed at the close of this presentation.

Poster Session I

12:00 p.m. - 2:00 p.m.

T1. COGNITIVE REMEDIATION ENHANCED BY AEROBIC EXERCISE CAN IMPROVE NEGATIVE SYMPTOMS IN FIRST EPISODE SCHIZOPHRENIA: A RCT

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Background: Meta-analyses have shown that the effects of cognitive training in schizophrenia patients go well beyond improvement in cognition to include benefits such as negative symptom reduction. In addition, evidence from a recent meta-analysis (Sabe et al., 2020) demonstrates the potentially beneficial effects of aerobic exercise on negative symptoms in individuals with schizophrenia. We examined the additive effects of combining these two interventions, cognitive training and aerobic exercise, on negative symptoms over a 6-month intervention with first-episode schizophrenia patients. As a check on the impact of the COVID-19 period on the findings, the analyses were also computed on the data collected prior to the pandemic and economic shutdown.
Methods: A RCT was used to compare Cognitive Training plus Aerobic Exercise (CT and E) to Cognitive Training plus Healthy Living training (CT and HL). The Aerobic Exercise intervention involved high intensity interval training and strength conditioning. Participant eligibility (n=62) included having had their first psychotic episode within two years of study entry. Participants were 64% male with a mean age at study entry of 23.1 (4.4) years and a mean education of 13.6 (1.9) years. All participants were provided four weekly sessions of internet-based cognitive training over a 6-month period. The two conditions were matched for time in the intervention. The 24-item Brief Psychiatric Rating Scale (BPRS) negative (Blunted Affect, Emotional Withdrawal, and Motor Retardation) and mood (Anxiety and Depression) symptoms and the Scale for the Assessment of Negative Symptoms (SANS) Expressive (Flat Affect and Alogia) and Experiential domains (Avolition/Apathy and Anhedonia/Asociality) were administered by trained raters every 2 weeks.
Results: Using General Linear Mixed Models, the trajectory (slope) over the 6-month intervention showed improvement that favored Cognitive Training and Exercise (CT and E) as compared to Cognitive Training and Healthy Living training (CT and HL) for the SANS Experiential Symptom domains of Avolition/Apathy (Mean change = -0.60 vs +0.30, P = <.01) and Anhedonia/Asociality (Mean change = -0.50 vs +0.10, P =.01). SANS Affective Flattening showed a strong tendency in the same direction of improvement (Mean change = -0.50 vs -0.07, P = 0.05). However, there was no significant difference in the trajectory (slope) of mood symptoms as both groups improved over time (Mean change -0.45 vs -0.35, P = 0.65. To examine the effects of the COVID-19 pandemic and economic shut down on symptoms, the analyses were computed with only the data collected prior to March 17, 2020. These analyses yielded virtually identical Results: to the full sample.
Discussion: Our findings suggest that the enhancing effect of adding aerobic exercise to cognitive training appears to extend beyond cognition to negative symptom improvement. Given the close

association between negative symptoms, motivation, and daily role and social functioning, perhaps engagement in aerobic exercise might be an indirect avenue to improving functional outcome.

T2. CO-MORBID SLEEP APNEA IN VETERANS WITH SCHIZOPHRENIA: PREVALENCE AND IMPACT ON COGNITION AND FUNCTIONAL CAPACITY

Stephen Ghazikhanian*[1], Toral Surti[2]

[1]Yale Medical School, [2]Schizophrenia Neuropharmacology Research Group at Yale

Background: The cognitive impairments of schizophrenia drive the functional disability of the illness but are difficult to treat. One barrier to cognitive intervention may be medical co-morbidities that affect cognition and are over-represented in people with schizophrenia. Obstructive sleep apnea (OSA) is treatable, causes reversible impairments in many cognitive domains also affected by schizophrenia, and is likely under-diagnosed. We have estimated the prevalence of OSA in schizophrenia, both by self-report and with a predictive model, and characterized the associations between OSA and cognition and functional capacity in schizophrenia, using a large dataset collected by the Veterans Administration Cooperative Studies Program (CSP).

Methods: We analyzed data collected by the multicenter initiative CSP #572: "Genetics of Functional Disability in Schizophrenia and Bipolar Illness" which included neuropsychological and functional capacity testing, diagnostic interviews, and self-reported demographic and medical history for 3942 patients with schizophrenia. Neuropsychological tests included TMT-A, BACS Symbol Coding, Category Fluency, verbal learning, working memory and NAB Mazes. Functional capacity measures were the UCSD Performance Skills Assessment Battery (UPSA-B) and the Everyday Functioning Battery- Advanced Finances (EFB-AF). Spearman correlations were used to assess association of reported OSA (R-OSA) with demographic and clinical factors. Self-reported diagnosis may underestimate prevalence of OSA in this sample, so we used a model by Utsun et al, (2016) to predict prevalence of OSA (P-OSA). Each participant's cognitive composite score (CCS) was calculated by averaging their age-and-gender-corrected T-scores for each cognitive test. T-tests compared assessments between reported and non-reported OSA (R-OSA v. nR-OSA) and predicted and non-predicted OSA (P-OSA v. nP-OSA). ANOVAs were used to examine differences in CCS, UPSA-B, and EFB-AF among R-OSA, predicted-and-not-reported OSA (PnR-OSA), and No-OSA. Binary logistic regression models of PnR-OSA with sociodemographic and clinical variables were used to characterize this vulnerable subgroup.

Results: The reported prevalence of OSA was 14.4% (n=566). R-OSA patients were more likely to have a college education, be married, and be functionally independent. The predicted prevalence of OSA was 71.9% (n=2834). R-OSA patients had higher CCS than nR-OSA, whereas P-OSA patients had lower CCS than nP-OSA (p's<0.0002). R-OSA patients performed better than nR-OSA in speed of processing assessments ($p<0.0005$), whereas P-OSA individuals performed worse than nP-OSA in speed of processing, verbal learning, and working memory (p's<0.0005). R-OSA had higher UPSA-B and EFB-AF than nR-OSA (p's<0.0001). P-OSA patients had a lower EFB-AF than those with nP-OSA ($p=0.003$). PnR-OSA patients performed worse than both R-OSA and No-OSA on CCS and EFB-AF (p's <0.05), and worse than R-OSA on UPSA-B ($p<0.05$). Veterans with PnR-OSA tended to be older, male, smokers, unmarried, and have higher BMI and less education that the rest of the sample.

Discussion: Our analyses suggest only 20% of OSA in schizophrenia is diagnosed. Self-reported OSA was associated with better performance on cognitive and functional measures, whereas predicted OSA was associated with worse performance on these measures. A possible explanation is that those with higher cognitive capacity are more likely to seek medical care, and those with less cognitive capacity are at greater risk for having co-occurring medical conditions that further compromise cognition. Patients vulnerable to under-diagnosis likely have the most to gain from treatment of their OSA.

T3. RESPONSE TO PSYCHOTIC EXPERIENCES: IMPACT OF PERSONALITY TRAITS ON EXPERIENCED LEVELS OF DISTRESS

Anne Neeltje Scholte-Stalenhoef[1], Lindy Lou Boyette[2], Marieke Begemann[3], Frederike Schirmbeck[4], Ilanit Hasson Ohayon[5], Wiepke Cahn[6], Lieuwe de Haan[4], Gerdina Hendrika Maria Pijnenborg[7], Anne Neeltje Scholte-Stalenhoef*[8]

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Background: Distress due to psychotic experiences is an important predictor of symptom exacerbation and need for care. In a large cross-sectional general population study, the personality traits Neuroticism, Extraversion and Openness to experience were found to moderate the relation between delusional ideation and secondary distress (Kuranova et al, 2020). The current study aims to expands on this finding by investigating whether 1) the personality traits predict distress due to the positive symptom dimension of psychotic experiences (hereafter referred to as 'positive symptoms') over a three-year period, 2) the personality traits moderate the relationship between positive symptom frequency and related distress, in both clinical and nonclinical groups, and while correcting for symptom levels.

Methods: Data pertain to the GROUP study, a Dutch longitudinal multicenter cohort study of vulnerability and resilience factors for variation in expression and course of non-affective psychotic disorders. Personality traits were assessed at baseline with the NEO-FFI questionnaire (Costa and McCrea, 1992) and the frequency of and distress due to subclinical psychotic symptom dimensions were assessed at baseline and follow-up with the CAPE questionnaire (www.cape42.homestead.com). The current sample consisted of 140 patients with psychotic disorders, 216 of their unaffected siblings and 102 healthy controls. Distress due to positive symptom was examined as a dichotomous variable, due to the skewed distribution. Logistic regression analyses were conducted to examine whether personality traits at baseline predicted positive symptom distress at follow-up, separate for patients, siblings and controls. Second, interaction effects between personality traits and positive symptom frequency on positive symptom distress were tested. Age, gender and relevant subclinical symptom dimensions were added to the models as potential covariates.

Results: Higher Neuroticism and higher Openness predicted higher positive symptom distress at three-year follow-up, in patients and siblings but not in controls. When relevant symptom dimensions were added to the logistic regression models, only Neuroticism still predicted positive symptom distress at follow-up, and only in the sibling group. Extraversion did not predict distress. Furthermore, in both patients and siblings, there was a statistically significant negative interaction between Openness and positive symptom frequency on positive symptom distress, also when

correcting for relevant symptom dimensions; indicating that higher Openness weakens the positive relation between positive symptom frequency and distress.
Discussion: Particularly the personality trait Openness to experiences may function as a protective factor for secondary psychotic symptom distress. However, this may be specific for individuals with higher subclinical psychotic symptoms. The relation between Neuroticism and secondary psychotic symptom distress appears to be confounded by symptom levels.

T4. NEUROCOGNITIVE FUNCTION IN SCHIZOPHRENIA SPECTRUM DISORDER PATIENTS WITH AND WITHOUT DELUSIONS

Christine Mohn*[1], Beathe Haatveit[2], Linn Sofie Sæther[3], Anja Vaskinn[4], Ingrid Melle[5], Ole A. Andreassen[5], Torill Ueland[6]

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Background: Delusions are core symptoms of schizophrenia spectrum disorders (SSD), but their origin and development is not well understood. Several studies report misattribution of meaning, jumping to conclusions, and deficient theory of mind in SSD patients with delusions suggesting that this symptom Results: from altered top-down cognitive processes. Apart from isolated findings of deficient working memory and visual memory, there is surprisingly little systematic investigation of basic neurocognitive functions that could form the foundation for this higher-order dysfunction. To our knowledge, there are no well-powered studies of the relationship between comprehensive neurocognitive function and delusions in SSD. Here, we aim to fill this knowledge gap.
Methods: In total, 240 SSD patients were included, of which 110 (71 males, 39 females, mean age 29.7 years) had moderate to severe delusions and 130 (74 males, 56 females, mean age 30.0 years) had no delusions according to item P1 of the Positive and Negative Syndrome Scale. Neurocognitive function was assessed with the MATRICS Consensus Cognitive Battery with additional tests of general intelligence, working memory, verbal and visual memory, and executive function.
Results: Compared to the patients without delusions, the patients with delusions displayed statistically significantly lower general intelligence (F 5.73, $p < .05$), verbal working memory (F 4.65, $p < .05$), visual working memory (F 7.56, $p < .01$), verbal learning (F 8.57, $p < .005$) and memory (F 8.64, $p < .005$), and visual learning (F 17.69, $p < .001$) and memory (F 11.94, $p < .001$). No significant group differences were detected in measures of processing speed, sustained attention, or executive functions.
Discussion: Moderate to severe delusions in SSD patients were linked to deficits in working memory, learning and retention memory for both verbal and visual stimuli. The practical and clinical implication of this finding is that delusions may, at least partially, result from dysfunctions

of the earliest stages of encoding of information, rendering these individuals vulnerable to biased reasoning due to the reliance of insufficient data.

T5. SHAKE MY HAND AND STAND UP: THE ROLE OF GRIP STRENGTH AND FUNCTIONAL MOBILITY IN SCHIZOPHRENIA

Federica Cuoco*[1], Giulia Agostoni[2], Silvia Lesmo[2], Mariachiara Buonocore[1], Margherita Bechi[1], Jacopo Sapienza[2], Francesca Martini[1], Ilaria Ferri[1], Federica Cocchi[1], Roberto Cavallaro[3], Marta Bosia[2]

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Background: Schizophrenia is one of the major global causes of disability. Cognitive deficits, poor physical health, and low activity levels can impact significantly on quality of life (QoL). On the one hand, physical health and cognition are known to be closely related. On the other, functional mobility and grip strength represent important measures of global physical status and recent literature suggests an association with cognitive performance, especially in the general older population, highlighting a potential role also in schizophrenia. In this perspective, these assessments may provide an easily-administered marker of cognitive functioning, as well as a target to improve the health of patients with schizophrenia. This study aims to analyze the effects of the maximal manual grip strength and functional mobility on cognition, symptoms, and QoL, also modeling their relationship with Metabolic Syndrome (MetS), in schizophrenia.
Methods: 103 adults with schizophrenia were recruited at the Schizophrenia Research and Clinical Unit, IRCCS San Raffaele, Milan, Italy. All people were assessed for psychopathology, cognition, QoL, physical performance status, functional mobility, and MetS. Correlation analyses were performed to evaluate the relationship between both physical performance and functional mobility, assessed respectively with the Jamar hand dynamometer and Time Up Go (TUG), and cognitive performance, symptoms, QoL, and MetS. Moreover, a forward stepwise multiple regression was used to evaluate the effect of Jamar and TUG as predictors of cognitive performance and QoL. Last, two mediation models were performed to test the effect of MetS as a predictor of Global Cognitive Index (GCI) and QoL, mediated by TUG score.
Results: Concerning grip strength, a significant positive correlation emerged with working memory and processing speed. As for functional mobility, several significant effects emerged showing an impact on negative symptoms, working memory, processing speed, GCI, QoL interpersonal relations, self-directedness and total score. Finally, mediation analyses showed that TUG score significantly mediated the negative effect of MetS on both the GCI and on QoL.
Discussion: Data showed a significant positive correlation between grip strength and two core cognitive deficits in schizophrenia, which are linked to quality of life, detectable since the early stages of neurodevelopment, and potential predictors of transition to psychosis in high risk populations.
Interestingly, data suggest also a key role of functional mobility with a direct impact on several domains of symptoms, cognition and functioning, as well as a mediator effect between MetS and quality of life.

Our findings are relevant and innovative. Indeed, to our knowledge, this is the first study that evaluates the role of both grip strength and functional mobility in schizophrenia. Grip strength and TUG test are non-invasive quick measures, that may be implemented in clinical practice, with important implications for prevention and monitoring, especially in the rehabilitative setting.

T6. SOCIAL PROCESSES ACROSS AUTISTIC AND PSYCHOSIS PHENOTYPE – A NETWORK ANALYSIS

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Background: Autism and schizophrenia are both characterized by heterogeneous psychopathology. Individuals with these conditions share difficulties in various social processes, such as social affiliation, communication, mentalizing, or attachment. Studying autistic traits and psychotic experiences in the general population can inform a better understanding of social dysfunction underlying autism and schizophrenia. The goal of the current study was to model complex associations between autistic traits, positive and negative symptoms, and various indicators of social processes in a large adult non-clinical sample.
Methods: The sample consisted of 649 participants with a mean age of M=40.23 and SD=13.09. The sample was representative of the 18 – 65 years old general population in the Slovak republic. The following scales were administered: Community Assessment of Psychic Experiences, The Comprehensive Autistic Trait Inventory, NIH Toolbox Adult Social Relationship scales, Five Item Mentalizing Index, Experiences in Close Relationships - Revised. Associations between variables were modeled using a network analysis approach. The importance of nodes (variables) was represented by the centrality index node strength.
Results: We found strong interconnections among autistic phenotype variables. Psychotic experiences domains were less densely interconnected. Social interaction difficulties, a part of the autistic phenotype, were more strongly related to negative symptoms domains (especially social withdrawal) than other autistic trait variables. Furthermore, paranoia was connected to perceived rejection, and hallucinatory experiences were more strongly associated with perceived hostility. The most central nodes were bizarre experiences, difficulties in social interactions, perceived rejection, loneliness, and social withdrawal.
Discussion: Connections within these domains were stronger than between domains. We found that more severe autistic and psychotic symptoms in the general population were associated with more profound problems in various social domains like loneliness, perceived rejection, perceived hostility, and lower social support. Overall, all domains formed a very dense network showing strong associations between symptom domains and difficulties in social processes. Results: need to be further replicated and extended in a clinical sample.
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T7. NEGATIVE SYMPTOMS IN SCHIZOPHRENIA DEPEND ON IMPAIRED MODEL-FREE REWARD PREDICTING, WHICH IS INFLUENCED BY STRIATAL DOPAMINE TRANSMISSION AND EXECUTIVE DYSFUNCTION

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Background: Negative symptoms are a core syndrome of schizophrenia, affecting about 60% of patients. They are a decisive factor for everyday functioning, but currently available pharmacological and cognitive-behavioral treatments still have limited effects. The development of successful therapies is hindered by a lack of understanding of underlying neurocognitive mechanisms. In this study, we tested one candidate for such a mechanism, namely reward-related decision-making (reward-DM). Reward-DM allows to analyze how motivational factors, i.e., expected rewards, influence different modes of decision-making, namely model-free (relying only on previous outcomes) and more flexible, but computationally demanding model-based behavior (implementing cognitive models). Furthermore, we investigated how model-based/model-free reward-DM is associated with two contributing factors: (i) associative striatum dopamine synthesis and storage (DSS), measured with 18F-DOPA positron emission tomography, which is the focus of dopaminergic aberrances in schizophrenia; and (ii) executive dysfunction, assessed with the symbol coding task (SCT), which influences decision-making processes.

Methods: 25 patients with chronic schizophrenia, currently without psychotic symptoms (to avoid bias from psychotic symptoms on reward-DM), and 24 healthy controls (matched by age and gender) were enrolled. Negative symptoms were quantified with the Positive and Negative Syndrome Scale (PANSS) negative sub-scale. Model-based/model-free reward-DM was investigated with a two-stage Markov decision task and computational modeling of subjects' decision-making behavior – the main outcome parameter quantified the influence of reward predictions on decisions (separately for model-based and model-free behavior). Associative striatum DSS was assessed by 18F-DOPA positron emission tomography and subsequent graphical Patlak analysis. Executive dysfunction was evaluated by SCT. Associations between variables were tested via regression analyses.

Results: The influence of model-free reward predictions on decisions was significantly reduced in patients compared to healthy controls ($p=0.02$), while there was no group difference for the influence of model-based reward predictions ($p=0.76$). In patients, the decreased influence of model-free reward predictions was (i) negatively related with negative symptoms quantified by PANSS-negative ($p=0.048$); (ii) positively related with associative striatum DSS ($p=0.04$), which was significantly reduced in patients ($p<0.001$); and (iii) positively related with SCT performance ($p=0.02$), which was significantly worse in patients ($p<0.001$).

Discussion: In patients with schizophrenia during remission of psychotic symptoms, selectively the influence of model-free reward predictions on decisions was impaired and related with negative symptoms, suggesting it as a mechanism for negative symptoms. Reduced associative striatum DSS and executive dysfunction constituted contributing factors for this aberrance. These more precise mechanistic insights could inform the development of future pharmacological and cognitive-behavioral treatments.

T8. COGNITIVE FUNCTIONING IN FIRST EPISODE PSYCHOSIS: THE RELATION WITH ANTIPSYCHOTIC MEDICATION

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Background: Although antipsychotic medication is the first line of treatment in first-episode psychosis (FEP), national guidelines are inconclusive about the type of antipsychotic that should be given as first choice drug. In addition, evidence regarding the effects of antipsychotic medication use on cognitive function remains inconclusive. Two specific mechanisms that have been implicated in the effect of antipsychotics on cognitive performance are dopaminergic and cholinergic binding properties. Therefore, this study examined the relation between cumulative and daily antipsychotic dose, dopamine D2 receptor affinity and anticholinergic burden score on patients' performance on a well-evaluated cognitive test battery.
Methods: Baseline data was used from the HAMLETT study. Patients were 3-6 months in symptomatic remission of their first psychotic episode and used antipsychotic medication. Recruitment took place in 24 Dutch mental healthcare institutions, covering different medication strategies and prescription practices. Cognitive performance was assessed with the Brief Assessment of Cognition in Schizophrenia (BACS). Use of antipsychotic medication was based on data from the Dutch Foundation for Pharmaceutical Statistics. Multivariate linear regression analyses were used to test for the relationship between cognitive performance and cumulative dose and daily dose of antipsychotic medication, anticholinergic daily burden and dopamine D2 receptor affinity. Covariates included were age, gender, years of education and symptom severity (PANSS).
Results: 90 patients were included, with an average age of 28.2 years (SD=9.3) and 74.4% were male. High dopamine D2 receptor affinity was significantly associated with reduced global cognitive performance (p=.029), and more specifically verbal fluency (p=.014). No significant associations were found between global cognitive performance and cumulative or daily dose of antipsychotic medication use, nor anticholinergic burden of antipsychotics (p-values >.05).
Discussion: This study provides important leads for choosing antipsychotic drugs in patients with FEP as higher dopamine D2 receptor affinity, but not anticholinergic burden, was related to lower cognitive performance. This underscores the importance of careful determination of the antipsychotic medication type in FEP in order to minimize the negative impact on cognition.

T9. OVERLAPPING BETWEEN SOCIAL COGNITION AND NEGATIVE SYMPTOMS: A CLUSTER ANALYSIS IN SCHIZOPHRENIA

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Background: Social cognition, which encompasses emotion recognition, theory of mind (the ability to infer others' mental states), or attributional style is particularly affected in schizophrenia. Negative symptoms are strongly correlated with these social cognitive impairments, both having a detrimental impact on social functioning. The extent of the interplay between social cognitive impairments and negative symptoms is a key question in schizophrenia-spectrum disorders since its clarification might provide new therapeutic options to address the resulting functional impairment. This study examined if distinct subgroups could be identified based on negative symptoms dimensions associated with social cognitive measures.
Methods: One hundred and thirty-five patients living with schizophrenia underwent clinical and neuropsychological assessment. Negative symptoms were divided into two dimensions: motivation and pleasure and expressivity. And three subdomains of social cognition (emotion recognition, theory of mind, and attributional style) were specifically evaluated. The standardized measures were included in hierarchical and k-means cluster analyses. The resulting clusters were then compared on remaining clinical and neuropsychological variables.
Results: A 3-cluster solution was identified with hierarchical cluster analysis with complete linkage (furthest neighbor) and optimized with k-means analysis. Cluster 1 (n=33) regrouped patients with amotivational symptoms and attributional biases. Cluster (n=72) included patients with few negative symptoms and relatively intact social cognition. And cluster 3 (n=30) was constituted of patients with a deficit in expressivity and impaired emotion recognition and theory of mind. Cluster 1 was significantly associated with more positive and depressive symptoms than Cluster 2, while Cluster 3 presented significantly more neuropsychological impairments (i.e., in speed of processing, working memory, executive functions, and visual and verbal memory) than Cluster 2.
Discussion: These results confirm the utility of combining negative symptoms and social cognitive data as it offers a further step to the existing conceptual frameworks and opens to more focused therapeutic approaches.

T10. ALTERED BODILY SELF IN CHRONIC SCHIZOPHRENIA AND FAMILIAL AT-RISK CHILDREN FOR PSYCHOSIS MEASURED BY BODILY MAPS

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Background: A recent study of embodied emotions using a topographic mapping tool (e.g. EMBODY) has shown that the bodily sensations that accompany emotional experience are altered in schizophrenia (Torregrossa et al, 2019). When asked to indicate where they feel body activation or deactivation while experiencing distinct emotions, individuals with schizophrenia (SZ) painted the same amount of pixels as controls, but reported less activations and more deactivations than controls for high-arrousal emotions. However, this pattern of body activations and deactivations

was highly variable between individuals, especially in the SZ group. To further explore altered emotional embodiment and address this problem of inter-individual variability in SZ, we developed a new analytic method that estimates the within-subject stability of bodily sensation patterns across different emotions. We hypothesized that SZ would exhibit alterations of body sensation stability. Given the association between bodily self disorders and conversion to psychosis, we also assessed the stability of bodily sensations of children at familial high-risk for psychosis (FHR).

Methods: Participants were 26 SZ and 26 matched CO (from Torregrossa et al's study), as well as 33 FHR subjects (18 girls, mean age = 11.85, 9-15 years old) who were offsprings of individuals with from schizophrenia, bipolar disorder or recurrent major depressive disorder from the INTERCEPT study, and 27 controls (17 girls, mean age = 11.93, 9-15 years old) with no family history of psychosis and no personal history of DSM-V disorder. For each emotion, subjects were instructed to color the body regions whose activity becomes stronger or faster in red on a body outline, and the regions whose activity becomes weaker or slower in blue in another body outline. Adults used the computerized body mapping tool to color in felt sensations while children completed the body mapping task on paper. Emotions (anger, disgust, fear, happiness, sadness, surprise and neutral) were induced by words, pictures and short stories to ensure proper induction in children. More emotions were used in adults (14) who were provided written definitions.

We selected 2 x 5 regions of interest (ROI) (head, arms, legs, upper torso and lower torso for the activation and the deactivation maps). If there is a stable body pattern for a given participant, the hierarchy of the 10 ROI intensities should be preserved (e.g. more intensity in the head than in the upper torso than in the arms etc) across all emotions. To estimate the stability of body pattern, we tested whether body-parts intensities were correlated between emotions, and derived a global score of connectivity strength for each emotion. The more correlations across emotions, the higher the score. The score is calculated for each individual, and can be high or low whatever the individual body pattern.

Results: The body pattern stability was very high in both adult and minor controls, with all emotions except the neutral one being strongly cross-correlated. Adult SZ as well as FHR children showed a globally lower body pattern stability than their matched controls, meaning that the pattern of body part intensities was less stable across emotions in adult SZ and FHR children than their matched controls.

Discussion: The pattern of body activations and deactivations is stable across emotions in control adult and minor, but unstable in SZ and in FHR children. This represents an easily accessible measure of whether individuals have a self-represention of an emotional body pattern, independent of the emotion type. This measure might complement other measures of the bodily self.

T11. EFFECTS OF NIGELLA SATIVA ON MITIGATING AGGRESSION INDUCED WITH AMITRIPTYLIN IN DROSOPHILA MELANOGASTER

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Background: Aggression is a feeling of anger or antipathy resulting in hostile or violent behavior or the action of attacking without provocation.Amitriptylin is a trycyclic antidepressant that can

induce aggression when an overdose is consumed. Nigella sativa oil is a widely known multi-therapeutic agent that is used in folklore medicine because of its anti-inflammatory abilities.
This study aims at investigating the possible prospects of Nigella sativa oil in mitigating aggression as modeled in Drosophila Melanogaster through exposure to Amitriptylin .

Methods: Four groups of virgin Drosophila melanogaster (Canton-S strain) shall be constituted, with each group containing 10vials, and each vial holding 20 flies.
The fly groups shall be exposed to either normal drosophila media for 7 days (A-control),

Amitriptylin overdose for 7 days (B),

Amitriptylin overdose for 7 days and pretreatment with Nigella Sativa oil for 7 prior days (C) or

concurrent Amitriptylin overdose and Nigella sativa treatment for 7 days (D). Fly media shall be based on yeast,cornmeal,molasses,and agar food at room temperature. Aggression, locomotion and neurotransmitter (GABA, Dopamine and glutamate) levels and difference in cells shall be measured using the Divider, RING,spectrophotometric and histological assays respectively.

Results: The level of aggression in the Drosophila be obtained in divider assay by recording their interaction in a slow mode video for 20minutes, the ring apparatus will be put in action and a timer would be to 3.0seconds to measure locomotion.
Discussion: Nigella sativa oil has been recorded to play a neuroprotective role as it has been used as an anti-anxiety and anti-aggression in it's previous studies. Therefore, we hypothesize that Nigella sativa would show protective effects on the behavioral, neurochemical and histological parameters in the amitriptyline-induced Canton-S flies.

T12. LONG-TERM COURSE OF COGNITIVE FUNCTIONS IN FIRST-EPISODE SCHIZOPHRENIA: A 10-YEAR FOLLOW-UP STUDY

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Background: Cognitive impairment in schizophrenia and its influence on functioning is well documented. Exploring the development of cognition over time in this disorder could give insights regarding illness-mechanisms and outcome prediction. The existing literature on long-term cognitive development in first-episode schizophrenia (FES) mainly points to stability, while some studies on first-episode psychosis find improvements during the first year after illness onset. However, to date there are fewer long-term studies on first-episode schizophrenia including a healthy control comparison group, and there is also a need for studies on the course of specific cognitive functions. The present study investigated the course of cognitive functioning in a FES group and healthy controls, over a 10-year follow-up period. We expected deficits in FES compared to controls as well as stability in cognitive functioning over time.
Methods: We analyzed data from 69 participants with FES and 92 healthy controls recruited from the same catchment area as part of the TOP study. Only participants with complete datasets were

included. Inclusion criteria were IQ > 70, adequate Norwegian language skills, and for controls no history of mental illness. Participants were assessed at baseline and at 10-year follow-up. The patient sample was assessed within 12 months of first treatment for schizophrenia-spectrum disorders (70.5 % schizophrenia, 16.7 % schizoaffective disorder, and 12.8 % schizophreniform disorder). We used a test-battery tapping 8 cognitive domains: learning, memory, attention, psychomotor speed, mental processing speed, working memory, verbal fluency, and executive functioning. Raw scores were converted to z-scores centered on controls at baseline. Standardized composite scores were entered in a repeated-measures ANCOVA with age as covariate, while domain scores were analyzed using a repeated-measures MANCOVA, covarying for age.
Results: ANCOVA of the composite score indicated a significant effect of time ($F(1) = 16.10$, $p < .000$) and of group ($F(1) = 94.90$, $p < .000$. We also found interactions between time and group ($F(1) = 6.07$, $p = .015$), indicating larger increase over time in the control group. MANCOVA of domain scores found significant multivariate effects of time ($F(8) = 3.07$, $p = .003$) and group ($F(8) = 12.10$, $p < .000$), as well as a time*group interaction ($F(8) = 2.97$, $p = .004$). Significant increases over time for both groups were found on memory, psychomotor speed, verbal fluency, and executive functioning. There were also interaction effects between time and group for attention ($F(1) = 13.34$, $p = .000$), and executive functioning ($F(1) = 6.43$, $p = .012$), such that controls increased while the patient group had slight declines.
Discussion: We found separate developmental courses for different cognitive functions. Schizophrenia patients performed significantly poorer than controls on all measures at both time points, but the most pronounced impairments were found on complex and speeded measures, such as psychomotor speed, mental processing speed and verbal fluency. Learning, working memory and mental speed held stable over time, but contrary to our hypothesis we found increases in several domains for both groups (fluency, psychomotor speed, and memory) and small decreases for the schizophrenia group on executive functioning and attention compared to controls. Our findings underscore the importance of investigating the developmental course of separate cognitive domains.

T13. SOCIAL COGNITION AND ITS ASSOCIATION WITH THE DURATION OF UNTREATED PSYCHOSIS IN ANTIPSYCHOTIC-NAÏVE INDIVIDUALS AT DIFFERENT STAGES OF THE SCHIZOPHRENIA SPECTRUM DISORDERS

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Background: To examine the temporal dynamic of social cognition (emotional management (EM)) on the schizophrenia spectrum and its association with duration of untreated psychosis (DUP) in never-medicated individuals at different stages of the disease.
Methods: This study included 101 individuals at clinical high-risk for psychosis (CHR), 85 patients with first-episode of psychosis (FEP) with a mean DUP of 15.9 (SD=14.4) weeks, 60

individuals with Chronic schizophrenia (CSz) with a mean DUP of 419.7 (SD=405.9) weeks, and 97 healthy controls (HC).
Results: A component analysis of the EM dominion score derived from the MATRICS Consensus Cognitive Battery revealed effective and ineffective EM factors under both private and social contexts. All clinical groups showed reduced effective EM, regardless of context, compared with the HC group (all $p \leq 0.003$) with no significant differences among them. Conversely, a progressive increase of ineffective EM as disease progresses was found: the CSz group showed higher scores compared with the FEP, and this group showed higher scores compared with CHR (all $p \leq 0.01$). DUP was positively associated with increased ineffective EM scores (all $p \leq 0.05$). For the FEP and CSz groups, higher ineffective social EM was associated with more severe positive and negative psychotic symptoms (all $p \leq 0.01$).
Discussion: These findings suggest a stable reduced ability to identify effective strategies for EM even from at-risk stages of the schizophrenia spectrum, with no changes among stages, and a parallel, progressive increase in choosing ineffective strategies for EM along the disease progression. Therefore, social cognition is mainly characterized by progressive deficits in schizophrenia.

T14. AFFECTIVE LABILITY IN PARENTS WITH SCHIZOPHRENIA OR BIPOLAR DISORDER AND THEIR CO-PARENTS - THE DANISH HIGH RISK AND RESILIENCE STUDY VIA 7

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Background: Affective lability is an aspect of affective dysregulation and refers to the frequency, speed, and range of changes in affective states. Studies have demonstrated associations between affective lability and various mental disorders with elevated affective lability being linked to a more complex and severe illness course and outcome.
Bipolar disorder and schizophrenia share some symptoms and genetics. In bipolar disorder, dysregulation of affects is a core feature and elevated affective lability is strongly associated with the disorder. Studies on affective lability in schizophrenia are sparse and less conclusive.

Assortative mating is common in individuals with mental disorders but to our knowledge, no research exists on affective lability in partners to individuals diagnosed with schizophrenia or bipolar disorder. When one parent is ill, the care for the child will often depend on the co-parent. Thus, elevated affective lability in co-parents is potentially a risk factor and may affect the children in these families.

Therefore, the objective of this study is to investigate affective lability in parents with schizophrenia, bipolar disorder or neither of these disorders. We expect to find elevated affective lability in parents with schizophrenia compared to the control group, but lower levels compared to

parents with bipolar disorder. Furthermore, we aim to investigate affective lability in co-parents to individuals with schizophrenia or bipolar disorder. Owing to the tendency to assortative mating, we expect higher levels of affective lability in co-parents to individuals suffering from bipolar disorder or schizophrenia compared with controls – but lower levels compared to their partners with bipolar disorder or schizophrenia.

Methods: This study is part of the Danish High Risk and Resilience Study –VIA 7, a population-based cohort study conducted in Denmark between 2013 and 2016. The VIA 7 cohort consists of 522 children aged 7 with parents diagnosed with schizophrenia or bipolar disorder in the Danish registries and their co-parents. This study focuses on the biological parents and includes data from 851 parents (305 parents where at least one of them have been diagnosed with schizophrenia, 187 parents where at least one of them have been diagnosed with bipolar disorder and 359 parents in the control group with neither of these disorders). The total score and sub-scores covering the domains of anxiety/depression, depression/elation, and anger of the Affective Lability Scale – short form (ALS- SF) questionnaire is used to measure affective lability. Higher scores in ALS-SF reflect elevated affective lability.

Results: Data analysis is ongoing, and data will be presented at the conference.

Discussion: Affective lability may help understand some of the underlying factors in bipolar disorder and schizophrenia and may provide important findings that may inform future treatment approaches. Furthermore, potential elevated levels of affective lability in co-parents to parents with schizophrenia or bipolar disorder may be an additional risk factor for children growing up with these parents and thus highlight the need for special focus on and support to families with bipolar disorder or schizophrenia.

T15. EXAMINING THE ROLE OF FAILURE AND SUCCESS EXPERIENCES ON TASK PERSISTENCE AND NEUROCOGNITION IN SCHIZOPHRENIA

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Background: Neurocognition is an important contributor to everyday functional outcomes, and thus is an important target for intervention; however, the mechanisms driving neurocognitive impairment in schizophrenia remain unknown. Many psychological mechanisms of neurocognitive functioning have been proposed that warrant investigation. In addition, the effect of failure and success experiences on neurocognition remains unknown. This study examined whether experiencing failure or success has an effect on persistence and neurocognitive performance and investigated whether motivation, defeatist performance beliefs, and mood act as mediating variables in this relationship.

Methods: The sample consisted of participants aged 18-60, including 21 participants with schizophrenia-spectrum disorders and 22 healthy controls. In this repeated-measures cross-over study, each participant completed a success and failure manipulation, a self-report of psychological status, an anagram persistence task, neurocognitive testing, and a clinical interview over two time points.

Results: Individuals with schizophrenia had lower persistence and processing speed relative to healthy controls, but this was not affected by the experience of failure or success. Individuals with

schizophrenia made worse decisions after failure, while healthy controls made better decisions after failure. We did not identify any significant cognitive-affective mechanisms which contribute to deficits in maintaining effort over time or impairments in processing speed and decision making.
Discussion: The results of this study demonstrate that the experience of failure may differentially affect the decision-making capabilities of healthy controls and individuals with schizophrenia, such that it worsens decision-making in schizophrenia and improves decision-making ability in HCs. Developing interventions to improve persistence in the face of failure, especially on cognitively complex tasks, may be important for improving neurocognition in schizophrenia.

T16. IMPROVED INDIVIDUALIZED IDENTIFICATION OF SCHIZOPHRENIA AND CLINICAL HIGH RISK FOR PSYCHOSIS WHEN COMBINING COGNITION WITH NATURAL LANGUAGE PROCESSING

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Background: Patients with schizophrenia have been shown to present with cognitive and language disturbances prior to the first psychosis onset. Previous studies have shown high classification accuracy using neurocognitive pattern classification to identifying patients with schizophrenia (SCZ) and individuals at clinical high risk (CHR) for psychosis (Zarogianni et al., 2017, Koutsouleris et al., 2012). However, few studies to-date have assessed the potential contribution of linguistic features to identify patients with early psychosis spectrum disorders. Recent advances in machine learning and natural language processing allow for rapid extraction of linguistic features from natural speech during clinical interviews. We recently showed disturbances in semantic coherence and syntactic complexity using natural language processing are predictive of transition to psychosis. In this study, we investigated the differential diagnostic value of combining linguistic features with cognition to discriminate patients with SCZ and CHR from heathy controls (HC).
Methods: Automated natural language processing (NLP) analysis was applied to speech samples obtained from 105 HC (mean [SD] age: 23.22 [3.64]; 46 male), 42 patients with SCZ (mean [SD] age: 23.76 [5.44]; 24 male), and 122 CHR (mean [SD] age: 20.90 [4.39]; 61 male) from 4 sites. CHR status was determined using the Structured Interview for Prodromal Syndromes, and patients with schizophrenia were diagnosed using the Structured Clinical Interview for the DSM-IV-TR. All individuals underwent neurocognitive assessment using the MATRICS Consensus Cognitive Battery (MCCB). The machine learning software NeuroMiner version 1.0 was used to set up a multiclass machine learning analysis pipeline to classify SCZ and CHR from HC combining linguistic and cognitive features using a linear class-weighted Support Vector Machine (SVM) algorithm (LIBSVM 3.1.2 L1-Loss SVC). Repeated-nested double cross-validation was employed, with leave-site-out cross validation in the outer cycle and 10-fold and 10-permutation inner cycle to avoid overfitting and test the estimation of the model's generalizability across sites.

Results: The groups significantly differed in age (F = 11.0; p<0.001) with CHR significantly younger than HC and SCZ, but not sex ($\chi 2$ = 2.29; p=0.32). The 3-group cross-validated classification balanced accuracies (BAC) in the cognition only analysis were 53.8% (HC vs SCZ), 51.7% (HC vs CHR), and, 50.0% (CHR vs SCZ) and 64.8% (HC vs SCZ), 68.0% (HC vs CHR), and 53.7% (CHR vs SCZ) in the linguistic features only analysis. As expected, combining linguistic markers with cognitive performance-based markers yielded higher classification accuracies with a BAC of 74.8% (HC vs SCZ), 69.5% (HC vs CHR), and, 56.0% (CHR vs SCZ).
Discussion: These findings suggest combining linguistic features with cognition contributes to the individualized identification of patients at various stages of psychosis spectrum disorders.

T17. HIGHER LEVEL EMOTION PROCESSING IN RECENT-ONSET SCHIZOPHRENIA AND RELATED DISORDERS: WHAT ARE THE COGNITIVE AND CLINICAL CORRELATES?

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Background: Social cognition refers to the mental processes underlying social interactions including perceiving, interpreting, and generating responses to the intentions, dispositions, and behaviors of others. The Social Cognition Psychometric Evaluation Study has highlighted four core domains of social cognition relevant for people with schizophrenia, including emotion processing. Emotion processing includes both lower-level (emotion perception/recognition) and higher-level (understanding and managing emotions) processes. While several prior studies have assessed lower levels of emotion processing, there are still very few information regarding the variables that could contribute to higher-level emotion processing. Higher-level emotion processes are complex functions that encompass a set of brain networks. For example, recent models of brain networks support that both mentalizing and emotion regulation rely on prefrontal and cingulate systems for attention, response selection, and mental state attribution. As a result, the brain networks involve in emotion regulation could also be involved in other cognitive functions, such as attention, memory, executive functions, speed of processing or theory of mind. Clinical variables such as anxiety or depressive symptoms have also demonstrated their impact on emotion regulation. The aim of this study is to explore the cognitive and clinical correlates of higher-level emotion processing in schizophrenia and related psychotic disorders.
Methods: Twenty-seven participants with recent-onset schizophrenia and related psychotic disorders were recruited. They were aged between 18 and 39 years old, with less than five years of treatment for their psychotic disorder and were clinically stable. Higher-level emotion processing was assessed using the Mayer Salovey Caruso Emotional Intelligence Test (MSCEIT). Cognitive variables included the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) to assess speed of processing, attention/vigilance, working memory, verbal and visual learning and problem solving as well as a theory of mind task (Combined stories

test). Clinical variables were assessed using the three dimensions scoring of the Positive and Negative Syndrome Scale (PANSS) (i.e., positive, negative, general psychopathology). Correlations were conducted between the MSCEIT and the cognitive (neurocognition, theory of mind) and clinical (three dimensions of the PANSS) variables.
Results: Regarding the correlations between higher-level emotion processing and cognitive variables, significant correlations were observed between the MSCEIT and theory of mind, ($r(27) = 0.599$. $p < 0.001$) as well as verbal learning ($r(27) = 0.403$. $p = 0.037$) and visual learning ($r(27) = 0.424$. $p = 0.028$). No significant correlation was found between the MSCEIT, and the three dimensions of clinical symptoms.
Discussion: The results are in line with previous studies that revealed associations between social cognition, episodic memory and affect regulation, due to commune brain networks underpinning these variables. For example, emotion regulation and episodic memory both rely on hippocampal networks. The absence of associations between emotion regulation and the clinical symptoms may be partly explained by the three dimensions of the PANSS used in this study. Using a five-dimension rating, we might expect associations between emotion regulation and the depression/anxiety and excitability/hostility dimensions. Future studies using larger samples and refined clinical variables would be helpful to disentangle the direction and nature of the associations with higher-level emotion processes.

T18. DO THOSE WHO JUMP TO CONCLUSIONS HAVE PROBLEMS IN THEIR SOCIAL COGNITION? A CROSS-SECTIONAL STUDY IN FIRST EPISODE PSYCHOSIS

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Background: Studying the most important components of the psychological treatments and their relationships could help for the development and personalisation of gold standard interventions that work together with reasoning biases in social decision-making processes in patients with psychosis. Two main cores of interventions in psychosis are the jumping to conclusions bias (JTC) and impaired social cognition (SC). However, the relationship between them is little explored in first-episode psychosis (FEP).
Methods: We conducted a cross-sectional multicenter study with 121 patients with FEP from 9 spanish mental health centers. Inclusion criteria: 1) schizophrenia spectrum (DSM-IV) 2) <5 years of the onset; 3) PANSS scores in delusions, grandiosity, or suspicions of ≥4 in the last year; and 4) 17-45 years old. Exclusion criteria: (1) traumatic brain injury, dementia, or premorbid IQ ≤70; (2) substance dependence; and (3) high PANSS in hostile, uncooperative, and suspiciousness.
We included a sociodemographic questionnaire, a battery of instruments regarding JTC, SC, and clinical measures: Beads task-computer version (easy, hard, and salient) to assess JTC; IPSAQ,

The faces test and Hinting Task to assess emotional recognition, attributional style, and ToM (domains of SC); PANSS for psychotic symptoms; BDI-II to assess the severity of depressive symptoms. Premorbid IQ was calculated with vocabulary subtest of the WAIS-III.

We conducted statistical analyses in three stages: 1) Descriptive analysis of the sociodemographic and clinical variables. 2) A Student's t-test to assess the differences between JTC/no JTC among SC subdomains. The effect sizes of all comparisons were calculated with Cohen's d using pooled SD. 3) We performed a binary logistic regression with the stepwise method for each of the three tasks of the JTC as the dependent variables, and the subdomains of the SC that were significant in the univariate analysis as independent variables, controlling for positive and depressive symptoms and, premorbid IQ.

Results: Firstly, people who did JTC in all three tasks scored lower in ER than NO-JTC (p=0.042-0.017, Cohen's d=0.088-0.721). Regarding ToM, we found no differencies between who do JTC and who do not. Considering AS, we had mixed findings: people who JTC made more internalized attributions for negative events (p=0.034-0.029; SD= 0.425-0.029). Likewise, we found a relationship between JTC and low externalized bias (p=0.042, SD 0.388), and with situational attribution of negative events in task 3 (p=0.004, SD 0.636). Doing JTC in Task 1 was explained by ER and AS (Internal attributions for negative events) ER has a B=-0.329, SE=0.134, p=0.014, R2=0.146, doing JTC was explained by ER B=-0.472, SE=0.171, p=0.006, R2=0.131. Finally, in the case of Task 3, doing JTC was explained by ER (B=-0.691, SE=0.228) p=0.002 and IQ (B=-0.061, SE=0.022) p=0.005, R2=0.426.

Discussion: These findings may suggest common psychopathological mechanisms between JTC, ER, and one-sided self-negative attributions that can be worked on in psychological interventions that address hasty reasoning style in FEP. Treatments addressed to reduce hast reasoning style should consider exercises and clinical examples that help patients with FEP improve processing social information and considering multiple causes for social and non-social events, and a good recognition of emotions in others.

T19. ADAPTATION TO THE INTERLOCUTOR DURING A CONVERSATION WITH INDIVIDUALS WITH SCHIZOPHRENIA

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Background: A deficit in social cognition - including theory of mind (ToM) - is one of the most disabling clinical characteristics of schizophrenia (SZ) (Sprong et al., 2007; Green et al., 2008). While ToM impairments have been well established using different tasks, very few studies have investigated these difficulties during social interactions (McCabe et al., 2004; Champagne-Lavau et al., 2009; Michelas et al., 2014). However, the attribution of mental states to others (ToM) is most often implicit, rapid and spontaneous in our daily interactions whereas the classical tasks used to assess this ability in schizophrenia mostly involve explicit, slow and cognitively costly processes (Frith and Frith, 2008). The aim of the present study was to better characterize the abilities of SZ individuals to attribute knowledge and beliefs to others during a conversation with

a partner. More specifically, we investigated whether SZ individuals adapt to their partner by changing their prosody when they know that he/she do not share the same knowledge as them.
Methods: Ten individuals with a DSM-V diagnosis of schizophrenia (SZ) and 29 healthy control (HC) participants matched for age and educational level made a collaborative game with a partner. All participants were native French-speakers with no previous neurological history. In this collaborative game, participants playing the role of director were asked to give instructions to an addressee about where to place a cross between different objects on a grid. Two conditions of objects presentation (shared knowledge, not-shared knowledge) were used. In the not-shared knowledge condition, unlike the shared knowledge condition, the director-participants knew that they did not have the same objects as their addressee. Global prosodic variations (i.e., pitch range and speech rate variations) were measured on speech productions from SZ and HC director-participants in both shared and non-shared knowledge conditions. Participants were also submitted to a neuropsychological assessment (e.g., memory, flexibility, attention, ToM).
Results: Log-transformed pitch span and speech rate values were analyzed with linear mixed-effects regression models including the group (SZ, HC), the knowledge condition (shared, not-shared) and their interaction as fixed effects. Participants and items were also included as random intercepts. The main Results: showed that, while HC participants spoke slower ($z=-9.92$ $p<.0001$) and with larger pitch excursions ($z=6.47$, $p<.0001$) in the not-shared knowledge condition compared to the share knowledge condition, SZ participants did not (speech rate: $z=-2.38$, $p=0.11$; pitch span: $z=1.17$, $p=1.00$). Spearman correlations were found in the SZ group between pitch span measures and attention performances in both knowledge conditions (shared knowledge: $p < .043$; not-shared knowledge: $p < .029$).
Discussion: These results confirmed that HC participants adapt their prosodic production to their addressee when they were aware of potential speech perception difficulties on their part (Michelas et al., 2019). By contrast, SZ individuals did not modify their pitch range and speech rate to facilitate their addressee's comprehension during the collaborative game. They seemed to have difficulties in adapting to their interlocutor, meaning they did not seem to take into account the knowledge and beliefs of their interlocutor to help them achieve the collaborative game. This pattern of performance was related to their attention ability. While these Results: need to be confirmed with a larger sample, the interactive task we used appears to be an original option for studying social cognition in schizophrenia since it is close to what happens in everyday interactions.

T20. JENESIS, GROW, THRIVE AND LIVE FULLY

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Background: Mental health disorders in subjects aged 15 to 25 represent the leading cause of disability and a major medical and economic issue.
Early intervention occurs during cerebral adolescence, a period of opportunity for preventive support and a change of paradigm (transdiagnostic and prospective vision) authorizing the ambition to be able to change the clinical trajectory of young users presenting clinical situations at risk through early and targeted support.

The JENESIS project is ambulatory early intervention device (DIP) proposed in the Hauts de France area.

Methods: To address the mental health of young adults (17-25 years) in the Oise area (France) with at-risk clinical conditions.
JENESIS will include a digital early intervention center (regional digital health platform, PREDICE), a mobile team of case managers and a center for consultations, assessments, and accompaniment.

Any user, frontline worker or family can contact JENESIS (by phone, email or e-appointment). A contact is established within 48 hours by a case manager (collection of the functional impact, screening).

The first step is based on the prodromal self-questionnaire (PQ16) in person or in the home. The second step verifies the eligibility criteria (functioning (GFS); basic symptoms (CAARMS)) and then schedules standardized evaluations (CAARMS, neuropsychological, functional) within 15 days.

Results: After the summary, a personalized support plan (face-to-face or videoconferencing) is proposed: therapeutic education for the patient (ETP), emotional management, cognitive remediation, support for daily life / studies and therapy.
JENESIS course: Illustration of risk situations concerning 3 participants (M = 18 years old).

Discussion: JENESIS appears to represent a departmental basis for validated assessments and diversified (content, delivery Methods: with dematerialization of care), individualized and proportionate care offers for adolescents and young adults in the department of Oise to support a chosen life course.
Feedback from users illustrates the feasibility and adaptability of such an early intervention support.

T21. EARLY DETECTION AND INTERVENTION OF PSYCHOSIS IN CHILDREN AND ADOLESCENTS IN ZURICH, SWITZERLAND: CLINICAL DATA FROM 2017-2021

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Background: The construct of a clinical high-risk (CHR) state of psychosis has been established to describe potentially prodromal symptoms which typically appear during adolescence and young adulthood. This is a very sensitive developmental period and the clinical high risk (CHR) is associated with increased functional impairment. To address the specialities in the care for this patient population a specialized outpatient care unit for early intervention in psychosis at the Department of Child and Adolescent Psychiatry and Psychotherapy, Psychiatric University Hospital, of the University Zürich (CAPS) is established. The interdisciplinary team (psychiatrists and psychologists) supports children and adolescents with psychotic disorders or at clinical high risk for developing psychosis. The early intervention service offers specialized assessment,

treatment and case management for minors with a first psychosis or CHR-state in an outpatient or inpatient setting as well as by day clinic care.
The evaluation main objective was to get a better understanding about this vulnerable patient group. Therefore, we analysed the clinical data about CHR-state, comorbid diagnosis, treatment, medication and hospitalisation of the patients who entered the service for early intervention in psychosis.

Methods: Participants who entered the service for early intervention in psychosis were followed up in the years 2017-2021 and descriptive analysis was used to summarize the data. For the evaluation of the risk construct the participants have been classified in "no increased risk", "CHR" or "early onset psychosis" (EOP). Additionally, ICD diagnosis, demographics and treatment (medication, psychotherapy, treatment setting) were assessed. Therapy was either psychotherapy and/or group training called DBT2P (Dialectical behavioral group training for adolescents, to prevent psychiatric disorders). Additionally, the use of a smartphone application "Robin Z"(add-on treatment tool to support the patients between the sessions) was assessed.
Results: In the last five years we saw 300 patients (112 female, mean age 15.7) who sought the care unit for early intervention. The evaluation of the risk showed that 44 patients had no increased risk, 205 were classified with a CHR and 51 fulfilled the criteria of an early onset psychosis (18.5%). Most of the patients showed comorbid diagnosis, mainly depressive disorders (42%).
The data about the treatment will be analyzed for the congress.

Discussion: Despite clinical implications, there is little data about early detection and early intervention in psychosis for children and adolescent. Therefore, the evaluation of the clinical data of the CAPS is of clinical importance and expected to add essential information in the fields of prevention and early intervention in psychosis.

T22. MEASURING ATTACHMENT IN PARENTS WITH SCHIZOPHRENIA OR BIPOLAR DISORDER AND ITS CLINICAL IMPLICATIONS FOR CHILDREN AT FAMILIAL HIGH RISK OF SCHIZOPHRENIA OR BIPOLAR DISORDER

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Background: According to attachment theory psychological functioning and affect regulations are influenced by the attachment patterns we have formed with other people. Attachment theory suggests that early relationships with parents/caregivers have a major impact on forming the foundations for attachment style. These styles are proposed to influence how an individual relates to other people through life although they can be modified by other relationships and experiences. Secure attachment style is associated with being able to manage distress, compose oneself with autonomy and the ability to form relationships with others, whereas insecure attachment can lead to negative self-image and negative expectations to the surroundings of the individual, meaning lowered self-esteem and lack of trust in other people. Insecure attachment style is a risk factor for the development of psychopathology, and it can also impact the ability to show positive commitment, supporting involvement and presence in the parental role, which are important for the development and well-being of the child. Attachment theory provides a useful framework to inform our understanding of relationship difficulties in people with e.g. schizophrenia spectrum psychosis or bipolar disorder, which is important when they are parents.

This study aimed to explore differences in attachment style between caregiver with schizophrenia spectrum psychosis (FHR-SZ), caregivers with bipolar disorder (FHR-BP) and caregivers with none of these (PBC – population-based controls). We also aimed to explore whether attachment style of the caregiver is associated with level of functioning of both the caregivers' and children, the children's psychopathology as well as caregivers disorganized caregiving representations.

We expect that the parents who have been diagnosed with a schizophrenia spectrum psychosis or bipolar disorder will show higher levels of anxious and/or avoidant attachment style compared to a healthy control group. We also expect to find associations between attachment style and level of functioning, psychopathology, and caregiving.

Methods: A population-based cohort of 522 seven-year-olds and their caregivers was established based on national registers. At baseline we included 202 children at familial high-risk of schizophrenia (FHR-SZ), 120 children at familial high-risk of bipolar disorder (FHR-BP), and 200 population-based controls (PBC). PBC could be registered with any other psychiatric diagnoses except for SZ or BP.

The adults' attachment styles were measured with the questionnaire Psychosis Attachment Measure (PAM, K. Berry). We measured the adult attachment style for both index parent and the

co-caregiver, and we will assess differences in attachment style between groups. We will use ANOVA to assess differences in adult attachment style between FHR-SZ, FHR-BP and PBC's. Secondly, we will assess whether adult attachment style is associated with level of functioning, psychopathology, and caregiving.

Results: Data analysis is ongoing and will soon be finalized.
Discussion: The implication of the Results: concerning parental role and social function will be discussed.
To have a parent or caregiver with mental illness is a risk factor for a child and therefore we hope that this study can inform us on whether insecure attachment style has a higher prevalence for parents, who at one point has been diagnosed with a mental illness and whether it is related to the well-being of the child. We hope that this study can identify a risk factor, which eventually can contribute in making "preventive interventions" in the long run.

T23. 18 MONTH FOLLOW-UP OF A COHORT OF CHILD AND ADOLESCENTS AT RISK FOR PSYCHOSIS: THE ROLE OF THE SOCIOECONOMIC STATUS

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Background: The role of socioeconomic status (SES) in the emergence of psychosis has long been debated. Studies pointed out that lower social class was associated with a worse course and prognosis in schizophrenic patients. In young adults at risk for psychosis (PRS), studies did not find baseline clinical differences or conversion rates differences in relation to parental SES but patients with lower SES presented a slower symptom recovery. There is no data evaluating the effect of SES in the emergence of psychosis and the presence of PRS states in children and adolescents.
We will examine how SES will affect the presence of a PRS state in a sample of children and adolescents and also if it influences the probability to transitate to psychosis in a 18 m follow-up. We hypothesize that low SES will be a risk factor to develop a PRS status and also, to transitate to a psychotic state.

Methods: Participants were recruited from the Child and Adolescent Psychiatry and Psychology departments of Hospital Clinic and Hospital Sant Joan de Déu (Barcelona, Spain) as part of the Child and Adolescent Psychosis Risk Syndrome (CAPRIS) Study.
PRS participants are children and adolescents (10-17 years old) help-seeking subjects who met PRS criteria. Inclusion criteria consist in meeting one or more of the following: 1) Attenuated positive symptoms (APS); or 2) Attenuated negative symptoms (ANS) in the previous 12 months; or 3) Brief intermittent limited psychotic symptoms (BLIPS); or 4) Genetic Risk: First- or second-

degree relative with schizophrenia or schizotypal disorder with impairment of functioning. Exclusion criteria: Intelligence Quotient (IQ) <70, autism spectrum disorder or traumatic brain injury.

A Healthy control (HC) comparison group was recruited from schools or community locations in the same area as PRS subjects. Exclusion criteria at baseline were: Presence of current axis I disorders of DSM-IV-TR, 1st or 2nd degree family members with a psychotic disorder and the same exclusion criteria as PRS subjects.

A total of 153 PRS were included in this study. 46 participants (30%) did not remain in the study. The remaining 107 participants had a mean age of 15.24±1.71. 24 subjects transitate to psychosis in the follow-up (PRS-P) and 83 did not (PRS-NP).

A total of 111 HC were also recruited, with 35 drop-outs (31.53%), mean age 15.66.

Assessment:

Age, gender, cohabitation, and academic performance were collected. Other clinical relevant variables were collected.

SES was measured with the Hollingshead-Redlich Scale. Information about higher education and occupation status of both parents were collected and registered as familial SES. A continuous variable was created following instructions on Hollinshead (1975). Five categories were created from 1(lower SES) to 5 (higher SES). The variable SES was codified into three groups, based on previous literature: Lower SES included categories I-II of SES; middle SES included SES III; higher SES included IV-V.

Results: Comparison between Lower (I-II); middle (III); Higher (IV-V):
We analyzed data using chi2 between groups. There were significant differences between PRS and H with a higher proportion of HC in the High SES group. There were differences between PRS outcomes (PSR-P and PRS-NP) and HC, with a higher proportion of HC in the High SES group. There were no differences in SES between PRS-P and PRS-NP.

Discussion: Our data suggest that in child and adolescent help-seeking PRS, low SES is a risk factor to develop a PRS status but, contrary to our hypothesis, it is not related with transition to psychosis.

T24. NEUROCOGNITION IN CHILDREN AND ADOLESCENTS AT CLINICAL HIGH RISK FOR PSYCHOSIS: A CLINICAL MARKER FOR TRANSITION?

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Background: According to the clinical staging model of psychosis (P. McGorry 1995), there are attenuated clinical presentations prior to the development of severe clinical symptoms identified

in the diagnosis of psychotic illness. The definition of clinical high-risk (CHR) states for the development of psychosis, has provided evidence of neural and neurocognitive alterations at this stage (Tyrone D Cannon 2015; Larry J. Seidman and Mirsky 2017). However, few studies provide evidence in children and adolescents. The analysis of cognitive factors in subjects with CHR in this particular group of age, could provide evidence contributing to the neurodevelopmental hypothesis, as childhood and adolescence could evidence alterations not observed in other stages of life.

Methods: The aim of this study is to identify a baseline cognitive profile of psychosis risk in children and adolescents compared to a healthy control (HC) group. Secondly, we aimed to differentiate cognitive profiles depending on the clinical outcome of children and adolescents with CHR, identifying possible cognitive markers of risk and protection in this population.

Methodology: A total of 98 CHR subjects were analyzed compared to 64 participants of a HC group. CHR state were determined as: having one or more of the clinical high-risk symptoms (positive attenuated symptoms, brief limited intermittent psychotic symptoms, and genetic risk), assessed by the Semistructured Interview for psychosis-risk syndromes (SIPS). CHR were divided according to their clinical outcome at 18-months follow up into three categories: subjects who developed a psychotic disorder to psychosis (CHR-P); subjects who still presenting attenuated positive symptoms after 18 months (CHR-NR); and patients who after 18 months have remitted from the risk state (CHR-R). A neurocognitive extensive battery had administered at baseline to assess general intelligence (verbal comprehension index, (VC) and Perceptual Reasoning index (PCI)), and cognitive areas of memory (verbal/visual), processing speed, working memory, attention, visuo-spatial abilities and executive function.

Results: General MANCOVA analysis of the CHR sample compared to the CS shows a generalized lower neurocognitive profile in the CHR group, with lower score in all cognitive variables in the CHR group. Significant differences were observed specifically in general intelligence and executive functioning. The analysis by groups according to clinical outcome identifies a specific baseline deficit in CHR-P compared to the HC, with baseline lower scores in processing speed (coding), visuospatial memory, attention (commissions), and executive function (cognitive flexibility/processing speed task). CHR-NR shows lower baseline scores in general intelligence (both VCI and PRI), verbal working memory and executive functions (verbal fluency task) compared to HC. Finally, CHR-R show only a difference in working memory compared to HC.

Discussion: Cognitive alterations were observed in CHR children and adolescents compared to HC. Specifically, cognitive deficits were observed both in participants who developed psychosis in the future (CHR-P), and in participants who still at risk after 18-months follow-up. Participants who remitted of the CHR state (CHR-R) shows a cognitive profile comparable to HC group. Thus, our Results: suggest the existence of cognitive deficits in children and adolescence that could be as a vulnerability marker for psychosis. The data of this work provide evidence of neurodevelopmental alteration in patients who will develop a psychotic disorder in the future.

T25. PERCEPTUAL PSUDONEGLECT IN ULTRA HIGH-RISK FOR PSYCHOSIS AND FIRST EPISODE SCHIZOPHRENIA

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Background: The phenomenon known as perceptual pseudoneglect refers to the leftward bias in visuospatial attention in non-clinical samples, possibly because of right hemisphere dominance for visuospatial attention. The expression of this phenomenon has been investigated in several psychiatric disorders, mainly in schizophrenia demonstrating schizophrenic patients have a deficit in leftward bias in comparison to healthy subject. No studies investigating the perceptual pseudoneglect were conducted in subjects at ultra-high risk of psychosis (UHR) and in those at the first stage of schizophrenia illness.
This study aims to analyze the associations between the perceptual pseudoneglect and early phase of psychosis in young adults.

Methods: Ninety-nine young adults (age: mean 22 years, SD 3; 55 women) were included. Intellectual disability and substance abuse disorders were considered exclusion criteria.
Subjects were grouped as follow: (1) 23 subjects for the First Episode Schizophrenia (FES), recruited from our outpatints program; (2) from the mental health help-seekers service, 18 subjects were at the Ultra High Risk for Psychosis (UHR), due to the presence of one or more attenuated psychotic symptoms (APS) or brief intermittent psychotic symptom (BIPS) or a genetic risk factor plus a functioning deterioration (GRD), and (3) 23 subjects were psychiatric controls (PC) due to the presence of a non-psychotic DSM-V disorder; and (4) 35 healthy controls (HC) from the general population. The condition of UHR was assessed using the Structured Interview for Psychosis-Risk Syndromes (SIPS). The degree of lateralized visuospatial attention bias was assessed using variants of the horizontal line bisection (LB) test.

Results: The four groups did not differ for age and gender. Performance at the LB test was significantly different between the four groups. As expected, FES showed a systematic error towards the right in visual-spatial attention. UHR patients presented a bimodal distribution of the systematic error. At the LB test FES and UHR presented significantly mean values more right-oriented than HC, whose values are physiologically shifted to the left.
PC had also a bimodal distribution of the performance at the LB test, but they did not show a significant difference from HC.

Discussion: Our findings demonstrated that FES and UHR had a systematic error towards the right in the visual-spatial attention, represented by a sign shifted to the right along the horizontal line. These Results: confirms that the presence of psychosis is associated with specific alterations of visuo-spatial performance.
Longitudinal studies would be necessary to evaluate transition rates in full psychosis among those UHR who showed an impairment of visual-spatial attention bias. If this will be observed, LB test might be used to improve the accuracy of psychosis prediction.

T26. OBSESSIVE-COMPULSIVE SYMPTOMS ASSOCIATED WITH CLINICAL AND FUNCTIONAL SEVERITY IN CHILDREN AND ADOLESCENTS WITH PSYCHOSIS RISK SYNDROME: RESULTS: FROM THE CAPRIS STUDY

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Background: Obsessive-compulsive symptoms (OCS) in adults with schizophrenia are associated with more severe psychotic and depressive symptoms, and lower social functioning (Tezenas et al, 2019). The prevalence of OCS in subjects with Psychosis Risk Syndrome (PRS) is 11-35% in adults, although it is unclear how this affects these individuals' clinical and functional outcomes (Soyata et al, 2018, Zink et al, 2014). To our knowledge, no studies in children and adolescents with PRS have measured the impact of OCS on these patients' clinical and functional status
Methods: This study will make use of the findings of a prospective longitudinal study (CAPRIS) in which helpseeking subjects who met PRS criteria were recruited from the Child and Adolescent Psychiatry and Psychology departments of Hospital Clinic and Hospital Sant Joan de Déu (Barcelona, Spain). Inclusion criteria were: 1) Attenuated positive or negative symptoms in the previous 12 months; 2) Brief intermittent psychotic symptoms; 3) First or second degree relative with schizophrenia or schizotypal disorder plus impairment of functioning; age:10-17 years. Exclusion criteria: IQ<70 and a diagnosis of neurodevelopmental disorder. At baseline, the Semistructured Interview for Prodromal Syndromes and Scale of Prodromal Symptoms (SIPS/SOPS) were administered, as well as a clinical scale battery including the Hamilton and Young scales and the Leyton Obsessive Inventory, child version (LOI-CV, Berg et al, 1988). A sample of age and gender matched HCs were also included. Subjects with LOI-CV≥21 were considered OCS+.
Results: 128 PRS subjects (15.3±1.6 years; 67.9% females) and 98 HC (15.5±1.5 years; 42.9% females) were included.64 PRS subjects (50%) were considered OCS+ while 19 HC (19.4%) scored higher than the threshold. When we compared, PRS-OCS +, PRS-OCS- and HC, they did not differ in age and gender but PRS-OCS + and - had lower socioecocomic status than HC. Clinically, PRS-OCS+ had significant higher scores on positive, negative, general and total SOPS and lower general functioning (GAF: 48.3±1.5 vs 54.1±1.5 vs 86.5±7.1; Wald statistic=11.822, p<0.001), compared to PRS-OCS- and HC, while no differences in affective symptoms were found between the groups. Among PRS subjects, OCS+ were significantly more frequently on antidepressants (37, 58.8%) than OCS– (20, 21.2%, Wald statistic 8.504, p=0.004).
Discussion: In children and adolescents with PRS, the prevalence of OCS is high (50%). Considering that PRS-OCS+ subjects had a more severe clinical and functional profile than PRS-OCS-, efforts should be made to assess OCS in minors at risk of psychosis.

T27. DO OBSTETRIC COMPLICATIONS PLAY A ROLE IN THE TRANSITION TO PSYCHOSIS IN CHILDREN AND ADOLESCENTS WITH PSYCHOSIS RISK SYNDROME?

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Background: Obstetric complications (OC) have helped predict which patients are more likely to have an early onset of psychosis (Baeza et al, 2021). OC have been associated with ultra-high risk of psychosis, also known as Psychosis Risk Syndrome (PRS),(Fusar-Poli et al, 2017) vs. controls. Additionally, some studies conducted mainly in young adults have found a relationship between OC and transition to psychosis (Kotlicka-Antczak et al, 2018; Mittal et al, 2009 and Yun et al, 2005). To our knowledge, there are no studies in children and adolescents with PRS measuring the impact of OC on the transition to psychosis.

Methods: This study will make use of the findings of an 18-month prospective longitudinal study (CAPRIS) in which help-seeking subjects who met PRS criteria were recruited from the Child and Adolescent Psychiatry and Psychology departments of Hospital Clinic and Hospital Sant Joan de Déu (Barcelona, Spain). Inclusion criteria were: 1) Attenuated positive or negative symptoms in the previous 12 months; 2) Brief intermittent psychotic symptoms; 3) At least one first or second degree relative with schizophrenia or schizotypal disorder plus impairment of functioning; age:10-17 years. Exclusion criteria: IQ<70 and a diagnosis of neurodevelopmental disorder. At baseline, the Semistructured Interview for Prodromal Syndromes and Scale of Prodromal Symptoms (SIPS/SOPS) were administered, as well as a clinical scale battery. To measure OC, the 15 item Obstetric Complications Scale (Lewis and Murray, 1988) was used, with all definite OC given a score of 2, and equivocal OC scored as 1, A sample of age and gender matched HCs were also included.

Results: 172 PRS subjects (15.2±1.6 years; 67.2% females) and 105 HC (15.4±1.6 years; 54.3% females) were included, with significant differences in sex ($\chi2$=4.531, p=0.041). Scores on the SOPS, GAF, and Hamilton and Young scales were all significantly higher in PRS than in HC. Ninety-six (55.4%) PRS subjects had suffered some type of definite or equivocal OC, which was not significantly different from HC (46.7%, $\chi2$=1.898, p=0.105; 1.5±2.2 vs 1.2±1.6, t=1.124, p=0.263). Similarly, no significant differences between groups were found when examining each specific type of OC.

We followed 107 PRS subjects for 18 months, during which time 23 individuals (21.5%), transitioned to psychosis (PRS-P). Compared PRS-P, PRS-NP and HC at baseline assessment, PRS-P had higher scores on general SOPS (9.5±4.4 vs.7.7±3.9 vs 0.5±1.3; PRS-P vs, PRS-NP: t=1.986, p=0.050), and lower GAF (45.8±1.6 vs 53±13.2 vs 86±7.5; PRS-P vs PRS-NP=t=-2.136, p=0.035) and GAF role scores (5.3±1.1 vs 5.9±1.2 vs 8.4±0.9; PRS-P vs PRS-NP: t=-2.220, p=0.029). No significant differences were found between the groups on OC except for a tendency towards significance in twin birth in PRS-P subjects ($\chi2$=5.464, p=0.065)

Discussion: In children and adolescents with PRS, the prevalence of OC is similar to HC. Twin birth was found to be associated with transition to psychosis, although this association did not quite reach statistical significance. More studies with larger samples are needed to identify the possible role of OC in the transition to psychosis in minors at risk of psychosis

T28. RALOXIFENE AS ADJUNCTIVE TREATMENT FOR SCHIZOPHRENIA-SPECTRUM DISORDERS: A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL

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Background: Several studies suggest that the adjunctive use of the selective estrogen receptor modulator (SERM) raloxifene improves psychotic and cognitive symptoms in postmenopausal women with schizophrenia-spectrum disorders. However, there are few well-designed clinical trials assessing the efficacy of raloxifene in premenopausal women and men. We aimed to assess the efficacy and safety of adjunctive raloxifene in male and female patients with a schizophrenia-spectrum disorders.

Methods: This randomized, double-blind, placebo-controlled, phase 3 trial was done in 5 in- and outpatient clinics in The Netherlands and Belgium. Participants, adult patients with schizophrenia-spectrum disorders on stable treatment with antipsychotic medication, were randomly assigned (1:1) to add-on once-daily oral raloxifene 120 mg or placebo for 12 weeks. Participants were stratified by age, sex and global functioning. The primary outcomes were psychotic symptoms, measured by the Positive and Negative Symptom Scale (PANSS) at 6 and 12 weeks of treatment and 6 months after treatment (follow-up), and cognitive functioning, measured by the brief assessment of cognition in schizophrenia (BACS) at 12 weeks of treatment and at follow-up. The BACS provides estimates of cognitive functioning based on 6 domains: verbal memory (List Learning), working memory (Digit Sequencing Task), motor speed (Token Motor Task), verbal fluency (Category Instances and Controlled Oral Word Association Test), attention/information processing speed (Symbol Coding Task) and executive functioning (Tower of London). Secondary outcomes were depressive symptoms (Beck Depression Inventory-II), global functioning (Personal and Social performance scale) and quality of life (EuroQol-5 dimensions) at 12 weeks of treatment and at follow-up. All analyses compared groups as randomised (intention-to-treat). The trial was registered with ClinicalTrials.gov, NCT03043820.

Results: Between November 2016 and July 2021, 159 patients entered the screening phase for eligibility, of which 102 patients were assigned to raloxifene (n=52) or placebo (n=50). Mean age was 42.0 (SD 11.9) years in the raloxifene group and 39.3 (11.2) years in the placebo group. From

baseline to week 12, negative symptoms as per PANSS negative score reduced in female patients assigned to raloxifene, compared to females assigned to placebo (treatment effect difference -2.88, 95% CI -5.02 to -0.74; p=0.01), but not in males assigned to raloxifene as compared to placebo (treatment effect difference -0.19, 95% CI -1.50 to 1.13; p=0.78). Compared with placebo, adjunctive raloxifene had no effect on ratings of positive and total symptoms. At follow-up, adjunctive raloxifene had a beneficial effect on working memory (treatment effect difference 0.77, 95% CI 0.09 to 1.46; p=0.03) and motor speed (treatment effect difference 1.05, 95% CI 0.21 to 1.90; p=0.02) in women, while in men, adjunctive raloxifene had a negative effect on working memory (treatment effect difference -0.53, 95% CI -0.95 to -0.113; p=0.01) at follow-up. We did not find any effects of raloxifene on depression, global functioning and quality of life. Rates of (serious) adverse events did not differ between groups. All admissions in the placebo group were for intensification of psychosis (n=7). In the raloxifene group, admissions were due to infection with the COVID-19 virus (n=1), bowel lavage (n=1), drug abuse (n=1) and intensification of psychosis (n=2). The most common adverse events were gastrointestinal (n=9 in the placebo group, n=12 in the raloxifene group), hypertriglyceridemia (n=14 in placebo group, n=6 in raloxifene group) and headache (n=6 in placebo group, n=5 in raloxifene group).
Discussion: Raloxifene is an effective adjunctive therapy for negative symptoms and cognitive deficits in women with schizophrenia-spectrum disorders. We found no evidence that raloxifene was superior to placebo for the treatment of schizophrenia-spectrum disorders in men. Future work is needed to identify patients who benefit most from augmentation with raloxifene.

T29. FEASIBILITY AND EFFECT OF VITAMIN D3 REPLENISHMENT IN PEOPLE WITH SCHIZOPHRENIA

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Background: Many people with chronic mental illness are Vitamin D deficient. Vitamin D is suspected to have wide-ranging effects in the areas of mood, cognition, and immunity. The use of 50,000IU of cholecalciferol (Vitamin D3) is one of the recommended Methods: of replenishment in the general population. Factors that may affect replenishment include magnesium levels, weight (as measured by BMI), cigarette smoking and alcohol usage. In a schizophrenia clinical research program, we sought to see if there was a relationship between these factors and replenishment and whether replenishment improved mood, symptoms and cognition.
Methods: Thirty-two participants with Vitamin D levels below 25ng/ml were recruited for participation in an open-label replenishment study with weekly Vitamin D3 50,000 IU. Prior to starting replenishment, baseline laboratory measures and self-report questionnaires of alcohol and cigarette consumption and state/trait anxiety (STAI) levels were obtained. At baseline and end of study (EOS), symptoms (BPRS) and cognitive assessments (RBANS) were performed. The research pharmacist called the participants weekly to remind them to take the medication. Vitamin D levels were checked at 8 weeks, along with calcium levels, as a safety precaution. Participants could remain in the study for up to 14 weeks to achieve replenishment, which was defined as ≥ 30ng/ml.

Results: Twenty-seven males and 6 females with a mean baseline Vitamin D level of 16ng/ml (min: 7; max.: 24.5) entered the study. At EOS, the mean Vitamin D level was 40ng/ml (min31; max 71). Twenty-five participants (21 male and 4 female) reached replenishment by week 8. Those who did not replenish by week 8 did not go on to meet replenishment at 14 weeks. There were no significant adverse effects from the cholecalciferol. One participant dropped out due to constipation.
Nineteen of the 33 participants met BMI "obesity" criteria with another 5 categorized as "overweight". Seven out of 8 non-replenishers were "obese"(i.e., BMI $\geq$ 30) vs 12/ 25 subjects who replenished. There was a statistically significant negative correlation between BMI and EOS Vitamin D (r=-0.39; p=.02). There were no significant effects of magnesium, cigarette smoking status or alcohol usage on successful replenishment. There was no significant change in hs-CRP, which was used as a general measure of immune status.

There was a correlation between Vitamin D and measured trait anxiety (Pearson correlation = 0.005), but not in the amount of change of that score from baseline to EOS. The STAI State measure trended in the same direction but did not reach significance. This was similar with the BPRS total and anxiety/depression subfactor scores, where, though no significance was found between change in Vitamin D and the subfactors, there was a trend in the expected direction. There were no significant correlations with the Anergia, Negative symptoms, Psychosis, Activation, and Hostile Suspiciousness subfactors. There were no significant findings between change in Vitamin D and the RBANS scores.

Discussion: Though there were few significant findings, many of the mood and anxiety measures changed in the expected direction of reduced symptomatology. We may have possibly been able to detect further significant relationships with a larger study size. In addition, there were too few participants who did not replenish to provide an adequate sample size for the between group comparisons. This had not been anticipated, as BMI has been found to relate to time to replenishment and the cohort included many subjects with obesity. We did not detect any improvement of cognition with change in Vitamin D, a result that goes against some previously published findings. The study does provide reassurance that chronically mentally ill patients with elevated BMIs can undergo weekly replenishment of Vitamin D stores in 8 weeks without adverse effects.

T30. WEIGHT AND METABOLIC CHANGES IN PATIENTS WITH SCHIZOPHRENIA WITH PALIPERIDONE PALMITATE 6 MONTHLY VERSUS PALIPERIDONE PALMITATE 3 MONTHLY TREATMENT: A POST-HOC ANALYSIS

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Background: Long-term use of atypical antipsychotics to treat patients (pts) with schizophrenia can cause common metabolic side effects such as weight gain, type 2 diabetes mellitus and lipid abnormalities, potentially leading to increased morbidity and mortality. The phase 3 double blind

(DB) study (NCT03345342) evaluated the efficacy and safety of paliperidone palmitate 6-month (PP6M) long-acting injectable (LAI) versus paliperidone palmitate 3-month (PP3M) LAI in pts with schizophrenia and demonstrated that PP6M was non-inferior to PP3M in preventing relapse, with no new safety concerns. We conducted a post-hoc analysis to assess changes in body weight (BW) from baseline (DB) to DB endpoint based on age and body mass index (BMI) and changes in blood lipid profiles during the 12-month DB phase.

Methods: This randomized, multicenter study was conducted across 20 countries enrolling pts with schizophrenia stabilized on shorter acting paliperidone formulations. Screened eligible adults (18-70 yrs) entered an open-label (OL)-maintenance (MA) phase to receive 1 injection cycle of paliperidone palmitate 1-month (PP1M) 100 or 150 mg eq. or PP3M (350 or 525 mg eq.) and were either matched or converted to an equivalent dose last received in OL-transition phase or prior to enrollment. In the 12-month DB phase, pts were randomized (2:1) to receive PP6M (700/1000 mg eq.) or PP3M (350/525 mg eq.). The mean change (SD) in BW and abnormal weight percent change was calculated at baseline, 6 months and 12 months by age (18-25 yrs; 26-50 yrs; 51-65 yrs; >65 yrs) and BMI (normal: <25; overweight: 25 to <30; obese: ≥30). Additionally, mean values for the four key lipid parameters (fasting low density lipoprotein [LDL], fasting triglycerides [TG], fasting total cholesterol [TC], and fasting high density lipoprotein [HDL]) over time were assessed and further stratified based on BMI sub-groups.

Results: In total 838/1036 screened pts entered the OL-phase and 702/838 (mean age: 40.8 yrs; men: 68.4%) were randomized to PP6M (n=478) and PP3M (n=224) groups. From DB baseline to endpoint, the changes in BW, waist circumference and BMI were numerically higher in the PP3M group vs PP6M group. The mean (SD) increase in BW from MA baseline to DB endpoint were 0.10 (4.959) kg and 0.96 (5.103) kg for the PP6M and PP3M groups, respectively. The change in BW from DB baseline to endpoint was highest in 18-25 yrs age group (PP6M vs PP3M: -0.65 [4.955] kg vs 4.33 [7.112] kg) and in BMI overweight category (-0.53 [4.386] kg in PP6M vs 1.15 kg [4.814] kg in PP3M). From DB baseline to endpoint, 50 pts (10.6%) in PP6M group and 29 pts (13.2%) in PP3M group experienced an abnormal increase in BW (≥7%) and 43 (9.1%) pts in PP6M group and 15 (6.8%) in PP3M group experienced an abnormal decrease in BW (≥7%). Furthermore, the treatment-emergent fasting lipid shift during DB phase from baseline (DB) were (PP3M vs PP6M): LDL: 1 vs 2; TG: 22 vs 22; TC: 2 vs 3; HDL: 28 vs 55, with a numerical advantage for all four key lipid parameters in the PP6M group, including in BMI sub-groups.

Discussion: Pts who transitioned to PP6M showed numerically less weight gain, BMI, waist circumference and more weight decrease compared to PP3M group during 12-month DB phase. This difference was more pronounced in the younger age group (18-25 yrs) and those who were overweight (BMI: 25 to <30). Beneficial effects with PP6M were also found in fasting blood lipids (HDL, LDL, TG and TC). This was surprising since both PP3M and PP6M contain the same active ingredient and may be explained by the differences in the release characteristics between the two formulations.

T31. D-SERINE AUGMENTATION OF NEUROPLASTICITY BASED AUDITORY LEARNING IN SCHIZOPHRENIA

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Background: Schizophrenia (Sz) is associated with core cognitive deficits that are related to impaired functional outcome. In addition, Sz patients show reduced auditory neuroplasticity, defined as reduced learning during training on exercises that place implicit, increasing demands on early auditory information processing. Enhancing neuroplasticity for better auditory processing represents an unmet clinical need and a rate-limiting first step prior to remediating cognition and overall function.

Brain NMDAR are known to mediate many forms of neuroplasticity and NMDAR dysfunction may play a key role in the pathophysiology of Sz. We recently demonstrated that two consecutive administrations of the NMDAR agonist D-serine (60 mg/kg) can enhance neuroplasticity-based auditory remediation (AudRem), along with the EEG plasticity measures mismatch negativity (MMN) and activity in the theta range. Limitations included a crossover design. We conducted an R61-R33 study to confirm target engagement and the optimal dose of D-serine combined with AudRem.

Methods: The study was conducted in 3 consecutive, 15 subject, double-blind, randomized, placebo-controlled dose cohorts of 12 subjects on D-serine (80, 100 or 120 mg/kg) and 3 on placebo. Study drug was administered 30 minutes before three AudRem sessions administered 1x per week to allow for training during peak levels. EEG was recorded pre/post and during sessions, to assess early auditory processing measures MMN and theta.

In AudRem, participants were presented with paired tones (e.g., Stimulus 1 ("reference") and Stimulus 2 ("test"): S1 and S2) and indicated which tone is higher in pitch (frequency). Milestones were designed to confirm target engagement, functional relationships and safety, and were assessed with three preplanned outcomes: plasticity, theta and MMN. As previously, plasticity was defined as improved pitch thresholds between successive auditory stimuli after AudRem, operationalized as (1) End of session plasticity: an improved (smaller) threshold (%change f, S2/S1) end of treatment visit, (2) Plasticity Improvement: change in threshold from initial plateau (trials 20-30 of 1st set) at end of treatment visit and (3) Plasticity maintenance: change in threshold from initial plateau (mean trials 20-30 across Visit 1) at end of treatment visit. MMN was defined as change from baseline after treatment and Theta as change during AudRem sessions. The prespecified analysis and go/no go milestones required at least a moderate effect size difference (d=0.5) between D-serine and placebo groups.

Results: 45 subjects were randomized, meeting our preplanned "n." Subjects were on a stable antipsychotic dose for at least 4 weeks, had normal kidney function and had moderate or lower cognitive disorganization (PANSS P2 less than or equal to 4).

As assessed by the Verbal Memory and overall composite domains of the MATRICS and the Tone Matching Task (TMT), subjects had impairments in both overall and auditory cognition. There were no significant between group or behavioral baseline behavioral or demographics differences.

All milestones were met.

All three dose cohorts showed statistically significant end of session plasticity ($p<0.001$) after three treatment visits, with the 80 and 120 mg/kg doses showing the smallest thresholds. D-serine treated subjects showed statistically significant plasticity improvement after a single treatment (11.7%,

p<0.001), and continued to improve through 3 treatments (12.5%, p<0.001). By contrast, placebo treated subjects showed non-significant changes across three treatments (4-5%, n.s.). Between-group, moderate effect sizes changes vs. placebo were seen for the 80 (d=0.74) and 100 mg/kg (d=0.59) doses. The 100 mg/kg dose also showed a moderate effect size difference in plasticity maintenance (d=0.77) on visit 2 and 3, but showed the largest (worst) end of session plasticity.

Target engagement was also demonstrated by moderate-large effect sizes vs. placebo for post baseline MMN change (d=0.77) for the 80 mg/kg dose and for theta change for the 80 mg/kg (d=0.85) and 120 mg/kg dose (d=0.86).

A statistically significant, moderate effect size correlation between plasticity maintenance and auditory cognition (r=0.40) and for end of session plasticity and TMT (r=0.41), which remained statistically significant within the D-serine group. Significant correlations were also seen between plasticity and overall cognition and reading.

Safety was demonstrated by a complete absence of renal toxicity or clinically significant adverse events.

Discussion: All prespecified Go/No Go milestones were met and strongly support engagement of the NMDAR system by D-serine. Plasticity, target engagement and safety were seen across all three cohorts. Results: were most robust at 100 mg/kg, and improve upon prior lower dose work by showing efficacy after a single treatment. Furthermore, while we focused on auditory plasticity and Sz in the present project, results are relevant across learning disorders and across conditions.

T32. METFORMIN FOR CLOZAPINE ASSOCIATED OBESITY

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Background: There is a paucity of evidence for effective interventions to ameliorate weight gain at time of clozapine commencement. We aimed to compare adjunctive metformin versus placebo at time of clozapine commencement to attenuate weight gain using data from two methodological approaches, a placebo controlled double blind RCT and a naturalistic retrospective chart audit.
Methods: In the RCT, participants were people with schizophrenia being commenced on clozapine, randomised to either metformin or placebo, for 24 weeks, with a primary outcome of difference in change in weight. Secondary outcomes included change rates of >5% weight gain, or weight gain/loss, and other metabolic and psychosis outcomes. For the naturalistic study, we retrospectively reviewed electronic medical records of people commenced on clozapine and recorded whether metformin was commenced by the treating team in the 12 months after clozapine commencement. Primary outcome was the effect of metformin on change in percentage bodyweight at 12 months after clozapine initiation, with secondary outcome being proportion with >5% or >7% bodyweight change.
Results: The RCT was closed prematurely in March 2020 due to COVID-19 restrictions. Twenty participants commenced the trial, with eight metformin group and five placebo group participants completing the trial. The study was insufficiently powered to detect difference between the metformin and placebo groups for the primary outcome of change in weight, however people in

the metformin group were significantly less likely to gain >5% of their body weight (12.5% vs 80%, p=0.015) and were more likely to lose weight (37.5% vs 0% p=0.024). There was no difference between the groups in terms of psychosis score or adverse drug reactions (ADRs). Among 90 patients initiated on clozapine in the naturalistic study, metformin use (n=48) was associated with a smaller increase in percentage bodyweight (1.32% versus 5.95%, p=0.031), lower rates of >7% gain in bodyweight (37.8% versus 63.0%, p=0.025) but not >5% weight gain. Sex, tobacco smoking, T2DM, clozapine dose and level and clozapine/norclozapine ratio were not associated with differences in change in body weight.

Discussion: Although the forced premature closure of the RCT due to COVID19 led to inadequate power to detect change, the initial findings are promising. When combined with the data from the naturalistic retrospective study, there is strong suggestion that clozapine and metformin co-commencement may be a promising treatment to prevent clozapine weight gain, particularly given the low rates of ADRs associated with metformin. Further studies are needed to confirm this finding.

T33. METACOGNITIVE TRAINING MODIFIED FOR NEGATIVE SYMPTOMS (MCT-N): A FEASIBILITY STUDY

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Background: The cognitive model proposes that negative symptoms in schizophrenia might be caused and maintained by dysfunctional beliefs arising as a consequence of repeated failures and setbacks, where individuals adopt coping strategies of 'shutting down' the cognitive-affective experience. This allows individuals to cope with overwhelming or aversive situations in the short-term, but leads to a reliance on negative symptoms including social withdrawal, avolition, and diminished expression to reduce exposure to, and the impact of, negative experience in the longer-term. These appraisals might include negative beliefs about social affiliations; low expectations of pleasure, success and acceptance; defeatist beliefs about performance; and a perception of limited resources (see Beck, Himelstein, Grant, 2019). Longitudinal studies have shown support for the model as defeatist performance attitudes and asocial beliefs are found to predict future negative symptoms (Luther et al., 2015; Thomas et al., 2017; Granholm, Holden and Worley, 2018).

In addition, there is evidence that suggests a link between metacognition and negative symptoms as limitations in complex metacognitive processes predict negative symptoms in first episode psychosis (Austin et al., 2019) and in more chronic samples, even after controlling for defeatist beliefs, affect recognition, and neurocognitive functioning (Lysaker et al., 2015). Metacognitive deficits are also associated with concurrent and future negative symptoms when controlling for verbal memory and education (Faith et al., 2020; Lysaker et al., 2020).

This suggests that negative symptom reduction may at least partially depend on improved metacognitive capacity, and that a metacognitive intervention specifically targeting the cognitions suggested to in the cognitive model may be beneficial. We therefore adapted a metacognitive training programme (MCT) to assess the acceptability and feasibility of the intervention, examine

variable change over the course of the intervention, and carry out a preliminary investigation of putative mechanisms of change.

Methods: We adopted a mixed Methods: case series design, providing detailed quantitative data on changes over time, to focus on potential mechanisms underlying the intervention in combination with qualitative exit interviews. The study used a combination of interviews (Brief Negative Symptom Scale (BNSS) (Kirkpatrick et al., 2010); Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987); (Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1990); Metacognition Assessment Scale (MAS-A) (Semerari et al., 2003); the Global Assessment of Functioning (GAF) (APA, 1987)) and self-rated questionnaires (Personal Belief about Illness Questionnaire (PBIQ) (Birchwood et al.,1993); Reflective Function Questionnaire (RFQ) (Fonagy and Bateman, 2016).
Non-parametric tests (Wilcoxon Signed Rank) were used to evaluate changes at pre, post and follow-up analysis due to the limited sample size and the repeated-measure nature of the data whilst multilevel modeling (MLM) was used to assess change over time and across cases. In addition, thematic analysis (Braun and Clark, 2006) was used to analyse the qualitative data.

Results: The intervention showed good feasibility as demonstrated by the attendance rate, the positive feedback from participants and the multidisciplinary team. Improvements on negative symptoms observed following the intervention (with large effect sizes post intervention and at follow-up) as well as on reflective functioning and stigma whilst MLM showed that depression, internalized stigma and reflective functioning explained the variance in negative symptoms and that a significant reduction in negative symptoms took place over time.
Discussion: The intervention appeared to be both acceptable to participants and feasible to implement. The triangulation of quantitative and qualitative Results: facilitated a thorough exploration of the feasibility of the intervention. In addition, there appeared to be symptomatic reduction over the course of the intervention. Significant changes were also observed in self-reported reflective function and internalised stigma which is consistent with our intention to offer an intervention targeting particular cognitions and mechanisms hypothesised to drive the development and maintenance of negative symptoms. The findings are also supported by the qualitative results.
Multilevel modelling showed that depression, internalized stigma and reflective functioning explained the variance in negative symptoms and that a significant reduction in symptoms took place over time. The findings are consistent with proposals that negative symptoms may develop in part as a consequence of diminished capacity for self-other mental state processing.

The study shows that MCT could be adapted to target negative symptoms, thereby holding the promise of a brief, structured and highly scalable intervention. Multilevel modelling allowed us to identify potential mechanisms and how these seem to interact to influence negative symptom expression, facilitating the future refinement of the intervention to target specific psychological processes that may underpin negative symptoms.

T34. CLOZAPINE AND COVID-19 VACCINATION: AN OBSERVATIONAL COHORT STUDY

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Background: Since the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has sparked, alarming evidence is found on the higher hospitalisation and mortality rates for patients with severe mental illness (SMI), especially for patients suffering from schizophrenia spectrum disorders (SSD) and bipolar disorder. Clozapine intoxication due to the sequelae of a cytokine storm syndrome, pneumonia and delirium are the three main complications, which require greater vigilance when patients using clozapine are infected with the SARS-CoV-2 virus. Due to these extra risks of COVID-19 in clozapine users, vaccination against SARS-CoV-2 is even more imperative for this patient group than for people with SMI in general.
Methods: In a multicentre observational cohort study (researchregistry6726), conducted from February 22nd 2021 to September 2nd 2021, we sought to explore the safety of COVID-19 vaccination in patients on clozapine. The trial consisted of only one phase for subjects receiving the single Johnson and Johnson vaccine, and of two phases for subjects receiving Moderna, BioNTech/Pfizer or AstraZeneca vaccines. Outpatients and long-stay inpatients of the Dutch Mental Health Centres Noord-Holland Noord, Rivierduinen and Reinier van Arkel who used clozapine and received COVID-19 vaccination were recruited by their treating psychiatrist, nurse practitioner or case manager. There were no exclusion criteria. Clozapine dosage and use of concomitant medications were at the discretion of the treating psychiatrist. Throughout the study changes in clozapine dose and other factors which could influence clozapine blood levels were documented. Primary outcomes were clinically relevant increase in clozapine blood levels (>100 µg/L increase compared to baseline, which was the final clozapine blood level determined before vaccination), and clozapine intoxication (>1000 µg/L). Secondary outcomes were granulocytopenia (mild granulocytopenia [1.5-2.0x109/L], moderate granulocytopenia [1.0-<1.5x109/L], severe granulocytopenia [0.5-<1.0x109/L] or agranulocytosis [<0.5x109/L]), leukocytopenia (<3.5 x109/L), and lymphocytopenia (<1.5 x109/L). Outcomes were measured approximately five days after the first and (when applicable) second dose of COVID-19 vaccine. We conducted the analyses using a per-protocol analytic approach. Protocol completion for both primary outcomes (clozapine blood levels) and secondary outcomes (WBC count and differential) was defined as having received a COVID-19 vaccine with blood samples between three to nine days following vaccination without a change in clozapine or fluvoxamine dose. Possible confounders were analysed.
Results: This study included 139 patients. Clinically relevant increases of clozapine blood levels occurred in 20/92 patients (22%) and in 16/56 patients (29%), three to nine days following the first and second COVID-19 vaccination, respectively. Post-vaccination clozapine intoxication occurred in two patients (2%) in the first phase, whose clozapine blood levels were already relatively high (670 µg/L) or toxic (1083 µg/L) before vaccination. In only one of these patients a significant increase in clozapine blood level of 430 µg/L (64%) was found. In the second phase, clozapine toxicity developed in a total of four patients (7%) (the same patient with the toxic level at baseline and three patients with clozapine blood levels approaching the upper limit of the therapeutic range (667-920 µg/L). Two of these patients showed a significant increase in clozapine blood level of 342 µg/L (51%) and 394 µg/L (56%), respectively. Moderate granulocytopenia (1.0-<1.5x109/L) was found in one patient (1%) following first and second vaccination, respectively. Two patients had leukocytopenia (<3.5 x109/L) after the first and second vaccination (2%). No significant increase was found in lymphocytopenia (<1.5 x109/L) after the first or second vaccination with 27

patients (21%) at baseline, 20 patients (21%) after the first vaccine and 14 patients (17%) after the second vaccine.

Discussion: At present, there is no compelling evidence that COVID-19 vaccination entails extra risks for clozapine users, such as a dangerous increase of clozapine blood levels, aplastic anaemia onset or granulocytopenia. To our knowledge, this is the first study evaluating the safety of vaccination against the SARS-CoV-2 virus in clozapine users. Based on the Results: of this small cohort study, we found no reason for concern as regards the safety of COVID-19 vaccination in clozapine users.

No extra monitoring is necessary following COVID-19 vaccination in clozapine users. However, psychoeducation on the symptoms of clozapine intoxication is prudent, especially in patients with clozapine blood levels approaching the upper limit of the therapeutic range, because a dangerous increase in clozapine blood level may occur. Moreover, there is no cause for concern that significant dangerous decreases in neutrophilic granulocytes, total leukocytes or lymphocytes occur after COVID-19 vaccination. Additional epidemiological studies are necessary to investigate the effects of vaccination against the SARS-CoV-2 virus on clozapine blood levels and WBC and differential in patients on clozapine.

T35. SLEEP DISTURBANCE IN MAINTENANCE TREATMENT FOR SCHIZOPHRENIA: EFFECT OF RESIDUAL SYMPTOMS

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Background: Sleep disruption is a cardinal symptom that bridges across psychiatric diagnostic categories (Goldberg et al., 2020). Sleep disturbance aggravates cognitive deficits (Ferrarelli, 2021), and may worsen psychotic, anxiety, and depressive symptoms (Nakajima et al., 2017), with debilitating effects on functioning and quality of life.

The objective of this post-hoc analysis was to investigate the long-term impact of sleep disturbance in stabilized patients with schizophrenia receiving flexible-dose lurasidone 40-160 mg/d or quetiapine XR 200-600 mg/d over a 6-month double-blind continuation study period. We also investigated whether residual sleep disturbance symptoms after the acute treatment phase predicted 6-month treatment outcomes.

Methods: This post-hoc analysis was based on patients with schizophrenia who completed six weeks of double-blind treatment with lurasidone (80 mg/d or 160 mg/d) or quetiapine XR (600 mg/d) (NCT00790192), followed by a 6-month double-blind extension trial (LUR-LUR or QXR600-QXR600) (NCT00789698). The treatment outcomes evaluated included PANSS total and subscales, functional remission (UPSA-B total > 75, “ability to live independently in the community”), and cognitive performance assessed by the CogState computerized cognitive battery. Sleep disturbance was assessed based on item 4 “reduced sleep” of the Montgomery-Åsberg Depression Rating Scale (MADRS). Daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS).

Results: A majority of patients (66%) with schizophrenia had "reduced sleep" symptom (MADRS item 4 > 0) at pre-treatment baseline. There was a significant correlation between "reduced sleep" and daytime sleepiness ESS total score (P = 0.006). Week-6 change in "reduced sleep" symptom significantly mediated changes in symptom severity (as assessed by PANSS total and subscale scores) as well as changes in the UPSA-B score and ranked CogState cognitive composite score with lurasidone or quetiapine XR treatment (vs. placebo) during the acute study phase.
An absence of residual sleep disturbance (MADRS item 4 "reduced sleep" = 0) at week 6 (end of acute treatment phase) predicted greater responses to LUR-LUR or QXR-QXR treatment compared to the presence of sleep as assessed by changes in PANSS total and subscale scores as well as symptomatic and functional remission rates at 6-month follow-up (all P values< 0.05).

In patients with residual symptoms (week 6 ESS < 6, normal), worsened insomnia mediated greater adverse changes in PANSS reduced emotional experience score (P < 0.05), cognitive performance (P < 0.05), and UPSA-B score (P < 0.05) at month 6 compared to those patients with week 6 ESS > 6.

Discussion: Our findings suggest the presence of sleep disturbance symptoms in stabilized patients with schizophrenia can affect cognitive performance, social engagement as well as rates of symptomatic and functional remission during maintenance treatment for schizophrenia.

T36. ANTIPSYCHOTIC DOSE AND POLYPHARMACY REDUCTION: TWO COCHRANE REVIEWS

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Background: Antipsychotic drugs are the mainstay treatment for schizophrenia, yet they are associated with diverse side-effects, such as extrapyramidal symptoms, weight gain, sedation and hormonal changes, which could be related to an increased burden and a lower quality of life. There may be a relationship between dose and side-effects, therefore, guidelines recommend using antipsychotics in monotherapy and at the lowest possible doses. In practice, however, polytherapy and higher doses are frequently used, especially in the acute phase. On the other hand, subtherapeutic doses could lead to an increased risk of relapse. Therefore, safe reduction of polypharmacy and dose is an important, yet neglected, goal of maintenance treatment, in order to minimize side-effect burden without increasing the risk of relapse.
Methods: We investigated dose and polypharmacy reduction in two separate Cochrane reviews with streamlined methodology. We searched the Cochrane Schizophrenia Group's register (up to February 2021) for open or blind randomized trials that compared reduction of dose or polypharmacy (any study-defined strategy was acceptable) versus no treatment change in stable patients with schizophrenia. The co-primary outcomes were quality of life, re-hospitalization, and premature discontinuation due to adverse events. We also investigated a long list of secondary efficacy and safety outcomes. Mean differences, standardized mean differences and relative risks were pooled using a random-effects model. The robustness of the Results: will be investigated in sensitivity analysis and potential effect-modifiers in predefined subgroup analyses. Publication

bias and small-study effects were investigated using funnel plot analysis. The protocols of these reviews were published in the Cochrane Library (ID: CD014383, CD014384).
Results: The search was updated and newly found records and data were incorporated. We identified 29 studies on reduction of dose and 5 studies on reduction of polypharmacy. The studies were published between 1963 and 2020, with sample sizes ranging from 13 to 374 participants and duration from 12 to 104 weeks. The Results: of these reviews will be presented in the poster.
Discussion: These Cochrane reviews could inform clinical practice with up-to-date evidence on the safety of antipsychotic dose and polypharmacy reduction in stable patients with schizophrenia.

T37. PATIENTS WITH SCHIZOPHRENIA'S SELF-ASSESSED FUNCTION IN RELATION TO STAFF ASSESSMENTS, IN A FORENSIC PSYCHIATRIC CONTEXT

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Background: Patients in the psychiatric care context tend to rate their symptoms as less palpable than staff. Patients diagnosed with schizophrenia also often overestimate their function. If the care is planned according to the patients' assessment it may result in the patients not receiving the care they need. The research on care and treatment in forensic psychiatry is deficient, most of the existing research aims to examine the staff's experiences. Giving good care in relation to the patients' function is essential to be able to support the patient in insight and ability to manage their illness and reduce the risk of recidivism. The aim of the study was to compare inpatients with schizophrenia's ability to self-assess their function to a control group with other diagnoses, the study will also examine patients' self-assessed function in relation to the staff's assessment.
Methods: The study was designed as a quantitative cross-sectional study with descriptive and analytical statistics. Patients have responded to the assessment tool short form survey-36 when assessing their function. The staff has used Global assessment of function's subscale 2, function, when assessing the patient's function. The participants were divided into two diagnostic groups, based on the cognitive function level that characterized their main diagnosis: patients diagnosed with schizophrenia (n=18) and the control group (n=16). The control group includes patients diagnosed with ADHD, personality syndromes and addiction. All patients in the study are being treated in a forensic psychiatric facility.
When comparing the two groups average measures Mann-Whitney U was used. When comparing the covariation between the patient assessments and the staff assessments, of the patient's function, Spearman's rank correlations was used.

Results: The results show that only one significant difference was identified when comparing the two groups, SF-36 subscale physical function (p=0.034). When the SF-36 was compared with GAF 2, SF-36 subscales physical function (rs = 0.387, p=0.031), physical role function (rs = 0.479, p=0.006) and social function (rs = 0.453, (p=0.012) covaried with GAF 2, for the total group. For the patients with schizophrenia significant covariations were found in the subscale physical function (rs = 0.688, p=0.003) and social function (rs = 0.602, p=0.018) when compared with GAF 2. For the control group only one significant covariation was found in the subscale physical function (rs = 0.830, p=0.001) when compared with GAF 2.

Discussion: Results: show that there is an inconsistency between the patients' and staffs' assessment of function. This indicates that there is a risk that the care given to the patient could have different outcomes depending on if it is based solely on the patients' assessment or solely on the staffs' assessment. The result also indicates that there is no significant difference between the patients with schizophrenia and the control group. The Results: are in line with other similar studies executed on psychiatric outpatients with schizophrenia and intellectual disabilities. The new finding also indicates that the same difficulties in assessing one's functions also occurs in the control group.

T38. INTEGRATIVE COGNITIVE REMEDIATION IN SCHIZOPHRENIA: IMPROVEMENT IN COGNITION, CREATIVITY, FUNCTIONAL OUTCOME, AND CLINICAL SYMPTOMS

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Background: Integrative cognitive remediation combining different trainings has been shown to improve cognition, functional outcome, and clinical symptoms in schizophrenia. However, the possible effectiveness of integrative cognitive remediation in improving primary negative symptoms and creative capacity, which has been associated with cognition and functional outcome, remains unknown. The aim of this study was to analyze the effectiveness of an integrative cognitive remediation program in improving cognition, creativity, functional outcome, and clinical symptoms in patients with schizophrenia.
Methods: Ninety-four patients with schizophrenia from the Mental Health Network from Álava (Spain) were randomly assigned to either an experimental group who performed integrative cognitive remediation with the REHACOP program (n = 47) or to an active control group who performed occupational activities (n = 47). Both the cognitive remediation and occupational activities were implemented during 20 weeks, in sessions of 60 minutes, 3 days a week. The REHACOP program combined cognitive remediation with social cognitive training and social and functional skill training. A comprehensive assessment of clinical symptoms, neurocognition, social cognition, creativity, and functional outcome was carried out at baseline and follow-up. The effectiveness of the cognitive remediation was analyzed with an analysis of covariance. Specifically, change scores (post-treatment - baseline) were compared between the REHACOP group and the active control group on each of the domains, controlling for baseline scores. A bootstrapping procedure was used (1,000 samples) with the Bonferroni adjustment.
Results: Analysis of covariance showed significant differences between the REHACOP and the active control groups in change scores of processing speed, working memory, verbal memory, inhibition, theory of mind, emotion processing, and figural creative strengths, as well as in functional competence and some clinical symptoms such as disorganization, excitement, and primary negative symptoms, with the REHACOP group showing greater improvement in these domains.
Discussion: This study provides initial data of the effectiveness of integrative cognitive remediation at improving primary negative symptoms and creativity. Results: suggest that integrative cognitive remediation combining trainings in neurocognition, social cognition, and

social and functional skills may be a key treatment to improve the primary negative symptoms that are so resistant to pharmacological treatment.

T39. THE EFFECT OF OXYTOCIN WITHIN A BRIEF MINDFULNESS-BASED GROUP THERAPY ON EMPATHY, AFFECT AND NEGATIVE SYMPTOMS IN INDIVIDUALS WITH A SCHIZOPHRENIA SPECTRUM DISORDER

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Background: Current treatment approaches for individuals with a schizophrenia spectrum disorder (SSD) remain limited regarding their effectiveness on negative symptoms and sociocognitive deficits. Research indicates improvements in negative symptoms and empathy for individuals with SSD after mindfulness-based group therapy (MBGT). Addtionally, after oxytocin (OXT) administration, especially in a positive social context, an increase in empathy could be shown in healthy controls. According to the social salience hypothesis the effect of oxytocin is dependent on the social context. Within an adversely perceived social setting, oxytocin can reduce empathy and enhance feelings of social anxiety and mistrust when administered. The effect of mindfulness in combination with OXT has not yet been examined. This proof-of-concept study investigated the augmented effect of OXT administration combined within a brief MBGT on empathy, stress and negative symptoms in patients with SSD.
Methods: A cohort of 41 patients with a diagnosis of SSD was recruited at the Charité – Universitätsmedizin Berlin. The study was based on an experimental, randomised, double-blinded and placebo-controlled design. Two MBGT sessions took place over one week. A dose of intranasal oxytocin with 24 I.U. or placebo was administered 45 minutes before each session. Empathy, stress and negative symptoms were measured using psychometric questionnaires at baseline and post-intervention. A 2x2 mixed-model ANCOVA design with time as within- and group as between-subject factor controlled for the respective baseline scores as covariates has been calculated to assess changes in the outcome variables.
Results: Our outcomes showed a significant decrease of stress and of negative affect measured with the Positive and Negative Affect Scale (PANAS) in both conditions. This effect is most likely explained by MBGT, regardless of the additional administration of oxytocin or placebo. No significant additional benefit of the oxytocin nasal spray on empathy was observed. However, a significant difference was observed between the oxytocin and placebo group in the reduction of the negative symptom domains avolition and diminished emotional range measured using the Self Evaluation of Negative Symptoms (SNS).
Discussion: In line with a previous study by our research group a significant effect of MBGT with regard to a reduction of stress and negative affect was shown in individuals with SSD. The effect could be observed regardless of the additional administration of oxytocin or placebo. For the first time, a significant additional benefit of oxytocin could be exhibited regarding a reduction of the two negative symptom domains avolition and diminished emotional range. These Results: could pave the way for OXT as a pharmacological augmented treatment option in the context of MBGT.

Outcomes are promising, however a larger trail with more participants and MBGT sessions is needed to be able to monitor our findings over the long-term course of therapy. Future research should focus on potentially influencing factors like the genetic variability of oxytocin receptor expressions in terms of a more personalised psychiatric treatment for individuals with SSD.

T40. LONGITUDINAL CHANGES IN COGNITIVE FUNCTIONING IN ANTIPSYCHOTIC-TREATED AND ANTIPSYCHOTIC-NAIVE PATIENTS WITH FIRST EPISODE PSYCHOSIS: A RANDOMISED, TRIPLE-BLIND, PLACEBO-CONTROLLED STUDY

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Background: Cognitive impairment occurs in antipsychotic-naïve first-episode psychosis (FEP), but antipsychotics confound interpretation of the longitudinal course of cognition in FEP. The study aim was to explore the effects of antipsychotic medication on cognition over the first 6-months of FEP treatment. A secondary aim was to investigate longer-term cognitive changes at 24-month follow-up.

Methods: A randomised, triple-blind placebo-controlled trial was conducted involving patients being allocated to receiving risperidone or paliperidone (N=38) or placebo (N=40) in conjunction with intensive psychosocial therapy for 6-months. A healthy control group (N=42) was also recruited. A cognitive battery assessing attention, working memory, processing speed, verbal fluency, cognitive control and verbal paired-associate learning and memory was administered at baseline, 6-, 12- and 24-months.

Results: Controls had higher mean performance than patients on all cognitive measures at baseline, but the two patient groups did not differ. For the majority of cognitive tests, there was a significant overall increase in performance over the 6-month treatment period without any interaction effects. However, a significant group-by-time interaction was observed in verbal paired-associate learning and memory. Both the placebo and healthy control groups showed improvement, but the medication group a deterioration, on immediate paired associate recall ($p=0.039$) and delayed cued recall ($p=0.005$). This result remained when only trial completers were included in the analysis.

Discussion: Although most areas of cognition remained unaffected, treatment with risperidone/paliperidone appeared to result in specific progression of memory impairment in FEP. While it remains to be determined if these findings apply to other antipsychotic medications, they do point to the need for careful consideration of the risks and benefits of antipsychotic prescription and the importance of accounting for the cognitive effects of medication in longitudinal research.

T41. CHARACTERIZING LATENT SOCIAL DATA-GATHERING BIASES IN SCHIZOPHRENIA AND SCHIZOTYPY WITH COMPUTATIONAL MODELLING

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Background: Schizophrenia patients show biases in data-gathering in probabilistic tasks: they respond more stochastically, overweight disconfirmatory information, and underweight expected evidence compared to controls. However, what is lacking is an understanding of social-data gathering biases which may underpin clinical symptoms such as paranoia and impairments in social cognition. Following our previous work (Adams et al., 2018) this study aimed to test hypotheses that (i) relative to controls SZ patients would show significant impairments in computational parameters (CP) characterising social decision-making which would (ii) be associated with positive symptoms; and (iii) a similar picture would exist for healthy high schizotypes.
Methods: 56 SZ patients and 112 controls (CTs) completed a computerised Prisoner's Dilemma game against both a mostly benevolent (80% cooperate) and a malevolent (20% cooperate) opponent. Participant's own actions (cooperate or compete - indices of trust) were acquired on every game round and hierarchical bayesian belief-updating modelling (HGF toolbox) was used to extract latent CP that characterised action decisions. The winning model contained parameters encoding response precision (nu), evolution rate (omega), and a drift parameter (rho; preference towards one action).
Results: SZ had significantly response precision ($p=0.011$) and higher drift ($p=0.005$) than CTs (sex and age matched). Lower response precision in SZ was significantly correlated with PANSS positive symptoms ($rs=.3$, $p<.05$). Within CTs, higher schizotypy total and all dimension scores were also associated with lower Nu.
Discussion: These findings suggest social decisions indexing trust are imprecise in SZ compared to CTs and greater imprecision predicts higher positive symptoms. As a similar relationship was also observed in high schizotypy, imprecise modelling of the actions of social agents may be a common foundation to 'positive symptom'-like mental experiences.

T42. ADVERSE CHILDHOOD EVENTS AND NEGATIVE SYMPTOMS IN GENERAL POPULATION

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Background: Adverse events in childhood increase the risk for developing schizophrenia. Specific adversity subtypes may also increase the prevalence of specific symptoms of schizophrenia. For instance, individuals with schizophrenia who report having experienced emotional neglect in childhood have more negative symptoms. Negative symptoms are suggested to manifest as a continuum across psychiatric diagnoses extending to the healthy population. Therefore, we tested in a general population sample, if exposure to childhood adverse events would

be associated with the severity of negative symptoms and whether there is adversity subtype specificity.
Methods: Four hundred fifty individuals living in the USA or Canada were recruited using an online tool (prolific.co). After quality control using infrequency items, 405 individuals (308 females, 87 males, mean age 27.85 ±10.20) were retained for the analyses. Exposure to childhood maltreatment was measured using the retrospective Maltreatment and Abuse Chronology of Exposure (MACE) scale. MACE divides maltreatment into 10 subtypes and also allows for quantification of the timing of the exposure. Negative symptoms were measured using the Self-Evaluation of Negative Symptoms (SNS) and The Motivation and Pleasure Scale-Self-Report (MAP-SR) scales. Participants' negative symptom scores were estimated using a multidimensional item response theory model. Standardized negative symptoms scores were then regressed against their standardized MACE scores while controlling for age, sex, education, and race.
Results: SNS and MAP-SR were strongly correlated (r=0.79, 95% CI 0.75 – 0.82). Overall exposure to any childhood adversity was associated with SNS (correlation r=0.39, regression coefficient = 0.38, 95% CI 0.29 – 0.48) and MAP-SR (r=0.37, regression coefficient = 0.36, 95% CI 0.27 – 0.45). Correlations between adversity subtypes and negative symptoms ranged between 0.1 and 0.3. Regression analyses including all subtypes showed that emotional neglect, and verbal abuse by parents and peers were especially associated with negative symptoms as measured with either one of the negative symptom scales.
Discussion: We found that overall adverse events in childhood are associated with more negative symptoms in a general population sample. Our analyses further suggest that emotional neglect and verbal abuse by parents and peers may be particularly important predictors of negative symptom severity. These findings were similar using two different scales for negative symptoms. If clinical and subclinical symptoms of schizophrenia share common etiological factors, studying how childhood adversity leads to negative symptoms in a general population sample may reveal important mechanisms underlying the development of negative symptoms in individuals with schizophrenia. In the future, using this sample, we will investigate how the timing and duration of childhood adversity is associated with negative symptoms. \

T43. IDENTIFICATION OF TEXTURE BRAIN MRI ABNORMALITIES ON CLINICAL HIGH-RISK PATIENTS USING EXPLAINABLE ARTIFICIAL INTELLIGENCE

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Background: Recent meta-analyses have reported brain volume differences and variability in clinical high-risk (CHR) subjects with and without transition to psychosis. Aim of the present study was to investigate the utility of radiomics texture features for a) identification of clinical high-risk state; and b) prediction of transition to psychosis. Structural MR images were acquired from 58 clinical high-risk subjects with no later transition (CHR_NT), 15 clinical high-risk subjects with a later transition (CHR_T), and 44 healthy controls (HC). We investigated two radiomics texture features providing the highest accuracy in preliminary analysis; a) difference of

entropy, which reflects the randomness of the intensity distribution and inherits characteristics of entropy in a second level, and b) contrast, which indicates large differences between neighboring voxels.
Methods: The wmp* image produced via SPM12 segmentation was used for discretization of intensities. Next, a voxel-by-voxel sliding 3D cube of 7x7x7 dimension was used for the grey level co-occurrence matrix (GLCM) calculation. Radiomics texture features were extracted and imported in a 10x10 nested cross-validation schema for the identification of CHR_NT vs. HC. The group of CHR_T was used for external validation. In the inner loop, cross-validated feature selection method selects 200 ranked-features. In order to perform localization, the positive relevance (PR) of voxels for CHR_NT subjects using the layer-wise relevance propagation (LRP) algorithm for multilayer neural network was applied. The explanation given by LRP was a map of voxels in the original texture feature map that contributed to diagnosis.
Results: The classification of a subject's clinical status was predicted with classification accuracy >73%. Caudate, putamen, thalamus, hippocampus, insula, cerebellum, vermis and pallidum, posterior limb of internal capsule and external capsule left showed PR for the corrected classified CHR_NT subjects in the difference of entropy map. Lingual, motor area, superior and posterior corona radiata left, and superior longitudinal fasciculus left showed PR for the CHR_NT subjects using the contrast feature map. The PR was not affected by volume changes in thalamus, insula, hippocampus, putamen and parahippocampal, caudate and amygdala (using the difference of entropy map). In addition, 10 out of 15 CHR_T subjects who classified as not HC presented uncorrelated volumetric changes with the PR in thalamus, olfactory cortex, cingulum left, parahippocampal left, amygdala left, cuneus left, lingual left, pallidum left, heschl left, temporal left, putamen and insula. These regions were the dominant regions for the prediction of psychosis using the difference of entropy map.
Discussion: The proposed framework enhances the classification decision for CHR_NT and HC subjects, verifies diagnosis-relevant features and may potentially contribute to identification of structural biomarkers for psychosis. The absence of PR correlations with volumetric changes enhances our notion that texture features can reveal a hidden neuro-biological pattern that expands beyond volumetric changes in the clinical high-risk state with potential relevance for future transition to psychosis but is hidden in the grey-matter (GM), white-matter (WM) and cerebrospinal fluid (CSF) relation and border determination.

T44. SYSTEMATIC REVIEW AND META-ANALYSIS ON PREDICTORS OF PROGNOSIS IN PATIENTS WITH SCHIZOPHRENIA SPECTRUM DISORDERS: AN OVERVIEW OF CURRENT EVIDENCE AND A CALL FOR PROSPECTIVE RESEARCH AND OPEN ACCESS TO DATASETS

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Background: Schizophrenia spectrum disorders have heterogeneous outcomes. If we could predict individual outcome and identify (modifiable) predictors of outcome, we could personalize and optimize treatment and care. Short- to medium- term outcome is most relevant for treatment goals in clinical practice.

Methods: We performed a systematic review and meta-analysis to identify predictors of outcome up to and including 1 year in prospective studies of patients with schizophrenia spectrum disorders. Interventions were excluded as predictors. Our literature search yielded 438 studies that reported on 1,281 outcomes. 134 of these studies provided information on possible predictors of the predefined outcomes; 32 on symptomatic remission, 30 on GAF-score, 47 on vocational functioning, 33 on social functioning, 11 on independent living and 21 studies on readmission. Sufficient information from included studies to calculate a common effect size for meta-analysis was only available for the outcome measure 'symptomatic remission' and the variables sex, age, positive symptoms and negative symptoms. For our systematic review we report frequency counts for the relationship between investigated variables and all predefined outcome measures.
Results: Our meta-analysis showed that the chance of symptomatic remission was lower in men (OR 0.69, 95%CI 0.56 to 0.84) and in patients with fewer positive (Cohen's d -0.24, 95%CI -0.45 to -0.03) and negative (Cohen's d -0.54, 95%CI -0.70 to -0.38) symptoms at baseline.
Our systematic review showed that the chance of symptomatic remission was lower in males, in patients with a longer duration of untreated psychosis, and in patients with more symptoms at baseline. The chance of readmission was higher for patients who had more previous admissions. The chance of functional recovery was higher in patients with better functioning at baseline. For personal recovery, not enough studies with comparable outcome measures were available to analyze predictors

Discussion: This study illuminates predictors of outcome of schizophrenia spectrum disorders. For all investigated outcomes, level of functioning at baseline in general and for that aspect of functioning specifically was the best predictor of outcome. Furthermore, we found no evidence for many proposed predictors in original research. Possible reasons for this include the lack of prospective research, between-study heterogeneity (sample, design, analysis) and incomplete reporting. We therefore recommend open access to datasets and analysis scripts, enabling other researchers to reanalyze and pool the data.

T45. PREDICTING TREATMENT OUTCOMES WITH COMPUTATIONAL SPEECH FEATURES IN HOSPITALIZED PATIENTS WITH SCHIZOPHRENIA

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Background: There is a critical need for biomarkers for schizophrenia that would guide personalized, evidence-based treatment decisions in a quantitative, cost-effective, and scalable way. In this study, we explore the use of computational acoustic and linguistic speech features as predictors of longitudinal treatment outcomes among hospitalized patients with schizophrenia.
Methods: Hospitalized patients with schizophrenia spectrum disorders were recruited during acute psychosis exacerbations. This interim analysis included N=23 patients who underwent a baseline assessment following admission and a follow-up assessment at discharge. Follow-up occurred at 0.9 – 3.7 weeks, with a mean of 2.0 weeks. DSM-5 diagnoses included schizophrenia (n=14), schizoaffective disorder (n=4), unspecified psychotic disorder (n=3), and schizophreniform disorder (n=2). Psychosis symptoms were assessed with the Brief Psychiatric Rating Scale (BPRS)

and language disturbance was rated with the Scale for the Assessment of Thought, Language and Communication (TLC). Language samples were collected with the Winterlight iOS app using structured tasks (paragraph reading, phonemic and category fluency) and open-ended questions (picture descriptions and prompted narratives). Recordings were diarized to isolate participant speech, transcribed, and processed through multimodal computational linguistic analysis to generate features describing vocal quality, speaking cadence, semantic coherence, parts-of-speech, and lexical characteristics. Elastic net regression models were used to predict psychosis symptoms at follow-up using baseline features. Linear mixed models were used to evaluate whether computational features predicted change in psychosis symptoms. All analyses were done in R.
Results: The main outcome of interest was positive symptoms on the BPRS. Compared to an elastic net model with which included baseline BPRS ratings alone, adding computational speech features to the prediction of positive symptoms at follow-up improved R-squared from 0.34 to 0.58. Higher positive symptoms at follow-up were predicted by a lower number of nodes in the largest strongly connected graph community, fewer prepositions, fewer filled pauses, longer maximum utterance length, and greater use of particles. For our secondary outcome of formal thought disorder symptoms, the addition of computational speech features similarly increased R-squared from 0.36 to 0.41. Examining individual computational features, an increase in positive symptoms was significantly predicted by increase in total words, use of demonstratives, and use of particles, as well as a decrease in the age of acquisition of nouns, location words, object words, noun to verb ratio, and prepositions. However, these relationships did not survive correction for multiple comparisons.
Discussion: We present preliminary evidence suggesting that computational linguistic features may aid in the prediction of hospitalization treatment outcomes for patients admitted for acute psychosis exacerbations. Given the small sample size and lack of validation sample, further investigations are needed to support these findings.

T46. NETWORK CLUSTERING OF SYMPTOM AND COGNITION SCORES IN CLINICAL HIGH-RISK FOR PSYCHOSIS

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Background: Unsupervised learning techniques have been applied to psychosis groups in the hope of finding meaningful but undiscovered groupings of patients. A literature exists on the clustering of Clinical High-Risk patients using cognitive and clinical scales. Using cognitive scales, such

work has generally shown there to be at least one subgroup with highly impaired cognition. Using clinical scales, research has shown distinct patterns of symptoms to differentiate between subgroups. The current study used the topological structure of a network of associations between patients to find network-based clustering solutions. It was hypothesised that network-based clustering would provide meaningful subgroupings of CHR subjects distinct from more traditional clustering.

Methods: In a sample of 261 CHR participants, networks of cognition and CAARMS symptom similarities (261x261) were formed using Pearson's correlations and thresholded at 10% sparsity. A Louvain community detection algorithm was used to find a 2-cluster solution for each network. Alternative clustering algorithms were used for comparison: K means clustering and Latent Profile Analysis. Simple t tests were used to explore whether clustering solutions separated the sample into groups with significantly different clinical / cognitive scores.

Results: For cognitive scores, network-based clustering produced one cluster with statically higher reasoning and social cognition scores, and another other cluster with significantly higher working memory, processing speed, attention / vigilance, and verbal learning scores. Alternative clustering algorithms produced one cluster with higher scores across domains. For symptom scores, network-based clustering produced one cluster with significantly higher positive symptoms, and one cluster with significantly higher negative symptoms. Alternative clustering algorithms produced one cluster with both higher positive and negative symptomatology.

Discussion: Network-based clustering provides an alternative approach to traditional unsupervised learning algorithms. In this study, network-based clustering solutions were shown to differentiate between domains, for instance separating CHR subjects with high positive and negative symptomatology. This is likely due to the characteristics of relational data modelled as a network. We propose network-based clustering to be a useful tool in searching for meaningful subgroups in psychosis. This study is limited in scope having only tested 2 cluster solutions.

T47. SPEECH DISTURBANCES IN SCHIZOPHRENIA: A CROSS-LINGUISTIC REPLICATION OF BERT AUTOMATED ANALYSIS OF COHERENCE

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Background: Language disorders have long been considered a distinctive feature of schizophrenia (SCZ). They range from reduced syntactic complexity to loss of semantic coherence and are often associated with thought disorders.

Natural Language Processing (NLP) has been used to provide quantitative and automated characterizations of language disorders in schizophrenia and has shown promising Results: in

identifying individuals at high risk, tracking symptoms, and targeting early intervention. The Bidirectional Transformer (BERT) architecture is a novel NLP approach used to encode longer sequence modeling and able to provide a deeper representation of the underlying semantic and discursive structure of a text. This is crucial as it can be used to identify broad dependencies within a text, potentially leading to more robust and generalizable Results: across different samples and languages. While previous studies have used BERT to detect linguistic disorder in schizophrenia, its robustness and cross-linguistic generalizability have yet to be assessed.

In this study, we analyzed a large cross-linguistic corpus of speech transcripts from patients with SCZ using BERT to provide quantitative measures of semantic coherence and to test the cross-linguistic generalizability of automated NLP measures of coherence.

Methods: We collected a Danish (DK) and Chinese (CH) cross-linguistic dataset including 161 participants with SCZ (111 DK, 60 CH) and 168 controls (HC) (129 DK, 39 CH) repeteadly producing video descriptions, for a total of 2776 transcribed texts. The Animated Triangle Task was used to elicit speech, and we then computed from transcripts the following measures of coherence (relying on previous studies) using BERT embeddings: Coherence 5-10 - average semantic similarity of each word in 5- or 10-word windows; coherence K5, K6, K7, K8 - word-to-word variability at "k" inter-word distances (k-range: 5-8).
We ran multilevel regression models with coherence measures as outcome, and language (DK, CH), diagnosis (SCZ, HC) or symptoms (SANS/SAPS; PANSS), and their interaction as predictors.

Results: We found the following effect of diagnosis (differences between patients with SCZ and controls): a reduced coherence-5 ($\beta = 0.003$ SE = 0.002 $p < 0.05$) in SCZ was found only for Danish, while decreased measures of other forms of semantic coherence in SCZ-K6 ($\beta = -0.021$ SE = -0.006 $p < 0.001$) and K7 ($\beta = -0.014$ SE = 0.007 $p < 0.05$)-were found only in Chinese. We found an association between symptoms and coherence measures, but no consistent pattern emerged.
Discussion: We used NLP and the BERT architecture to quantitatively measure and compare semantic coherence in patients with schizophrenia and control subjects. Consistent with previous studies, we found reduced semantic coherence in schizophrenia. However, we found important cross-linguistic differences: the reduced coherence measures differ across languages. This suggests that quantitative coherence measures may vary depending on the language studied and may not be universally present. Further work is needed to test how the NLP Results: generalize to different samples and languages, and to clarify the relationship between the different coherence measures and the different clinical symptoms that characterize schizophrenia.

T48. REDUCED VOLUME OF INFERIOR FRONTAL GYRUS IS ASSOCIATED WITH DECREASED CONTRIBUTION OF MODEL-BASED LEARNING IN EARLY PSYCHOSIS

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Background: Psychosis patients show impaired goal-directed learning and reduced volumes of prefrontal and parietal cortical areas. Although impaired goal-directed learning has been linked with reduced volumes of prefrontal areas in healthy subjects, the relationship between goal-directed learning and the volume of brain structures in psychosis remains unclear. We hypothesized that impaired goal-directed learning of psychosis patients is associated with volume reductions of anterior cingulate, dorsolateral prefrontal and posterior parietal cortex as well as of right inferior frontal gyrus. These areas exhibit reduced volume in psychosis patients and constitute a fronto-parietal network for different cognitive abilities that are pivotal in goal-directed learning.
Methods: Here we use morphometric magnetic resonance imaging along with a 2-stage decision task in early psychosis patients and healthy controls. With the 2-stage task, the interaction of model-free and model-based learning in terms of their relative contribution to decision-making can be quantified. While model-free learning regards only the prior reward history, model-based learning also considers future consequences of actions and thereby formalizes goal-directed learning. Gray matter volume of anterior cingulate, dorsolateral prefrontal and posterior parietal cortex as well as of right inferior frontal gyrus were incorporated in a general linear model (GLM) to predict the interaction of model-based and model-free learning across healthy controls and patients. In addition, gray matter volume of these areas was compared between controls and patients, along with the interaction of model-based and model-free learning.
Results: Our preliminary Results: suggest that the relative contribution of model-based learning in healthy controls and patients correlates positively with the volume of the right inferior frontal gyrus. In addition, patients compared to controls show reduced relative contribution of model-based learning and reduced gray matter volume in the right inferior frontal gyrus.
Discussion: Our preliminary data suggest that the impaired ability of psychosis patients to learn prospective, goal-directed decision making is linked with reduced volume of an area for response inhibition. Response inhibition is a key component of goal-directed learning which critically depends on the ability to learn withholding of reflexive habitual actions. These findings advance our understanding of cognitive deficits in psychosis patients.

T49. PREDICTING WHO BENEFITS FROM COGNITIVE-BEHAVIOURAL THERAPY FOR PSYCHOSIS USING ROUTINE DATA: A MACHINE LEARNING STUDY

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Background: Cognitive-Behavioural Therapy (CBT) is the primary psychological intervention for psychosis (CBTp). However, only approximately 50% of patients experience a clinically significant improvement. Although many studies have investigated which factors are associated with response to treatment, they have mostly relied on traditional group comparisons or regression-type approaches aimed at maximising a measure of model fit between a small set of hypothesis-driven predictors and treatment outcome in the same data used to generate the model (i.e. models are not tested for generalisability). This approach is not suited for inferences about unseen individual patients, which may partially explain why findings from these studies have had limited impact on clinical practice so far. Machine learning is a multivariate data-driven approach capable of finding intricate patterns in the data that can then be used to make predictions in unseen individuals. This is a promising approach for personalised psychological care where treatment

recommendations are guided by a patient's unique profile. Being able to predict whether a patient is likely to benefit from CBTp before treatment commences would also allow for optimisation of clinical resources. The aim of this study was to predict response to CBTp at the individual level using routine clinical data in a specialised psychological service for psychosis.

Methods: Response to treatment was investigated in 209 patients experiencing hallucinations, delusions or both receiving CBTp at the Psychological Interventions Clinic for outpatients with Psychosis (PICuP), a specialist CBT service based at the Maudsley Hospital (London, United Kingdom) for help-seeking individuals with distressing positive symptoms of psychosis. Information on demographics, individual items on Psychotic Symptom Rating Scales (PSYRATS), psychological distress (Clinical Outcomes in Routine Evaluation, CORE), Illness Perception Questionnaire (IPQ), Depression Anxiety Stress Scales (DASS), Warwick-Edinburgh Mental Wellbeing Scales (WEMWBS) and functioning (Work and Social Adjustment Scale, WSAS) were used as input features, totalling 92 variables. Improvement following CBTp was defined as a 30% increase in the total score of the Choice of Outcome In CBT for Psychoses questionnaire (CHOICE), assessing psychological recovery, from pre- to post-treatment. Input features were first normalised, missing data (0.5%) were imputed with k-nearest neighbours, and data dimensionality was reduced via principal component analysis (PCA). The resulting components were analysed with a regularised logistic regression implemented via elasticnet in a stratified nested 5-fold cross-validation scheme repeated 10 times, totalling 50 models. The most informative features were extracted by first identifying which PCA components had the largest average weights across all models, and then retrieving the items with the highest loadings on these PCA components. Analyses were carried out in Python 3.8 using sklearn (v 0.24). The code is available at https://github.sandramv/cbtp.

Results: Before treatment, 54% of service users were experiencing delusions and hallucinations (DH), 27% hallucinations only (H) and 19% delusions only (D); 109 improved following CBTp (DH: 53%, D: 28% and H: 20%). The machine learning model was able to predict who improved after CBTp with 71.7% (4.2) balanced accuracy ($p<.001$), 70.7% (7.6) sensitivity and 72.7% (7.2) specificity. The most informative features were grouped into five categories in decreasing order of importance: 1) low duration, loudness and amount of distress associated with hallucinations; 2) low levels of hopelessness, low mood and anhedonia (e.g. CORE "I have felt despairing or hopeless"); 3) attributing illness to psychosocial factors such as having "family problems" and "no close friends" (IPQ); 4) low duration and amount of preoccupation with delusional beliefs; 5) feeling hopeful towards therapy and believing that addressing unhelpful cognitions and behaviours will be helpful (e.g. IPQ "How much do you think looking at things differently can be helpful?").

Discussion: This study provides the first evidence that it is possible to predict who will benefit from CBTp at the individual level using routine data with good accuracy. These findings highlight the translational value of routine data for prediction modelling, as similar Results: have been found for other disorders albeit using more expensive and difficult to acquire data such as brain function. Patients with less severe psychotic and depressive symptoms and psychologically orientated views of their problems were more likely to benefit from treatment. The latter is expected given that addressing distressing thoughts, feelings and behaviours associated with psychotic and depressive symptoms, social withdrawal, and family/interpersonal conflict is a central part of CBT. Results: from this study should be validated prospectively. Overall, these are promising findings for personalised psychological care in psychosis.

T50. INDIVIDUALIZED PREDICTION OF TRANSITION TO PSYCHOSIS FROM CLINICAL AND NEUROCOGNITIVE DATA IN INDIVIDUALS AT ULTRA-HIGH RISK FOR PSYCHOSIS: A MACHINE LEARNING STUDY

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Background: Identification of individuals at high risk for psychosis is an important step that raises the possibility of early diagnosis and preventive treatment for psychotic disorders. However, there is currently no single marker that reliably predicts prognosis in these individuals. Machine learning provides general tools that can aid clinical decision making by learning multivariate models that can predict diagnosis and prognosis for a novel subject, based on historical data that includes multiple characteristics. Our main aim in this study is to use machine learning algorithms to build models that can accurately predict who will develop psychosis among individuals at high risk for psychosis, based on the baseline clinical and neurocognitive data.

Methods: We recruited thirty-six help-seeking individuals who were at ultra-high risk (UHR) for psychosis, according to the Comprehensive Assessment of At Risk Mental States (CAARMS) instrument, and 35 age-, gender- and education-level matched healthy subjects (HC). A battery containing clinical scales and neurocognitive tests were administered at the time of admission. Of the 36 individuals at UHR for psychosis, 18 transitioned to psychosis by the end of the first year. We trained two different support vector machine (SVM) models for two tasks: a) to discriminate UHR subjects from HC and b) to discriminate UHR subjects who transitioned to psychosis (UHR-T) from the ones who do not (UHR-NT). For task (a), we used baseline cognitive information to distinguish individuals at UHR for psychosis versus HCs. For task (b) – distinguishing UHR-T versusUHR-NT, we trained 3 different classifiers, each based on the data used:the clinical data alone, cognitive data alone and combination of both clinical and cognitive data. For each of these tasks, we used SVM to learn a model, based on the most discriminative subset of features found using a LASSO-based recursive feature elimination, within the training set. We use a 5-fold internal cross validation (CV) within each fold to identify the best features, then a leave-one-out external CV in the outer layer to evaluate the generalizability performance of the models.

Results: Using cognitive data, our model could discriminate between the individuals at UHR and HCs with an accuracy of 76%. For distinguishing UHR-T versus UHR-NT groups, the highest performance was achieved by using cognitive and clinical data together, with an accuracy of 81%. The model that used cognitive data alone produced an accuracy of 63%, whereas the model that used clinical data alone produced an accuracy of 72%. In the prediction of transition to psychosis, cognitive features that contributed the most were the ones related to executive functions. Severity of the positive symptoms and avolition were among the most discriminative clinical features.

Discussion: Our findings suggest that machine learned tools based on clinical and neurocognitive information can be helpful in the individualized prediction of transition to psychosis among at-risk

help seeking populations. Further studies are needed to externally validate the performance of our models.

T51. FORMAL THOUGHT DISORDER IN SCHIZOPHRENIA AND BIPOLAR MANIA: A LONGITUDINAL PHENOMENOLOGY STUDY

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Background: Formal Thought Disorder (FTD) represents disruptions in conscious thinking and limits to speech production. To date, most FTD studies have focused on chronic schizophrenia; it is known, however, that FTD affects people across the schizophrenia-bipolar spectrum. Further, FTD is at its most severe when persons present acutely, with ~90% of patients expressing various subtypes of FTD symptoms. There is limited work examining FTD longitudinally, therefore a comprehensive understanding of which subtypes of FTD symptoms resolve, and which remain is still relatively unknown. This study will examine the phenomenology of FTD over time in patients with schizophrenia and bipolar mania, examining for longitudinal changes and differences across diagnostic conditions.

Methods: Two patient samples were recruited from the inpatient department of Liverpool Hospital, Sydney. Patients were diagnosed as DSM-IV schizophrenia (N=33) and bipolar disorder I – mania phase (N=29), and were recruited in an acute phase of illness as part of an inpatient admission. Detailed clinical interviews were obtained at baseline (session 1) and in two subsequent interview sessions, at 8 weeks (session 2) and 16 weeks (session 3) after baseline. All had been discharged after session 1. FTD phenomenology was assessed using the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS). Twelve individual symptoms of FTD were examined across the three sessions in the two groups (Poverty of Speech, Poverty of Content of Speech, Blocking, Increases Latency of Response, Derailment, Tangentiality, Incoherence, Illogicality, Circumstantiality, Pressure of Speech, Distractible Speech, and Clanging). General linear models examining symptom severity across the twelve symptoms by diagnostic group by session were run with appropriate post-hoc follow up tests.

Results: The analyses established that A) FTD severity in schizophrenia was equivalent over the three sessions (means scores of 0.63, 0.66, 0.63), whereas in bipolar mania, FTD reduced over time (means scores of 0.72, 0.43, 0.40). B) Over all sessions, poverty of speech was more severe in schizophrenia than bipolar mania (mean scores of 0.56 and 0.10, respectively $p=0.03$), whereas pressure of speech was more severe in bipolar mania (mean scores of 0.6 and 1.24, respectively $p=0.007$). C) Tangentiality and circumstantiality remained high in schizophrenia across all three sessions, whereas in bipolar mania, tangentiality, circumstantiality and pressure of speech were high during session 1 only.

Discussion: These data speak to the chronicity of FTD in schizophrenia in the immediate months following psychiatric discharge, and possibly over the course of their illness. In contrast, FTD symptoms in bipolar mania are restricted to acute phases and gradually resolve. Negative symptoms of thought disorder were only present in schizophrenia.

T52. MULTIMODAL CLINICAL DEEP PHENOTYPING (CDP) TO IDENTIFY BIOTYPES OF MENTAL ILLNESS - A TRANSLATIONAL AND RDOC-BASED NATURALISTIC (COHORT) STUDY

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Background: Psychotic-spectrum disorders (PSD) are defined by operationalized symptom clusters which lack sensitive and specific biomarkers to distinguish between different diagnoses or disease states. Moreover, PSD often have substantial symptom overlap and common biological underpinnings, which make a precise differentiation between different disease entities challenging. To address these limitations in the diagnostic process and nosological characterization of psychiatric disorders we aimed to investigate multimodal relations between clinical data, clinical scores, neurocognitive findings, and multimodal Magnetic Resonance Imaging (MRI) measurements in a large patient cohort in an RDoC-based approach. Additional assessments include the retinal domain using optical coherence tomography (OCT) and electroretinogram (ERG), neurophysiological assessments through electroencephalography (EEG), transcranial magnetic stimulation (TMS), and (epi)genetic profiling. Through multivariate analyses, machine and deep learning algorithms, we aim to stratify patient subgroups to better distinguish between disease phenotypes and prospectively optimize treatment strategies. Finally, using human induced pluripotent stem cells (hiPSC) from our cohorts, we aim to link cellular findings to clinical data to develop a translational approach to precision medicine that can be integrated into psychiatric diagnostic and treatment algorithms.

Methods: Following a broad naturalistic approach, participants with PSD from both outpatient and inpatient settings as well as healthy controls (HC) aged 18-65 years are enrolled. Multimodal phenotyping includes collection and laboratory analysis of blood and cerebrospinal fluid samples, in-depth deep clinical characterization with standard diagnostic tools, collection of socio-demographic data as well as pertinent validated clinical assessment scales and a neurocognitive test battery (BACS). Moreover, subjects are characterized using a wide array of neurophysiological and imaging tools such as: multimodal MRI including structural (T1-MPRAGE, T2-SPACE, DTI diffusion tensor imaging) and functional sequences (resting-state fMRI, task-fMRI), Magnetic Resonance Spectroscopy (MRS), EEG, TMS, assessment of retinal anatomy and electrophysiology by OCT and ERG. Finally, participants may undergo genetic sequencing as well as donate somatic cells to obtain hiPSC. Data is collected and shared in collaboration with the Munich Mental Health Biobank (MMHB). Both the MMHB and CDP study are approved by our local ethics committee (ref. nr. 18-716 and 20-528 respectively).

Results: Between December 2020 and November 2021 a total of 217 subjects were enrolled, including 113 patients (64.6% male) and 104 HC (53.8% male). Patients showed predominantly a multi-episode psychotic disease course. Preliminary data was analyzed and showed a mean age of 38.5 (±10.7) years for PSD patients and 35.8 (±12.3) years for HC.

Discussion: The Clinical Deep Phenotyping (CDP) study will collect multimodal data from a large-scale naturalistic cohort. Results: from this study will provide novel and critical insights into the understanding of complex psychiatric disorders, greatly supporting translational,

individualized, RDoC-based research from bench to bedside. Immediate goal of the CDP study is the definition of sensitive and specific biomarkers or biomarker-clusters to support diagnostic and treatment algorithms of complex psychiatric disorders. Future goals include developing biomarker-stratified clinical trials as well as follow-up data collection for longitudinal studies.

T53. MENTAL HEALTH, RISK AND PROTECTIVE FACTORS AT MICRO- AND MACRO-LEVELS ACROSS EARLY AT-RISK STAGES FOR PSYCHOSIS: THE MIRORR STUDY

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Background: The clinical staging model states that psychosis develops through subsequent stages of illness severity. To better understand what drives illness progression, more extensive comparison across clinical stages is needed. To this end, the Mapping Individual Routes Of Risk and Resilience (Mirorr) study was designed, an in-depth study of individuals with different levels of risk for psychosis (i.e., representing different early clinical stages) that uses a multimethod approach of cross-sectional assessments and daily diary reports. This study presents how psychopathology, well-being, functioning and factors of risk and protection are expressed at the baseline assessment across different early clinical stages, using cross-sectional questionnaires and in-depth daily diary assessments.

Methods: Data came from the Mirorr study that includes N=96 individuals, divided across four subgroups (n1=25, n2=27, n3=24, n4=20). These subgroups, each with an increasing risk for psychosis, represent clinical stages 0-1b. Cross-sectional data and 90-day daily diary data assessed at baseline on psychopathology, well-being, psychosocial functioning, risk and protective factors were statistically compared across subgroups (stages) and descriptively compared across domains and assessment.

Results: The subgroups reported increasing psychotic severity as well as general psychopathological severity, confirming their interpretation as representing increasingly severe (though still early) clinical stages. The subgroups displayed a nuanced profile of differences and similarities. The largest gap between subgroups was sometimes between subgroups 1 versus the other subgroups (suggesting largest differences between non-clinical and clinical populations), sometimes between subgroups 1 and 2 versus subgroups 3 and 4 (suggesting largest differences between those with and without substantial psychotic experiences) and sometimes between subgroup 4 versus the other subgroups (suggesting specific patterns for those at UHR for psychosis). Psychopathology increased across subgroups, although not always linearly and nuanced differences were seen between assessment methods. Well-being and functioning differed mostly between subgroup 1 and the other subgroups, suggesting differences between non-clinical and clinical populations. Risk and protective factors differed mostly between the two highest and lowest subgroups, especially regarding need of social support and coping, suggesting differences between those with and without substantial psychotic experiences. Subgroup 4 (stage 1b) reported especially high levels of daily positive and negative psychotic experiences. Functional challenges already exist in early clinical stages, as individuals in the clinical subgroups were less likely to have contact with their parents, have a partner, friends, or a job/study. However, if individuals did have a partner, friend or job/study, they were generally just as satisfied as individuals from the

non-clinical subgroup. This highlights the importance of supporting individuals to maintain these domains as much as possible, as they may form important sources of life satisfaction.
Discussion: Risk for psychosis exists in larger contexts of mental health and factors of risk and protection that differ across stages and assessment methods. Taking a broad, multi-method approach is an important next step to understand the complex development of youth mental health problems.

T54. PSYCHIATRIC ADMISSION AMONG MIGRANTS: A RETROSPECTIVE STUDY IN ACUTE PSYCHIATRIC WARD IN BOLOGNA, ITALY

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Background: Further evidences underlined higher rate of psychiatric admissions because Schizophrenia Spectrum Disorders (SSD) in migrants compared to natives and differences in psychiatric services use between the two groups of patients.
Our study aims are evaluating incidence and characteristics of psychiatric hospitalizations of migrant patients compared to natives in a well-defined area of the metropolitan city of Bologna and evaluating the effect of the Covid 19 pandemic on the incidence and characteristics of psychiatric hospitalizations.

Methods: This is an observational and retrospective study on migrant and natives urgent psychiatric admission to the psychiatric unit "SPDC-Malpighi" Local Health authority from 01/01/2018 to 31/12/2020.
Results: Both men and women with a migratory background had higher rates of hospitalization due to any psychiatric cause and the difference between migrants and natives was particularly pronounced among the youngest age group (15-24 years), as in this age-band rates were 3 times higher for migrants.
Rates of compulsory treatments were generally similar between the two groups but migrants aged between 15-24 years had a 4-times greater risk of compulsory admission.

With regard to admissions due to a specific disorder, we found relevant differences in hospitalization rates for SSD (Schizophrenia Spectrum Disorder) and MD (Mood disorders). Specifically, migrants had a 1.55 IRR of being admitted for SSD compared with natives. IRR were increased for both males and females of migrant origin and they were particularly high in the youngest age-group (15-24 years) in which the risk is 5 times greater.

Furthermore, migrants were more likely to be admitted via ED and less likely to be referred from a CMHC or from non-psychiatric hospital unit compared with natives. Most migrants were discharged at home while natives more frequently chose to self-discharge.

Discussion: We confirm the presence of differences in access to care, type of discharge and type of diagnosis between migrants and natives. We found higher hospitalization incidence rates for SSD in migrants. Interestingly, we found that differences in hospitalization rates for SSD between migrants and natives was not more statistically significant in 2020 pandemic.

Further studies to investigate changes in pre and post Covid admissions in migrants would be needed.

T55. STATE PARANOIA CHANGES IN LESS FAMILIAR SOCIAL COMPANY: AN EXPERIENCE SAMPLING STUDY

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Background: Paranoia can be understood not only as a stable trait, but it can have substantial day-to-day fluctuations. It often fluctuates in connection to the company an individual is with. Experience sampling studies have identified an important role of present social distress, self-esteem, and type of social company in relation to changes in momentary paranoia, both in clinical and healthy samples. This was most evident in individuals with low and medium levels of trait paranoia, and not in highly paranoid people, in whom paranoia fluctuations are more independent from social context. Building on the previous evidence, we expected that state paranoia levels will be predicted by the type of current social company and that this relationship would be moderated by the level of trait paranoia.
Methods: The present sample consisted of 60 individuals (34 patients with schizophrenia, depression, or anxiety disorders and 26 healthy controls) who completed the selected Methods: in two phases, as a part of a larger study. The Paranoia scale was administered to measure trait paranoia in the survey phase. In the ESM part, participants repeatedly reported state paranoia and social context ten times per day, over six consecutive days. The type of current social company represents how close the present individuals were.
Results: The average compliance to the ESM protocol was 71%. In a multilevel linear regression model, we found all included variables to significantly improve the model fit [$\chi2(4) = 31.04$, $p < 0.001$]. State paranoia was negatively predicted by the type of company [β (S.E.) = -0.10 (0.03), $p < .001$] and was moderated by trait paranoia [β (S.E.) = -0.07 (0.03), $p = .024$]. Trait paranoia also independently predicted state paranoia [β (S.E.) = 0.45 (0.14), $p = .001$]. Moreover, there was a significant positive effect of the presence of diagnosis [β (S.E.) = 0.39 (0.03), $p < .001$], meaning patients experienced higher levels of state paranoia than healthy controls.
Discussion: Individuals experienced higher state paranoia in situations when with less familiar company. The relationship was stronger when taking trait paranoia into account. This is in line with the previous findings showing the importance of social context in explaining and understanding momentary fluctuations in paranoia.
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T56. TRAIT DISSOCIATION CORRELATES WITH INDUCED FEELINGS OF BODY DIS-OWNERSHIP ARISING FROM DISRUPTED MULTI-SENSORY INTEGRATION

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Background: Dissociative experiences, including sensations of detachment from the body, the self, or reality, occur frequently in schizophrenia and are closely associated with other psychotic experiences in clinical and non-clinical groups. Previous research induced dissociative states, namely sensations of body dis-ownership, in otherwise healthy individuals by using augmented or "mixed" reality to delay the visual perception of self- and other-generated touch. This study aimed to test the hypothesised association between induced sensations of body dis-ownership and trait dissociation, and explored behavioural and cardiac responses to multisensory disruption, in a non-clinical sample.
Methods: We recruited 100 participants with no previous psychiatric diagnosis to take part. In the study, a webcam mounted to a virtual reality headset allowed participants to view their body and surroundings through the webcam in real time, as if they weren't wearing the headset at all. During the task, the participant's arms were stroked with a brush by themselves or by the researcher. A delay, ranging from 0-1s, was applied to the visual image on the headset, causing a delay between the sight and feel of the tactile sensation. Participants rated the perceived synchrony of the visuo-tactile experience and their sense of ownership over their own body. Electrocardiography recorded cardiac response to the task. Trait measures of dissociation (Cambridge Depersonalisation Scale) and anomalous perceptions (Cardiff Anomalous Perceptions Scale) were also completed.
Results: Increased visual delay led to greater feelings of dis-ownership over the body, and these induced feelings of dissociation significantly correlated with trait measures of dissociative experiences ($r = 0.35$) and anomalous perceptual experiences ($r = 0.29$). On average, asynchrony between vision and touch was noticed at earlier times for self-generated touch ($M = 261$ms) compared to other-generated touch ($M = 290$ms), and sensitivity to the asynchrony for self-generated touch was significantly correlated with trait dissociation ($r = -0.26$). Distinct cardiac signals arose for self- and other-generated touch, but this distinction was less apparent for people with higher scores on trait dissociation measures.
Discussion: Our findings suggest that induced dissociative experiences have relevance for trait dissociative experiences which are common in psychosis. Furthermore, the Results: point to a particular role for disrupted multisensory integration of self-touch in dissociative experiences, as demonstrated by both behavioural and physiological responses. Not only does this work enhance our understanding of dissociation, a common experience in psychosis, but it also offers the first evidence that inducing dissociation in a controlled manner may prove to be a useful tool in clinical practice to assess and train effective ways of coping with dissociative experiences.

T57. CLINICAL VALIDATION OF RATINGS ON THE SIX-ITEM POSITIVE AND NEGATIVE SYNDROME SCALE OBTAINED VIA THE SIMPLIFIED NEGATIVE AND POSITIVE SYMPTOMS INTERVIEW AMONG OUTPATIENTS WITH SCHIZOPHRENIA

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Background: The six-item Positive and Negative Syndrome Scale (PANSS-6) is a scalable measure of the severity of core symptoms of schizophrenia, which can be obtained via the brief semi-structured Simplified Negative and Positive Symptoms Interview (SNAPSI). A recent study of inpatients with schizophrenia confirmed the validity of PANSS-6 ratings obtained via SNAPSI. However, research has not yet tested the validity of the PANSS-6+SNAPSI combination among outpatients.
To test the clinical validity of PANSS-6 ratings obtained via SNAPSI (PANSS-6-SNAPSI) among outpatients with schizophrenia using PANSS-6 ratings extracted from the 30-item Positive and Negative Syndrome Scale and obtained via the Structured Clinical Interview for the Positive and Negative Syndrome Scale (PANSS-6-SCI-PANSS) as the gold standard reference.

Methods: PANSS-6-SNAPSI and PANSS-6-SCI-PANSS ratings were obtained by independent raters with established inter-rater reliability (group-wise). Agreement between PANSS-6-SNAPSI and PANSS-6-SCI-PANSS was estimated via the intra-class coefficient (ICC). Post hoc analyses included the "leave-one-out" approach in which one rater at a time was excluded from the ICC analysis.
Results: Seventy-three outpatients with schizophrenia participated in the study (mean age 38.3 years, 56% males). The ICC for PANSS-6-SNAPSI versus PANSS-6-SCI-PANSS was 0.67 [95%CI = 0.56–0.76], with ICC at item level ranging from 0.40 (item P2 - conceptual disorganization) to 0.83 (item P3 - hallucinatory behavior). When excluding one specific rater, the ICC increased to 0.75 [95%CI = 0.63–0.83], with ICC at item level ranging from 0.49 (item P2 - conceptual disorganization, item N1- blunted affect and item N4 - passive/apathetic social withdrawal) to 0.81 (item P3 – hallucinatory behavior). Detailed Results: of the study will be presented at the SIRS 2022 Conference.
Discussion: We found acceptable clinical validity of PANSS-6-SNAPSI ratings, suggesting that PANSS-6-SNAPSI can be used for both inpatients and outpatients with schizophrenia.

T58. PROGNOSTIC ACCURACY AND CLINICAL UTILITY OF PSYCHOMETRIC INTERVIEWS FOR INDIVIDUALS AT CLINICAL HIGH RISK FOR PSYCHOSIS: A META-ANALYSIS

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Background: Accurate detection of individuals at clinical high risk for psychosis (CHR-P) is the essential initial step for effective primary indicated prevention. However, current knowledge is limited by a lack of an up-to-date synthesis of the available evidence. We aimed to summarise the prognostic accuracy and clinical utility of psychometric instruments for primary indicated psychosis prevention.
Methods: We first identified studies from the previous meta-analysis before searching Web of Knowledge databases until 29th November 2021. We then manually searched references of identified articles. Longitudinal studies were considered for inclusion if they followed-up individuals assessed with psychometric and clinical instruments for CHR-P, reporting transition to psychotic disorders in both those who meet CHR-P criteria (CHR-P+) and those who do not (CHR-P-).
We conducted a prognostic accuracy meta-analysis compliant with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines; independent data extraction. Primary outcome was prognostic accuracy, indexed by area-under-the-curve (AUC), sensitivity and specificity, estimated by the number of true positives, false positives, false negatives and true negatives at the longest available follow-up time. Primary outcome was prognostic accuracy, indexed by area-under-the-curve (AUC), sensitivity and specificity, estimated by the number of true positives, false positives, false negatives and true negatives at the longest available follow-up time. Prognostic accuracy meta-analyses were conducted using the MIDAS package in STATA 14. Further prognostic accuracy analyses included: summary receiver operating characteristic curves, study quality assessment, meta-regressions and sensitivity analyses. Clinical utility analyses included: probability modifying plots, likelihood ratios and Fagan's nomogram.

Results: A total of 19 studies including 4,700 individuals assessed by CHR-P instruments were included. Prognostic accuracy was excellent: AUC=0.85 (95% CI: 0.82-0.88) at a mean follow-up time of 35 months. This result was driven by an outstanding sensitivity (0.93, 95% CI: 0.88-0.96) and a poor specificity (0.57, 95% CI: 0.49-0.65). Being CHR-P+ was associated with a small likelihood ratio (LR)+ (2.17, 95% CI: 1.81-2.60). Being CHR-P- was associated with a large LR- (0.11, 95% CI: 0.06-0.21).
Discussion: These findings consolidate the use of psychometric instruments for CHR-P in help-seeking individuals for primary indicated prevention of psychosis. There is still insufficient evidence to determine the prognostic accuracy of clinical instruments. Future research should improve ability to rule in psychosis, either through changes to the assessment instruments themselves or enriching pre-test psychosis risk.

T59. AUTONOMIC AND SUBJECTIVE RECOVERY AFTER AN EXPERIMENTAL STRESSOR IN PSYCHOSIS AND HEALTHY CONTROLS

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Background: Individuals with psychotic disorders (PSY) experience heightened levels of autonomic and subjective arousal, which are linked to the occurrence of psychotic symptoms. To prevent high stress levels, it is decisive to determine how these build up. One mechanism can be

deficits in the downregulation of arousal after the exposure to a stressor (i.e., deficient recovery). This appears likely since a reduced resting-state heart rate variability (HRV) and difficulties in volitional emotion regulation are observed in PSY and are both associated with stress recovery in non-clinical samples. Some studies so far suggest a prolonged stress response in PSY, however, it remains unclear whether PSY show deficits in both the autonomic and subjective recovery and which characteristics predict the recovery. Thus, we compared autonomic and subjective recovery in PSY to healthy controls (HC) and examined whether a higher resting-state HRV and more functional emotion regulation are predictive of a faster recovery.

Methods: We assessed resting-state HRV and self-reported functional emotion regulation one week before a stress induction paradigm with a combined physical and cognitive stressor. After the stress exposure, we investigated autonomic recovery (i.e., decrease in heart rate, increase in HRV) and subjective recovery (i.e., decrease in subjective stress and negative affect) in PSY (n = 50) and HC (n = 50) over the recovery phase of one hour. We analyzed group differences in a) initial recovery (i.e., 7min post stressor) and b) total recovery (i.e., 60min post stressor) with repeated-measures ANOVAs and c) conducted paired t-tests to analyze whether PSY returned to baseline later than HC. We used linear regressions to analyze whether resting-state HRV and functional emotion regulation predict recovery rates of autonomic and subjective arousal.

Results: The expected time × group interactions only emerged for subjective stress: a) initial recovery, $F(2.55, 250.28) = 3.20$, $p = .03$; b) total recovery, $F(1.97, 193.08) = 3.65$, $p = .029$). Post-hoc tests revealed that HC showed a steeper decline in subjective stress than PSY. During total recovery, heart rate, subjective stress, and negative affect decreased and HRV increased in both groups. Generally, PSY showed higher levels of subjective stress and negative affect than HC but there were no group differences in levels of autonomic arousal. In both groups, all parameters c) returned to baseline at the first measurement-point after the stressor, with no significant group differences. Resting-state HRV predicted the recovery rate of heart rate, $b = -0.01$, $SE = .00$, $p = .005$ ($f = 0.28$), and functional emotion regulation predicted the recovery rate of HRV, $b = 0.09$, $SE = .04$, $p = .021$ ($f = 0.21$).

Discussion: No evidence of general deficits in stress recovery in PSY emerged, which suggests that hyperarousal in PSY is not satisfactorily explicable by a prolonged acute stress response. Nevertheless, the study points to a delayed recovery in the subjective experience of stress, which could contribute to constantly heightened stress levels. Future research needs to examine whether this generalizes to other types of stressors in ecologically more valid designs. Interventions to increase resting-state HRV and emotion regulation seem a promising approach to improve autonomic recovery, but further research is needed to explore whether this could prevent the occurrence of psychotic symptoms.

T60. IMPLICATIONS OF AWARENESS OF ILLNESS IN THE SELF-ASSESSMENT OF PSYCHOTIC SYMPTOMS IN PATIENTS WITH SCHIZOPHRENIA AND OTHER RELATED DISORDERS

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Background: As new patient-reported outcome measures (PROMs) and symptom self-report scales are being developed in psychiatry, concerns about their reliability and validity in patients with schizophrenia and other related disorders still arise. Patients suffering from psychotic symptoms are typically believed to be an unreliable source of information for self-reported tools because of low awareness of illness, also known as lack of insight or anosognosia, which is considered a key feature of psychotic disorders. The aim of this study is to elucidate the effects of insight on the accuracy of self-reported psychotic symptoms in patients with schizophrenia and other related disorders, using a recently developed and validated, digital computerized adaptive testing (CAT) tool to evaluate severity of psychotic symptoms (CAT-Psychosis).
Methods: Patients diagnosed with schizophrenia and other related disorders were recruited from inpatient units and outpatient clinics to ensure a broad range of symptomatology severity. Clinicians conducted semi-structured interviews to rate psychosis severity and awareness of illness using the Brief Psychotic Rating Scale (BPRS) and the Scale of Unawareness of Mental Disorders (SUMD), respectively. Patients rated themselves with the self-administered version of the CAT-Psychosis using tablet computers with touch screens. Since both psychosis assessments can potentially make patients more aware of their symptoms, testing order (BPRS first or CAT-Psychosis first) was randomly assigned to control for bias. Pearson correlation coefficients were used to analyze the convergent validity of CAT-Psychosis and BPRS ratings. SUMD scores were used to median-split patients in two groups regarding their insight level. Finally, a moderated regression analysis was performed to quantify the impact of insight in the correlation between the two psychosis severity measures.
Results: Eighty-eight patients with schizophrenia and other related disorders (n = 76 schizophrenia, n = 7 psychosis not otherwise specified, n = 5 schizophreniform disorder) completed the self-administered version of CAT-Psychosis and the clinician-rated BPRS and SUMD, and thus were included in this analysis. For this sample, self-administered CAT-Psychosis showed convergent validity with total BPRS scores ($r = 0.547$; 95% CI: 0.367–0.726; $p < 0.001$). SUMD scores were found to moderate this correlation ($\beta = –0.560$, $p = 0.041$). Patients with lower insight showed less agreement between clinician-rated and self-reported psychosis severity scores ($r = 0.645$, 95% CI: 0.415–0.874, $p < 0.001$ for high insight patients, and $r = 0.441$, 95% CI: 0.150–0.732, $p = 0.002$ for low insight patients). No statistically significant differences were found in BPRS ($U = 892$, $z = -0.599$, $p = 0.549$) and CAT-Psychosis ($U = 871$, $z = -0.774$, $p = 0.439$) scores between high and low insight patients.
Discussion: Our results indicate that insight modifies the accuracy of self-reported psychotic symptoms in patients with schizophrenia and other related disorders. In our sample, patients with lower insight were found to have a slightly worse correlation between self-reported and clinician-rated symptomatology, even though psychosis severity scores were similar between high and low insight patients. Noteworthy, patients with lower insight were still able to correctly and accurately identify their symptoms, as correlations between CAT-Psychosis and BPRS scores remained statistically significant in both groups.

T61. CURRENT HOT TOPICS IN DELUSIONAL DISORDER MANAGEMENT: A SYSTEMATIC REVIEW FOCUSED ON CLINICAL OUTCOMES

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Background: For many decades, delusional disorder (DD) has been considered a difficult-to-treat disorder with poor clinical outcome. Prior research indicates that antipsychotics and antidepressants are the main treatments used for DD, while psychotherapy, particularly cognitive behavioral therapy (CBT), is the treatment based on the best efficacy evidence. Recently, several investigators have tried to redefine and to optimize treatment outcomes in DD. One intriguing question is the precise role played by antidepressants.

Methods: A systematic review of the literature available on PubMed from its inception until October 2021 was carried out according to the following the PRISMA directives. Search terms: (delusional disorder) AND (depression OR antidepressants). Inclusion criteria: systematic reviews, original studies or case series addressing at least one of the following questions concerning DD: (1) What comes first in DD, depression or delusion? (2) Is depression a comorbidity or is it part of the psychopathological structure of DD? (3) Should antidepressant prescription be restricted to the presence of depressive symptoms? (4) Do enduring affective symptoms contribute to the traditional concept of DD as a treatment resistant disorder?

Results: A total of 2,215 records were initially identified, of which 26 fulfilled our inclusion criteria.

(1) Time sequence. The onset of mood symptoms can precede or follow the onset of DD (<50%) (2 studies). Patients with affective symptoms were younger, showed an earlier age at onset, and sought treatment earlier than those without affective symptoms.

(2) Comorbidity. Factor analyses of DD symptomatology revealed that core depressive/irritability symptoms were present in the structure of DD (two studies). One study identified 5 psychopathological dimensions of the psychosis spectrum in DD, one of the five being depression. Internalizing attributional styles in DD were seen in two studies. The fact that depressive symptoms are frequent in DD (21-55.8%), and past history of depression in relatives, however, suggests comorbidity.

(3) Antidepressants. Rates of antidepressant prescription are low in DD, 80% of which are given to patients seen as suffering from comorbid depression; 20% in somatic type. Response to antidepressants is rarely reported in studies. (<10%).

(4) Treatment resistance. This has not been investigated through the lens of depression or antidepressant efficacy. It is usually attributed to cognitive deficits.

Discussion: Future research should elucidate whether depressive symptoms are a core part of the psychopathological structure of DD, and not merely a psychiatric comorbidity. The first hypothesis is supported by the fact that antidepressants are also prescribed in DD cases who do not show depressive symptoms (e.g. DD, somatic type). Obtaining an accurate timeline for onset and progression of symptoms, perhaps from a 3rd party, may lead to early antidepressant or CBT treatment, potentially preventive of delusion formation - a form of staged treatment for DD.

T62. TELEHEALTH OF COORDINATED SPECIALTY CARE IN EARLY PSYCHOSIS DURING COVID-19

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Background: During the coronavirus (COVID-19) pandemic, mental health transitioned to telehealth to comply with social distancing guidelines. While telehealth is not a novel health care delivery. COVID-19 has accelerated wide-scale use and facilitated implementation due to policy changes and recent technological advances. Over the past 10 years, telehealth has been promoted for mental health interventions, including psychotherapy and medication management. It is particularly important to evaluate telehealth delivery in coordinated specialty care (CSC) clinics treating individuals with early psychosis (EP). In this population accessing care can be challenging and longer duration of untreated psychosis is associated with poorer clinical and functional outcome.

Methods: Young persons 16-30 years who are experiencing EP characterized by meeting threshold psychosis symptoms within 24 months prior to admission, (i.e., FEP) or attenuated psychosis symptoms (i.e., CHR). Participants are eligible for CSC for a period of two years and may transition to our 12-month "stepped care" program while establishing care with other providers.

Beginning in March 2020, transition to telehealth only occurred using HIPAA-approved video telehealth services with gradual opening to hybrid virtual and in-person visits by July 2020.

We compared use of core clinical services pre-COVID (Sep2019-Feb 2020) to services during COVID (Mar2020-Jul2021), including medication management, recovery-oriented cognitive therapy and case management, supported education and employment services, certified peer-support, and monthly family educational groups.

Results: New enrollment at the Psychosis Evaluation and Recovery Center (PERC) at the University of Pennsylvania included 19 persons during the pre-COVID and 33 person during the COVID periods. As of July 2021, 49 persons were enrolled in CSC. Comparing specific services, we found that after an initial decrease in utilization and new referrals, was an quick acceptance or virtual services.

Discussion: The abrupt onset of COVID-19 restrictions in March 2020 posed unforeseen challenges to ensure mental health care during the pandemic, from a public health perspective and, in particular for health care personnel and clinical populations. Our CSC for EP program quickly implemented telehealth services and we were impressed by the positive acceptance by our clients. For most participants telehealth provided an effective delivery of care option with less disruption

in other daily activities and obligations, such as school or work. Ongoing data review will offer support to continue a hybrid model of telehealth and in-person services within CSC for EP beyond COVID-19, as clinically and economically feasible.

T63. A NOVEL NEUROIMAGING SCORE TO AID IN EARLY DETECTION OF PSYCHOSIS

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Background: Structural brain alterations in adults with psychosis are well-established. However, case-control differences of individual brain regions account for only a small amount of the variance. By leveraging Methods: used in psychiatric genetics (i.e., polygenic scores), we can use the schizophrenia vs. control group difference effect sizes in brain structure and enhance our ability to identify youth in the earliest phases of psychosis. Furthermore, by considering age associated changes in brain structure, we may improve the portability of this score in youth.
Methods: FreeSurfer was used to calculate cortical thickness, cortical surface area, and subcortical volumes (N measures=152) in two independent samples of adults with schizophrenia vs. healthy controls (COBRE, BSNIP). We weighted the participants' brain region measures by the effect size associated with group differences reported in ENIGMA schizophrenia working group publications. From these weighted scores, we created a cumulative score, i.e., the "Psychosis Neuroimaging Score" and optimized this score in the two samples. For both cohorts, we iteratively tested the number of individual brain regions that provided optimal discriminability between case-control strongest effect size, calculated the Psychosis Neuroimaging Score using that number of regions. Using five-fold cross-validation, we created a receiver operating characteristic curve, and estimated the area under the curve (AUC) to determine the accuracy of the classifier. We used DeLong's test to assess if classification performance in these two samples was better than chance. Next, in a large archival sample of aggregated sample of youth with harmonized structural neuroimaging scores, we used generalized additive models to characterize the normative neurodevelopmental trajectory of the Psychosis Neuroimaging Score. Then, based on chronological age, we calculated the 'expected' Psychosis Neuroimaging Score for youth in the Philadelphia Neurodevelopmental Cohort. For each individual, we subtracted the predicted Psychosis Neuroimaging Score from the true Psychosis Neuroimaging Score, i.e., the Psychosis Deviance Index. We then assessed the ability of this score to differentiate between youth with psychosis spectrum symptoms and typically developing youth.
Results: In two samples, COBRE (N schizophrenia=76; N control=90) and BSNIP (N schizophrenia=124, N control=136), the Psychosis Neuroimaging Score discriminated between schizophrenia and controls with good accuracy (AUC COBRE=0.75, AUC BSNIP=0.72). Classifiers performed significantly better than chance (COBRE: Z=6.4,p=1.4e-10; BSNIP: Z=6.7,p=2.4e-11). In each sample, this score accounted for >10% more of the variance in case-control status than the individual measure with the greatest effect size. In the large aggregated cohort of youth (N=5268, 1-30 years) we found that the Psychosis Neuroimaging Score significantly increased with increasing age (15-30 years old). Finally, in the PNC cohort, we found that youth with psychosis spectrum symptoms (N=426) had a greater Psychosis Deviance Index in comparison to typically developing youth (N=783,p<.001).

Discussion: The Psychosis Neuroimaging Score improves our ability to discriminate between individuals with and without a diagnosis of schizophrenia. The Psychosis Deviance Index may help improve our ability to detect early stages of psychosis in youth.

T64. DEVELOPMENT AND IMPLEMENTATION OF CONVERT: A DIGITAL ALGORITHM TO FACILITATE LARGE-SCALE RESEARCH IN SUBJECTS AT CLINICAL HIGH RISK FOR PSYCHOSIS

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Background: Clinical High Risk for Psychosis (CHR-P) is a construct that captures the pre-psychotic phase, when an individual presents with at-risk symptoms. There is enormous interest to identify CHR-P subjects to effectively intervene before the potential transition to psychosis occurs. For this reason, psychometric (semi-structured) interviews have been developed to detect CHR-P (CAARMS 12/2006 and the SIPS 5.0 are mostly used). However, operationalisation differences exist between both instruments, leading to potential inconsistencies for CHR-P research. To overcome this problem, an algorithm to convert outcomes between the two interviews has been developed (CONVERT) and previously externally validated in a retrospective dataset, demonstrating a substantial accuracy. To date, no study has implemented the algorithm in a new prospective multi-centre dataset.
Methods: Therefore, the aims of this project were two-fold. First, we fine-tuned the algorithm code in Python to refine it by improving its functionality according to new psychometric updates of the CHR-P interviews, as well as its user experience and accessibility (algorithm development). Second, we implemented the algorithm on data from PSYSCAN, a multi-centre study comprised of 243 referrals to 10 clinics assessed for a CHR-P state in the period September 2016 – March 2020. The CONVERT algorithm (CAARMS-to-SIPS) was run on Python 3.8.2, to convert diagnostic outcomes (CHR-P−, CHR-P+ [GRD, APS, and BLIPS], and Psychosis) from CAARMS to SIPS (algorithm implementation). To compare the diagnostic outcomes IBM SPSS Statistics 22 was used. Percentage overall agreement, Fleiss's Kappa (an adapted kappa for multiple rather than binary categories), and the McNemar-Bowker $\chi 2$ test were calculated. The quantitative analysis was followed by a qualitative analyses to investigate any sources of disagreement between the CAARMS and the converted-SIPS outcomes.
Results: The refined algorithm displayed an overall adequate CAARMS versus- converted SIPS agreement in the identification of subject's outcomes (n=187, overall agreement=67.91%; Fleiss's kappa=0.153, 95% CI=0.043-0.263; McNemar-Bowker $\chi 2$=45.231, p<0.001). The qualitative analysis suggests that the algorithm accurately captures real disagreement which is due to core psychometric differences between the two interviews.
Discussion: The present study is the largest CONVERT implementation study since the tool was created.
Changes were made to the algorithm code to improve accessibility and usability for future

researchers and clinicians. Moreover, a multi-centre study like PSYSCAN enhances generalisability due to varied patient populations and recruitment strategies. We hope these findings will inform the next phase, which will consist of an external validation study, currently under planning. Ultimately, we anticipate the algorithm will be useful to facilitate large-scale analyses across different CHR-P datasets by enable data-merging to ensure adequate statistical power and therefore improve the validity of research findings in this field. Standardising the CHR-P interview is especially relevant in a field like clinical psychiatry, where no objective measures/exams exist to establish a diagnosis, other than clinical impression. Moreover, this tool would reduce the time/cost burden of repeating both the CAARMS and SIPS for each subject in future research.

T65. CANNABIS USE AS A POTENTIAL MEDIATOR BETWEEN CHILDHOOD ADVERSITY AND PSYCHOSIS: RESULTS: FROM THE EU-GEI STUDY

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Background: Childhood adversity and cannabis use are considered independent risk factors for psychosis, but whether cannabis use may be acting as mediator between adversity and psychotic disorders has not yet been explored. The aim of the study is to examine whether cannabis use in adolescence mediates the relationship between childhood adversity and psychotic disorders.
Methods: 853 first-episode psychosis patients and 1,174 controls were recruited as part of the EU-GEI study. Detailed history of cannabis use was collected with the Cannabis Experience Questionnaire. The Childhood Experience of Care and Abuse Questionnaire was used to assess exposure to household discord, sexual, physical or emotional abuse and bullying in two periods: early (between birth and age 12), and late (between 12 -17 years). Following Baron and Kenny's criteria, we performed mediation analyses to assess whether the association between childhood adversity and psychosis was mediated by (1) lifetime cannabis use, (2) cannabis potency, and (3) frequency of use. Each putative mediator was entered in separate models to investigate their individual impact on the relationship.
Results: The association between household discord and psychosis was partially mediated by lifetime use of cannabis (indirect effect coef. 0.064, 19%), its potency (indirect effect 0.059, 20%), and totally mediated by frequency of use in adolescence (indirect effect 0.103, 42%). Similar findings were obtained when the analyses were restricted to early exposure to household discord. Both lifetime cannabis use (indirect effect coef. 0.081, 17%) and potency (indirect effect coef. 0.084, 18%) totally mediated the association between early psychological abuse and psychosis.
Discussion: The mediational role of cannabis use was particularly robust for experiences of household discord and psychological abuse relative to other types of trauma, such as physical and sexual abuse, and bullying. For that reason, children and adolescents exposed to particularly

challenging environments in their household could benefit from psychosocial interventions aiming at preventing cannabis misuse, particularly during adolescence.

T66. HYPERPROLACTINEMIA IN DRUG-NAïVE FIRST EPISODE PSYCHOSIS AND ITS POSITIVE ASSOCIATION WITH SERUM BDNF LEVELS AT BASELINE

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Background: The relationship between prolactin and schizophrenia has been largely studied and it is widely accepted that hyperprolactinemia is a frequent adverse event of antipsychotic treatment. However, the relationship between hyperprolactinemia and schizophrenia might be more complex, and not only a consequence of antipsychotic treatment.
Studies in drug – naïve first episode psychosis (FEP) show contradictory Results: in this issue. Whereas some initial studies reported lower or normal serum prolactin levels, recent other works have found higher prolactin levels in these patients and even in individuals at clinical high risk for developing a psychotic disorder.

It is known that brain derived neurotrophic factor (BDNF) has a key role in neural survival and network plasticity and has been involved in the etiopathogenesis of psychotic disorders. Nevertheless, the association between BDNF and prolactin has been poorly studied.

With this study, we want to know how BDNF levels at baseline in drug-naïve FEP are influenced by prolactin.

Methods: Fifty drug-naïve FEP treated between April 2013 and July 2017 at the ETEP Program at Hospital del Mar were included. Inclusion criteria were: 1) age 18-35 years; 2) fulfillment of DSM-IV-TR criteria for brief psychotic disorder, schizophreniform disorder, schizophrenia or unspecified psychosis; 3) no previous history of severe neurological medical conditions or severe traumatic brain injury; 4) presumed IQ level > 80, and 5) no substance abuse or dependence disorders except for cannabis and/or nicotine use. All patients underwent an assessment at baseline including sociodemographic and clinical variables (substance use, DUP, PANSS, GAF and CDSS). Fasting blood samples were obtained before administering any medication at baseline and used to determine prolactin levels and BDNF levels. SPSS program was used for statistical analyzes.
Results: In our drug-naïve FEP sample, the 43.5% of patients had hyperprolactinemia (> 530 mcIU/mL) at baseline and prolactin levels showed a significative positive correlation with BDNF levels at baseline ($r = 0.521$; $p = 0.011$). Moreover, we did a lineal regression model (STEP-WISE METHOD) that showed that the baseline variables that better predict BDNF levels were prolactin levels (B = 0.14, 95% CI 0.01 to 0.02; $p = 0.012$) cannabis use (B = -1.23, 95% CI -2.21 to -0.26; $p = 0.016$) and DUP (B = -0.12, 95% CI -0.22 to -0.02; $p = 0.020$).

Discussion: Our Results: suggest that could be a dysregulation of prolactin secretion in drug-naïve FEP, thus the frequent hyperprolactinemia in FEP patients would not be only related to antipsychotic treatment.
Moreover, it has been shown that prolactin has extensive effects on the central nervous system, including metabolism of neurotransmitters and neuropeptides, and stress responses. One study found that prolactin could inhibit hippocampal neurons apoptosis in a mouse model of induced depression through the activation of JAK/STAT signaling pathway.

The JAK/STAT signaling pathway is involved in processes such as immunity, cell division and cell death, and it is also activated by BDNF [8]. Taking this into account and our results, we suggest that the prolactin neuroprotective effect could be mediated through the increase of BDNF levels.

Nevertheless, it is also possible that both prolactin and BDNF levels were increased as a stress response. Unfortunately, the nature of this study can't elucidate this fact, and neither if the relationship between BDNF and prolactin is a cause or a consequence. More studies have to be done to clarify this issue.

T67. HIPPOCAMPAL SUBFIELDS ARE DIFFERENTIALLY ASSOCIATED WITH CORTISOL AND DAILY STRESSORS IN INDIVIDUAL AT CLINICAL HIGH-RISK FOR PSYCHOSIS

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Background: Robust literature implicates the hippocampus as an important structure affected by stress during psychosis pathogenesis. Both biological and environmental indicators of stress are associated with reduced hippocampal volumes in individuals with psychosis. While evidence suggests that hippocampus is affected, cortisol levels altered, and exposure to environmental stress prominent prior to illness onset, investigations on the critical links between stress and hippocampal volumes during the psychosis risk period are lacking.
Methods: A total of 51 clinical high-risk (CHR, mean age 18.61, SD=1.83) and 70 healthy control (mean age 18.30, SD=2.57) participants completed all study procedures. Structural scans were acquired using a 3-Tesla magnetic resonance imaging. Hippocampal subregions (cornu amonis (CA)1, CA2_3, CA4_dentate gyrus (DG), presubiculum, and subiculum) were extracted using Freesurfer hippocampal segmentation package. Three saliva samples were collected the morning of clinical interviews to assess resting cortisol levels. The mean value of the samples was used in analyses. Daily stress inventory (DSI) was used to assess distress of daily stressor exposure. Partial correlations were used to examine the relationship between hippocampal volumes and stress measures in the CHR group. Multiple linear regressions were employed to explore the group differences in the relationship between hippocampal subfield volumes and stress measures. Age and intracranial volume were used as covariates in all analyses.
Results: Correlational analyses in the CHR group indicated divergent associations between hippocampus and cortisol and hippocampus and environmental stressors. Specifically, greater resting cortisol levels were significantly associated with reduced volume in presubiculum ($r=-.4$, $p=.006$) and at a trend level in subiculum ($r=-.22$, $p=.13$). Cortisol was not associated with volumes

in CA1 (r=.09, p=.58), CA2_3 (r=.1, p=.52), or CA4_DG (r=-.005, p=.97). Conversely, correlational analyses demonstrated significant associations between higher DSI and lower volumes in CA1 (r=-.37, p=.009) and CA2_3 (r=-.29, p=.04) and at a trend level in CA4_DG (r=-.28, p=.06). DSI was not significantly associated with volumes in presubiculum (r=-.09, p=.56) or subiculum (r=-.17, p=.2).
Further, multiple linear regressions indicated stress by group interactions predicted relevant subfield volumes. In the first model (R2=.38, F(5, 102)=12.29, p<.0001), cortisol (□=-.72, p=.007), group (□=-.16, p=.047), and cortisol by group interaction (□=.61, p=.02) significantly predicted presubiculum volume. In the second model (R2=.38, F(5, 96)=11.83, p<.0001), main effect of DSI (□=-.68, p=.01) but not group (□=.11, p=.18) significantly predicted CA1 volume, and their interaction was a significant predictor (□=.57, p=.03). Lastly, in the third model (R2=.48, F(5, 96)=17.46, p<.0001), only DSI significantly predicted CA2_3 volume (□=-.51, p=.03); group was not a significant predictor (□=.12, p=.12), and their interaction was at trend level (□=.47, p=.051).

Discussion: Taken together, the Results: indicate that biological and environmental indicators of stress are related to hippocampal atrophy prior to psychosis onset. Moreover, different subfields were differentially affected. Whereas subiculum and presubiculum were associated with cortisol, CA1, CA2_3, and CA4_DG were associated with daily stressors. These findings suggest possible diverging mechanism by which different areas in the in the hippocampus are damaged by stress. Lastly, these effects were specific to the CHR group implicating hippocampal atrophy via alterations in the stress systems as risk factor for developing psychosis.

T68. INTACT MISMATCH-NEGATIVITY IN EMERGING PSYCHOSIS: EVIDENCE FROM MAGNETOENCEPAHLOGRAPHY

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Background: Auditory Mismatch Negativity (MMN) is an event related potential that is elicited by irregularities in a constant auditory stream, such as during an oddball paradigm, where repetitive standard sounds are interspersed with infrequent deviants (Näätänen et al. 2007). Reductions in MMN-responses are well established in schizophrenia (Umbricht and Krljes, 2005). However, evidence for MMN impairments in participants at Clinically High Risk for Psychosis (CHR-P) is less well-established. Here, we examined magnetoencephalographically (MEG) recorded MMN-responses in a CHR-P group as well as in a sample of patients with a first-episode of psychosis (FEP) to establish whether MMN responses are impaired during emerging psychosis.
Methods: We recorded 248 channel whole head MEG data from a total of 236 subjects (140 females): 116 CHR-P, 33 FEP, 38 low risk for psychosis and 49 healthy controls. They were

presented with trains of sequences of 5 harmonic tones (400 Hz + 800 Hz sinusoids, 80 ms long and 150 ms sound onset asynchrony, probability of 60%) with infrequent duration deviants (40 ms long, probability of 20%). To control for potential attentional differences between groups, participants were presented with a rapid visual letter detection task time locked to auditory stimuli where targets.
Evoked response fields (ERF) were computed on -0.7s to 1.2s long epochs, 20 Hz low pass filtered, with baseline correction. Linearly Constrained Minimum Variance beamformer was used for source localisation and time series extraction from virtual electrodes. Time-frequency representations (TFRs) as well as inter-trial phase-coheren (ITPC) was computed for each virtual electrode using the multitapers algorithm ranging from 1 to 20 Hz with a sliding 500 ms time window.

Results: Task performance for all participants was at ceiling (97.8% accuracy), although the FEPs were less accurate than controls (p=0.05). Sensor-level ERFs showed that all groups had a significant MMNm response between 165-185 ms and there were not differences between groups. Virtual electrode time series indicated that both CHRs and FEPs showed a significant MMNm response in Heschl's Gyrus (HG), Superior Temporal Gyrus (STG), Rolandic, Thalamus on the right hemisphere but not on the left hemisphere while MMNm was present bilaterally in controls. However, MMNm response was not reduced in CHRs and FEPs as compared to controls.

In TFRs, enhanced theta power during MMN response was observed in HG, STG, Rolandic bilaterally in CHR-P and controls while only on the right hemisphere in the FEPs. However, similarly to ERF-data, there were no group differences.

In CHRs, ITPC was enhanced during MMN response in theta (4-8 Hz) band in HG, STG, Rolandic on the right hemisphere and bilaterally in alpha (8-12 Hz) band while there was no such enhancement in FEPs or controls. However, similarly to ERF-data, there were no group differences.

Discussion: In summary, we detected robust MMN responses in both CHR-P and FEP-groups that were not reduced in amplitude relative to controls. Similarly, there were no reductions in spectral power and ITPC at theta- and alpha-band frequencies. The lack of MMN-related deficits in the current study are discussed in the context of attentional manipulations and the utilization of different auditory paradigms to elicit MMN-responses.

T69. EVIDENCE OF METABOLIC SUBGROUPS IN FIRST-EPISODE PSYCHOSIS: A META-ANALYSIS OF VARIABILITY

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Background: First-episode psychosis (FEP) is associated with metabolic alterations. However, it is not known if there is heterogeneity in these alterations beyond what might be expected due to

normal individual differences, indicative of subgroups of patients at greater vulnerability to glucose/lipid dysregulation.
Methods: We employed meta-analysis of variance, indexed using coefficient of variation ratio (CVR), to compare variability of the following metabolic parameters in antipsychotic naïve FEP and controls: fasting glucose, glucose post-oral glucose tolerance test (OGTT), fasting insulin, insulin resistance, haemoglobin A1c (HbA1c), total-cholesterol, low density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL)-cholesterol, and triglycerides. Standardised mean difference in metabolic parameters between groups was also calculated; meta-regression analyses examined physiological/demographic/psychopathological moderators of metabolic change.
Results: 28 studies were analysed (1716 patients, 1893 controls). Variability of fasting glucose (CVR=1.32; 95%CI:1.12-1.55;p=0.001), glucose post-OGTT (CVR=1.43; 95%CI:1.10-1.87;p=0.008), fasting insulin (CVR=1.31; 95%CI:1.09-1.58;p=0.01), insulin resistance (CVR=1.34; 95%CI:1.12-1.60;p=0.001), HbA1c (CVR=1.18; 95%CI:1.06-1.27;p<0.0001), total-cholesterol (CVR=1.15; 95%CI:1.01-1.31;p=0.03), LDL-cholesterol (CVR=1.28; 95%CI:1.09-1.50;p=0.002), and HDL-cholesterol (CVR=1.15; 95%CI:1.00-1.31;p<0.05), but not triglycerides, was greater in patients than controls. Mean glucose, glucose post-OGTT, fasting insulin, insulin resistance, and triglycerides were greater in patients; mean total-cholesterol and HDL-cholesterol were reduced in patients. Increased symptom severity and female sex were associated with worse metabolic outcomes.
Discussion: Patients with FEP present with greater variability in glucose/lipid parameters relative to controls, consistent with a subgroup of patients with more severe metabolic changes than others. Understanding determinants of metabolic variability could help identify patients at risk of developing metabolic syndrome. Female sex and severe psychopathology are associated with poorer metabolic outcomes, with implications for metabolic monitoring in clinical practice.

T70. GENDER DIFFERENCES IN FIRST EPISODE PSYCHOSIS PATIENTS WITH AND WITHOUT HIV IN DURBAN, SOUTH AFRICA

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Background: According to the Global Burden of Disease Study 2013 mental disorders are among the main contributors to the increase in years lived with disability (YLD) rates per person. Importantly, HIV was also identified as especially contributing to increasing YLDs in sub-Saharan Africa. Women are more vulnerable to HIV in South Africa. There is a need to understand the interrelationships between gender, HIV, and mental illness in a region with a high HIV prevalence. We examined psychotic, cognitive, and depressive symptoms, and duration of untreated psychosis in people with first episode psychosis (FEP) living with and without HIV. Secondly, we reviewed the preliminary data for associations between gender, HIV and clinical features of FEP.
Methods: The study was conducted at 5 hospitals in the province of KwaZulu-Natal, South Africa. Male and female patients, aged between 18 to 45 years, with first presentation for a psychotic disorder, were invited to participate. The study utilized a clinical interview, physical examination, and several psychiatric tools, including the MINI to confirm psychosis diagnosis, the PANSS (Positive and Negative Syndrome Scale), PHQ-9 to measure symptom variables. Cognition was

measured using the Cognitive Assessment Tool (CAT-Rapid) and International HIV Dementia Scale (IHDS). Measures were carried out within 6 weeks of first presentation.
Results: Of the 156 participants, 109 were males (median age = 23 years) and 47 females (median age = 30 years) with FEP. There were 24 females and 12 males living with HIV. The participants were acutely ill with median total PANSS Scores of 78.08 and a one-month DUP. There were no statistically significant gender differences between males and females for PANSS, CAT or DUP scores. The female patients had higher depression symptoms (p=0.002) and lower IHDS scores (p=0.01). The females with FEP and HIV had a higher PANSS negative scores (p =0.04), compared to the females without HIV. The females with FEP and HIV had higher depression scores (p=0.002) and lower IHDS scores (p=0.01) compared to females without HIV.
Discussion: Living with HIV and FEP is a double burden that perhaps heralds the onset of HIV Associated Neurocognitive Disorders. The poor cognitive function in FEP and HIV patients may be a legacy effect of the so-called viral escape.

T71. DOES OXIDATIVE STRESS MEDIATE THE ASSOCIATION BETWEEN STRUCTURAL BRAIN CHANGES AND WORKING MEMORY IMPAIRMENT IN ADOLESCENTS WITH A FIRST-EPISODE-PSYCHOSIS?

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Background: We have recently reported on decreased frontal left grey matter (FLGM) volume predicting decreased working memory (WM) performance in adolescents with a FEP over the first two years after the appearance of the first psychotic symptom, as a function of age (Rapado-Castro et al. 2021). However, there is still a limited understanding on how these two processes might intertwine Brain volume loss has previously been associated with oxidative stress at baseline in our sample (Fraguas et al. 2012). In particular, a greater brain volume decrease in the left frontal volume was associated with lower total baseline glutathione (GSH), levels at the time of the FEP (Fraguas et al. 2012). Oxidative stress has also been related to cognitive deficits in FEP (Martínez-Cengotitabengoa et al. 2012). This study investigated if GSH levels at baseline mediated the association between brain volume loss in the left frontal lobe and WM impairments over time in adolescents with FEP.

Methods: Participants

A sample of 31 FEP individuals (mean age 16 [13-17]) from the original CAFEPS sample (Castro-Fornieles et al. 2007), who completed both baseline and longitudinal cognitive and neuroimaging assessments and had valid baseline GSH levels at baseline were included for this study purpose

Neuropsychological assessments

WM function was assessed at baseline and two-years follow up by means of the digits backwards and letter-number sequencing subtests from the Weschler Intelligence Scale, WAIS-III (Rapado-Castro et al. 2021).

Brain imaging

An anatomical brain MRI was obtained at baseline and at the 2-year follow-up visit (mean [SD], 25.7 [2.7] months) in 5 different 1.5-T scanners (Reig et al. 2009). LFGM volume was obtained using an automated method based on the Talairach´ atlas. The longitudinal change in LFGM volume was described as a percentage calculated as follows: Longitudinal Change = [(follow-up, vol2) - (initial volume, vol 1) / vol1] x 100

Oxidative stress evaluationB

Total GSH was measured using the Bioxytech GSH-420 assay kit, which uses a method based on the formation of a chromophoric thione by specific elimination of GSH-thioether; the absorbance measured at 420 nm is directly proportional to the total GSH concentration.

Statistical Analyses

Mediation analyses were performed to assess whether oxidative stress (GSH levels at baseline) mediated the relationship between FLGM volume loss and WM impairment over time in our sample. These analyses were performed using a macro developed by Preacher and Hayes (Hayes 2008).

Secondary mediation analyses were conducted to explore the potential effects of confounding variables. These variables were selected based on previously reported associations with longitudinal brain volume changes, working memory function or oxidative stress (i.e. Age, months of inter-scan interval, interscan ICV change, gender, baseline smoking status, psychopatology, antipsychotic medication or length of illness prior to baseline assessment) (Fraguas et al. 2012; Martínez-Cengotitabengoa et al. 2012; Rapado-Castro et al. 2021). The potential confounding variables that demonstrated significant associations with the primary variables of interest were entered as covariates and mediation analyses were re-run. (i.e. age and baseline smoking status).

Results: In the primary model, GHS levels at baseline displayed a significant positive path coefficient for path a (a= 9.879, t= 2.0931, p=0.0466) and non-significant effect for path b (b= 0.0008, t= 0.5022, p=0.6201). In addition, there were significant total and direct effects of X on Y (c=0.0974, t= 2.5047, p=0.0191; c'= 0.0891, t=2.0817, p=0 .0482). Partial effects of control variables on WM were significant for age (Coeff=0.042, p<0.01) and non-significant for smoking status (Coeff=0.336, p=0.49). The mediation effect (a*b path) of GSH levels at baseline was not significant (bias corrected 95% CI -.020, 0.81). The model explained the 24% of the variance of WM performance over the first two years after the FEP.
Discussion: Although FLGM volume loss was significantly associated with lower baseline GSH levels and reduced FLMG volume significantly predicted WM impairments when controlling for the effect of GSH, no mediation effect was observed. Results: indicate associations between FLGM volume and GSH, and between decreased FLGM volume and WM function over time. However, the associations between FLGM volume loss and GSH, and FLGM decrease and WM performance appear to be independent of each other. Further longitudinal studies are needed to precisely understand the neurobiological mechanisms that link brain volume changes to the working memory dysfunction observed in adolescent psychosis.

T72. EARLY-LIFE TRAUMA ASSOCIATION WITH PARVALBUMIN (PVALB) PROMOTER DNA METHYLATION IN FIRST EPISODE PSYCHOSIS PATIENTS

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Background: Deficits in parvalbumin-containing GABA neurons are a well-established pathological finding in schizophrenia as well as animal models of psychosis induced by administration of phencyclidine (PCP) or methamphetamine, isolation rearing and neonatal inflammation. Recent findings indicate that elevated methylation of the parvalbumin gene (PVALB) promoter sequence provides a correlate of these deficits [1–3]. A study of blood-derived DNA in depression patients, however, demonstrated a deficit of PVALB methylation at one CpG methylation site [4]. To study this further, we have investigated the relationship of PVALB methylation to two inter-related factors - first episode psychosis (FEP) and early life trauma.
Methods: This study is part of the epidemiological investigation "Schizophrenia and Other Psychoses Translational Research: Environment and Molecular Biology", conducted in Ribeirão Preto catchment area, Brazil, between April 2012 and March 2015, which is included in the EU-GEI consortium. We used blood-derived DNA of 35 FEP and 35 age-, sex- and years of schooling-matched population-based controls recruited in Brazil. Bisulfite conversion and pyrosequencing were used to determine methylation levels in 4 CpGs within the promoter sequence of PVALB. The history of early life trauma was assessed by using the Childhood Trauma Questionnaire (CTQ)[5]. We used general linear model including methylation levels as dependent variables, groups (FEP x controls) and childhood trauma (yes or no) as fixed factors.

Results: Investigating the association of psychosis and childhood trauma with PVALB methylation, we observed a trend to reduced methylation associated with trauma (p=0.057 by multivariate analysis) with no significant relationship with psychosis. This primarily reflected a significant effect only in CpG4, one of the four CpG sites studied (F=5.09, p=0.027). This result is also consistent with our previous findings in a study of early life stress in healthy men [6]. No significant association with age, years of schooling or sex was apparent. Exploration of the components of the CTQ by correlation showed that this association of reduced CpG4 methylation with trauma was significantly related to a history of abuse (Spearman's rho=-0.238, p=0.049) rather than neglect (Spearman's rho=-0.119, n.s.)

Discussion: Our results shows reductions in PVALB methylation at a specific site are associated with trauma, particularly child abuse, which is consistent with previous findings of reduced methylation at the same CpG site in both depressed subjects [4] and healthy men exposed to childhood trauma [6]. Interestingly, CpG4 is at a transcription factor recognition site for the glucocorticoid receptor, changes in which contribute to the effects of stress on the HPA axis. Changes in PVALB methylation may reflect the effects of traumatic events and result in the changes in protein/mRNA expression seen in schizophrenia and other psychosis. Future work to follow up this preliminary study should aim to clarify further the effect of early life trauma on PVALB methylation and how this it may relate to the development of mental disorders including psychosis and depression.

T73. TRANSITION AND NEURODEVELOPMENTAL OUTCOME AT 18-MONTHS FOLLOW-UP IN A CHILD AND ADOLESCENT SAMPLE WITH PSYCHOSIS RISK SYNDROME

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Background: The study of child and adolescent (CAD) population at risk for developing a psychotic disorder is of particular interest (Schultze-Lutter et al., 2017), as could open a window in the neurodevelopmental definition of the illness, assessing patients during a critical period of brain development (Murray, Bhavsar, Tripoli, and Howes, 2017), that show the first symptoms of the illness.

The aim of this study is to extend the current knowledge on transition rates in a sample of CAD with risk psychosis syndrome (PRS) in a follow-up of 6, 12, and 18 months. Secondly, we aimed to examine aspects of neurodevelopment variables, clinical symptoms, and functioning outcomes that could predict the development of a psychotic disorder in 18 months follow-up in a sample of CAD with PRS and community controls (CC).

Methods: It was included a total of 103 PRS and 87 CC's age and sex-matched. PRS were help-seeking CAD between 10 and 17 years who meet one of the following criteria: 1) Attenuated positive symptoms; or 2) Attenuated negative symptoms in the previous 12 months; or 3) Brief

intermittent limited psychotic symptoms; or 4) Genetic Risk: First- or second-degree relative with schizophrenia or schizotypal disorder with impairment of functioning. Exclusion criteria were: Intelligence Quotient (IQ) <70, diagnosis of autism spectrum disorder or traumatic brain injury.
It was assessed the neurodevelopmental variables at baseline; and prodromal and functional outcome were follow-up at 6, 12, and 18 months. Prodromal symptoms were assessed by the Scale for Prodromal Symptoms (SOPS) (Mcglashan and Miller 2001) and functioning was assessed by the Global Assessment of Functioning. A total of 63 PRS conducted all the visits of the study, and 60 PRS has only assessed their clinical status at the follow-up.

Results: A total of 24 PRS participants developed a psychotic disorder during the follow-up (PRS-P), being the transition rate at 18 months follow-up of 23.30%. Four participants developed psychosis before or at 6 months follow-up visit (16.6%), 10 between 6 to 12 months visit (41.67%), and 10 between 12 to 18 months visit (41.67%).
The variables that predict transition to a psychotic disorder (differences between the PRS-P and the PRS that not developed a psychotic disorder during the 18 months follow-up samples (PRS-NP)), were the P3 punctuation in SOPS (grandiosity) and the use of antipsychotic medication, featured as a risk factor to develop psychosis.

Significant differences were observed in neurodevelopmental outcomes, specifically in the proportion of PRS-P participants who present a delay in language development; showing PRS-P a higher proportion of this neurodevelopmental delay with respect to the PRS-NP / CC.

Discussion: Our transition rate is 23.30% at 18 months follow-up. This is a result similar to that presented in a recent meta-analysis that analyzes transition rates in CAD (Raballo et al., 2020), and suggests that rates are similar to those found in adult population studies recently published (Glenthøj et al. 2021), validating the risk criteria in the adolescent population.
At the neurodevelopmental level, there is a delay in language development in the PRS that develop psychosis, and not in the PRS-NP or the CC. These data have been previously collected in studies with CAD with schizophrenia (Asarnow, 1999) but also in prospective studies (Gur et al., 2014). It could be linked to the lower verbal performance or to the existing verbal memory deficit, Results: that are found in previous studies focused on at risk mental states (Tor et al 2018; Frangou, 2013; Siedman 2017, NAPLS-II).

T74. PATHWAYS TO CARE AT FIRST-EPISODE PSYCHOSIS: A CROSS-CULTURAL COMPARISON BETWEEN BOLOGNA AND SOUTH LONDON

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Background: Pathways to Care (PtC) are useful indicators about how patients access to mental health care, especially in the context of a first-episode psychosis (FEP). In this study we aimed to

explore how PtC are associated with patients' characteristics and clinical presentation and to assess the cross-cultural differences of the PtC predictors between South London and Bologna.
Methods: This study included 427 FEP individuals recruited in Bologna and South-East London, in the context of EUropean network of national schizophrenia networks studying Gene–EnvironmentInteractions (EU-GEI) study. We performed logistic regression to test the associations between our outcome variables (PtC) and the independent study variables.
Results: More patients were referred by GPs or specialists in London and more patients followed the emergency route of care in Bologna Despite study centres differences, older patients were more likely to be referred by primary care; patients referred by emergency services were more likely to be in a relationship; migrant patients were less likely to be referred via an informal route (e.g. self-referred or referred by friends and/or family). Patients referred by the specialist route were more likely to experience positive symptoms, while patients following informal referral were more likely to experience mania.
Discussion: Pathways to care of people facing FEP were found correlated with several socio-demographic and clinical variables in both centres and despite study centres differences in health services organization. The socio-demographic variables found correlated with pathways to care highlight the importance of social network and social services more than primary care in easing the help seeking behaviours.

T75. DISORGANIZATION IN FIRST EPISODE SCHIZOPHRENIA: 2-YEAR TREATMENT RESULTS: FROM THE 2-YEAR "PARMA EARLYPSYCHOSIS" PROGRAM

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Background: Disorganization is a core dimension of schizophrenia, yet it is relatively under-investigated compared to positive and negative ones, especially at the illness onset. Indeed, most of the empirical studies investigating the disorganized domain included patients with prolonged schizophrenia. Therefore, the aims of this research were (1) to monitor the longitudinal stability of disorganized symptoms in young patients with First Episode Schizophrenia (FES) along a 2-year follow-up period, and (2) to examine any significant association of disorganization with functioning, psychopathology and the specific treatment components of an "Early Intervention in Psychosis" (EIP) program across the 2 years of follow-up.
Methods: At baseline, 159 FES individuals (aged 12–35 years) completed the Positive And Negative Syndrome
Scale (PANSS) and the Global Assessment of Functioning (GAF). Spearman's correlation coefficients and multiple linear regression analysis were carried out.

Results: During the follow-up period, disorganization had relevant enduring positive associations with PANSS negative symptoms, lack of judgment/insight and positive symptoms representing delusional thought contents, as well as significant enduring negative correlation with GAF scores. Along the 2 years of follow-up, FES patients also showed a relevant improvement in

disorganization symptoms. This reduction was specifically associated with the number of individual psychotherapy sessions provided during the first year of treatment.
Discussion: Disorganization is a prominent clinical feature in FES at the recruitment in specialized EIP services,
but its temporal trajectory reveals a decrease over time, together with the delivery of specific, patient-tailored EIP interventions.

T76. THE RELATIONSHIP BETWEEN BRAIN-DERIVED NEUROTROPHIC FACTOR, PSYCHOTIC SYMPTOMATOLOGY, COGNITION AND FUNCTIONING IN FIRST-EPISODE PSYCHOSIS: TARGETING THE INFINITELY SMALL VARIATION TO PREVENT THE LARGER

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Background: Cognitive impairments are among main symptoms of first-episode psychosis and occur long before other psychotic symptomatology, such as positive symptoms. If not treated, cognitive impairments tend to persist during the chronic phase, resulting in a possible obstacle to the return to optimal functioning. Brain-derived neurotrophic factor (BDNF) is a neurotrophin involved in neurogenesis and neuroplasticity. It has been demonstrated that BDNF occupies a role in modulation of numerous neurotransmitters, such as dopamine, which is involved in the pathophysiology of schizophrenia. BDNF is particularly present in cerebral areas responsible of cognitive functions, like memory and learning skills. Moreover, epigenetic mechanisms, such as DNA methylation, reduce BDNF levels already decreased in psychotic disorders. However, only few studies examined the association between cognitive impairments and BDNF levels, more notably with DNA methylation of the BDNF, in first-episode psychosis. The aim of this study was to examine the association between BDNF levels, cognitive impairments, cognitive complaints, psychotic symptomatology, social and occupational functioning.
Methods: 27 patients with first-episode psychosis were recruited. To participate in the study, patients had to meet the following inclusion criteria: aged between 18 and 35 years old, diagnosed with a psychotic disorder within the last five years, and sufficiently clinically stable for a neuropsychological assessment, as measured by the Clinical Global Impression – Severity (CGI-S). Exclusion criteria were no history of cerebral trauma or neurological disorder. BDNF levels were collected through saliva samples. The cognitive domains were assessed using the MATRICS Consensus Cognitive Battery (MCCB), the cognitive complaints were assessed using the Subjective Scale to Investigate Cognition (SSTICS), the psychotic symptomatology was assessed using the Positive and Negative Syndrome Scale (PANSS), the social and functional functioning was assessed using the Social and Occupational Functional Assessment Scale (SOFAS). Pearson's correlation analyzes were conducted on the data using the Statistical Package for the Social Sciences (SPSS) software.
Results: Statistical analyzes showed significant correlations between a BDNF gene variant level and the SOFAS score ($r(27) = 0.465$, $p = 0.045$), the PANSS positive symptoms subscale score

(r(27) = 0.466, p = 0.045), the PANSS negative symptoms subscale score (r(27) = 0.468, p = 0.044), the PANSS general psychopathology subscale score (r(27) = 0.464, p = 0.046), the total PANSS score (r(27) = 0.463, p = 0.046), and the SSTICS score (r(27) = 0.465, p = 0.045). Results: also showed significant correlations between DNA methylation of BDNF's promoter IV (position 1) and the SOFAS score (r(27) = 0.520, p = 0.022), the PANSS positive symptoms subscale score (r(27) = 0.526, p = 0.021), the PANSS negative symptoms subscale score (r(27) = 0.531, p = 0.019), the PANSS general psychopathology subscale score (r(27) = 0.527, p = 0.020), the total PANSS score (r(27) = 0.531, p = 0.019), and the speed of processing (r(27) = -0.559, p = 0.013). In addition, DNA methylation of BDNF's promoter IV (position 2) significantly correlated with the SSTICS (r(27) = 0.509, p = 0.026), while DNA methylation of BDNF's promoter IV (position 3) significantly correlated with the speed of processing (r(27) = -0.466, p = 0.044). No significant correlation was found between other cognitive domains assessed by the MCCB and BDNF levels, DNA methylation of BDNF's promoter IV (position 1) and SSTICS, DNA methylation of BDNF's promoter IV (position 2) and PANSS or SOFAS and, finally, DNA methylation of BDNF's promoter IV (position 3) and PANSS, SOFAS or SSTICS.
Discussion: These Results: suggest that different patterns of DNA methylation of the BDNF and BDNF gene variation may be involved in the severity of the psychopathology, the level of functioning, as well as some objective cognitive impairments and subjective cognitive complaints. These findings underline previous findings and thus support the convergent validity that underlies these relationships. However, the nature of the link between BDNF and cognition remains unclear. Further studies should examine more in detail the models of interaction between objective cognitive impairments, as well as subjective cognitive complaints, and different BDNF levels.

T77. TOBACCO SMOKING IN CLINICAL HIGH RISK (CHR-P): A SYSTEMATIC REVIEW AND META-ANALYSIS OF THE EVIDENCE

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Background: There is converging evidence that youths at clinical high risk (CHR) are not only likely to develop the first episode of psychosis but also to develop poor physical outcomes. Some physical health risk factors - such as smoking - have been shown to increase the probability of a frank onset of psychosis in those at risk. A meta-analysis conducted on psychotic patients confirmed that daily tobacco use is associated with an increased risk of psychosis. A significant association between any attenuated psychotic symptoms (that characterize CHR state) and cigarette smoking has been recently shown in a study conducted in South London.
Nowadays, it is not completely clear how these findings would translate to the CHR population but a better understanding of how physical health parameters could affect psychopathological outcomes could be beneficial for these vulnerable clinical populations. To shed light on the percentage of smokers in CHR populations, an updated systematic review and meta-analysis of

the literature has been carried out. Our main aim was to test whether the probability of being a smoker was higher in the CHR subjects or in the control group.

Methods: The literature search was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. We systematically scrutinized from literature inception to October 2021 the following online databases: Web of Science Core Collection, BIOSIS Citation Index, KCL-Korean Journal Database, MEDLINE, Russian Science Citation Index, SCiELO Citation Index.
We have considered all the relevant studies reporting the smoking status in CHR subjects and in control groups.

We used the odds ratio as the effect size measure and data were pooled using a random effect approach.

Results: Preliminary data show that CHR individuals were more likely to use tobacco than matched healthy controls. Specifically, the overall OR of 2.016 ($p<.001$ 95%CI=1.476-2.749) indicated a higher likelihood that CHR individuals would use tobacco compared to controls. Heterogeneity was not significant ($I2=30.193$ $p=0.11$). The visual inspection of funnel plots did not reveal a clear suggestion for publication bias and the Egger's test was non-significant ($p=0.10$).
Discussion: Our systematic review and meta-analysis suggest that is crucial to investigate physical health outcomes such as tobacco use as part of clinical practice in CHR services. Unfortunately, current CHR assessment tools are entirely based on the measurement of psychopathological features and do not always include an assessment of these parameters on a regular basis.

T78. RECREATIONAL DRUG USE AFFECTS THE RISK OF DISTRESSING HALLUCINATIONS IN THE GENERAL DUTCH POPULATION

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Background: Auditory (AH) and visual (VH) hallucinations experienced by patients with psychotic disorders are often perceived as distressing. While both AH and VH also occur in healthy individuals, they are rarely accompanied by the hallucinatory distress experienced by psychotic patients. The current examination investigates AH and VH in the general Dutch population (≥ 14 years of age) with the aim to identify factors that predict whether AH and VH will be experienced as distressing by the individual or not. This information is of importance in un¬derstanding the transition of transient and harmless hallucinations towards distressing ones, which is a crucial step in the development of psychosis. Particularly, we examined the effect of drug and alcohol use on the risks of experiencing distress from AH and/or VH across the Dutch population by means of an online survey.
Methods: Participants filled out the Questionnaire for Psychotic Experiences (QPE) and a questionnaire about drug use during the past week and month. Only participants who reported having experienced AH (N = 3032) or VH (N = 2208) during the past month were included in the analysis. Prevalence rates were calculated, and binary logistic regression was performed to analyze odds ratios (ORs, with sex, age, and years of education as covariates). To this end, the ordinal variables that originally measured distress from hallucinations (separately for AH and VH) were

dichotomized based on a median split, resulting in a variable depicting 'distressing' vs. 'non-distressing' hallucinations, separately for each hallucinatory modality.
Results: The current sample consisted of 7033 participants. First, a significant interaction between sex and age on the risk of experiencing distressing hallucinations in the past month was found for AH (OR = 0.983; p = 0.004) but not for VH (OR = 0.988; p = 0.110). Assessing the effect of recreational drug use in the past month on the risk of experiencing stressful AHs separately for males and females revealed a significant effect of alcohol (OR = 0.736; p = 0.000) and cannabis (OR = 1.419; p = 0.009) for females. That is, while the consumption of alcohol during the past month significantly decreased the risk of experiencing distressing AH in women, the use of cannabis during the past month significantly increased the risk of experiencing distressing AH for females. Interestingly, no effect of drug use on the risk of experiencing stressful AH was found in males. However, it is worth noting that the absence of a significant effect of drug use in males may also be due to a lack of power. Finally, there was no significant effect of drug use on the risk of experiencing distressing VHs.
Discussion: The present investigation suggests a crucial role of recreational alcohol and cannabis consumption in the past month on the risk of experiencing distressing AH. The risk of experiencing stressful VH, however, did not turn out to be affected by the use of drugs or alcohol in the past week or month. Intriguingly, the effect of drug and alcohol use on the risk of experiencing stressful AH was only found for females, not for males. In conclusion, current Results: suggest that recreational alcohol and cannabis use by females is associated with the level of distress caused by AH in the general population. As such, the consumption of alcohol and cannabis could be important targets for early interventions aimed at individuals who are not yet but may be at risk of becoming part of a clinical population. Whether this effect holds true for men as well remains to be established in further research.

T79. PERSISTENT USE OF CANNABIS AND PSYCHOTIC-LIKE-EXPERIENCES IN THE GENERAL POPULATION. PRELIMINARY RESULTS: OF THE SICILIAN GENETIC AND PSYCHOSIS (SGAP) FOLLOW-UP STUDY

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Background: The most recent research approaches on psychosis go beyond the classical nosographic dichotomy health/illness, focusing at the psychosis continuum. Indeed, attenuated subclinical psychotic symptoms or psychotic-like experiences are common and distributed as a continuum in the general population. Relationship between cannabis use and the onset of psychosis is well established as well as the effect of continued cannabis use on clinical outcome. Less is still known regarding the effect of cannabis on subclinical psychotic manifestations in the general population overtime. This study aimed to test the association between continued cannabis use and psychotic-like-experiences in population-based controls over 8-year-follow-up.

Methods: 15 population-based controls from the SGAP case-control study were followed up after 8 years. Sociodemographic, clinical and neuropsychological assessments were performed at baseline and 8-year-follow-up. Persistent cannabis use was assessed through CEQmv, psychotic-like-experiences were measured using CAPE. In STATA 15, non-parametric Wilcoxon test was used to test differences between the two measurements of CAPE over the two time points, and non-parametric Mann-Whitney test was performed to test association between continued cannabis use over the follow-up period yes/no and changing scores of CAPE.
Results: Participants (7 males and 8 females, aged 39±12.2) were re-assessed after 7.8±1.2 years. 5/10 individuals displayed continued cannabis use from baseline to follow-up. CAPE scores differed between the two time points for total (0.8 vs. -0.5; $z=2.3$, $p=0.02$), negative (0.7 vs. -0.3; $z=2.4$, $p=0.017$) and depressive (0.8 vs. -0.4, $z=2.6$, $p=0.009$) scores, but not for positive dimension ($p=0.33$). Continued use of cannabis was associated with increasing in scores of CAPE positive ($z=-2.1$, $p=0.0367$) and CAPE depressive ($z=-2.1$, $p=0.0367$) between baseline and follow-up.
Discussion: Preliminary Results: suggest that psychotic-like-experiences tend to decrease over time, especially for depressive and negative dimensions. Moreover, individuals who displayed a steady pattern of cannabis use tend to increase subclinical psychotic experiences, in particular for positive and depressive dimensions. Further research is required to investigate the psychotic continuum, trajectories of psychotic-like-experiences overtime and factors, as cannabis use, that can contribute to different pathways.

T80. AN INTERSECTIONAL APPROACH TO ETHNORACIAL DISPARITIES IN PATHWAYS TO CARE AMONG INDIVIDUALS WITH PSYCHOSIS IN COORDINATED SPECIALTY CARE

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Background: Disparities in pathways to care, typically characterized by source of referral and type of first mental health contact, have been found between majority White individuals and underserved ethnoracial groups. Several US-based studies suggest that Black Americans experience more negative pathways to care. Yet, previous research examining duration of untreated psychosis (DUP) across ethnoracial groups is inconsistent. Previous research on ethnoracial correlates of care pathways has largely focused on differences between disadvantaged ethnoracial groups and non-Latinx White individuals. By examining multiple sociodemographic characteristics (including ethnoracial Background:) that simultaneously interact with a person's first-contact experience, we can potentially identify more meaningful clusters of individuals shaped by multiple dimensions of disadvantage and/or privilege.

In a large ethnoracially diverse sample of individuals with recent-onset psychosis this study aimed to: (1) examine differences in sociodemographic characteristics and first-contact experience (source of referral, referral contact type, and reason for first contact) by ethnoracial groups; (2) empirically cluster individuals based on how their first-contact experience intersects with their sociodemographic characteristics; and (3) compare DUP and DRP by ethnoracial groups and the newly identified intersectional clusters of individuals.

Methods: This study utilized data from OnTrackNY, a network of coordinated specialty care (CSC) programs in New York State providing recovery-oriented, evidence-based psychosocial interventions and medications to young people experiencing early psychosis. OnTrackNY provides CSC to individuals ages 16–30 who have experienced non-affective psychosis for two years or less. The total study sample consisted of 1,726 individuals enrolled at one of 21 OnTrackNY sites from October 2013 to January 2020. Using standardized forms, baseline assessments on the person's sociodemographic characteristics, living situation, family involvement, and clinical information were collected. Ethnoracial categories were operationalized as: Latinx, and all the following non-Latinx White, Black, Asian, Multiracial, and Other/Unknown. Latent class analysis was used to empirically identify clusters of individuals based upon multiple dimensions of their first-contact experience, i.e. referral source, type of service, and symptoms at referral, and social position rather than isolating the impact of each characteristic separately. Main outcomes of interest were the time from onset of psychotic symptoms to first service contact in days (DUP) and the time from first service contact to OnTrackNY admission in days (DRP).

Results: White individuals had the shortest DUP (median days=17.0), a significantly shorter duration than Black and Asian individuals (30 and 34 median days, respectively). However, White individuals also had the longest DRP (median days=102.5), compared to Black, Latinx, and Asian individuals (76, 62, and 57 median days, respectively). Latent class analysis suggested five clusters of individuals fit the data well. The "Predominantly White, non-metropolitan, more economically advantaged cluster" and the "Youngest, emergency department without hospitalization cluster", possibly the most advantaged groups, had the shortest DUP (17 and 25 median days), while the "Predominantly Asian and Latinx, depression and psychotic symptom"
and "Predominantly Black, structurally disadvantaged cluster" had the longest DUPs (36 and 44 median days). Of note, the DUPs for the latter two clusters were longer than any single ethnoracial group (17-34 days). Regarding DRP, an opposite pattern emerged with longer DRPs for more advantaged clusters, and a relatively short DRP for cluster which consisted predominantly of ethnoracially minoritized individuals.

Discussion: Comparing the findings on the association between DUP and DRP by ethnoracial group and by clusters revealed several differences. The White group mainly diverged from other groups, whereas the cluster analyses yielded more information on various parameters that appear to be intertwined with ethnoracial Background: in impacting DUP and DRP, including first contact type, proxies of social class and clinical presentation. Moreover, the differences between clusters in DUP were more substantial than those between ethnoracial groups, emphasizing that ethnoracial Background: is one element in a larger set of interconnected social and clinical indicators dynamically impacting the period between illness onset and enrolment into mental health services for psychosis.

Our study findings underscore the importance of, and greater depth of understanding that may be gained through, intersectional approaches. We demonstrated that DUP and DRP may differ across ethnoracial group and intersectional clusters, supporting the position that future studies should

include multiple time-to-treatment factors, including proportion of time spent in the pathway in various types of services before entering CSC services.

T81. THE ASSOCIATION BETWEEN TRANSIENT CHILDHOOD PSYCHOTIC EXPERIENCES AND PSYCHOSOCIAL OUTCOMES IN YOUNG ADULTHOOD: EXAMINING THE ROLE OF MENTAL DISORDER AND ATTACHMENT

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Background: Psychotic experiences (PE) are hallucinations or delusions which occur below threshold of psychotic disorder. PE are generally transient, and occur most often in childhood. PE have been associated with poor mental health and functional outcomes. Mental disorders and PE often co-occur. Evidence shows individuals with mental disorders and PE, even transient PE, show higher need for care and worse health outcomes.
Attachment is hypothesized as a mechanism for coping in times of need. Attachment has been found to attenuate the relationship between PE and certain risk factors, but its role in the relationship between PE and psychosocial outcomes is unknown.

This study aimed to examine two issues:

1. The relationship between transient childhood PE and adult psychosocial outcomes, comparing those with and without mental disorders.

2. To examine the role of attachment in this relationship.

Methods: A sample of 103 attended baseline (age 11 – 13) and 10-year follow-up. PE and mental disorders were collected using the Schedule for Affective Disorders and Schizophrenia for School-aged Children, Present and Lifetime Version. Multiple psychosocial measures were included, covering a range of potential difficulties faced in adulthood. This includes: General Health Questionnaire (mental distress); Rosenberg Self-Esteem Scale (self-esteem); The Multidimensional Scale of Perceived Social Support (support from friends, family, relationships); The Perceived Stress Scale and Stressful Life Events Scale (stress). Analysis compared those with PE, mental disorder, both PE and mental disorders, and controls. All analysis was conducted using linear and Poisson regression. One model controlled for sex and victimisation in childhood, and the second controlled for these and attachment dimensions.
Results: PE was associated with lower self-esteem (β= -2.28, p=0.03), and perceived social support from friends (β=-2.80,p= 0.01), and higher stress in non-romantic relationships (IRR=1.64). PE and mental disorders with lower self-esteem (β=-5.74, p=0.002), higher stress in romantic (IRR=1.40) and non-romantic (IRR=1.59) relationships, general stress (β= 5.60, p=0.006), and mental distress (β=5.67, p=0.001). Mental disorders without PE were not associated with any psychosocial measure.
Attachment dimensions attenuated some models; In those with PE stress in non-romantic relationships (IRR = 1.62) remained significant. In those with both PE and mental disorders, mental distress (β=4.01, p = 0.02) and stress in romantic relationships (IRR = 1.36) remained a robust finding.

Discussion: This paper illustrates the significant association between transient PE and adult psychosocial outcomes, independent of the effect of co-occurring mental disorders. It further validates the necessity to measure PE when screening for mental disorders, as they may represent a more severe trajectory. Finally, this study demonstrates the role of attachment dimensions in PE, which is currently under examined.

T82. CLINICAL HIGH-RISK CRITERIA IN CHILDREN AND ADOLESCENTS: NEITHER A PLURIPOTENT NOR A TRANSDIAGNOSTIC RISK MARKER, OR GENERAL SEVERITY MARKER

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Background: Clinical high-risk of psychosis (CHR) criteria and symptoms are more prevalent but less psychosis-predictive and less clinically relevant in children and adolescents compared to adults. Based on high rates of non-converters, it was suggested that CHR criteria were (1) pluripotential, (2) a transdiagnostic risk factor, or (3) simply a severity marker of mental disorders rather than specifically psychosis-predictive. If any of these three alternative explanatory models were true, their prevalence should differ between persons with and without mental disorders, and their severity should be associated with functional impairment as a measure of severity. Thus, we compared the prevalence and severity of CHR criteria/symptoms in 8- to 17-year-olds of the community and inpatients.

Methods: Community subjects (n=233) randomly chosen from the population register of the Swiss Canton Bern, and inpatients (n=306) with primary diagnosis of attention-deficit/hyperactivity (n = 86), eating (n = 97), anxiety incl. obsessive-compulsive (n = 94), or autism-spectrum disorder (n = 29), not clinically suspected to develop psychosis, were examined for CHR symptoms/criteria. The Structured Interview for Psychosis-Risk Syndromes (SIPS) and the Schizophrenia Proneness Instrument, Child and Youth version (SPI-CY) were used to assess the 5 positive items relevant to the symptomatic ultra-high risk criteria and the 14 basic symptoms relevant to basic symptom criteria. We examined group differences in frequency and severity of CHR symptoms/criteria using Chi-square- and nonparametric tests, and their association with functioning using correlation analyses.

Results: The 7.3%-prevalence rate of CHR criteria in community subjects did not differ significantly from the 9.5%-rate in inpatients. Frequency / severity of CHR criteria never differed between the community and the four inpatient groups, while the frequency / severity of CHR symptoms differed consistently in only four CHR symptoms:

- suspiciousness/persecutory ideas of the SIPS (Chi-square(4)=9.425; P=0.051, Cramer's V=0.132; and Z=-4.281, P<0.001; Rosenthal's r = 0.184), and
- thought pressure (Chi-square(4)=11.019; P=0.026, Cramer's V=0.143; and Z=-2.639, P=0.008; Rosenthal's r=0.114),

- derealization (Chi-square(4)=32.380; P<0.001, Cramer's V=0.245; and Z=-3.924, P<0.001; Rosenthal's r=0.169) and
- visual perception disturbances (Chi-square(4)=10.652; P=0.031, Cramer's V=0.141; and Z=-2.822, P=0.005; Rosenthal's r=0.122) of the SPI-CY.

These were consistent with a transdiagnostic risk factor or dimension, i.e., displayed higher frequency and severity in inpatients, in particular in those with eating, anxiety/obsessive-compulsive and autism-spectrum disorders. Low functioning, however, was at most weakly related to the severity of CHR criteria/symptoms, with the highest correlation yielded for suspiciousness/persecutory ideas (Kendall's Tau=-0.172, P<0.001).

Discussion: The lack of systematic differences between inpatients and community subjects does not support suggestions that CHR criteria/symptoms are pluripotential or transdiagnostic syndromes, or merely markers of symptom severity.

T83. RELAPSE PREDICTION DURING TAPERED ANTIPSYCHOTIC DISCONTINUATION

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Background: The etiology and development of schizophrenia remains largely unknown, but research during the last decades has suggested an involvement of inflammation and the immune system. It has been established that patients with schizophrenia may have a distinctive molecular signature in serum compared to healthy control subjects, and that the molecular signature may be used to predict symptom improvement and time to relapse.
Most current guidelines advocate for maintenance treatment. This has increasingly been questioned during the last decade, where several longitudinal studies on first episode psychoses found large subgroups of patients doing well without medication. Further, patient and patientorganisations advoate for gradual tapering of antipsychotics. However, tapering of antipsychotics is associated with increased risk of relapse, suicidal and violent behavior. Therefore, the danish health system established a specialized Clinique offering gradual tapering of antipsychotic medication for patients with schizophrenia. In addition, we initiated a longitudinal non-interventional trial. We aim to examine wheter differential early molecular signatures can be indicative of relapse and identify subjects for whom further dose reduction cannot be recommended.

Methods: Patients following the specialized 18-month treatment program for schizophrenia patients undergoing gradual tapering of antipsychotics in the capital region of Denmark will be offered participation in the study. Blood sample will be drawn every month, along with thorough clinical assessment rating level of symptoms and function. Based on this information we segregate patients in 3 groups, mainly according to their PANSS score.

- Group A: No worsening in PANSS. The medical discontinuation will go on for one year, with blood samples and ECG monthly. The patient will be categorized as "Non-relapse". We expect this group to be 30% of the total sample.
- Group B: Patient and/or therapist want to pause the discontinuation, without obvious worsening in psychotic symptoms. This could be a prodromal state, before a relapse, where we will intensify the monitoring, with blood samples every 2. weeks. We expect this group to be 40% of the total sample size, and that half of them stabilize with no further relapse.
- Group C: Significant detoriation in the patient's condition indicating relapse measured as: Significant worsening in PANSS score or level of function (>10 %), need for intensive psychiatric care (ie admission to a psychiatric ward) or risk of suicide or violence.

We expect this group to be 50% of the total sample size.

In this case the patient will be considered as having a relapse. The patient's medication will be adjusted, and more intensive clinical contact will be established, until stabilization. Blood samples and ECG will be collected weekly for the next four weeks after which the patient will have two monthly checkups.

The blood samples include lipids, leptin, supar, cytokines and standard inflammatory parameters.

Results: The project is awaiting ethical approval; we expect recruitment of patients to start in February 2022.

Discussion: Hypotheses:

1) Approximately 50% of the included patients will experience significant clinical relapse during antipsychotic medication tapering

2) In this group of patients, a change in specific markers (LDL, HDL, leptin, proinsulin, TGF-alpha as well as cytokines considered as state markers) will be seen in the last blood test before relapse.

3) These markers will remain altered during the period of destabilization, but will normalize as symptoms improve and condition stabilizes

T84. PHYSIOLOGICAL STRESS AND COGNITION IN INDIVIDUALS AT ULTRA-HIGH RISK FOR PSYCHOSIS

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Background: Cognitive deficits are a well-known to be present in schizophrenia. Moreover, cognitive impairments are present in ultra-high risk (UHR) individuals for developing psychosis. Higher levels of stress have been observed in UHR individuals compared with healthy controls (HC). UHR individuals exhibit a hyperactive and dysfunctional HPA-axis, with elevated cortisol

and a blunted CAR. In addition, UHR individuals perceive daily events more stressful. Increasing stress levels and decreasing cognitive function, might be linked together by excess glutamate availability in hippocampus and prefrontal cortex, causing brain changes and atrophy, which could cause cognitive changes. No previous studies have examined the association between physiological stress biomarkers and cognition in UHR individuals. This study aims to examine this association.

Methods: The study sample is a part of the FOCUS trial. This study will use data from 72 help-seeking individuals, aged 18-40, who all met the inclusion criteria of the comprehensive assessment of at-risk mental state (CAARMS) and 36 age and gender matched HC. Participants were assessed with cognitive tests indexing the 7 core domains as stated by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB). The participants underwent an extensive testing of their physiological stress levels in their home environment for one day at baseline. We measured saliva cortisol and saliva alfa-amylase (SAA) at awakening, 30 min, 60 min after awakening and at bedtime and heartrate variability (HRV) during sleep and before awakening. We examined the relationships using generalized linear models.

Results: We found that impaired cognition in verbal learning and memory (N=70 B=-0.79 [-1.6 to -0.03] p=0.041), visual learning and memory (N=66 B=1.53 [0.37 to 2.7] p=0.010), working memory (N=68 B=0.67 [0.05 to 1.3] p=0.035, N=70 B=1.38 [0.12 to 2.6] p=0.032) and sustained attention (N=69 B=-159.2 [-274.4 to -44,0] p=0.007, N=70 B=-372.1 [-637.9 to -106.4] p=0.006) were significant associated with increased SAA at multiple time points in UHR individuals (higher SAA suggests increased stress). Furthermore, impairments in BACS composite score were associated with increased SAA (N=69 B=-10.6 [-18 to -3.2] p=0.005). Moreover, impaired cognition in executive function was significant associated with low HRV (low HRV suggests increased stress) measured 60 min before awakening on two measures (N=37 B=0.17 [0.02 to 0.32] p=0.024, N=37 B=0.19 [0.01 to 0.36] p=0.035) .

We found no significant association between cortisol and cognitive domains in UHR individuals.

Discussion: Eight studies have previously examined the relationship between stress and cognition in: schizophrenia patients, first episode psychosis patients and children at risk for developing psychosis. The Results: showed significant associations between measures of cortisol levels and the cognitive domains of working memory, verbal memory, executive functioning, and processing speed, suggesting increased stress to be associated with impaired cognition.

Our Results: did not indicate an association between cortisol and cognition as in previous studies. However, it might indicate associations between stress, expressed by the sympathetic nervous system (SAA and HRV), and impaired cognition in UHR individuals. It could be that the dysfunction of the HPA-axis seen in schizophrenia and in UHR individuals, are not yet prominent enough in our sample to identify a significant relationship.

T85. COGNITIVE FUNCTION AND TREATMENT RESPONSE TRAJECTORIES IN FIRST EPISODE SCHIZOPHRENIA: EVIDENCE FROM A PROSPECTIVE COHORT STUDY

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Background: Treatment response in the first few weeks of antipsychotic treatment is strongly associated with future response. Cognitive impairments in verbal memory and language functions measures have been associated with treatment response in the first episode, with impairments in these domains observable prior to disease onset.
Methods: 89 participants with first episode schizophrenia who had recently started antipsychotic medication were recruited, with 46 included in the main analysis. Over 6 weeks participants attended 3 visits, at each completing version A of the Brief Assessment of Cognition in Schizophrenia (BACS), as well providing data on symptom severity assessed by the Positive and Negative Syndrome Scale (PANSS).
Results: Trajectory analyses were used to classify the participants by treatment response; 84.78% of the sample were classified as treatment responsive, and the remaining 15.22% as treatment non-responsive. Unadjusted and adjusted logistic regressions observed no significant relationship between baseline cognitive performance and antipsychotic response. No change in the pattern of results was observed when using >20% PANSS reduction criteria.
Discussion: This investigation identified two clear trajectories of treatment response in the first six weeks of antipsychotic treatment. Responder and non-responder groups did not significantly differ on performance on the BACS, suggesting that larger samples may be required or that brief cognitive batteries for schizophrenia may not be a useful predictor of response in the first two-years of illness onset.

T86. PSYCHOTIC-LIKE EXPERIENCES AND THEIR CORRELATES IN A NATIONALLY REPRESENTATIVE STUDY OF GENERAL POPULATION ADOLESCENTS

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Background: Subclinical psychotic-like experiences (PLEs) are common among general population adolescents but have been found to correlate with heightened risk of mental health problems and various problems in well-being. Due to limited sample sizes, however, these effects have not been well differentiated by age and gender. We therefore studied endorsement frequencies of PLEs in different age and gender adolescent groups in a nationally representative survey. Secondly, we investigated what the PLEs tell about the adolescents´ broader well-being concerning other mental health and health in general; problems at home, in school, or with friends; adversity or traumatic experiences; and service need / use.
Methods: We investigated the prevalence and correlates of PLEs in the nationwide Finnish School Health Promotion study with over 158 000 pupils and students (aged 14–20 years). PLEs were investigated with three questionnaire items, one each for auditory and visual hallucinatory experiences and suspicious thought content. The response scale addressed frequency, with the

response alternatives Many times a day / Daily / Several times a week / Weekly / Monthly / Less often or never. A latent factor was also estimated to represent overall PLE intensity. Intercorrelations were calculated with the following measures of mental health and well-being: depressive symptoms, anxiety symptoms, burnout symptoms, covid-19-related worries, social anxiety, eating disorder symptoms, self-harm, family adversity, being a crime victim, sexual violence, parental mental violence, parental physical violence, violence in the family, bullying, loneliness, discrimination experiences, immigration status, substance use, problems in school work, self-esteem, positive mental health, participation, and engagement.
Results: Suspicious thought content was the most commonly reported of the three PLEs and visual hallucinatory experiences the rarest. We therefore coded having recurrent PLEs as having perceptual abnormalities at least weekly, or unusual thought content at least several times a week. Recurrent PLEs were reported by 12 % of the adolescents, more often in girls (14%) than boys (10%) and in the younger age group (ages 14–16; 15%) compared to the older adolescents (ages 16–20; 8%). The latent PLE factor represented the three assessed PLEs with good fit. PLE endorsement was associated with other concurrent mental health symptoms, especially symptoms of eating disorder and depressive and anxiety symptoms; self-harm; substance use; and trauma and adversity history, especially sexual violence and parental physical violence. We report these correlations by age and gender adolescent group.
Discussion: This cross-sectional study reaching the whole age group of 14–20 years in schools in Finland offers new data on PLEs in general population adolescents and the meaning and relevance of these experiences as general markers of distress. Our data shows that a substantial fraction of adolescents experiences PLEs recurrently and these experiences are associated with a wide variety of burden in the adolescent's everyday life. We discuss the meaning of PLEs in girls and boys and younger versus older adolescents.

T87. DOES LEAD-TIME BIAS CONFOUND THE ASSOCIATION BETWEEN DURATION OF UNTREATED PSYCHOSIS AND OUTCOME IN SCHIZOPHRENIA?

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Background: Duration of Untreated Psychosis (DUP) is understood as the time from onset of frank psychotic symptoms until the start of treatment for these symptoms and it has been found to be associated with later outcome.
The association have previously been explained either by the neurtoxity theory, where the psychosis leads to neurological damage, functional decline and a chronic trajectory, or prolonged DUP could be a marker of a more severe illness trajectory marked by insidious onset and more severe outcome. Jonas et. Al. (APJ 2020) proposed that the association could be explained be lead-time bias, where the association is caused by moving the observational window forward prior to the inevitable functional decline and chronicity of the illness.

Jonas et. al find in their study that patients with a short DUP have higher functional scores at baseline, and that patients with a long DUP experience most of their functional decline prior to

onset of treatment, while participants with a short DUP experience most of their decline after initiation of treatment. These findings are in line with the third explanation that the effect of DUP seen on outcome primarily is due to the observational time frame of the baseline assessment, e.g. lead time bias.

In this study we aimed to reproduce the findings of the Jonas et. al study while also addressing some of the comments raised as a critic of the study.

Methods: For this study we used data from the OPUS trial, including 547 participants with schizophrenia spectrum disorders recruited and randomized to either standard treatment (n: 272) or intervention treatment (n: 275). Participants were between 18 and 45 of age.
DUP was assessed with the IRAOS. The onset of adequate treatment, and thus the end of DUP, was operationalized as the inclusion date. Functioning were at baseline and the subsequent follow-ups assessed using the GAF. We used the PAS for measuring premorbid functioning. For premorbid functioning the PAS was used and rescaled to correspond to the GAF.

We conducted multilevel spline regression models similar to the Jonas et al. analytical setup, using a data-driven approach to find the optimal inflection point.

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 in OPUS, and including not just a slope change but a level change in the model. This model indicated a slow decline (-0.31 (SE 0.08) per year) until first-OPUS treatment, at which point there was a sharp decrease (-16.13 (SE 0.77)) in GAF, and after which GAF gradually improved again (0.92 (SE 0.11)). Both in this model and in models accounting for potential lead-time bias, however, longer DUP was associated with a decrease in function (-0.01 (SE 0.003)) for each additional week of DUP). This is in contrast with the Jonas et al. study. Also, in contrast with the Jonas et al. study, we found a significant interaction between DUP and time before baseline in OPUS.
Discussion: In this study, we did not find evidence of a lead-time bias, but rather found that onset of treatment in OPUS occurs at the time when people are doing the worst, and is consequently not random. Longer DUP is associated with reduced function, and the decline before onset of treatment interacts with DUP in the expected direction. In conclusion, DUP is an important predictor of poor outcome, and reduction of DUP is thus likely to reduce the functional decline and improve prognosis in patients with first-episode psychosis. Moreover, we find that onset of treatment occurs at a significant time, when patients are doing poorly, which would not be consistent with the lead-time bias hypothesis.

T88. MOTOR BEHAVIOR DURING SPEECH TASKS IN BRAZILIAN INDIVIDUALS WITH AT-RISK MENTAL STATES — A MOTION ENERGY ANALYSIS

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Background: Motor abnormalities are observed in patients with schizophrenia, being frequently associated with social impairments. Recent studies have pointed to the presence of these disturbances also in individuals with at-risk mental states (ARMS) for psychosis. Our aim was to use motion energy analysis (MEA) to compare motor behavior during speech tasks videos in ARMS and control individuals and test for associations with symptoms domains.
Methods: Thirty-two ARMS and forty-six controls individuals 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. Data was submitted to an automated MEA software, and mean amplitude, frequency, and coefficient of variability of head and torso movements were obtained. Correlation between these metrics and relevant SIPS symptoms were also assessed, including social anhedonia (N1), avolition (N2), expression of emotion (N3), experience of emotions and self (N4).
Results: Independent-samples tests – Mann-Whitney U and t Student - were used to analyze differences between ARMS and control group. For ARMS, regarding the ROI of the head, a significantly lower mean amplitude (SO: $U=422$, $p<0.001$, $d=0.414$; MR: $U=418$, $p=0.009$, $d=0.323$) and increased coefficient of variability (SO: $U=477$, $p=0.006$, $d=0.338$; MR: $U=347$, $p<0.001$, $d=0.443$) was observed even after Bonferroni correction ($p<0.0125$). For the torso, this group presented a lower amplitude ($U=539$, $p=0.031$, $d=0.251$) and lower frequency ($U=504$, $p=0.013$, $d=0.300$) for the SO video, and higher variability in both tasks (SO: $U=490$, $p=0.009$, $d=0.319$; MR: $U=412$, $p=0.007$, $d=0.339$), but only the latter survived the Bonferroni correction ($p<0.0125$). In MR video, negative correlations were seen for head movement frequency with symptoms N1, N3 and N4 ($\tau = -0.180$, $p=0.046$, $\tau = -0.203$, $p=0.030$ and $\tau = -0.185$, $p=0.044$, respectively), and for torsos frequency with N3 ($\tau = -0.199$, $p=0.033$). N5 was negatively correlated with head's amplitude in both videos (SO: $\tau = -0.236$, $p=0.009$; MR: $\tau = -0.268$, $p=0.004$). Inversely correlation was seen for some positive symptoms and movement frequency and amplitude (p-values varying from 0.048 to <0.001) and positive correlation between these symptoms and movement variability (p-values ranging from 0.029 to 0.002). None of the correlations survived Bonferroni correction for multiple comparisons.
Discussion: These results are consistent with our hypothesis, that ARMS individuals have marked differences in their motor behavior during speech as compared to controls. Also, significant associations of movement metrics with symptoms were found, supporting the importance of movement analysis in the ARMS diagnostic. Despite having a lower movement energy, the ARMS group presented more variability in movements during the videos when compared to controls. The increase in this variability may be caused by the increase in involuntary movements - that are more erratic - whereas voluntary movements related with blunted affect, such as gesticulation, are scarcer. MEA analysis proved to be a potential tool to the investigation of abnormal movements, and it could enhance the screening of risk mental states in a more naturalistic way.

T89. DOPAMINERGIC ALTERATIONS IN POPULATIONS AT INCREASED RISK FOR PSYCHOSIS: A SYSTEMATIC REVIEW OF IMAGING FINDINGS

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Background: Approximately 1-3% of the population suffers from schizophrenia and related psychotic disorders. Often, identifiable symptoms and functional alterations precede the development of a first psychotic episode. The longer the time between the occurrence of the first psychotic symptoms and the start of adequate treatment, the smaller the subsequent improvement in psychopathology and quality of life. Since striatal dopamine dysfunction is the leading theory for the pathogenesis of positive symptoms in schizophrenia, alterations of the dopaminergic system may be important neurobiological correlates of vulnerability and transition to psychosis.
Methods: A systematic search was performed by use of PubMed and PsycINFO databases. We systematically reviewed the evidence for dopaminergic alterations demonstrated by in-vivo imaging studies in humans at increased risk of developing psychosis, covering clinical (e.g. individuals meeting clinical criteria for being at ultra-high-risk of developing psychosis), genetic (e.g. relatives of schizophrenic patients), and environmental high-risk groups (e.g. individuals who are highly exposed to environmental risk factors associated with schizophrenia, such as cannabis use). The case-control and cross-sectional versions of the Observational Study Quality Evaluation (OSQE) were used for the risk of bias assessment of observational studies. All 63 included studies utilized Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT), or neuromelanin-sensitive Magnetic Resonance Imaging (NM-MRI) Methods: to collect data concerning the dopaminergic system during rest and/or following pharmacological, behavioural, or cognitive challenges.
Results: The current evidence highlights that 1) Striatal dopamine synthesis capacity is increased in clinical and genetic high-risk individuals relative to controls, while findings in environmental high-risk individuals were inconsistent, with a decreased striatal dopamine synthesis capacity in cannabis users compared to healthy individuals; 2) Striatal dopamine D2/3 receptor availability is unaltered in all three high-risk groups compared with healthy individuals; 3) Other aspects of the dopamine system (e.g. neuromelanin levels, cognitive task-induced dopamine release) have been investigated by a limited amount of studies and firm conclusions cannot be drawn.
Discussion: In line with imaging findings in schizophrenic patients, the present Results: show that presynaptic dopaminergic abnormalities occur in high-risk individuals before they develop psychosis. It seems likely that the whole at-risk group can be stratified into multiple subgroups, with varying risks to develop psychosis, transition rates, and underlying neurobiology. Furthermore, this study suggests that the detection of a hyperdopaminergic state, as indexed by molecular imaging, may facilitate early detection and intervention of psychosis.

T90. PREVALENCE OF FIRST EPISODE PSYCHOSIS IN TOBACCO USERS AND NONUSERS: A EUROPEAN MULTICENTRE STUDY (EU-GEI)

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Background: Tobacco is a highly prevalent substance of abuse in patients with psychosis (1). Approximately between 50-70% of patients with first episode psychosis (FEP) report using tobacco (2), with 60-80% of patients with psychosis presenting heavy use (20 or more cigarettes per day) as opposed to 11% in the general population (3). The aims of this study were: 1) to analyse the relationship between tobacco use and FEP prevalence, and 2) to analyse the relationship between heavy and non-heavy tobacco use and FEP.

Methods: A total 1105 FEP patients [613 FEP users (males: N=425(69.3%); age: mean=29.8±10.0) and 492 FEP nonusers (males: N=256 (52.0%); age: mean=33.1±11.1)] and 1355 healthy controls (HC) [329 HC users (males: N=173 (52.6%); age: mean=35.1±12.3) and 1026 HC nonusers (males: N=466 (45.4%); age: mean=36.6±13.2)] participated in this multicentre study, which is part of the European Network of National Schizophrenia Networks studying Gene-Environment Interactions (EU-GEI project). We used the modified version of the Medical Research Council (MRC) Sociodemographic Schedule to collect the sociodemographic data; the 90-item computerized Operational CRITeria (OPCRIT) system for the diagnosis of psychosis; the Tobacco and Alcohol Questionnaire to measure substance use and the Cannabis Experience Questionnaire to measure concurrent cannabis use. Data about the use of tobacco were limited to the 12 months prior to enrolment in the study. Frequency of tobacco use in the FEP user group was categorized in two groups (heavy and non-heavy users) using the Fagerström Test for Nicotine Dependence (FTND) (a cut-off ≥20 cigarettes per day was established to identify heavy users). We used chi-square tests for comparisons in categorical variables, t-test in the case of continuous variables and binary logistic regression model analyses to examine the association of tobacco use with case-control groups. These analyses were adjusted for sociodemographic variables, alcohol use, and frequency of cannabis use.

Results: FEP users were significantly younger than FEP nonusers ($p \leq .001$), HC users ($p \leq .001$) and HC nonusers ($p \leq .001$); they used more alcohol than FEP nonusers ($p \leq .001$) and HC users ($p = .001$) and they used more cannabis than the rest of the groups (FEP nonusers: $p \leq .001$; HC users: $p \leq .001$; HC nonusers: $p \leq .001$). Concerning tobacco use, FEP users smoked more daily units of tobacco than healthy control tobacco users ($t = 3.3$; $p \leq .001$) and there was a higher proportion of heavy users in the FEP user group than in the HC user group ($\chi 2 = 7.6$; $p = .006$). Logistic regression models showed that the prevalence of FEP was 3.3 times higher in tobacco users than in non-users ($p \leq .001$; OR=3.3; 95%CI 2.7-4.0) [the OR was still significant after including frequency of cannabis use within the group of confounding variables ($p \leq .001$; OR=2.6; 95%CI 2.1-3.2) and 1.7 times higher in FEP heavy tobacco users than in FEP non-heavy users ($p = .002$; OR=1.7; 95%CI 1.2-2.4).

Discussion: FEP prevalence is higher in tobacco users than in tobacco non-users and in heavy tobacco users than in non-heavy users. Assessment of tobacco use and provision of adequate treatment should be encouraged in the general population, particularly in those subjects with psychosis vulnerability.

T91. PREDICTION OF ONE-YEAR OUTCOME AFTER A FIRST EPISODE OF PSYCHOSIS: A CROSS-OVER VALIDATION APPROACH IN EUFEST AND PSYSCAN

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Background: In order to enhance the development of tools to give more personalized advice on prognosis and outcome as well as to facilitate clinical decision-making, machine learning techniques are increasingly being used in the research field of psychiatry and psychosis in particular. Promising prognostic models have been published to predict outcome in patients with first episode psychosis (FEP). However, since these models are rarely validated in large, independent samples, it is as yet unclear whether these predictions generalize well to the population as a whole. We therefore aimed to validate a previously developed prognostic model for predicting one-year functional outcome after a first episode of psychosis (EUFEST) in an external FEP cohort (PSYSCAN).

Methods: The present work used data from EUFEST as well as the FEP cohort from the PSYSCAN study. EUFEST is an international, multicenter, pragmatic, open-label, randomized controlled trial comparing the effectiveness of second-generation antipsychotic drugs with that of a low dose of haloperidol in patients with first-episode schizophrenia. PSYSCAN is an international, multicenter, longitudinal study on the early stages of psychosis, in which FEP patients were followed for a one-year period in a naturalistic, prospective design. The open-source pattern recognition tool NeuroMiner was used to develop two prognostic classification models based on the cross-validation and machine learning pipeline from Koutsouleris et al. (2016). The primary outcome measure was one-year functional outcome as assessed with the Global Assessment of Functioning (GAF current score). GAF scores were dichotomized to differentiate patients with a poor outcome (GAF <65) from patients with a good outcome (GAF ≥ 65). To determine the validity of the models beyond the original sample, a cross-over validation approach was adopted; a model was trained and cross-validated using data from one study and then applied on to the external dataset, and vice versa. To test model validity from a different approach, we pooled both samples and performed a leave-project-out cross-validation analysis. We additionally evaluated geographical generalizability of the models, selecting a leave-site-out approach.

Results: A total of 339 EUFEST subjects and 226 subjects from PSYSCAN were included in the analyses. After a year of follow-up, 78 patients from the EUFEST sample (23%) achieved the poor outcome threshold as compared to 113 patients (50%) in PSYSCAN. The pooled non-linear SVM classifier trained on EUFEST data correctly identified patients with a poor outcome with a cross-validated BAC of 66.3%, $p < .002$. The prognostic model trained on PSYSCAN participants achieved a slightly higher BAC of 69.5%, $p < .002$. However, when applying the models onto the study cohort not included in the discovery and cross-validation phase, classification accuracy dropped up to 18%. The Results: of the leave-project-out cross-validation approach produced a similar and non-significant prediction performance (BAC = 52.8%, $p = 0.186$). Remarkably, the highest balanced accuracy was achieved by the leave-site-out inner pooled model (71.3%).

Discussion: The present study showed that two models for the prediction of one-year outcome based on a previously published machine learning algorithm classified patients from a new sample into a good functional outcome versus a poor functional outcome group with modest accuracy, suggesting limited generalizability of these models to other samples. If we are to eventually use such prognostic tools in daily clinical practice, it is of utmost importance to test these models in independent datasets. Future high quality external validation studies are therefore recommended.

T92. SELF-REPORTED MOTOR DEFICITS SHOW GOOD UTILITY IN THE CONTEXT OF PSYCHOSIS-RISK SCREENING: VALIDATION AND INITIAL FINDINGS FROM THE SENSORIMOTOR AND ACTIVITY PSYCHOSIS-RISK (SMAP-R) SCALE

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Background: Sensorimotor abnormalities precede and predict the onset of psychosis. Despite the practical utility of sensorimotor abnormalities for early identification, prediction, and individualized medicine applications, there is currently no dedicated self-report instrument designed to capture these important behaviors. The current study assessed and validated a questionnaire designed for use in individuals at clinical high-risk for psychosis (CHR).
Methods: The current study included exploratory (n = 3,009) and validation (n = 439) analytic datasets– that included individuals with a CHR syndrome (n = 84)- who completed the novel Sensorimotor Abnormalities and Psychosis-Risk (SMAP-R) Scale, clinical interviews and a finger tapping task. The resulting scales were assessed for discriminant across the CHR group (n=84) compared other disorders that report motor disturbances (i.e., depression; n=35 and anxiety; n=78), and community sample volunteers (n=78) samples among the validation analytic dataset.
Results: The scale showed a consistent structure with two facets (Physical Activity and Sensorimotor Abnormalities) with two Motor Abnormality subfacets (Coordination, Dyskinesia) across exploratory (Crohnbach's α = .67-.71) and validation (Crohnbach's α = .64-.71) datasets consistent with conceptual models of sensorimotor pathology in psychosis. Facets predicted risk calculator scores (p's=.01-.008) and performance on a finger tapping task (p's=.015-.016). Sensorimotor Abnormalities facet and subfacets discriminated CHR from community sample volunteers (Cohen's d's = .63-.87) and clinical samples (Cohen's d's = .31-.67). Items also distinguished anxiety and depression groups from community sample volunteers on particular facets (Cohen's d's = .35-.43), showing potential for a broad application.
Discussion: The SMAP-R scale may be used as an initial screening to focus further clinical sensorimotor assessment and targeting individualized treatment. This measure provides unique insight into sensorimotor abnormalities (accounting for 2% of variance in current risk assessment approaches), which is largely under-utilized in current approaches to researching and treating the psychosis risk syndrome. Features of the scale may facilitate widespread incorporation of sensorimotor screening into psychosis-risk research and practice.

T93. A PROXY MEASURE OF PREMORBID ADJUSTMENT IN PSYCHOSIS FOR LARGE-SCALE EPIDEMIOLOGICAL STUDIES AND ELECTRONIC HEALTH RECORD-BASED RESEARCH

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Background: Premorbid adjustment (PA) is an important predictor of functional outcome in psychosis. The Premorbid Adjustment Scale (PAS) is considered the gold standard for measuring PA. The PAS was developed for research, but its use would not be feasible in certain settings, such as large epidemiological studies or medical record review studies. Therefore, a proxy measure of premorbid adjustment (PMPA) is needed in such scenarios. Several authors have proposed the sum of the following sociodemographic variables as an indicator of poor PA: unmarried (and without a partner), unemployed (and not studying), and having a secondary or lower education. However, this PMPA method has not been compared to existing validated procedures for evaluating PA. The aim of the present study was to compare it with the PAS gold standard.

Methods: The data for these analyses were taken from the PAFIP study, conducted at the Marqués de Valdecilla University Hospital, Spain. The cohort included patients with first-episode psychosis (FEP) diagnosed according to DSM-IV criteria, aged 18 to 60. Baseline sociodemographic and clinical information was recorded for the total sample. PA was categorized as 'poor' or 'non-poor' following the PMPA criteria described above, and also by the PAS (higher score means worse adjustment). Statistical differences between patients with 'poor' or 'non-poor' PA according to the PMPA methodology were analyzed with the chi-square and the Student's t-test. A point-biserial correlation coefficient was used to measure the relationship between PMPA categorization and PAS scores. Regression analysis was conducted to determine how well the PMPA classification predicted PAS scores (dichotomized into 'high' or 'low' values by median split for easier interpretation). The accuracy and discrimination ability of the model were checked with a classification table and area under the receiver operating characteristics curve (AUC), respectively. The significance level was 0.05. MedCalc Statistical Software was used for statistical analyses.

Results: The sample consisted of 521 patients (288 [55.3%] males, mean age 33.18 [± 9.98] years). Of these, 27.3% (n = 142) were rated as having poor PA following PMPA criteria. The mean PAS score of the cohort was 0.32 (± 0.22). Bivariate analysis showed statistical differences between 'poor' and 'non-poor' PA groups in age, gender, marital status, employment, education, substance use, PAS scores, premorbid intelligence, age at onset, type of psychotic disorder, and psychiatric symptom severity (level of functioning, global cognitive functioning, severity of positive, negative, and general psychopathology symptoms, and illness insight). The point-biserial correlation coefficient was 0.57 (95% CI: 0.51-0.63, $p < 0.001$), indicating a moderate to strong correlation between the PMPA and PAS. Logistic regression analysis revealed that poor PA according to the PMPA significantly predicted high PAS scores (OR = 13.78, 95% CI 8.57-22.16;

$p < 0.001$). The classification table showed that 81.9% of patients were classified correctly and the AUC was 0.78 (95% CI: 0.74-0.81; $p < 0.001$), indicating good PMPA predictive power.
Discussion: The PMPA may be considered an easy, reliable method for estimating PA in FEP when its assessment with the gold-standard PAS is unfeasible or unavailable. The proposed PMPA methodology may be implemented both in clinical practice and in epidemiological research, and would be potentially useful in large-scale epidemiological studies and electronic health record-based research.

T94. COMMON GENETIC VARIATION RELATED TO SCHIZOPHRENIA IS ASSOCIATED WITH COGNITIVE PERFORMANCE IN CHILDREN AND ADOLESCENTS

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Background: Genetic risk for schizophrenia (SZ), whether familial or based on common polymorphisms, is associated with cognitive performance. Previous reports have shown that an increased genetic risk for SZ is also associated with an impairment in neurocognitive and socio-cognitive performance, way before the typical age of onset of SZ (e.g., before 10 years old). A recent study identified genetic variants associated with low SZ liability despite high genetic risk. These newly discovered variants may promote resilience to SZ. Based on foregoing findings, we hypothesized to find higher SZ polygenic risk scores to be associated with poorer cognitive performance in adolescents, whereas we expected an opposite association with polygenic resilience scores, i.e., higher polygenic resilience scores would be associated with better cognitive performance in the same tests associated with risk.
Methods: We included genomic and neurocognitive data of 5120 Caucasian participants ranging in age between 8 and 22 years from the naturalistic Philadelphia Neurodevelopmental Cohort, who underwent 14 different neurocognitive tests from the Penn computerized neurocognitive battery (CNB). For each participant, we calculated SZ polygenic risk and resilience scores based on genome wide association studies from the Psychiatric Genomics Consortium. We then investigated the association between neurocognitive performance at each test, and both polygenic risk and resilience scores using linear models. Our models included a total of 113 different reaction time (RT) and correct response measures from the CNB as a dependent variable, and genetic risk and resilience scores, as well as their interaction, as independent variables. Furthermore, we included participants' sex, age, parental education level, intelligence quotient and the first ten principal components derived from whole-genome SNP data as nuisance covariates. All p values were $p<0.05$, False Discovery Rate (FDR) corrected.
Results: We identified significant associations of SZ polygenic risk scores with 15 cognitive indices, mainly RT, belonging to six different CNB tests, covering the domains of emotion identification, emotion differentiation, verbal reasoning, visual object learning, spatial processing, and face memory tasks (all $pFDR<0.05$). Across all tests, poorer performance was associated with higher risk scores. We found polygenic resilience scores positively associated only with performance at a line orientation RT task ($pFDR<0.05$). Interestingly, we did not find any

significant interaction between risk and resilience scores on cognitive performance (or either of them with age) after multiple comparison correction.
Discussion: Our Results: show significant associations between cognitive deficits and SZ higher polygenic risk scores in adolescents, namely in emotion processing, verbal reasoning, spatial memory and processing and face memory abilities. On the other hand, higher polygenic resilience scores were positively associated only with spatial processing. These findings show that genetic variants associated with SZ via risk or resilience have functional correlates in cognition during childhood and adolescence. Specifically, SZ genetic variation modulates cognitive performance way before the typical onset age of disease, matching the expected direction of higher performance corresponding to lower risk and higher resilience. Moreover, the association we found between cognitive deficits and higher polygenic risk scores in adolescents supports the neurodevelopmental hypothesis of SZ, suggesting that genetic risk factors may potentially interact with the physiology of neurodevelopmental processes years before the onset age for SZ.

T95. SONIC HEDGEHOG PATHWAY GENES IN SCHIZOPHRENIA AND BIPOLAR DISORDERS: ANALYSIS OF THEIR ROLE IN BRAIN AND FACE INTERRELATED DEVELOPMENT

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Background: Brain and facial tissues are both derived from the same ectodermal layer, and they are developed in an interrelated way under the influence of the Sonic Hedgehog (Shh) signalling pathway. SHH, SUFU and GLI3 genes are key elements of the Shh pathway and have been associated with schizophrenia (SZ) and bipolar disorder (BD). We aimed: i) to test the association of SHH, SUFU and GLI3 with SZ and BD; ii) to assess the correlates between facial shape and neuroanatomical measures in individuals diagnosed with SZ/BD and healthy controls (HC), and iii) to analyse whether these genes modulate face-brain relationships.
Methods: The sample comprised 437 subjects (113 diagnosed with SZ, 129 with BD and 195 HC). In all, we genotyped 3 SNPs (SUFU-rs10786679, SHH-rs10949808, GLI3-rs3735361) and conducted a case-control genetic association approach (Plink). In a subsample (53 patients with SZ, 22 with BD and 47 HC), we obtained facial 3D reconstructions and neuroanatomical measures from 1.5T MRI scans. We recorded the 3D coordinates of 20 anatomical facial landmarks in each facial reconstruction (Amira 5.2). Neuroanatomical measures (brain cortical thickness, volume and area) were obtained from the grey-matter segmentation of 34 ROIs (FreeSurfer). Geometric Morphometrics and multivariate statistical techniques were used to assess the influence of cortical

regions on facial shape. A three-way interaction between genotype, cortical regions and diagnosis on global facial shape was conducted (Procrustes ANOVA).
Results: The genetic association analyses revealed allelic and recessive effects of the T allele of the SHH-rs10949808 on the risk for SZ (p=0.026 and p=0.031, respectively). The A allele of the SUFU-rs10786679 was associated with BD (under allelic (p=0.03) and dominant (p=0.026) models). No genetic association was found with the GLI3-rs3735361.
Regarding morphometric analyses, we detected a significant association of superiorfrontal region thickness (p=0.044) and volume (p=0.035) with the facial shape when comparing SZ and HC subjects. These associations explained 1% of facial shape variance and were not conditional to the diagnosis. When the GLI3 genotype was included in the ANOVA model, we observed a significant three-way interaction effect of superiorfrontal area, SZ diagnosis and genotype on global facial shape (p=0.001). This interaction explained up to 4.8% of total facial shape variance.

In relation to BD and HC, a trend towards significance was found in the association of superiorfrontal volume with facial shape (p=0.056). However, when adding the GLI3 genotype, a significant three-way interaction between superiorfrontal area, diagnosis and genotype on facial shape was found (p=0.045). This interaction explained up to 7.3% of total facial shape variance.

Discussion: Our data confirm the contribution of central genes of the Sonic Hedgehog pathway (SUFU and SHH) to the risk for SZ and BD disorders. Our findings also indicate the role of GLI3 in the modulation of brain and face development in these disorders, as revealed by the significant three-way interaction found among GLI3 genotype, superiorfrontal area and diagnosis on facial shape.
Overall, the association of genes implicated in the face and brain development, such as SHH and SUFU with SZ and BD, and the influence of brain measures on facial shape modulated by GLI3, support the notion of facial shape as an indirect neuroanatomical marker for SZ and BD.

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T96. GENOME-WIDE METHYLATION ANALYSIS FOR TREATMENT RESISTANT SCHIZOPHRENIA

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Background: Approximately 20%-30% of patients with schizophrenia who receive antipsychotics are resistant to treatment, and a further 30% are only partially responsive (Miller et al, 2006; Farooq et al., 2019. Lieberman et al., 1993; Kane et al., 1988). Thus, treatment resistant schizophrenia (TRS) poses a significant barrier to symptom management and clinical care, as well as substantial social and economic burden (Kennedy, 2014). This study aims to use epigenome-wide association studies (EWAS) to investigate the role of DNA methylation in TRS and to identify regions or positions associated with increased treatment resistance.

Methods: 119 patients diagnosed with schizophrenia spectrum disorder were recruited from the Centre of Addiction and Mental Health (CAMH) in Toronto, Canada. Data on antipsychotic use was gathered through self-report, then verified using patient medical records and medication history to categorize patients into treatment resistant (TR) and non-TR groups. Genome-wide methylation was determined through DNA samples collected for MethylationEPIC array profiling. The functions dmpFinder and bumphunter from the minfi package were used to examine the relationship between DNA methylation level and treatment resistance status.
Results: We did not find CpG sites signficantly associated at genome-wide level with treatment TRS.
Discussion: Based on this, genome-wide methylation may provide a powerful explanation for variability in TRS, with clinical applications that can be used to better tailor antipsychotic treatments to individuals based on their DNA profiles. However, further, larger scale analyses of DNA methylation in TRS are needed to replicate, support, and validate our findings presented here.

T97. INFLAMMATION AND BRAIN STRUCTURE IN SCHIZOPHRENIA AND NEUROPSYCHIATRIC DISORDERS: AN INTERROGATION OF CAUSAL PATHWAYS AND TRANSCRIPTOMIC PROFILES

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Background: Evidence to support immune activation in neuropsychiatric disorders is suggested by elevated IL-6 in childhood being associated with later risk of depression and psychosis, and present before the initiation of medication. Previous in-vitro and post-mortem research suggests a mechanistic relationship between inflammation and structural brain changes in mental disorders. Our objective is to investigate a possible causal relationship between inflammation and changes in brain structures in-vivo, and to explore a transcriptome-driven functional basis for these changes.
Methods: We leverage two datasets: the UK Biobank, a population-based cohort, containing clinical, genomic and neuroimaging data on around 500,000 UK residents aged 40-69 at baseline, and gene expression data taken from the Allen Human Brain Atlas. Genetic variants regulating levels/activity of circulating interleukin-1 (IL1), interleukin-2 (IL2), interleukin-6 (IL-6), C reactive protein (CRP), and brain-derived neurotrophic factor (BDNF) used as exposures in Mendelian randomization (MR) analysis, while grey matter volume (GMV) and cortical thickness measures were used as outcomes. Differential gene expression was modelled in regions mapped to areas significant in MR analysis; genes were tested for biological and disease over-representation in annotation databases and connectivity in protein-protein interaction networks.
Results: Genetically determined levels/activity of IL-6 were associated with GMV in the middle temporal (z-score = 5.76, $p<1.1x10-4$), inferior temporal ($z=3.38$, $p<0.001$), fusiform ($z=4.70$, $p<1.1x10-4$), and frontal ($z=-3.59$, $p<0.001$) cortex; and with putamen ($z=-3.78$, $p<0.001$) and

cerebellum (-3.64, p=0.001). No association with other biomarkers survived multiple testing correction. Brain-wide co-expression analysis showed a highly interconnected network of genes preferentially expressed in the middle temporal gyrus (MTG), which formed an interaction network with IL-6. MTG-expressed genes were functionally enriched for abnormal brain, cognition, anxiety, affective-related traits in mouse and neurologically-driven mental disorders in humans.
Discussion: These results suggests that innate immune system functioning, particularly IL-6 related pathways, may impact key areas of brain development. Elevation of IL-6 may impact structures who highly express neuroactive genes which, as a group, preferentially interact with each other and IL-6. A large part of this neurogenetic pathway may be mediated across neuropsychiatric disorders.

T98. GET ON RECOVERY DESPITE COVID-19: CREATION OF AN INTEGRATIVE PSYCHOEDUCATIONAL PROGRAM FOR PEOPLE WITH SCHIZOPHRENIA TO COPE WITH

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Background: Psychoeducation plays a key role in psychosocial rehabilitation programs towards recovery among people with schizophrenia. Since 2019 a national psychosocial rehabilitation network has been implemented in France offering several validated therapeutic tools, as part of personalized recovery-oriented program. In march 2019, faced with the urgency of the health measures linked to the pandemic and their impact on the continuity of care for people suffering from schizophrenia, the 2 recovery-oriented psychosocial rehabilitation expert centers in Hauts de France area, CRISALID and CSN2R, based on their experience in therapeutic education, have proposed an adaptation of the "Lifestyle" program by including specific sessions related to covid-19 while emphasizing coping strategies, continued care, health, recovery and quality of life.
Methods: Therapeutic education programs are built taking account cognitive impairments as well as clinical characteristics specific to schizophrenia. They are inspired by cognitive remediation techniques and cognitive and emotional behavioral therapy. Evaluations as well as home exercises between sessions are carried out. So when the epidemic arrived, and faced with the multitude of contradictory information and the fragility of people suffering from schizophrenia, we built a program to face and live with covid 19, “Livingstyle and COVID19’. During the second half of 2020, we included 12 patients (8 women, 4 men) meeting the criteria for schizophrenia (DSM IV-TR) who participated to 12 sessions, in small groups, including knowledge of the virus, treatments, barrier measures and above nutritional balance, addiction, management of emotions, overall health. We worked around cognitive biaises in a fun and hopeful atmosphere. We used some psychological assessments before and after the program. Statistical analyzes have been carried out with a level of significancy < 0,05.
Results: Patients perceived a significant improvement in their sense of self-efficacy (p=0.04). Participants felt more able to achieve their goals. Similarly, there is a significant trend regarding coping strategies (p=0.25) with a slightly greater use of external support.

Discussion: "Lifestyle and COVID19" is a new psychoeducational program who helps people with schizophrenia to cope with the pandemic crisis, helping them to live with the virus and to continue their goals of recovery. This program is easy to use and adaptable according to the evolution of knowledge and the health crisis. The satisfaction of the participants at the end of this program, and in particular their feedback on their empowerment capacity, underlines the importance of the continuation and the co-construction of recovery-oriented therapeutic education programs taking into account the reality of life.

T99. 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, with recent estimates suggesting a more than two-fold greater risk of psychotic disorder among first-generation migrant groups; however, the mechanisms underlying this association remain elusive. Migrant language has recently been proposed as a novel factor that may hold promise for improving our understanding of the relationship between migration and psychotic disorders. 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 linked population-based health administrative data, we constructed a retrospective cohort of first-generation migrants to Ontario over a 20-year period between 1992 and 2012. We obtained information on first language and fluency in Canada's official languages (English and French), in addition to other variables known to be associated with the risk of psychotic disorders among migrant groups. First language was categorized using several different approaches, due to the lack of a validated approach for measuring linguistic distance – these approaches included classification based on language trees, language acquisition difficulty, and syntax-based distance. First onset non-affective psychotic disorders were identified using a validated algorithm. We used Poisson regression models to compute incidence rate ratios for each language variable to assess the magnitude of effect on the risk of developing psychosis, relative to migrants who did not develop psychotic disorder, after adjusting for multiple risk factors.
Results: Our cohort included over two million first-generation migrants over the 20-year observation period, and nearly 700 different languages were represented in the dataset. Preliminary findings suggest that migrants who speak neither of Canada's official languages at the time of arrival (35%) have higher rates of psychotic disorder, relative to those who speak English (IRR=1.13, 95%CI=1.10,1.17). Full Results: for each of the language classifications will be presented at the conference.
Discussion: The excess rates of psychotic disorders among migrant and ethnic minority groups have persisted for nearly a century with little progress toward prevention. The findings from this study could potentially identify modifiable markers of risk for psychotic disorder to inform public mental health strategies.

T100. SOCIAL ANHEDONIA IN MALAYSIAN SCHIZOPHRENIA PATIENTS AND HEALTHY PARTICIPANTS

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Background: The reduced capacity for social and interpersonal interactions, or social anhedonia (SoA), is regarded as an important aspect of various psychiatric disorders, especially schizophrenia-spectrum disorders. As an indirect measure of SoA, the Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS; Gooding and Pflum, 2014) is relatively short and easy to administer, rendering it useful in both research and clinical settings. The goal of the present study was to validate the Malay translation of the ACIPS (adult version).
Methods: This cross-sectional study included 95 (47 male, 48 female) schizophrenia patients and 300 (77 male, 223 female) healthy subjects. Participants were given Malay versions of the ACIPS, Snaith Hamilton Pleasure Scale (SHAPS-M), and Beck Depression Inventory (BDI-M).
Results: The ACIPS exhibited good internal consistency (Ordinal alpha = 0.966). Total ACIPS scores were inversely correlated with BDI-Malay scores, and positively correlated with total SHAPS-M scores. Factor analysis yielded a three-factor solution which accounted for 52.06% of the variance. As expected, the schizophrenia patients scored significantly lower than the healthy community participants on the ACIPS, $t(130) = 4.26$, $p < 0.001$.
Discussion: The Malay version of the ACIPS showed good concurrent validity and excellent internal consistency. The patient data will be discussed in the context of other patient data from various countries (China, France, U.S.). Taken together, these data provide further validation for the utility of the ACIPS in both Western and Eastern contexts.

T101. THE INTERNATIONAL PSYCHOSIS EPIDEMIOLOGY CONSORTIUM – A PILOT RETROSPECTIVE HARMONIZATION PROJECT

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Background: Carrying out cross-country epidemiological research is costly. An alternative strategy is to pool existing data from high-quality early psychosis studies at an individual patient level. In this pilot project, data from 3 early psychosis cohorts from 3 different countries will be retrospectively harmonized into a virtual databank. This study aims to investigate the predictors of functional, symptomatic and personal outcome in patients with early psychosis, as well as the moderating effects of, amongst others, sociodemographic factors and illness duration.
Methods: This study uses individual patient data of >2000 patients with early psychosis from OPUS (Denmark, RCT), EPPIC (Australia, prospective cohort study) and a combination of PROGRs/PHAMOUS/RQ-MIS (The Netherlands, prospective cohort studies). These studies contain data on socio-demographic, socio-economic, premorbid, diagnostic, clinical, family and

medication baseline characteristics and follow-up measurements regarding functioning, symptoms and personal wellbeing. A virtual databank including the 3 abovementioned cohorts will be built. Based on this databank, a meta-analysis of individual patient data will be conducted. Advanced statistics, such as ensemble machine learning Methods:, will be used to investigate associations between the candidate predictor variables and functional, symptomatic and personal outcomes. Second, it will be evaluated if the associations between predictors and outcome are moderated by, amongst others, sociodemographic factors and illness duration.
Results: As a first step in building the virtual databank, a catalogue that comprises information on amongst others study design, population characteristics, Methods:, ethical and legal procedures and variables was made. Second, a set of target variables has been defined, based on consensus within the consortium. Third and currently, the harmonization potential for the variables is determined and a harmonization manual is developed. In the meantime, ethical and legal procedures are completed and the projects' technical infrastructure is developed and implemented. This infrastructure allows remote and non-disclosive analyses on the individual patient data of the cohorts without the need of transporting the data to another site, thereby safeguarding the participants' privacy. In a next step, cohort data will be transformed to the target format. A description of the technical infrastructure and the method for data harmonizing will be presented as well as some preliminary analyses.
Discussion: This pilot project shows that it is possible to build a virtual databank with data of individual early psychosis patients and to implement a technical infrastructure for remote analyses. The process so far has also revealed how time-consuming retrospective data harmonization is. Specific obstacles, step-by-step procedures and suggestions for future projects are proposed. This retrospective harmonization will allow large-scale international epidemiological research on early psychosis. In a later stadium the databank will be expanded with cohorts of a larger international collaborative psychosis research network as initiated by the SIRS Epidemiology Research Harmonization Group.

T102. THE ASSOCIATION BETWEEN SUBSTANCE-INDUCED PSYCHOSIS AND SUICIDE ATTEMPT

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Background: The current knowledge of substance-induced psychosis is still relatively limited. It has been suggested that individuals with substance-induced psychosis are a vulnerable population with a higher mortality, including death from suicide, compared with the general population. Even though not fatal, suicide attempt is an important risk factor for subsequent suicide. A better understanding of early stages of suicidal behavior in this population may have important implications to prevent suicide.
The aims of this study were to quantify the risk of suicide attempt after an incident substance-induced psychosis, and to compare the risk with the general population. Additionally, to examine whether psychosis caused by a specific substance increases the risk of suicide attempt more than

others. Lastly, we wanted to investigate if a specific period is associated with a greater risk of suicide attempt than others.

Methods: This was a Danish prospective, register-based study using information from the nationwide Danish Registers. All people living in Denmark aged 13 or more during 1995 to 2017 were included. Outcome was suicide attempt registered as a hospital contact. Cox proportional hazard regressions, adjusted for relevant confounders, were performed to estimate hazard ratios. An analysis regarding history of substance use disorders was conducted to examine if the combination of preceding substance use and substance-induced psychosis interacts on the incidence of suicide attempt.

Results: The study included a total of 5,806,700 individuals, and 8,900 people diagnosed with a substance-induced psychosis were identified. Preliminary Results: show that people with a substance-induced psychosis compared to the general population have a higher risk of having a subsequent suicide attempt (hazard ratio (HR) = 13.39, 95 % CI = 12.44 – 14.41). A similar pattern is seen when looking at the individual types of substance-induced psychosis. Opioid-induced psychosis had the highest hazard ratio (HR = 26.06, 95% CI = 18.01-37.79), while the lowest ratio was noted for cannabis (HR = 8.82, 95% CI = 7.61-10.22).
Further data are expected in 2022.

Discussion: The association between substance-induced psychosis and the risk of suicide attempt has to our knowledge not previously been investigated. Although the results are preliminary, they indicate that people with a substance-induced psychosis have a higher risk of suicide attempt.

T103. THE GENDER DISTRIBUTION OF PSYCHOTIC DISORDERS: EVIDENCE FROM A META-ANALYSIS

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Background: Incidence of psychotic disorders is highest in young men, and this has influenced both public perception of the disorders as well as service provision. Using existing epidemiological data, this paper will examine the age- and gender-distribution of pyschotic disorders in more detail, and will take a public health approach to challenge the perception of psychotic disorders as occurring predominantly in young men.

Methods: We used an existing meta-analysis which searched four databases to obtain citations of original research on the incidence of non-organic adult-onset psychotic disorders published from 2002 onwards. Data was extracted by sex, and incidence rate ratios (IRRs) and corresponding 95% confidence intervals (CIs) were computed. We pooled data using random-effect meta-analysis, and assessed the quality of studies included.

Results: Of the 177 citations meeting our inclusion criteria only 70 (39.5%) reported incidence for men and women separately. For all psychotic disorders, 26 estimates of IRRs in men compared with women were available from 10 citations with a pooled IRR of 1.44 (95% CI: 1.27-1.62). For non-affective psychoses, the pooled IRR of 1.60 (95%CI: 1.44-1.77) was estimated using 27 estimated from 11 citations. For affective psychoses, 20 estimates from six citations yielded a pooled IRR of 0.87 (95%CI: 0.75-1.00). At the conference, Results: using an updated search

strategy will be presented, as well as more detailed Results: in terms of diagnoses and across the life-course (age x sex interactions).
Discussion: Whereas the incidence of psychotic disorders is higher in men compared with women, this appears to be driven by the non-affective psychoses as there is no statistically significant difference in incidence rates for the affective disorders. This indicates that the public perception of psychotic disorders as a male group of disorders deserves more nuance. Service provision would also benefit from a public health approach: whereas incidence might peak in young men, they are a relatively small part of the population, so the majority of new cases will occur outside this narrow demographic.

T104. FACTORS ASSOCIATED WITH NEET-STATUS AFTER A DIAGNOSIS OF A PSYCHOTIC DISORDER IN ADOLESCENCE

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Background: Psychotic disorders are common reasons for unemployment and disability pension. However, it is not known whether the risk factors of not being in employment, education or training are similar in young people with and without psychotic disorder.
Methods: We used the register-based 1987 Finnish Birth Cohort study, which includes all live births in Finland during that year. The analyses comprised 55,171 individuals. Of these 288 had been diagnosed with psychotic disorders during 2004-2007 when they were 16-20 years old. We compared the association between several sociodemographic factors and being outside of education, employment, and training (NEET) for at least five years during 2008-2015 among those with and without a diagnosis of psychotic disorder.
Results: The odds ratio for being NEET for at least five years was 23.1 (95% CI 18.0-29.5, p<0.001) for those diagnosed with a psychotic disorder compared with the full cohort. Of those diagnosed with a psychotic disorder 65.6% had been NEET for at least one year and 35.8% for at least 5 years. Of those without a history of psychotic disorder 16.4% had been NEET for at least one year and 2.2% for at least five years.
All studied potential risk factors for long-term NEET status, but male sex, were more common in the group with a history of psychotic disorders than in the rest of the cohort. There was a statistically significant association between long-term NEET status, and all studied sociodemographic factors among those who had not been diagnosed with a psychotic disorder. Among those with psychotic disorders there was a significant association only between not having applied for upper secondary education (OR 2.7 (95% CI 1.1.-6.5, p 0.027)), not having a diploma from secondary education (OR 4.0 (95% CI 2.3-7.0, p <0.001)) and having a parent who had got welfare support (OR 1.7 (95%CI 1.1-2.8, p 0.030)). There was a significant interaction between psychotic disorders and placement outside of the home, not applying for upper secondary education, not having a diploma from upper secondary education and parents not being married. The associations between these factors and being long-term NEET were significantly weaker for those with a psychotic disorder than for the full cohort.

Although the associations between the sociodemographic factors and being NEET were weaker in the psychosis group, the proportion who were NEET was bigger. Being long-term NEET was most common among those with a history of psychotic disorder who had not applied for upper secondary education (56.5%) or had no diploma from upper secondary education (47.6%).

Discussion: The associations between several sociodemographic factors and being long-term NEET were significantly weaker for those with a psychotic disorder than for the full cohort. The findings highlight the serious long term functional morbidity associated with a diagnosis of psychosis in adolescence independent of sociodemographic Background: factors.

T105. GENDER, AGE AND GEOGRAPHICAL REPRESENTATION OVER THE PAST 50 YEARS OF SCHIZOPHRENIA RESEARCH

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Background: Previous studies have suggested that subjects participating in schizophrenia research are not representative of the demographics of the global population of people with schizophrenia, particularly in terms of gender and geographical location. We here explored if this has evolved throughout the decades, examining changes in geographical location, gender and age of participants in studies of schizophrenia published in the last 50 years.
Methods: We examined this using a meta-analytical approach on an existing database including over 3,278 publications collated for another project.
Results: We found that the proportion of studies and participants from low-and-middle income countries has significantly increased over time, with considerable input from studies from China. However, it is still low when compared to the global population they represent. Women have been historically under-represented in studies, and still are in high-income countries. However, a significantly higher proportion of female participants have been included in studies over time. The age of participants included has not changed significantly over time.

Discussion: Overall, there have been improvements in the geographical and gender representation of people with schizophrenia. However, there is still a long way to go so research can be representative of the global population of people with schizophrenia, particularly in geographical terms.

T106. NEIGHBORHOOD-LEVEL PREDICTORS OF AGE AT FIRST PRESENTATION FOR PSYCHOTIC DISORDERS USING NATIONWIDE SWEDISH REGISTER DATA

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Background: The relationship between neighborhood-level factors and the incidence of psychotic disorders is well established. However, it is unclear whether neighborhood characteristics can also influence the age at first presentation of these disorders.
Methods: We used longitudinal Swedish register data to identify a cohort of persons diagnosed with a psychotic disorder between 1997 and 2016. Using multilevel mixed-effect linear modelling we investigated whether neighborhood deprivation and population density at birth were associated with the age-at-first diagnosis of a psychotic disorder, which we used as a proxy for the age-at-onset.
Results: Our final cohort included 13,440 individuals. In an unadjusted model, we found no evidence of an association between neighborhood deprivation and the age-at-first diagnosis of psychosis (p=.069). However, when adjusted for sex, family history of psychosis, obstetric complications, family disposable income at participants' birth and parental migration status, the age-at-first diagnosis was predicted to increase by .13 years (95% CI: .05 to .21; p=.001), for 1 standard deviation increase in neighborhood deprivation. This was equivalent to a later presentation of 47 days (95% CI: 18 to 77). We found no evidence of a different relationship for non-affective compared to affective psychoses (LRT $\chi2(1) = .14$; p= .712). Population density was not associated with the age-at-first diagnosis of psychosis in unadjusted (p=.814) or adjusted (p=.282) models.
Discussion: Individuals born in more deprived neighborhoods are first diagnosed at a later age than those born in more affluent areas; this potentially highlights the presence of barriers to equitable psychiatric care.

T107. DEVELOPMENT OVER TIME OF THE POPULATION ATTRIBUTABLE RISK FRACTION FOR CANNABIS USE DISORDER ON SCHIZOPHRENIA

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Background: Cannabis use and potency of cannabis has increased over the past years. If the association between cannabis and schizophrenia is causal, this should be reflected in an increase in the proportion of cases of schizophrenia being attributable to cannabis, the population

attributable risk fraction (PAR%). Objective: To determine whether the PAR% for cannabis use disorder on schizophrenia has increased over time.

Methods: Design

Nationwide, register-based historical prospective cohort study.

Setting

Population-based.

Participants

All people in Denmark born before December 31st, 2000, and alive and aged 16 or above at some point between January 1st, 1972, and December 31st, 2016.

Exposure

Diagnosis of cannabis use disorder.

Main outcome and measures

Diagnosis of schizophrenia. We estimated PAR% of cannabis use disorder on schizophrenia from 1972 to 2016.

Results: We included 7,186,834 individuals, including 3,595,910 (50.0%) women. The adjusted hazard ratio for schizophrenia fluctuated around 4 (with 95% CI's ranging from approximately 3 to 6) throughout most of the study period when comparing people diagnosed with cannabis use disorder with people without cannabis use disorder. The PAR% of cannabis use disorder schizophrenia also fluctuated, but with clear evidence of an increase from around 1995 (where the PAR% was relatively stable around 2%, with 95% CI of approximately 0.3% to either side) until reaching some stability between 6% and 8% (with 95% CI of approximately 0.5% to either side) since 2010.

New, unpublished data will be presented on the sex-differences in this association.

Discussion: Assuming causality, the proportion of cases of schizophrenia attributable to cannabis use disorder has increased three to four-fold over the past two decades, which is fully what would be expected given previously described increases in use of cannabis and potency of cannabis. Our Results: from longitudinal analyses of the associations over time between cannabis use disorder and schizophrenia provide some evidence that some of this association may be causal. This has important ramifications regarding legalization and control of use of cannabis.

T108. ACUTE FUNCTIONAL AND BEHAVIORAL EFFECTS OF INCREASED ASTROCYTE ACTIVITY IN THE MPFC

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Background: The pathophysiology of schizophrenia appears to involve molecular and functional abnormalities in glial cells, including astrocytes. Whilst astrocytes have the capacity to critically affect key neurodevelopmental processes, they have been proposed to contribute to some of the alterations in the glutamatergic neurotransmitter system associated with schizophrenia.

Methods: Using the "designer receptor exclusively activated by designer drugs" (DREADDs) system, we developed a hM3DGq-DREADD-based mouse model to investigate the acute functional effects of increased astrocyte activity in the medial prefrontal cortex (mPFC).
Results: We found that hM3DGq-DREADD-mediated activation of astrocytes in the adult mPFC impaired mPFC-dependent cognition, including temporal order memory and spontaneous alternation in the Y-maze. Furthermore, DREADD-based activation of mPFC astrocytes increased the animals' sensitivity to the non-competitive N-methyl-d-aspartate receptor (NMDAR), MK-801.
Discussion: The data presented here suggest that astrocytes are directly involved in regulating cognitive processes pertaining to the mPFC. Moreover, the increased sensitivity to MK-801 in response to enhanced astrocyte activity indicates altered glutamatergic neurotransmission as seen in psychosis.

T109. THE HYPERDOPAMINERGIC STATE INDUCED BY ADOLESCENT STRESS IS HIGHLY CORRELATED WITH DEFICITS IN DIFFERENT BEHAVIORAL DOMAINS

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Background: The onset of some psychiatric disorders, such as schizophrenia, often occurs in late adolescence and/or early adulthood, which is a period of greater vulnerability to socio-environmental factors. Evidence suggests that stress during this period may affect brain structures that are important in regulating stress response, such as the ventral hippocampus (vHipp), leading to hyperactivation of the ventral tegmental area (VTA) dopamine system, which has been associated with psychotic symptoms. Here, we assessed the long-lasting effects of the exposure to stress during adolescence or adulthood on behavior and VTA dopamine system activity through in vivo electrophysiology.
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 (adolescence: PND 31-40; adulthood: PND 61-70), and three 1-hour restraint stress sessions (days 1, 2 and 10), right after the footshock session. Between 2-3 weeks after the end of the stress, the animals were submitted to different behavioral tests to evaluate anxiety [elevated plus-maze (EPM) and light-dark box], sociability (social interaction test), cognitive function [novel object recognition (NOR) test], anhedonia (splash-test), and hyperresponsivity to psychostimulants (locomotor response to the NMDA receptor antagonist MK-801). The in vivo electrophysiological activity of dopamine neurons in VTA was also recorded.
Results: Adolescent stress exposure (n=12 naïve and 12 stressed) produced in adult rats anxiety responses in the EPM and light-dark box, decreased social interaction, impaired cognitive function in the NOR test, and increased locomotor response to MK-801. These behavioral deficits were not found in animals exposed to stress in adulthood (n= 12 naïve and 12 stressed). Furthermore, electrophysiological recordings indicated that adolescent stress increased the number of spontaneously active VTA dopamine neurons, with no changes in the firing rate and burst activity. Adult stress did not induce long-lasting electrophysiological changes. Correlation matrix analysis indicated that the hyperdopaminergic state was highly correlated with anxiety behaviors, impairments in social interaction and cognitive function induced by adolescent stress.

Discussion: Our findings indicate that adolescent stress induced a schizophrenia-like hyperdopaminergic state which was highly correlated with long-term anxiety-like behaviors, cognitive and social interaction impairments, suggesting that adolescence may be a period of higher vulnerability for the development of schizophrenia in adulthood. Financial support: Sao Paulo Research Foundation (18/17597-3; 21/03391-7).

T110. KETOGENIC DIET BASED METABOLIC THERAPY FOR SCHIZOPHRENIA

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Background: Recent research revealed that deficit in brain energy metabolism, oxidative stress and inflammatory processes may play a role in the pathophysiology of schizophrenia. The classic pharmacological approaches focus on neurotransmitter receptors and do not have a direct impact on the above processes. In addition, antipsychotics cause systemic metabolic abnormalities ultimately leading to early cardiovascular death. Therefore, there is a pressing need to develop novel treatment approaches that directly address energy metabolism, oxidative stress and inflammatory processes. Ketogenic Diet (KD) is a high-fat, medium protein and very low-carbohydrates diet that has been shown to beneficially influence the neurobiological processes underlying the pathophysiology of schizophrenia. We hypothesized that KD and related metabolic therapeutic approaches alleviate behavioural abnormalities in pharmacological and neurodevelopmental models of schizophrenia and control psychotic symptoms and general functioning in individuals with schizophrenia and schizoaffective disorders.
Methods: Several KD based metabolic therapeutic approaches, such as ketogenic diet, beta-hydroxybutyrate (BHB; the main circulating ketone body) supplementation, as well as supplementation with triheptanoin (an anaplerotic agent to re-fill the tricarboxylic acid cycle) and with trihexanoin (a short-chain triglyceride metabolized to the short chain fatty acid [SCFA] hexanoate in the intestines) were tested in a pharmacological mouse model of schizophrenia. A single injection of the irreversible NMDA receptor antagonist dizocilpine (MK-801) was administered following three weeks of the above interventions, to induce a variety of schizophrenia-like behaviours. Furthermore, the effects of ketogenic diet were also tested in the poly-I:C-induced maternal immune activation (MIA) neurodevelopmental model. In the clinical arm of the study, 6 patients with schizophrenia or schizoaffective disorder were instructed to follow a ketogenic diet and their symptoms and general functioning were measured using the Positive and Negative Symptom Scale (PANSS) administered by an experienced psychiatrist.
Results: Ketogenic diet prevented a wide spectrum of schizophrenia-like behaviours induced by MK-801 administration, including locomotor hyperactivity, social interaction deficits, impaired sensorimotor gating and working memory. BHB supplementation largely replicated the effects of ketogenic diet in mice models. Triheptanoin and trihexanoin normalized MK-801-induced social withdrawal but not the locomotor hyperactivity. Furthermore, ketogenic diet administered during young adulthood normalized schizophrenia-like behaviours in the MIA model. Consistently with the preclinical finding, individuals with schizophrenia on a ketogenic diet demonstrated significant symptom improvement on PANSS and better general functioning as long the metabolic ketosis was maintained.

Discussion: Our translational work and the presented case studies strongly indicate that ketogenic diet based metabolic therapeutic approaches carry significant therapeutic benefit potential in schizophrenia.

T111. RETINAL MACULAR VOLUME IN SCHIZOPHRENIA

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Background: Schizophrenia is a neurodevelopmental disorder, and several studies have shown longitudinal decreased volume in white and grey matter. At the moment there are not any biological markers that can predict the course of the disease, nor treatment strategies that can prevent neurodegeneration. The evaluation of retinal fiber nerve layer (RNFL) in the retina represents an affordable opportunity to infer nerve changes in the brain - "the eyes are a window to the brain". Some authors have already demonstrated, for example, through Optical Coherence Tomography (OCT), the reduction of retinal nerve fiber layer thickness (RNFL) in neurodegenerative diseases such as Parkinson's disease, Alzheimer's, and multiple sclerosis. A few studies have also identified reduced RNFL in Schizophrenia, but little attention has been drawn to changes in macula volume, which could also be associated with neurodegeneration.
Methods: Schizophrenia group and control were sex and age matched. Subjects with intellectual disability, substance abuse, reported severe head trauma, uncontrolled medical condition, neurological condition, rheumatological condition, autoimmune condition, chronic infectious disease such as HIV/AIDS and hepatitis, myopia greater than 6 degrees, glaucoma, or other ocular pathologies that would hinder OCT examination were excluded. Individuals with any diagnosed mental disorder or taking psychotropic medication were not included in the control group. All participants underwent the Structured Clinical Interview for DSM-5 (SCID-5) in order to confirm the diagnosis of schizophrenia, diagnose possible comorbidities in the patient group, and exclude possible mental disorders in the control group. Anthropometric data (weight, height, BMI), information on physical health, medication use, use of alcohol, tobacco, and other psychoactive substances were also collected.
A single experienced ophthalmologist performed the ophthalmologic evaluation and OCT examination of all participants, thus minimizing possible examiner bias. Images of the retinal macula were acquired and processed by Spectral Domain OCT (SD-OCT) - Spectralis OCT, Version 6.0, Heidelberg Engineering, Germany applying standard protocol 1, 3, and 6 mm diameter Early Treatment Diabetic Retinopathy Study (ETDRS).

Comparisons were made using Student's t-test for continuous variables, running SPSS Statistics version 25 software for IOS Mac.

Results: Subjects were 35 patients with schizophrenia, 20 males and 15 females, aged 18 to 52 years, with a mean age of 36.51 years (SD = 12.41) and 35 healthy controls, 23 males and 12 females, aged 18 to 58 years, with a mean age of 36,74 years (SD = 11.94). Patients with schizophrenia had a lower macular volume of the right eye than controls (mean 8,48, sd 0,318 in

schizophrenia; mean 8.68, sd 0.415 in control group; t= 2.23; p = 0.029); no significance was found in left eye (8.47, sd 0.332 in schizophrenia; 8,62, sd 0.36 in control group; T 1.78; P 0.08).
Discussion: This study demonstrated a reduction in macular volume in the right eye of patients with schizophrenia. Since the retina is the visualization of neurons in vivo, this result could be related to the loss of volume in neurons and synapses. Retinal volumetric reduction in the right eye alone has also been identified in other studies evaluating individuals with schizophrenia, and may reflect the existence of asymmetry in the functioning and structure of the cerebral hemispheres. In addition, the small sample size and the fact that the examination always started with the right eye (implying a possible decrease in the quality of the left eye examination) may have contributed to the Results: only reaching statistical significance in one eye. Future studies of macular alterations observed in optical coherence tomography and cerebral cortex changes in schizophrenia might contribute to a better interpretation of our results.

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T112. ULOTARONT IMPROVES METABOLIC PARAMETERS IN RODENT MODELS OF WEIGHT GAIN AND HYPERGLYCEMIA

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Background: Ulotaront (SEP-363856) is a TAAR1 agonist with 5-HT1A agonist activity currently in Phase 3 clinical trials, with FDA Breakthrough Therapy Designation, for the treatment of schizophrenia. Metabolic Syndrome (e.g. central obesity, dyslipidemia, hypertension, hyperglycemia, etc.), which can be induced or exacerbated by antipsychotic drugs (APDs), is highly prevalent in schizophrenia patients. The need for novel treatments that lack APD class-specific metabolic side effects is therefore apparent. As a new pharmacological class, ulotaront has no significant activity at receptors commonly associated with APD-induced metabolic alterations (i.e. D2, 5-HT2C, H1 and M3). Intriguingly, recent preclinical evidence has identified TAAR1 as novel regulator of metabolic control and a promising target for obesity and type 2 diabetes. Here we evaluated the risk-benefit profile of ulotaront for the treatment of schizophrenia by assessing its effects on metabolic parameters in rodent models of Iatrogenic weight gain and hyperglycemia.
Methods: Effects of 15-day oral ulotaront treatment on body weight, food intake and metabolic parameters were investigated in Sprague Dawley rats on high-fat diet (HFD). In addition, body weight effects were determined in a rat (8-day treatment) and mouse (21-day treatment) model of olanzapine-, and corticosterone-induced body weight gain, respectively. Glucose tolerance was assessed in C57Bl6 and diabetic db/db mice following acute oral dosing. The acetaminophen absorption test was used to evaluate effects on gastric emptying in C57Bl6 mice. To obtain insights into the neurocircuits modulated by ulotaront, whole-brain 3D c-fos imaging was performed in C57Bl6 mice.
Results: Administration of ulotaront to rats on HFD resulted in a dose-dependent reduction in body weight, food intake and liver triglyceride content compared to vehicle controls. A more rapid reversal of olanzapine-induced weight gain and food intake was observed in rats switched to ulotaront treatment compared to vehicle alone. Consistent with the body weight-lowering effects

in rats, chronic treatment with ulotaront normalized corticosterone-induced body weight gain in mice. Acute ulotaront dosing dose-dependently reduced plasma glucose excursion in C57Bl6 and diabetic db/db mice during an oral glucose tolerance test (oGTT). Neither glucose nor insulin levels were changed in response to ulotaront during an ivGTT. Acute TAAR1 activation delayed gastric emptying in mice, which is likely the main mechanism driving reductions in glucose excursion during the oGTT. Ulotaront increased neuronal activity (c-fos expression) in several brain regions associated with the regulation of food intake and integration of peripheral metabolic signals (i.e. arcuate and paraventricular nucleus of the hypothalamus, and dorsal vagal complex). The brain-wide c-fos signature of ulotaront was distinct from that of the typical APD haloperidol.
Discussion: Our data indicate that ulotaront not only lacks APD-induced metabolic liabilities but can reduce body weight and improve glucose tolerance in rodent models. The underlying mechanisms are not fully elucidated but may include TAAR1-mediated peripheral effects on glucose homeostasis and gastric emptying, and/or direct modulation of homeostatic and hedonic neurocircuits regulating energy balance. The beneficial metabolic effects of ulotaront suggest a substantially improved risk-benefit profile compared to established APDs. Thus, TAAR1 agonists may not only represent a novel therapeutic class for the treatment of schizophrenia, but potentially also for metabolic disorders.

T113. AGGREGATION AND CO-AGGREGATION OF SPECIFIC PROTEINS IN POSTMORTEM BRAIN SAMPLES

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Background: Schizophrenia and other chronic mental illnesses (CMIs), such as major depressive disorder, are complex conditions with hereditary and non-genetic components. Since depressive episodes are a common clinical characteristic in schizophrenia, schizophrenia patients diagnosed with depression have a worse outcome, compared to patients without depression. Hence, investigating their shared elements could provide insight into shared biological pathways. As a result of overlapping symptoms between neurodegenerative disorders and CMIs, protein aggregation could be a possible pathological mechanism. Several proteins have so far been implicated as aggregating in CMIs, including Collapsin Response Mediator Protein 1 (CRMP1), Disrupted in Schizophrenia 1 (DISC1), Neuronal PAS domain-containing protein (NPAS3), and TRIO and F-actin-binding protein (TRIOBP-1). Most of these have been detected in multiple CMIs, suggesting aggregation to cross diagnostic boundaries. So far, the aggregation of one of these proteins alone was investigated, but some data suggests the idea of one protein stimulating aggregation of the others or co-aggregation.
Methods: We investigated the presence of aggregation of these proteins simultaneously in human brain samples, using suicide as an alternative, discrete non-subjective measure that spans diagnoses. Studies were performed on brains samples from 14 victims of suicide and 14 control individuals. 6 samples each from patients with depression and Alzheimer's disease were also included for context. Brains were donated as part of the Hungary-wide Lenhossék Program, after granting of family or a legal permission. Samples of the insular cortex were isolated, and flash-frozen after a post-mortem interval of 4.60±0.28 hours. Ethical approval for each stage of this work was obtained from the ethical committees and boards from the Ministry of Health of

Hungary, the Semmelweis University, and/or the University of Rijeka, as appropriate. Brain samples were homogenized, and the insoluble (including aggregating) protein fraction was purified with a series of solubilization buffers and ultracentrifugation. Both the original homogenates and this purified insoluble fraction were analyzed by Western Blot. All procedures were performed under blinded conditions.
Results: In our study, we have seen TRIOBP-1, previously only seen to aggregate in schizophrenia, as insoluble in suicide victims or depression patients. However, specific species of DISC1 (n=2) and CRMP1 (n=3) were found insoluble in suicide victims relative to control samples. Additionally, levels of CRMP1 were seen to vary in the whole sample between depression patients and control individuals or victims of suicide (in both cases $p<0.05$ by one-way ANOVA). Neither sex nor age showed any significant effect on the results. Notably, many of these samples showed multiple proteins to be aggregating simultaneously. We, therefore, performed follow-up in vitro studies in neuroblastoma cells, to determine if any of these proteins can co-exist in the same intracellular aggregates. In most instances, aggregation of each protein was independent of each other, although DISC1 co-aggregated with CRMP1 (confirming a previous result) and also with TRIOBP-1 (a novel interaction).
Discussion: Protein aggregation could be a common factor in major mental illness, with most instances of simultaneous aggregation arising from common underlying factors, rather than direct co-aggregation of the proteins, with the notable exception of DISC1 that can induce aggregation of some other proteins. Replication studies, as well as confirmation in additional brain regions, are now required to examine further this phenomenon and understand its pathological relevance.

T114. DETERMINATION OF THE DOMAIN STRUCTURE OF DISC1 IN MAMMALIAN CELLS IDENTIFIES A REGION CRUCIAL FOR ITS AGGREGATION IN SCHIZOPHRENIA

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Background: To date, the pathophysiology of schizophrenia remains incompletely understood. While traditionally investigated using genetics, disrupted protein homeostasis has been suggested as a complementary approach to determine biological basis for schizophrenia in at least a subset of patients. Several proteins previously implicated by genetic studies have been shown to form insoluble aggregates in this illness, including Disrupted in Schizophrenia 1 (DISC1). DISC1 is a multi-functional scaffolding protein of significant importance for neurodevelopment and synaptic function. However, delineation of the domain structure of DISC1 has only recently been attempted, using high-throughput analysis in E. coli. This approach identified four distinct stable domains named D, I, S and C. Here, we used this knowledge to confirm and refine the structure of DISC1 in mammalian cells, as well as to identify the region of DISC1 responsible for its aggregation.
Methods: DISC1 domain borders were refined by combining previously published theoretical data with the recent empirical data. Constructs encoding variants of domains D, I and C were cloned, with various alternative domain boundaries, based on theoretical predictions. These were transfected into HEK293 cells and tested for stability via proteasome inhibition assay. Results: were obtained by immunoblotting. In order to investigate which structural region(s) might be responsible for its aggregation, previously cloned fragments of DISC1, their combinations, and

interaction partners were expressed in SH-SY5Y neuroblastoma cells. Localization patterns and aggregation were assessed by fluorescent microscopy. Binding to interaction partners was tested using the nanoscale-pulldown assay.
Results: A proteasome inhibition assay showed that modified versions of D and C domains show improved stability over their empirically-derived counterparts, with evidence that the I region may not represent a stable folded domain by itself. The D, S and C domains were further shown to be functional in isolation, based on interaction with known protein binding partners. Single domains exhibited cytoplasmic localization with no aggregate formation. In contrast, the combination of domains D and I showed clear signs of aggregation, with full length DISC1 used as a positive control. Based on this, we hypothesized that the unstructured region between these two domains, D and I, is responsible for DISC1 aggregation propensity, which was verified using further truncation constructs. Deletion of this region also resulted in abolished aggregation.
Discussion: Previous theoretical predictions of DISC1 sequence repeats indicate the existence of conserved structural loops. These loops are in overlap with some of the experimentally proposed domains. Here, we have shown that the loops are indeed essential for the domain stability. Moreover, changing the boundaries of some experimental domains to match the end of theoretical structural motifs noticeably increased their expression, suggesting that current DISC1 domain boundaries should be redefined. Additionally, we were able to narrow the aggregating region of DISC1 down to a cluster of amino acids near the center of the protein. Taking into consideration how aggregation affects the brains of patients with neurodegenerative diseases, these findings could present a powerful insight into pathological mechanisms of mental illness, thus enabling future therapeutic development.

T115. MACHINE LEARNING BASED PREDICTION AND THE INFLUENCE OF COMPLEMENT - COAGULATION PATHWAY PROTEINS ON CLINICAL OUTCOME: RESULTS: FROM THE NEURAPRO TRIAL

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Background: Functional outcomes are important measures in the overall clinical course of psychosis and individuals at clinical high-risk (CHR), however, prediction of functional outcome remains difficult based on clinical information alone. In the first part of this study, we evaluated whether a combination of biological and clinical variables could predict future functional outcome in CHR individuals. The complement and coagulation pathways have previously been identified as being of relevance to the pathophysiology of psychosis and have been found to contribute to the prediction of clinical outcome in CHR participants. Hence, in the second part we extended the analysis to evaluate specifically the relationship of complement and coagulation proteins with psychotic symptoms and functional outcome in CHR.

Methods: We carried out plasma proteomics and measured plasma cytokine levels, and erythrocyte membrane fatty acid levels in a sub-sample (n=158) from the NEURAPRO clinical trial at baseline and 6 months follow up. Functional outcome was measured using Social and Occupational Functional assessment Score (SOFAS) scale. Firstly, we used support vector machine learning techniques to develop predictive models for functional outcome at 12 months. Secondly, we developed linear regression models to understand the association between 6-month follow-up levels of complement and coagulation proteins with 6-month follow-up measures of positive symptoms summary (PSS) scores and functional outcome.

Results: A prediction model based on clinical and biological data including the plasma proteome, erythrocyte fatty acids and cytokines, poorly predicted functional outcome at 12 months follow-up in CHR participants. In linear regression models, four complement and coagulation proteins (coagulation protein X, Complement C1r subcomponent like protein, Complement C4A and Complement C5) indicated a significant inverse association with functional outcome; and two proteins (complement C5 and Protein Z dependant protease inhibitor) positively associated with the PSS score.

Discussion: Our study does not provide support for the utility of cytokines, proteomic or fatty acid data for prediction of functional outcomes in individuals at high-risk for psychosis. However, the association of complement protein levels with clinical outcome suggests a role for the complement system and the activity of its related pathway in the functional impairment and positive symptom severity of CHR patients.

T116. GABA AND GLUTAMATE RECEPTOR ALTERATIONS IN THE PATHOPHYSIOLOGY OF SCHIZOPHRENIA-LIKE PHENOTYPES

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Background: Multiple lines of evidence suggest that abnormalities in inhibitory and excitatory neurotransmission are involved in the hippocampal hyperactivity that is associated with the hyperdopaminergic state commonly found in schizophrenia. Specifically, NMDA and GABAA receptor abnormalities have been found by human post-mortem examination and in some in vivo PET imaging studies. Previous research on the methylazoxymethanol acetate (MAM) developmental disruption model pharmacologically targeted GABAA receptors, by both the general GABAA receptor positive allosteric modulator diazepam and by a more selective positive allosteric modulator of the α5 subunit-containing GABAA receptor (α5GABAAR). Such experiments resulted in prevention or reversal of the hyperdopaminergic state and the associated schizophrenia-like behaviours in MAM-treated rats, suggesting GABAAR and specifically α5GABAAR may be involved in the development of psychosis. However, whether abnormalities at these receptors are involved in the pathophysiology of schizophrenia in the context of MAM was unknown. Here, we investigated NMDA, general GABAA and more specific α5GABAAR density in the MAM model using quantitative autoradiography. Putative preventive effects of chronic administration of diazepam during the peripubertal stage on these receptors' density at adulthood were also assessed.

Methods: Male MAM- and control (SAL)-treated rats were divided by either administration of diazepam (DZP; SAL:DZP n = 20; MAM:DZP n = 17) or vehicle (VEH; SAL:VEH n = 19; MAM:VEH n = 15) during puberty (PD31-40). Adult rats were then assessed for psychosis-relevant behaviours (amphetamine-induced hyperlocomotion (AIH) and the elevated plus maze (EPM)). To quantify the density of NMDA, GABAA and α5GABAAR, we used quantitative receptor autoradiography with [3H]MK801, [3H]Flumazenil, and [3H]Ro15-4513, respectively. Autoradiographs were sampled to ascertain receptor densities in the following hippocampal subfields: dorsal and ventral CA1, and ventral subiculum. Group (MAM vs SAL) and condition effects (DZP vs VEH) were analysed using three-way mixed ANOVA with region of interest as repeated measure. Finally, we analysed correlations between any significant receptor density differences and behavioural measures. The significance threshold was set to p=0.05, with Benjamini-Hochberg correction for multiple comparisons.

Results: MAM-treated rats exhibited psychosis-relevant behaviours in terms of increased amphetamine-induced hyperlocomotion (p=0.003) and anxiety-like behaviour (p=0.027) compared to SAL-treated rats. Diazepam administration only rescued anxiety-like behaviour (p=0.006). Autoradiography analyses revealed a reduction of α5GABAAR across all hippocampal subfields (p=0.005), an increase of NMDA receptors in the dorsal CA1 (q=0.030), and no differences in general GABAA receptors. Furthermore, reduced hippocampal α5GABAAR densities were associated with increased amphetamine-induced hyperlocomotion ($q<0.05$) and reduced ventral hippocampus CA1 α5GABAAR density was associated with increased anxiety-like behaviour (p=0.039). Finally, increased dorsal hippocampus CA1 NMDA receptor density was associated with increased amphetamine-induced hyperlocomotion (p=0.007).

Discussion: These data demonstrate that NMDA and α5GABAAR densities are abnormal in the context of the MAM model of schizophrenia and correlated with schizophrenia-relevant behavioural alterations. This suggests that such receptor abnormalities may be part of the molecular mechanisms underlying hippocampal dysfunction in schizophrenia and support prior evidence for α5GABAAR as a potential novel therapeutic target for schizophrenia.

T117. CHILDHOOD TRAUMA AND CANNABIS INTERACTIONS IN AFFECTING PSYCHOSIS ONSET AND ROLE OF THE ANTERIOR-POSTERIOR AXIS OF THE HIPPOCAMPUS: A BSNIP STUDY

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Background: A history of childhood trauma (CHT) has been shown to increase the risk of developing major psychiatric disorders. Structural deficits of the hippocampus (HP) have been observed in individuals with a history of CHT, with or without psychopathology suggesting that exposure to early life stress directly affects the development of the hippocampus. Other environmental factors influencing the risk of psychosis include use of cannabis (CU). The HP primarily contributes to cognitive functioning processes. Thus, here we predict that CHT adds on to the effects of psychopathology, mediating a reduction in volume of the aHP and pHP and a corresponding decline in cognitive function. Considering the shared genetic Background: of major psychiatric disorders, we explore the interaction of CU and CHT on the risk of psychosis and age onset (APO) in relation to the aHP and pHP volumes by use of path analysis in a large transdiagnostic sample of psychotic probands (PRO) and controls (HC).

Methods: PRO (n=1138; including: Bipolar with psychotic features, schizoaffective and schizophrenia) and HC (n=535) were recruited by the BSNIP2 and PARDIP studies. A structural 3 Tesla T1 image acquired from each participant, was processed using FreeSurfer 7.1 to calculate aHP and pHP volumes. Childhood trauma severity, total and subscale scores, were assessed using the Childhood Trauma Questionnaire (CTQ); cognition with the composite BACS score. PRO and HC were further divided by CU and group comparisons were made for CTQ measures, APO, and cognition. Statistical analysis was done using R (4.0.3), with HP volumes adjusted for age, sex, race, scanner, and eTIV. A Pearson correlation was used to relate HP with CTQ, BACS with CTQ, and APO with CTQ. Males/females divergence was examined. All analyses were corrected for multiple comparisons using FDR correction.

Results: The total CTQ score, and the five CTQ subscores (including emotional, physical, sexual abuse; and emotional and physical neglect) were significantly lower in HC compared to PRO, across DSM diagnoses. Data also showed significant inverse correlations between trauma score and volumes of aHP and pHP, but only in PRO; as well as with APO (the higher the CTQ score, the lower the APO). Analysis of trauma scores in PRO with/out CU showed significantly higher emotional abuse score and younger APO in PRO with, compared to PRO without CU. In HC, emotional as well as sexual abuse scores were higher with cannabis use. Exploration of the effect of trauma on cognition showed a significant inverse relation between higher BACS and lower CTQ scores. The positive relation between aHP and pHP with BACS did not change with/out controlling for severity of trauma but the association differed in male and female PRO where only the aHP in

males and both aHP and pHP in females correlated with the BACS. Structural equation modeling indicates contribution of cannabis, trauma and cognition in lowering the age of psychosis onset; with some direct effects on the HP.
Discussion: Here we report a significant effect of trauma on aHP and pHP in PRO, with differences in males and females and earlier APO. Lower cognition in PRO is related to higher trauma, but positive association between BACS and HP volume appears not to be mediated by trauma. PRO with history of cannabis use have higher trauma scores and an earlier APO. The structural equation modeling indicates direct effects of both cannabis and trauma on psychosis onset and the HP.

T118. PERCEIVED THREAT AND ALTERED INTERPERSONAL SPACE IS LINKED TO REDUCED VENTRAL HIPPOCAMPAL VOLUME IN SCHIZOPHRENIA

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Background: Perceived threat is a core symptom in schizophrenia and is often linked to tremendous individual burden and requires novel treatment interventions. As perceived threat is hard to detect in a clinical setting we used a behavioral measure to investigate alterations in interpersonal space in patients with schizophrenia. Therefore, we implemented an interpersonal space measure to quantify perceived threat in schizophrenia patients and controls and compared whole brain grey matter volume between patients with high interpersonal space, normal interpersonal space and healthy controls.
Methods: To test the effect of interpersonal space on grey matter volume we applied an interpersonal space test on a total sample of 114 (33 healthy controls, 81 schizophrenia patients). Based on their interpersonal space measure, patients were separated into two subgroups; one group of patients with increased interpersonal space and one group with normal interpersonal space. Then, we tested group effects on grey matter volume using a one-way ANOVA with age and total intracranial volume as covariates. Post-hoc tests were used to calculate grey matter differences between the three groups. Results: were corrected for multiple comparisons (p (FWE) < .05).
Results: One-way ANOVA between the three groups revealed significant differences in grey matter volume within the limbic network including bilateral hippocampus, amygdala, ventral tegmentum, and thalamic nuclei. Post-hoc comparisons, between high interpersonal space patients and controls revealed significantly reduced volumes in hippocampus, thalamus, putamen, temporal gyrus, and cerebellum in patients with high interpersonal space. Hippocampus, thalamus, putamen and temporal gyrus also show significantly reduced volume in patients with high interpersonal space compared to patients with normal interpersonal space. In contrast, no differences in grey matter volume were observed between controls and patients with normal interpersonal space.
Discussion: High interpersonal space in schizophrenia patients is linked to reduced grey matter volume in key areas of the limbic network. In particular, the association of high interpersonal space and hippocampus supports animal models of delusion formation. Our Results: further support the notion that grouping patients according to a quantified measure of perceived threat allows for

testing structural anomalies in the limbic network related to perceived threat in schizophrenia patients.

T119. THALAMOCORTICAL CONNECTIVITY IN WORKING MEMORY IMPAIRMENT IN SCHIZOPHRENIA, CONVERGING EVIDENCE FROM FMRI AND EEG

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Background: People with schizophrenia (PSZ) exhibit diminished working memory (WM) task performance compared to healthy controls (HC; Gold, 2004). The neurophysiological processes underling WM deficits remain unclear, which could be due to the variability in tasks and methodologies used. In the present study, we address this gap by examining commonalities in the EEG and fMRI indices of WM storage elicited by the same visual change detection task. Using this paradigm, we measured event-related alpha desynchronization (α-ERD) from the EEG, and modulation of the fMRI BOLD signal in the posterior parietal cortex (PPC) and middle occipital gyrus (MOG). These EEG and fMRI BOLD measures have exhibited significant WM load-dependent modulation in HC and reduced modulation for PSZ (Erickson et al., 2017; Hahn et al., 2018). Importantly, the load-dependent α-ERD and PPC/MOG modulation signals appear to be strongly correlated in PSZ but not HC, suggesting a potential shared psychopathological origin (Erickson et al., 2021). The present study has two aims: 1) to replicate the findings of a significant correlation between α-ERD and PPC/MOG modulation in PSZ but not HC observed in Erickson et al. (2021); and 2) to test the hypothesis that thalamocortical hyperconnectivity in PSZ accounts for abnormally elevated α-ERD and BOLD correlations.

Methods: 8 PSZ and 10 HC completed the study. Participants completed EEG and fMRI sessions on separate days, while performing an identical change detection task with set sizes 1, 3, and 5 items. α-ERD was calculated separately for each set size, and α-ERD slope reflects the modulation in α-ERD with WM load. Similarly, BOLD modulation as a function of set size was calculated by estimating % signal change at each set size and calculating the slope of change as a function of WM load. The correlation between the α-ERD and BOLD slopes was then examined. Resting state and task-related connectivity between the posterior thalamus and the PPC and MOG were examined to test for thalamocortical hyperconnectivity in PSZ.

Results: There was trend-level difference in behavioral performance between PSZ and HC ($F(1,16)=3.29$, $p=0.09$) with PSZ performing worse than HC. For α-ERD we conducted a hemisphere x set size x group (2 x 3 x 2) repeated measures ANOVA. As expected, there were no significant effects of hemisphere ($F(1,16)=0.18$; $p=0.68$), and there was a trend-level effect of set size ($F(2,32)=2.68$; $p=0.08$), with smaller α-ERD at smaller set sizes. Although there was a qualitative pattern of PSZ exhibiting reduced α-ERD, this group effect did not reach statistical significance ($F(1,16)=0.78$; $p=0.39$). Similarly, although HC had a qualitatively larger negative α-ERD slope compared to PSZ as a function of WM load, this effect also did not reach statistical significance ($F(1,16)=2.11$; $p=0.17$).

For BOLD we again conducted a hemisphere x set size x group (2 x 3 x 2) repeated measures ANOVA separately for PPC and MOG. There was no significant effect of hemisphere for either

PPC or MOG (F's<1.27; p's>0.28). There was a significant main effect of set size for PPC and MOG (F's>10.97; p's<0.001), with smallest % signal change at set size 1 and the largest % signal change at set size 5. Finally, as with the α-ERD effects, PSZ had qualitatively reduced BOLD modulation compared to HC, but this effect did not reach significance (F's<1.31; p's>0.27). There was a significant difference between HC and PSZ for MOG slopes as a function of WM load ($F(1,16) = 7.22$; $p = 0.02$), and a qualitatively similar pattern of PPC slopes that did not reach statistical significance ($F(1,16) = 2.32$; $p = 0.15$).

Consistent with our previous observations, we observed large, negative correlations between α-ERD and BOLD modulation slopes for PSZ that reached the level of a trend in the PPC (r's = -0.62 to -0.91; p's ≤ 0.10), but not the MOG (r's = -0.35 to -0.58; p's ≤ 0.41). Contrary to our predictions, we also observed large, negative correlations between α-ERD and BOLD modulation slopes in HC as well in both the PPC (r's = -0.70 to -0.72; p's ≤ 0.05) and MOG (r's = -0.62 to -0.73; p's ≤ 0.06). There were no significant differences in the task or resting-state thalamocortical connectivity between PSZ and HC.

Discussion: Our findings lend support to previous work indicating that (a) α-ERD modulation as a function of WM storage is reduced in PSZ; (b) PPC/MOG BOLD modulation as a function of WM storage is reduced in PSZ; and (c) the magnitude of the α-ERD and BOLD modulation are strongly correlated. However, unlike previous work, we observed that HC also exhibit a strong correlation between these signals. Furthermore, we did not observe the expected hyperconnectivity between posterior thalamus and cortical areas in PSZ. The present work therefore indicates that α-ERD and BOLD are functionally related in WM function in health as well as in clinical populations. It should be noted that the present conclusions are of a preliminary nature given the small, and likely underpowered, present sample size.

T120. DEVELOPMENTAL OXIDATIVE STRESS LEADS TO T-TYPE CA2+ CHANNEL HYPOFUNCTION IN THALAMIC RETICULAR NUCLEUS OF MOUSE MODELS PERTINENT TO SCHIZOPHRENIA

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Background: The thalamic reticular nucleus (TRN) is composed of GABAergic neurons that receive synaptic inputs from cortex, thalamus and subcortical regions and exert inhibition onto thalamic neurons projecting to the cortex or subcortical areas. Therefore, it occupies a key position to modulate thalamo-cortical information flow, and is involved in sleep-arousal states, sensory filtering, attention, and emotion-related behaviors. Anomalies of TRN neurons expressing parvalbumin, the larger population of TRN neurons, are reported in schizophrenia (SZ) patients. As impairment of parvalbumin interneurons induced by oxidative stress (OxS) is a "hub" on which converge several genetic and environmental risk factors associated with SZ, we hypothesized that OxS affects also the integrity and function of TRN. TRN neurons, in particular parvalbumin-expressing ones, can exhibit oscillatory burst discharges which mediate sleep spindles, known to be affected in SZ. The excitability and rhythmic bursting activity of TRN neurons depend on two sub-types of low voltage-activated T-type Ca2+ (T-Ca2+) channels (CaV3.2 and CaV3.3), and on

their coordinated activity with small-conductance Ca2+-activated K+ (SK) channels. Here, we investigated in mice the impact of OxS on the burst firing behavior of TRN neurons and function of their T-Ca2+ and SK channels.
Methods: TRN integrity and function was assessed during peripuberty and/or adulthood in 1) mice (Gclm knockout, KO) with a chronic glutathione deficit, 2) mice with a transient glutathione deficit induced by buthionine sulfoximine (BSO) during early postnatal development, 3) offspring mice from mothers having received an intraperitoneal injection of methylazoxymethanol acetate at gestational day 16 (MAM mice). We evaluated the mode of firing activity (tonic versus phasic) and excitability of TRN neurons, and quantified their T-Ca2+ and SK currents, using in vitro whole-cell recordings. In parallel, we used immunohistological techniques to assess OxS, integrity of parvalbumin-immunoreactive neurons and extracellular perineuronal net (PNN), as well as the expression of CaV3.2 and CaV3.3 in the TRN.
Results: In Gclm KO mice, which display OxS, reduced parvalbumin-immunoreactive neurons and weakened PNN in TRN, we found a reduction of T-Ca2+ currents with a concomitant decrease of SK currents in TRN neurons of adult, but not peripubertal individuals. In KO adults, the decrease in T-Ca2+ currents was accompanied with a decrease of Cav3.3 expression and a shift towards more hyperpolarized membrane potentials for burst firing leading to less prominent bursting behavior. In young Gclm KO mice, but also BSO-treated mice, an early-life oxidative challenge (induced by the dopamine uptake inhibitor GBR12909) precipitated the hypofunction of T-Ca2+ channels. This was prevented by a treatment with N-acetylcysteine that also abolished OxS and normalized parvalbumin expression and PNN. Increased oxidation of extracellular redox sites, presumably on CaV3.2 channels, also contributed to the reduced T-Ca2+ currents in TRN neurons of these mice. Likewise, a concomitant presence of OxS and hypofunction of T-Ca2+ channels in TRN neurons of MAM mice was found.
Discussion: Our Results: strongly suggest that OxS-mediated T-Ca2+ channel hypofunction in TRN, via reduced CaV3.3 expression and oxidation of redox-sensitive sites on CaV3.2, represent a convergent mechanism contributing to early thalamo-cortical anomalies and SZ pathogenesis. Together with genetic associations between SZ and CACNA1I (encoding CaV3.3) and to a lesser extent CACNA1H (encoding CaV3.2), these suggest that T-Ca2+ channel dysfunction in TRN could represent an early pathological feature of this psychiatric disorder.

T121. THE ASSOCIATION OF A POLYGENIC SCORE INDEXING A DRD2-RELATED CO-EXPRESSION NETWORK WITH STRIATAL DOPAMINE SYNTHESIS CAPACITY: A PET IMAGING STUDY

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Background: The D2 dopamine receptor (D2R) is the primary site of action of antipsychotics and is involved in essential brain functions relevant to schizophrenia, such as attention, memory,

motivation, and emotion processing. Furthermore, the gene coding for this receptor (DRD2) has been associated with schizophrenia at a genome-wide level.
A polygenic index (PCI) predicting the brain-specific expression of a network of genes co-expressed with DRD2 has been associated with response to antipsychotics, brain function during working memory in patients with schizophrenia, and with the modulation of prefrontal cortex activity after pharmacological stimulation of D2 receptors.

We aimed to investigate the relationship between the DRD2 gene network and in vivo striatal dopaminergic function, which is a phenotype associated with psychosis and schizophrenia.

Methods: To this aim, a sample of 92 healthy subjects underwent 18F-DOPA PET and was genotyped for genetic variations indexing the co-expression of the DRD2-related genetic network in order to calculate the PCI for each subject.
Results: The PCI was significantly associated with whole striatal dopamine synthesis capacity ($p = 0.038$). Exploratory analyses on the striatal subdivisions revealed a larger effect of the PCI on dopamine function for the associative striatum.
Discussion: These Results: are in line with a possible relationship between the DRD2-related co-expression network and schizophrenia and extend it by identifying a potential mechanism involving the regulation of dopamine synthesis. Future studies are needed to clarify the molecular mechanisms implicated in this association.

T122. MEASUREMENT OF BRAIN GLUTATHIONE AND ITS RELATIONSHIP WITH PERIPHERAL OXIDATIVE STRESS MARKERS IN SCHIZOPHRENIA-SPECTRUM DISORDERS

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Background: Oxidative stress may contribute to the declining course and poor outcomes observed in psychosis, with oxidative damage affecting the neuronal membrane and impairing neurotransmission. However, Results: from in vivo Magnetic Resonance Spectroscopy (MRS) studies have been disparate, potentially reflecting differences in clinical stage, sample demographics, neuroanatomical focus, sample size, and variability in acquisition Methods:. In this study we aim to conduct a systematic review and meta-analysis of all existing evidence investigating differences in glutathione measured in the brains of people with psychosis , and assess if this is related to key clinical and demographic features. We also investigate the effects of differences in MRS acquisition method and voxel placement.
Methods: Data Sources:
PubMed, PsycINFO, Web of Science, Ovid MEDLINE and EMBASE to identify journal

articles published until May 30th, 2021.

Study Selection:

A literature search revealed 28 studies, with 24 eligible for inclusion in the meta-analysis, providing in vivo measurement of glutathione using magnetic resonance spectroscopy in individuals with a clinical diagnosis of a schizophrenia spectrum disorder, or individuals at clinical high risk for psychosis.

Data Extraction and Synthesis:

Independent researchers (AM and CH) extracted levels of oxidative stress metabolites, clinical and demographic characteristics and magnetic resonance spectroscopy methodologies from the 24 studies. A random effects model of standardised mean differences across variables was used to calculate overall effect using comprehensive meta-analysis software.

Results: GSH levels were not significantly different across all psychosis patients (N=723) when compared to healthy controls (N=709) (k=33, d=-0.096, CI=-0.23 to 0.03, p=0.15) but were significantly different for patients with established schizophrenia (n=379; k=16, d=-0.21, CI=-0.38 to -0.04, $p<0.05$) compared to healthy controls. Meta-regression analyses indicated no effect of age, sex, antipsychotic medication, or symptom severity. No effect of methodological variables was found, including echo time and voxel size.

Discussion: A reduction in brain glutathione levels is present in established schizophrenia and may provide novel treatment targeted at this stage of illness rather than heterogeneous early phases of illness. Furthermore, the variability in MRS acquisition modalities may not be having as strong an impact on glutathione quantification as previously thought.

T123. FRONTAL POLE VOLUMES AND COGNITIVE INSIGHT IN SCHIZOPHRENIA, REVISITED

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Background: Lack of insight is one of the cardinal features of schizophrenia (SCZ). It is an important determinant of functional outcome in schizophrenia. Cognitive insight is commonly measured using the Beck's Cognitive Insight Scale (BCIS), which has two components- Self Reflectiveness (SR) and Self Certainity (SC). The frontal pole (FP; Broadman Area 10) has been shown to play a role in complex cognitive functions including meta-cognition. Since FP is implicated in self-referential tasks, it is worthwhile to examine its role in cognitive insight in schizophrenia. Hence, we aimed to study the relationship between FP volumes and cognitive insight in a large sample of schizophrenia patients and healthy controls.

Methods: We recruited 41 healthy volunteers (HV) and 57 patients with schizophrenia (SCZ). We assessed cognitive insight using the BCIS and clinical severity using the positive and negative syndrome scale (PANSS), the Calgary depression rating scale for schizophrenia. Imaging was performed using a 3T magnetic resonance scanner. A standard 3D T1 MPRAGE sequence was acquired with isometric voxels We used a previously validated morphometric method to perform FP parcellation and to obtain volumes. The posterior limit of the FP was identified as the coronal section of the anterior termination of the olfactory sulcus (ATOS), perpendicular to the AC-PC plane. This was manually outlined on successive coronal slices anterior to this section, till the most

rostral section containing GM. A single rater blind to the diagnostic status of the subject performed the morphometric analysis on coded images. An intraclass correlation coefficient of 0.96 (95% CI-(0.93-0.99),$p<0.001$) was established indicating excellent intra-rater reliability. To assess the relationship between GM volumes in the FP and BCIS scores, multiple linear regression analyses were performed with BCIS sub-scores and composite score as dependent variables and hemisphere specific FP volume, age, sex, years of education, and ICV as explanatory variables.

Results: On multiple regression analysis within SCZ group, the model was significant for SC ($R2=0.21$; $F=2.33$; $p=0.04$) with age and ICV being significant predictors. The model was also significant for BCIS composite scores ($R\ 2 =0.32$; $F=4.00$; $p=0.002$) with left FP volume ($\beta=0.44$; $t=2.04$; $p=0.04$). However, the model was not significant for SR ($R2=0.14$; $F=1.45$; $p=0.21$). In HV, the overall regression model was significant for SR ($R2=0.40$; $F=4.02$; $p=0.004$) with years of education and sex being significant predictors. However, the model was not significant for SC ($R2=0.26$; $F=2.07$; $p=0.08$) or composite scores ($R2=0.14$; $F=0.99$; $p=0.44$) in HV. Partial correlation demonstrated no significant relation between age and FP volumes in neither SCZ nor HV. Left and right FP volumes did not show any relation with PANSS sub-scores, SANS score, duration of illness or antipsychotic dose ($p>0.05$).

Discussion: Findings of the study suggest a relationship between BCIS composite score and left FP volume in SCZ. We had previously reported a relationship between cognitive insight and FP volumes in a previous study. The current study in an independent larger sample with both sexes further supports the existing literature suggesting the critical role of frontal pole in cognitive insight. The current study reports anatomical substrate that could be targeted in intervention strategies, such as brain stimulation, for improving cognitive insight. Considering the important role of insight in functional outcome, the current finding of anatomical correlate has potential clinical implications.

T124. GRAY MATTER VOLUME CHANGE IN EARLY-ONSET PSYCHOSIS – AN ENIGMA MULTICENTER VOXEL-BASED MORPHOMETRY STUDY

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Background: Structural brain alterations have been reported in early-onset psychosis (EOP, age of onset before 18 years of age), however, due to small sample sizes and heterogeneity, findings are inconsistent. A previous mega-analysis from the ENIGMA EOP group revealed lower intracranial volume and subcortical volumes changes. Voxel based morphometry (VBM) examines changes in brain volume on a voxel-by-voxel basis and thus provides complementary

information to FreeSurfer analysis commonly used in the ENIGMA consortium. In this study, we introduce the newly developed ENIGMA VBM tool (sites.google.com/view/enigmavbm) and investigate gray matter volume alterations in EOP.
Methods: The ENIGMA VBM tool has been developed to apply DARTEL VBM with standardized settings, conduct case-control comparisons, investigate correlations of clinical variables within the patient group, conduct automatic quality control (QC) procedures and output statistical images. T1-weighted brain images were processed locally at each participating site with the ENIGMA-VBM tool and the resulting statistical maps were sent to the coordinating site. Comparison of regional gray volume between patients and controls (modelling intracranial volume and age as covariates of no interest) and the correlation to clinical variables in patients were meta-analysed at the coordinating site using Seed-based d Mapping (version 6.21). 472 EOP patients (54.9% female) and 458 healthy controls (43.7% female) were included in the analysis from 13 independent sites. Mean age of onset was 15.3 years with a mean duration of illness of 1.9 years.
Results: The VBM analysis revealed lower gray matter volume of the cortex in EOP which passed $p<0.05$ family wise error (FWE) corrected threshold. While significantly lower cortical volumes were observed in all lobes of the brain, the greatest alteration was in the right medial cingulate (Hedges $g=0.55$, $p<0.001$). An older age of onset in patients ($n=428$) was associated with lower gray matter volume in post central gyrus (Hedges' $g=0.20$, $p<0.01$) and thalamus (Hedges' $g=0.17$, $p<0.01$). In patients ($n=343$), widespread lower frontal lobe gray matter volume was associated with a higher chlorpromazine equivalent dose (Hedges' $g=0.20$, $p<0.01$).
Discussion: The Results: confirm robust lower cortical volume in EOP compared to healthy controls, which is consistent with other studies. The findings relating to age of onset and medication are more novel and require replication by future studies. Finally, this study demonstrates the effectiveness of the ENIGMA VBM tool in determining structural brain changes in large multicenter samples.

T125. ALTERED EEG ACTIVITY AT BASELINE DURING A P300 TASK AND IN THE RESTING STATE IN PATIENTS WITH SCHIZOPHRENIA. ARE THEY COMPARABLE AS A CONTROL CONDITION?

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Background: We can find in the literature ample evidence that patients with schizophrenia show alterations in EEG activity both during the performance of a cognitive task and during the resting state. On the other hand, there are also studies that have found that the modulation of bioelectrical activity in these patients is altered during the performance of cognitive tasks. In this line, our previous work has demonstrated a deficit in EEG activity modulation, calculated as the difference between the P300 task-related response and the immediately preceding baseline state. However, these works assume baseline as a valid control condition when it is likely to be influenced by task-related cognitive expectancy activity. It is therefore questionable whether basal activity is analogous to that of the true resting state, i.e., when the subject is not performing any cognitive or motor task. Despite its relevance to research, to the best of our knowledge no preceding study has compared both states of EEG activity.

Methods: 89 patients with schizophrenia (28 of them first-episode) and 76 healthy controls performed a dual task during an EEG recording: 1) five minutes of resting state, and 2) an oddball task for P300 event-related potential elicitation. Absolute power across the entire scalp (29 electrodes) was then assessed for each of these paradigms. Statistical analysis consisted of a repeated measures General Linear Model where the effect of 'Condition' (baseline P300 and rest) as within-subjects factor, and 'Group' (patient and healthy control) as between-subjects factor were studied. The statistical analysis was repeated for each of the relevant frequency bands: theta, alpha, beta-1 and -2, and gamma-1 and -2. In order to rule out the possible effect of illness chronicity and/or medication, this analysis was also performed for first-episode patients vs healthy controls.
Results: A significant effect was found for the factors 'Condition' and 'Group', as well as for their interaction. Patients with schizophrenia showed, in all frequency bands, significantly higher EEG activity in both P300 baseline and resting state compared to healthy controls. Second, regardless of study group, absolute power in the fast bands (beta-2 and gamma-1 and -2) was significantly higher during P300 baseline than during the resting state. However, in the slower frequency bands (theta, alpha and beta-1), no significant differences were found between the two conditions. Finally, the study of the Condition*Group interaction indicated that only in the intermediate frequency bands beta-1 and beta-2, patients with schizophrenia and controls differed in these results: the former showed no significant differences between conditions, while the latter did.
Discussion: Previous studies have demonstrated decreased modulation of EEG activity in patients with schizophrenia using measures such as spectral entropy or connectivity strength, studied as the change between P300 task-related baseline and response. These Results: have been especially significant in slow frequency bands such as theta. The present work confirms a hyperactivation in patients with schizophrenia in both task-related baseline and resting state. We believe that it is relevant to have found, at least in the slow frequency bands, similar alterations in the task-related baseline and in the resting state. This would confirm that the deficits in the modulation of bioelectrical activity found in previous studies are probably due to hyperactivation already present from the resting state itself.

T126. INVESTIGATION OF NEUROPHYSIOLOGICAL ASPECTS OF PSYCHOTIC DISORDERS BASED ON RESTING STATE EEG-ANALYSES IN CORRELATION TO COGNITIVE ABILITIES IN PATIENTS AND CONTROL SUBJECTS

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Background: The prospective CDP (“Clinical Deep Phenotyping”) study at the Department of Psychiatry and Psychotherapy of the LMU Munich aims to identify endophenotypes from the psychotic spectrum. The phenotyping of the study participants is performed multimodally using techniques from MR neuroimaging, neurophysiology and neuropsychology.
Schizophrenia is a severe mental illness of the psychotic type. In addition to positive and negative symptoms, patients with schizophrenia also show impaired cognitive performance. This domain is covered in the CDP study by the standardized BACS (Brief Assessment of Cognition in Schizophrenia) test, which is performed on patients with schizophrenia and on healthy control

subjects. Abnormalities in the EEG have also been shown in patients with schizophrenia. The resting state EEG performed in the CDP study will show to what extent patients with schizophrenia differ from healthy control subjects in terms of EEG frequencies and amplitudes.

Methods: Participants had a resting state EEG recorded with 21 Electrodes. The recording was made using the BrainAmp amplifier (Brain Products, Martinsried, Germany) and Cz served as the reference electrode. In total the recording of the resting state EEG lasted 10 minutes (min), the first 5 min with eyes closed and another 5 min with eyes open. Participants were instructed to remain as calm and relaxed as possible during the recording. Before analysis, all resting state EEG data were carefully cleaned. In order to reject as few EEG segments as possible, de-artifacting was performed with a semi-automatic ICA (independent component analysis) using BrainVisionAnalyzer 2.2. After ICA, almost the entire 10 min of artefact-free EEG remained (~90%), so that the analyses can be carried out on this basis.
The BACS test was performed on participants by trained personnel under standardized circumstances. In the BACS test, the cognitive domains "verbal memory and learning", "working memory", "motor skills", "attention and processing speed", "word fluency" and "executive functions" were tested in different subdomains.

Results: The preliminary analyses of the rsEEG showed highly significant ($p<0.001$) Results: at the single-electrode level in the theta frequency range (4-8 Hz). Here it could be shown that in patients with schizophrenia there is a significant increase in the mean theta amplitudes (given in μV). Clustering the electrodes into 3 left-hemispheric and 3 right-hemispheric clusters also revealed a significantly ($p<0.01$ in the left and right central clusters, $p<0.05$ in all other clusters) higher mean amplitude of theta waves in patients with schizophrenia.
For the alpha (8-12 Hz), beta (12-30 Hz), gamma (30-70 Hz) and delta (1-4 Hz) frequency ranges, no significant difference could be observed at the single-electrode level between patients with schizophrenia and healthy control subjects.

At the source level (left insula, right insula, dACC, and complete salience network), not only the mean amplitudes of theta waves but also the mean amplitudes of alpha and delta waves showed a significant increase in patients with schizophrenia.

A negative correlation ($r = - 0.269$; $p = 0.04$) between the mean amplitudes of theta waves and the score achieved in the BACS task "digit sequencing" was shown in healthy control subjects in the left hemisphere.

Discussion: Based on these preliminary results, it can be suggested that the cognitive performance of healthy control subjects is directly associated with neurophysiological correlates. Direct comparison with other observational levels, such as evoked potentials (P300), retinal neurophysiology, and multimodal MRI will increase exploratory power and possibly generate complementary evidence.

T127. PSYCHOPATHOLOGICAL SYNDROMES ACROSS AFFECTIVE AND PSYCHOTIC DISORDERS CORRELATE WITH GRAY MATTER VOLUMES: RESULTS: FROM THE FOR2107 COHORT

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Background: More than a century of research on the neurobiological underpinnings of affective (major depression, bipolar disorder) and psychotic disorders (schizophrenia, schizoaffective disorder) has been unable to identify diagnostic "markers". An alternative approach is to study dimensional psychopathological syndromes that cut across categorical diagnoses. Previously, we have identified a transdiagnostic factor model including depression, negative symptoms, positive formal thought disorder, paranoid-hallucinatory syndrome, and increased appetite. The aim of the current study was to identify gray matter volume (GMV) correlates of these factors across affective and psychotic disorders.
Methods: We tested the association of 5 psychopathological factors with GMV using multiple regression models (in SPM) in a sample of N=1069 patients. T1-weighted brain images were acquired with 3-Tesla magnetic resonance imaging and preprocessed with CAT12. Results: were suggested significant at $p<.05$, family wise error corrected. To rule out confounding effects of unequally distributed diagnostic categories, interaction analyses (diagnosis × psychopathological factor) were performed. We further tested syndrome specific regions of interest (ROIs).
Results: The factor positive formal thought disorder was negatively associated with GMV in the right middle frontal gyrus, while the paranoid-hallucinatory syndrome was negatively correlated with GMV in the right fusiform, and the left middle frontal gyri. ROI analyses revealed further negative associations, including the negative syndrome with bilateral frontal opercula, positive formal thought disorder with the left amygdala-hippocampus complex, and the paranoid-hallucinatory syndrome with the left angular gyrus. No interaction of diagnostic category x psychopathological factor was present.
Discussion: Volume changes underlying psychopathological syndromes are independent of diagnosis. We could confirm previous Results: from much smaller studies which have restricted themselves to single diagnoses. Our findings open a new avenue for neurobiological research of affective and psychotic disorders, using syndrome based, dimensional approaches rather than categorical diagnoses.

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T128. PATIENTS WITH SCHIZOPHRENIA AND THEIR PROCESSING OF PERCEPTUAL (UN)CERTAINTY – EVIDENCE FROM BEHAVIOR AND EEG

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Background: The world is not as we perceive it. Actually, the sensory information is inherently incomplete and to varying degrees ambiguous and noisy. In order to provide a stable and reliable perception, the brain integrates this limited sensory (bottom-up) information with endogenous

(top-down) information. This integration mechanism seems to be deficient in patients with schizophrenia and might explain social and perceptual impairments.
The integration of bottom-up with top-down information was investigated in neurotypicals by contrasting perceptual processing of ambiguous/low-visibility with unambiguous/high-visibility stimuli while measuring the electroencephalography (EEG). Large event-related potential (ERP) differences were found and named the "ERP Uncertainty Effects", which reflect the differential integration of bottom-up and top-down information.

Methods: We compared patients with schizophrenia and matched controls by investigating behavioral and ERP Uncertainty Effects. We evoked those effects by presenting smiley stimuli with different visibility levels of their emotional expressions that could be either happy or sad. We evoked uncertainty by low-visibility emotional expressions and certainty by high-visibility emotional expressions.
In Experiment 1, participants indicated the perceived emotion (happy/sad) of 10 smileys with different levels of visibility. The stimuli were presented in random order. In Experiment 2, we recorded EEG. Participants were presented with high-visibility or low-visibility stimuli and performed a one-back comparison task. Currently we collected data from 14 patients and 13 neurotypicals and data collection is on-going.

Results: In Experiment 1, increasing stimulus uncertainty was correlated with increasing reaction times in neurotypicals. In patients, reaction times were not dependent on stimulus uncertainty. In Experiment 2, we replicated the ERP Uncertainty Effects in neurotypicals and found a tendency for smaller effects in patients. An additional exploratory analysis revealed that the ERP starts to differ between groups already 115ms after stimulus onset. This difference was found during lower-level visual processing at occipital electrodes.
Discussion: The reaction time Results: suggest that in patients with schizophrenia the subjective perceptual certainty seems to be decoupled from stimulus quality. The EEG Results: suggest that uncertainty processing is similar between groups but that its intensity differs between them. The exploratory Results: suggest that processing differences between groups occur at a surprisingly early, low-level step for a such a high-level disorder like schizophrenia.

T129. RESTING-STATE ELECTROENCEPHALOGRAPHY MICROSTATES DYNAMICS AND RELATIONS TO COGNITION IN ANTIPSYCHOTIC-NAïVE INDIVIDUALS ACROSS THE PSYCHOSIS SPECTRUM

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Background: Resting-state electroencephalography (EEG) microstates are recurrent scalp potential configurations that are stable for around 60 to 100 ms before transitioning in a non-continuous manner. Temporal parameters of EEG microstates as well as their order of occurrence have previously been shown to differ in individuals across the psychosis spectrum and have even been suggested as endophenotypes for schizophrenia. A recent paper showed abnormally random transitions between microstates in patients with early course psychosis compared to heathy controls using sample entropy as a measure of sequence complexity. However, most EEG studies have been undertaken in medicated patients and the clinical implications of microstate aberrations are poorly understood. To fill this gap, we investigated microstate temporal parameters as well as microstate sequence complexity and their correlation to cognitive performance in antipsychotic-naïve individuals across the psychosis spectrum and in healthy controls.

Methods: We included 44 antipsychotic-naïve first-episode patients with schizophrenia (SCZ), 22 individuals at ultra-high risk for psychosis (UHR), and 87 healthy controls (HC) matched to SCZ on age, sex, and parental socioeconomic status. We performed modified K-means clustering on eyes closed resting-state EEG data to derive four microstates. Individual microstates where matched according to literature microstates commonly found in both HC and SCZ and labelled A, B, C, and D. Each sample in the original EEG recording was then mapped to its most similar microstate resulting in a sequence of microstates of the same length as the original EEG signal. From the microstate sequence, we calculated the temporal microstate parameters: duration, occurrence, and coverage. We analysed the temporal parameters using a repeated measures ANOVA. Sample entropy was calculated as a measure of complexity of the microstate sequences and their random permutations. We correlated temporal microstate parameters as well as sample entropy with eleven cognitive tests, including verbal- and performance intelligence and subtests of the Brief Assessment of Cognition in Schizophrenia (BACS) and Cambridge Neuropsychological Test Automated Battery (CANTAB), using z-scores based on HC.

Results: We observed no differences in temporal microstate parameters between HC, SCZ and UHR. Sample entropy of the microstate sequences was significantly lower than random permutations of the sequences for all three groups. However, there were no differences in sample entropy between the three groups. Duration of Microstate A was positively correlated with reaction time ($rs = 0.24$, $p = 0.028$) and sustained attention ($rs = 0.22$, $p = 0.045$) in healthy controls. Conversely, duration of Microstate A was negatively correlated with spatial working memory in SCZ ($rs = -0.37$, $p = 0.028$) and negatively correlated with verbal intelligence in UHR ($rs = -0.43$, $p = 0.047$). No significant correlations remained after adjusting for multiple comparisons. Microstates B, C and D showed no significant correlations with cognitive performance.

Discussion: Our data does not replicate previous findings of differences in temporal microstate parameters and sample entropy between SCZ, UHR and HC. This negative finding might be caused by the fact that individuals included in this study are naïve to antipsychotic treatment at the time of testing. To rule out this possibility, we currently investigate follow-up data on 79 HC and 27 SCZ after six weeks of treatment. The observed negative correlations between Microstate A and cognitive functions in the patient groups could suggest that Microstate A represents a broad marker for cognitive functioning in patients in the psychosis spectrum.

T130. RESTING STATE ACTIVITY AND THE RESPONSE TO COGNITIVE TRAINING IN PATIENTS WITH PSYCHOSIS: RESULTS: FROM AN EXPERIMENTAL TRIAL

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Background: Cognitive impairment is a major attribute of psychotic patients that directly correlate with poor social and work outcomes. Since pharmacological therapies can only target positive and negative symptoms, showing almost no effect in ameliorating these deficits, a treatment that aims directly at them is needed. Cognitive remediation (CR) is a non-pharmacological intervention designed to halt the pathological neural systems that characterize major psychotic disorders, and its main objective is to assure cognitive rehabilitation, as well as amelioration of the psychosocial functioning, thus improving the overall patients' quality of life.
There are two broad categories of computerized CR approaches: neuropsychological model and neuroplasticity-based CR, where neuroplasticity refers to the changes in cortical organization and interaction between brain systems in response to learning. This work focuses on a neuroplasticity-based type of CR, the auditory training. Available evidence regarding the efficacy of CR shows a considerable variability in individual treatment response,up to 40%, which may undermine the effectiveness of CR in real-world settings. Several studies identified psychological, cognitive, and biological variables that predicts improvement following cognitive remediation interventions. The aim of this work, however, given the unique features of neuroplasticity-based CR, was to identify neurophysiologic factors that may directly predict the cortical pattern reorganization induced by CR.

Methods: So far, we analyzed the data coming from 11 adult participants with a diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder or other psychotic disorders according to DSM-V criteria (using SCID-5-CV) who underwent 10 hours of auditory training. At baseline, assessments of demographic and neurocognition functions were conducted. Resting state electroencephalogram (EEG) was measured before the intervention. Functional networks were estimated by computing the magnitude square coherence (MSC) and the cross correlation (CCOR) between the time series of all available cortical sources. A statistical model was used to form characteristic weighted and binary graphs. The introduced modulation was assessed primarly by networks density, networks degree and link level.

Results: Results found linear correlation between beta band (12–30Hz) and best performance on measures of centrality (network degree and network density; $p < 0.05$, uncorrected) and inverse linear correlation between weighted delta performance and link levels in beta band between the nodes E52 and E57 ($p < 0.05$, multiple comparison corrected).

Discussion: Our analysis identifyed new potentially exploitable tools that could be used to select patients that most stand to gain from auditory training and patients that instead would benefit more from a different treatment approach.
These findings enrich the understanding of functional connectivity networks, as it seems one of the first study supporting the theory that resting state oscillations can predict cognitive

performance, specifically in the context of neuroplasticity-based CR. Our Results: provide preliminary evidence for a future personalized medicine approach in which each patient would receive a different cognitive remediation therapy to specifically target his or her own cognitive profile.

T131. EFFECTS OF CANNABIDIOL ON MEMORY-RELATED FUNCTIONAL CONNECTIVITY IN PEOPLE AT CLINICAL HIGH RISK OF PSYCHOSIS

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Background: Preclinical models place dysfunction within a hippocampal-midbrain-striatal circuit at the centre of the pathophysiology driving psychosis onset. People at clinical high risk for psychosis (CHR) show altered activation as well as functional connectivity between these regions during cognitive tasks and resting state conditions. Cannabidiol (CBD) is a non-intoxicating constituent of the cannabis plant with antipsychotic and anxiolytic properties. Previous work suggests that CBD partially normalises aberrant hippocampal-prefrontal functional connectivity in people with established psychosis. We recently showed that CBD also normalises activation in these regions in CHR individuals during memory processing, but whether CBD modulates memory-related functional connectivity in CHR patients is unknown.
Methods: Using a randomised, double-blind, parallel-group design, 33 CHR patients were randomised to a single oral dose of CBD (600 mg) or placebo. Healthy controls (n=19) were studied under identical conditions but did not receive any drug. Participants underwent functional magnetic resonance imaging (fMRI) at 3T during a verbal memory (encoding and recall) paradigm. Seed-to-voxel (wholebrain) functional connectivity was examined for three seeds derived from our previous fMRI task results right caudate head, left parahippocampal gyrus, right inferior frontal gyrus. Differences in connectivity related to the CHR state (controls vs placebo), the effects of CBD (placebo vs CBD), and linear between-group relationships (controls>CBD>placebo or vice versa; primary analyses) were examined using a nonparametric approach to minimise assumptions.
Results: In preliminary analyses, we observed a linear pattern of functional connectivity between the three groups, such that controls (n=19) > CBD (n=15) > placebo (n=16), between the caudate head seed and the caudate body during encoding; the parahippocampal seed and the bilateral caudate body during recall; and between the inferior frontal gyrus seed and the parahippocampal gyrus and putamen during recall. The opposite linear pattern was observed between the parahippocampal seed and the bilateral striatum, midbrain, parahippocampal gyri and hippocampus during recall, where functional connectivity was lowest in the control group, highest in the placebo group and intermediate in the CBD group. Final analyses are ongoing and Results: will be presented at the conference.
Discussion: Preliminary results suggest that CBD modulates functional connectivity between key nodes of the neural circuitry strongly implicated in psychosis onset and in a direction indicative of

'normalisation'. These Results: provide further neurophysiological evidence to support the idea that CBD may be a promising novel therapeutic for CHR patients. Further research is required to examine whether these acute neurofunctional effects translate into clinical efficacy after a period of treatment.

T132. EEG BAND POWER AND CLINICAL SYMPTOMS OF ANTI-PSYCHOTIC NAïVE, FIRST-EPISODE PATIENTS WITH SCHIZOPHRENIA

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Background: Schizophrenia is characterized, among others, by disturbances in electrophysiological brain activity. Previous research has indicated changes in neural oscillatory patterns in medicated schizophrenia patients, which could potentially provide objective biomarkers signaling neural processes underlying different aspects of symptomatology. As a first step, these deviant patterns need to be confirmed in anti-psychotic naïve, first-episode schizophrenia patients, to rule out possible influences of medication or progress of the disease.
Methods: Spectral band analyses (δ, θ, α, β) of 82 antipsychotic-naïve, first-episode patients with schizophrenia (age 18-41) were performed in the 10 s intertrial periods of a typical P50 suppression paradigm and compared with those from 60 age and gender matched healthy controls.
Results: As expected, we found significant group*scalp-region interactions for all 4 assessed spectral bands, indicating higher activity in the temporal and occipital regions in patients than in healthy controls yet similar or lower activity in the other (frontal, central and parietal) regions. These patterns were found in both the (absolute) power and amplitude data yet was more pronounced in the amplitude data. The increased temporal activity in patients reached statistical significance only for the amplitude data, and only when all 4 band frequencies were combined. Last, no significant correlations between the patients' symptomatology and spectral measures were found.
Discussion: Spectral analyses of the intertrial intervals of a typical P50 suppression paradigm revealed deviant patterns of activity in a relatively large population of antipsychotic-naïve, first-episode patients with schizophrenia. This shows that deviant electrophysiological activity in schizophrenia is neither caused by medication nor by progress of the disease and is also present in other than resting state data. Future studies are needed to further investigate the clinical relevance and the potential predictive validity of our current findings.

T133. REDUCTIONS IN SYNAPTIC DENSITY MARKER SV2A IN EARLY COURSE SCHIZOPHRENIA

Late-Breaking Poster

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Background: One of the most influential models of schizophrenia is the synaptic pruning hypothesis, which proposes that aberrant pruning occurs during adolescence, preceding the formal onset of illness. Two recent publications have demonstrated reductions in binding of [11C]UCB - J, the first in-human PET synapse marker. However, they were conducted with chronic patients, leaving unanswered whether these reductions are confounded by illness chronicity and present in earlier phases of illness. The absence of synaptic reductions in earlier phases of illness would be inconsistent with synaptic abnormalities playing a causal role for schizophrenia, while their presence would lend support for the synaptic pruning hypothesis and for future efforts aimed at defining the timeline of synaptic abnormalities in schizophrenia.
Methods: To address these questions, we completed [11C]UCB-J scans on a sample of early-course schizophrenia patients (n = 9, average duration of illness = 3.4 years) and demographically matched 9 healthy individuals. We quantified specific binding (BPND) with white matter reference region normalization and compared binding between groups in a priori-specified, pre-registered set of brain regions, (hippocampus, superior temporal gyrus, dorsolateral prefrontal cortex and striatum). We also completed exploratory ROI and voxel-wise comparisons. The secondary goal of the study was to obtain preliminary evidence of the functional impact of synaptic abnormalities by testing the association between [11C]UCB-J binding with cognitive ability and symptom levels.
Results: We observed highly significant, widespread C11-UCB-J binding reductions in a priori-specified (hippocampus, caudal and middle frontal gyrus, putamen, Heschl's gyrus, and superior temporal gyrus) and additional ROIs identified by exploratory analyses (amygdala, pars triangularis, medial and lateral orbitofrontal, and insula cortex). The percent reduction ranged between 16.5% - 21.5%. ROIs met Bonferroni corrected significant levels, $P < 0.0036$, and effect sizes for group difference were > 1.4. We also observed significant positive correlations between cognitive functioning (BACS score) and [11C]UCB-J binding in higher order cortical ROIs (middle frontal, superior temporal and Heschl's gryus), $R > 0.55$, $P < 0.019$, and inverse correlation between C11-UCB-J binding in Heschl's gyrus with psychosis severity (SAPS total), $R = -0.675$, $P = 0.046$.
Discussion: This is the first report of decreased [11C]UCB-J binding in a non-chronic schizophrenia sample. The consistency and robustness of findings across all [11C]UCB-J schizophrenia studies to date indicate that synaptic reductions are robust. The presence of synaptic reductions in early phase illness is consistent with the pruning hypothesis of schizophrenia and lends support for future efforts to define the timeline of synaptic abnormalities in schizophrenia.

T134. TRANSCRIPTOMIC DECODING OF CELLULAR AND MOLECULAR SIGNATURES OF IN VIVO NEUROIMAGING MEASURES OF GABAERGIC NEUROTRANSMISSION

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Background: Post-mortem investigations of GABAergic dysfunction in schizophrenia found expression changes of specific GABAA receptors (GABAARs) and reductions in parvalbumin (PVALB) and somatostatin (SST) GABAergic inhibitory interneurons. These post-mortem findings must be corroborated by in vivo studies to minimise the potential effects of medication and illness duration. Positron emission tomography (PET) is the only non-invasive method for in vivo imaging of GABAAR function. However, it remains to be fully characterised whether the basic principles of GABAergic system organisation are reflected in measurements with the two gold-standard radiotracers [11C]flumazenil and [11C]Ro15-4513. Such knowledge would help understand the potential of GABA PET to investigate distinct GABAergic abnormalities in schizophrenia. Here, we aimed to (1) uncover the co-expression patterns between GABAAR subunits and proteins commonly expressed by major interneuron types (interneuron markers) in the human brain, and (2) use imaging transcriptomics to decode molecular and cellular signatures of [11C]flumazenil and [11C]Ro15-4513 imaging.
Methods: First, co-expression patterns between the main GABAAR subunits (GABRA1-5, GABRB1-3, GABRG1-3, GABRE and GABRD) and major interneuron markers (GAD1, PVALB, SST, VIP and CCK) were examined. To this end, Weighted Gene Co-expression Network Analysis (WGCNA) was performed on microarray data on 15,633 genes extracted from the Allen Human Brain Atlas, and Results: for genes of interest were extracted. Second, Partial Least Squares (PLS) regression analysis was applied to determine the patterns of covariance between the gene expression data (separately for WGCNA clusters and the 15,633 genes) and the parametric maps of [11C]flumazenil and [11C]Ro15-4513 binding from healthy volunteers, and Results: for genes of interest were extracted. The parametric maps of [11C]flumazenil and [11C]Ro15-4513 binding were respectively, an open-access dataset from the Neurobiology Research Unit at Copenhagen University Hospital, and one obtained at the Institute of Psychiatry, Psychology and Neuroscience (King's College London).
Results: WGCNA Results: revealed co-expression between SST, GABRA5, GABRA2, and GABRB1. PVALB was assigned to a cluster not containing any other genes of interest. VIP and CCK shared cluster assignment but not with any other genes of interest. In the cluster-wise PLS, [11C]flumazenil binding covaried most strongly with a cluster containing GABRB2, GABRG3, GABRA1, GABRG2, and GAD1 ($Z=7.48$, $pFDR<0.001$). It was also associated with expression of GABRD, GABRA4, VIP, CCK and PVALB in the gene-wise PLS ($Z=5.64$-2.26, $pFDR<0.032$). [11C]Ro15-4513 binding covaried most strongly with a cluster containing GABRA5, GABRA2, SST and GABRB1 ($Z=6.18$, $pFDR<0.001$). Other genes of interest which expression covaried with [11C]Ro15-4513 binding included GABRB3, VIP, CCK and GABRA3 ($Z=4.20$-2.71, $pFDR<0.016$).
Discussion: Our analysis showed that a large proportion in [11C]flumazenil and [11C]Ro15-4513 binding regional variation can be explained by the expression of distinct genes encoding GABAergic system components. [11C]flumazenil binding tracked genes encoding subunits of the most abundant GABAAR in the brain (GABRA1, GABRB2, GABRG2) and the interneuron marker PVALB. Conversely, [11C]Ro15-4513 tracked genes encoding less widespread subunits (GABRA5, GABRA2, GABRA3) and the interneuron marker SST. Both radiotracers were associated with the inhibition-regulating interneuron markers VIP and CCK. These findings suggest that alterations in distinct GABAergic system components may be investigated with [11C]flumazenil and [11C]Ro15-4513 in schizophrenia.

T135. IDENTIFYING PRODROMAL BIOMARKERS OF SCHIZOPHRENIA AND BIPOLAR DISORDER USING MAGNETOENCEPHALOGRAPHY

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Background: Schizophrenia (SZ) and bipolar disorder (BD) are severe mental illnesses with large overlapping heritability. Both disorders are associated with altered neurophysiological responses, as measured with magnetoencephalography (MEG) or electroencephalography (EEG), particularly reduced mismatch negativity (MMN) and 40 Hz auditory steady-state responses (ASSR). These deficits could potentially both serve as early markers of illness and provide insight into the underlying pathophysiology as endophenotypes. First-degree relatives to patients with SZ and BD also show some neurophysiological deficits, however whether these deficits can be detected in adolescent offspring of patients is undetermined.
Methods: Our investigations are part of The Danish High Risk and Resilience Study - VIA (VIA15), a population-based longitudinal cohort study integrating social, psychological and biological risk factors and outcomes for schizophrenia and bipolar disorder. Here, we will investigate auditory MMN and 40 Hz ASSR in 15 year old adolescents ($n \approx 175$) born to parents diagnosed with either SZ (FHR-SZ), BD (FHR-BD), or neither SZ or BD (population-based controls, PBC) using MEG. We will first perform sensor-level analyses and apply dynamic causal modeling (DCM) to investigate effective connectivity and make inferences about underlying neurobiological mechanisms [3]. The latter will be supported by structural magnetic resonance images. Moreover, we will investigate whether polygenic risk scores for SZ and BD predict neurophysiological responses in the adolescents and investigate correlations with state psychopathology and cognitive performance.
Results: Final results are expected in 2024.
Discussion: The VIA15 study will allow for unprecedented insight into the neurobiological development of schizophrenia and bipolar disorder. Particularly, our study will allow integration of genetics, epigenetic, structural and functional neuroimaging, psychopathology and cognition to characterize the development of SZ and BD.

T136. THE IMPACT OF CUMULATIVE PRENATAL COMPLICATIONS AND CHILDHOOD TRAUMA ON BRAIN STRUCTURE IN SUBJECTS WITH PSYCHOTIC EXPERIENCES

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Background: Psychotic experiences (PEs) occur in 5-10% of the general population and present an increased risk for later mental health disorders including psychosis. Psychotic disorders and PEs are caused, in part, by exposure to adverse environments both prenatally and during childhood. However, it is not clear whether environmental risk factors impact brain development to cause psychosis. This study examines whether cumulative prenatal complications and childhood trauma are associated with altered grey matter volume in subjects with psychotic experiences.

Methods: 401 participants were drawn from the UK Avon Longitudinal Study of Parents and Children. PEs were assessed using the Psychosis-Like Symptom Interview. Cumulative polynatal risk was calculated by summing 24 binary prenatal and perinatal risk factors (Davies 2020), including season of birth, birth weight, number of antenatal visits, maternal infection, obstetric complications, paternal and maternal age. Cumulative trauma was calculated by summing 6 binary trauma variables reported from infancy to age 17 years (physical cruelty, domestic violence, sexual abuse, emotional neglect, emotional cruelty and bullying). T1-weighted MRI images were preprocessed using the Computational Anatomy Toolbox for SPM 12 to obtain grey matter volumes. Voxel-cluster analyses examined the effect of PE group on brain volume, whereby PE status is classified on a 4-point ordinal scale (no PEs n=267 > suspected PEs n=47 > definite PEs n=52 > clinical disorder n=35). We also assessed the effect of polynatal risk score and cumulative trauma on brain structure, and their interaction with PE. Age, gender and total intracranial volume were included as covariates. Thresholds for analyses were set at $p < 0.001$ at the voxel level, together with a family-wise error (FWE) correction for multiple comparisons at $pFWE < 0.05$ at the cluster level. Significant clusters were extracted using the MarsBaR toolbox and analysed in R (version 4.0.5).

Results: PEs were associated with reduced grey matter volume in the bilateral posterior cingulate (pFWE<0.001; -12, -51, 5; Z=4.05; 2192 voxels, 32, -72, 8; Z=3.85; 1129 voxels) and a trend for reduced volume in the thalamus (pFWE=.030; -12, -12, 5; Z=3.71; 690 voxels). Polynatal risk score was associated with increased volume in the putamen (pFWE=.008; -27, -3, 6; Z=3.67; 421 voxels) and a trend for reduced volume in the insula (pFWE=.08; 42, -11, 24; Z=4.03; 256 voxels). There was a significant interaction between PE and polynatal risk in the caudate (pFWE=0.02; 11, 12, -8; Z=4.08; 351 voxels) and insula (pFWE=<0.001; 57, -26, 21; Z=4.79; 1313 voxels), whereby higher polynatal risk was associated with increased caudate volume in clinical cases but not in healthy volunteers. Reduced insula volume was found in those with suspected PEs, definite PEs and clinical cases in a dose-dependent manner, but in healthy volunteers increased insula volume was associated with higher polynatal risk. Cumulative trauma was associated with increased volume in the putamen (pFWE=.001; -24, -5, 9; Z=3.79; 602 voxels), prefrontal cortex (pFWE<.001; 36, 59, 12; Z=4.70; 756 voxels) and medial frontal gyrus (pFWE<.001; 0, 36, 48; Z=3.98; 820 voxels). There was a significant interaction between PE and cumulative trauma (pFWE=0.002; -26, -77, -32; Z=3.67; 536 voxels), as increased Crus II cerebellar volume was associated with higher cumulative trauma in clinical cases but not in other groups.

Discussion: This study demonstrates that cumulative exposure to prenatal risk factors or childhood trauma is associated with increased grey matter volume in the putamen. These effects are non-specific to mental health, whereas the effect of cumulative trauma on cerebellar volume was specific to cases with psychosis. The cerebellum Crus II is linked to social mentalising (Van Overwalle 2020) and thus may contribute to impairments in social cognition in schizophrenia. The

finding of increased caudate volume with polynatal risk was specific to clinical cases and could possibly represent a mechanistic pathway between polynatal risk and the development of schizophrenia, as this is the locus of excessive dopamine release in schizophrenia. Reduced insula volume has previously been reported in schizophrenia and high-risk subjects (Liloia 2021), and is consistent with our finding of reduced insula volume with polynatal risk in those with psychotic experiences and clinical symptoms. Insula volume may serve as a biomarker of poor mental health outcomes in those with adverse prenatal conditions, whereas increased insula volume appears to be protective as this was observed in healthy volunteers. The insula integrates external sensory input with the limbic system and generates prediction errors regarding interoception. Its disruption may lead to rigidity in affective states and weaken discrimination between self-generated and external information, relevant to schizophrenia symptomatology. In summary, prenatal risk factors and cumulative trauma may increase the risk of schizophrenia due to their effects on grey matter in the cerebellum Crus II, caudate and insula.

T137. CLOZAPINE PLASMA LEVELS ASSESSMENT USING A POINT OF CARE DEVICE: FEASIBILITY AND VALIDITY

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Background: Clozapine is the only drug approved for refractory-psychosis; however, the compound is underused in spite of its notable advantages. Therapeutic drug monitoring (TDM) can assist overcoming some of the barriers through personalized dosing. Blood levels are associated with clinical response, identification of drug-related toxicity and adherence monitoring. Clozapine TDM is usually performed by LC-MS/MS, hence requiring venous blood sample and multi- step laboratory outsourcing. New and advanced technologies can enable rapid and easier way to measure clozapine serum levels. MyCare InsiteTM by Saladex © is a Point of Care (POC) device utilizing a method based on capillary sampling immunoassay. The test is conducted as an office procedure and the results are received immediately following finger prick. In this exploratory study we assessed the validity of the POC MyCare Insite device in comparison to the standard LC-MS/MS method. In addition, we assessed the feasibility of this methodology among both patients and healthcare practitioners.

Methods: Study population included 44 patients, diagnosed with schizophrenia spectrum disorders and treated with clozapine for at least four weeks of a stable dose. Participants were assessed using questionnaires about feasibility of blood sampling. Thereafter venous and capillary blood samples were collected at the same time and analyzed. Additionally, both caregivers and healthcare providers filled clinical and feasibility questionnaires. Clozapine plasma levels were compared between Methods: using linear regression model. SPSS version 20 software was used for data analysis.

Results: Of the total sample (44 patients), 61% were males and 39% females. Mean age was 43± 12 years and mean daily clozapine dose was 293± 134 mg/day (ranging between 50-600 mg/day). According to clinical global assessment, most of the patients (79%) presented moderate to severe psychotic symptoms as well as negative symptoms. Moderate or severe side effects were reported

among 37% of them. Linear regression model of TDM measurements from the two Methods: demonstrated high correlation with R2 = 83% ($p<0.0001$) and mean dispense of 26±162 ng/dl (median of 4.5 ng/dl). More than 60% of the patients found the TDM of clozapine to be important. Most of the participants (58%) favored the capillary sampling, with 11% even claimed that testing method would affect their adherence to TDM. Moreover, a larger portion (72%) strongly preferred to be tested in the physician's office rather than the lab. Healthcare providers also thought patients would prefer the capillary testing.
Discussion: Clozapine TDM is a valuable tool to ascertain both efficacy and safety of treatment. The POC device offers a rapid, accessible and satisfactory measure of clozapine serum levels. Both patients and healthcare providers reported preference of capillary sampling as well as office procedure TDM. Using POC immunoassay may contribute to increase treatment adherence and therefore improving rate and outcome of clozapine treatment among this difficult-to-treat population.

T138. INVESTIGATING THE EFFECTS OF ACUTE DOPAMINERGIC AND GLUTAMATERGIC CHALLENGE IN THE SUB-CHRONIC PHENCYCLIDINE MODEL

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Background: The sub-chronic phencyclidine (scPCP) model is a well-established model of relevance to cognitive impairment associated with schizophrenia. Our lab, and others, have evidenced robust behavioural and molecular changes in 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. Hypersensitisation to stimulants such as amphetamine has been evidenced in schizophrenia, and current research provides conflicting Results: regarding whether the scPCP model Results: in such hypersensitisation. Therefore, the aims of this research are to 1. Develop an animal model suitable to test novel drugs targetting both positive and cognitive symptoms. 2. Identify whether scPCP animals have a hypersensitised state to acute challenge with amphetamine or PCP. Following this, a pharmacology study will be completed to test a drug compound, which is known to reverse cognitive deficits in the scPCP model, in its efficacy against hyperlocomotion (positive symptoms).
Methods: 80 female Lister-hooded rats were dosed with vehicle or phencyclidine (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. In study one, rats were then randomised into 8 experimental groups (n=10 per group), acute treatment groups were: aVehicle, aAmphetmine 0.25mg/kg, aAmphetamine 0.5mg/kg, and aAmphetamine 0.75mg/kg. In study two, rats were randomised into 4 experimental groups (n=10 per group). Acute treatment groups were: aVehicle and aPCP 2mg/kg. Locomotor activity (LMA), a correlate for psychosis in rats, was measured in studies one and two following acute treatment. For NOR, the discrimination index (DI) between groups were analysed using a student's t-test. The area under the curve (AUC) for

the LMA were analysed using a two-way ANOVA followed by Tukey's multiple comparisons test.

Results: In the NOR test, there was a significant reduction in the DI in scPCP animals (0.1059 ±0.0425) compared with scVehicle animals (0.413 ±0.045) ($t(18)=4.728$; $p<0.001$), evidencing a cognitive deficit. All animals displayed similar levels of baseline LMA. In study one, groups treated with acute amphetamine had significantly greater activity levels than vehicle groups ($p<0.001$, Tukey). There were no significant differences when comparing scVehicle and scPCP groups with the same acute treatment. In study two, groups treated with acute PCP had significantly greater activity levels than acute vehicle groups in the first 30 minutes ($p<0.05$, Tukey), this activity dramatically reduced in the scVehicle animals over the last 60 minutes.

Discussion: Acute treatment with either amphetamine or PCP increased the LMA of scVehicle and scPCP rats. Acute PCP locomotion reduced after 30 minutes in both scVehicle and scPCP groups, however the activity of scPCP rats remained higher than scVehicle rats. We did not observe any hypersensitisation in the scPCP rats. Given the conflict in the literature, dopaminergic sensitisation is likely dependent on the dose and administration pattern utilised. When stimulants such as amphetamine or PCP are administered to scPCP rats, rats display both cognitive dysfunction (evidenced from NOR test) and positive symptoms (evidenced by increased hyperlocomotion) relevant to schizophrenia. Currently, a drug study employing this acute amphetamine scPCP model to test novel treatments for their efficacy against cognitive and positive symptoms is underway.

T139. INVESTIGATING PARVALBUMIN INTERNEURONS AND PERINEURONAL NETS IN TWO PRECLINICAL MODELS FOR COGNITIVE IMPAIRMENT ASSOCIATED WITH SCHIZOPHRENIA

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Background: Schizophrenia is a debilitating neuropsychiatric disorder with a complex aetiology. Despite the diverse risk factors associated with disease onset, most patients present with characteristic cognitive deficits. Presently, no drugs are clinically available to alleviate these cognitive impairments associated with schizophrenia (CIAS). As such, CIAS is classed as an unmet clinical need.

There is a growing body of evidence implicating the role of parvalbumin interneurons (PVI) and their associated perineuronal nets (PNN) in cognition. In post-mortem studies of schizophrenia patients, both PVI and PNN are decreased in regions related to cognition, though it is not clear what is driving these reductions. We used two models of relevance to schizophrenia to further understand this pathology: the sub-chronic phencyclidine (scPCP) and maternal immune activation (MIA) models. Both are established in vivo models that induce a reliable cognitive deficit. This work aimed to characterise PVI and PNN in these mechanistically distinct models and determine if PVI and PNN are a point of convergence in models relevant to CIAS.

Methods: In the scPCP model, sixty female Lister Hooded rats were dosed with saline or phencyclidine (2 mg/kg bodyweight i.p.) bi-daily for seven days. Rats were culled twelve weeks after sub-chronic dosing.
In the MIA model, a total of twelve Wistar dams were dosed with saline or polyinosinic-polycytidylic acid (poly(I:C), Invivogen, 10 mg/kg bodyweight i.p.) at gestational day 15 (n=6 per group). Plasma was taken three hours after dosing to assess maternal interleukin-6 (IL-6) and tumour necrosis factor alpha (TNFα) response. Offspring were weaned at postnatal day (PD)28 and culled at postnatal day (PD)35 and PD100.

For both models, qPCR, simple western analysis (WES) and immunohistochemistry (IHC) were used to measure parvalbumin (PV), PNN or its components in the prefrontal cortex (PFC). For the scPCP cohort, data were analysed using a univariate general linear model (GLM). For the MIA cohort, data were analysed in a general linear mixed model (GLMM) with the dam as the subject, treatment, age, sex as factors, and IL6 and TNFα responses as co-variates.

Results: In the scPCP cohort, qPCR analysis showed an increase in PV mRNA in scPCP-treated rats ($F1, 19 = 5.424$, $p = 0.038$, GLM). This increase contrasts with the outcome from IHC, which showed a significant decrease in PVI cell density in the PFC ($F1, 19 = 24.237$, $p<0.0001$, GLM). WES studies are ongoing to ascertain whether the total PV protein in the PFC is changed after scPCP dosing. In the scPCP group, there was no change to the PNN components aggrecan, brevican, neurocan, or versican mRNA expression. Labelling PNN using wisteria floribunda agglutinin (WFA) for IHC revealed that PNN density mirrored clinical findings and was reduced in the PFC ($F1,19 = 5.536$, $p = 0.030$, GLM).
In the MIA model, there was no change in PV mRNA or protein. We found a high maternal TNFα response was a significant predictor of increased aggrecan ($F1, 36 = 8.412$, $p = 0.006$, GLMM) and neurocan ($F1, 36 = 5.953$, $p = 0.020$, GLMM) mRNA in the offspring. This increase was replicated in the IHC results; high maternal TNFα predicted a significant increase in WFA labelling of PNN when including age as a factor ($F1, 34 = 21.123$, $p<0.0001$, GLMM).

Discussion: Although functionally distinct, the present work shows that both the scPCP and MIA model result in PVI and PNN dysfunction compared to respective controls. Given the presence of cognitive symptoms in both models, we hypothesise that the low PVI and PNN state seen in scPCP and the high PNN state seen in MIA-R impairs the regular activity of PVI. Therapeutics targeting the PVI and the PNN may prove beneficial in treating a complex disease like CIAS.

T140. GLUTAMATE/GLUTAMINE (GLX) CONCENTRATION INCREASE IN AUDITORY CORTEX AND DECREASE IN ANTERIOR CINGULATE CORTEX CORRELATE WITH FREQUENCY AND SEVERITY OF AUDITORY HALLUCINATIONS: A 1H-MRS REPLICATION STUDY

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Background: There has been an increasing interest over the last couple of years in the underlying neurochemistry of auditory verbal hallucinations (AVH), as a complement to established functional neuroimaging findings of aberrant altered activation patterns in language areas. Using proton magnetic resonance spectroscopy (1H-MRS) several studies have reported deviant Glutamate+Glutamine (Glx) concentrations in temporal and frontal areas in AVH compared to non-AVH, and healthy control subjects (Ćurčić-Blake et al., 2017; Hjelmervik et al., 2020; Hugdahl et al., 2015). Hjelmervik et al. correlated Glx levels from left auditory (superior temporal gyrus, l-STG) and midline anterior cingulate cortex (m-ACC) with scores on the PANSS P3 item, measuring severity of AVHs, and found positive correlations for l-STG Glx, contrasting a significant negative correlation for m-ACC Glx. Furthermore, m-ACC Glx has been shown to correlate with interhemispheric STG functional connectivity in subjects with more severe AVH (Weber et al., 2021). These findings were interpreted as supporting an excitatory bottom-up / top-down inhibitory imbalance model for AVHs (Hugdahl, 2009; Jardri et al., 2016). Considering the intrinsic variability of MRS data, it is important that these Results: are replicated – in particular the Hjelmervik et al. (2020) findings, which directly relate to existing theoretical models. We therefore re-analyzed data from a recent fMRI study (Hugdahl et al., 2020), where subjects pressed a button when an AVH episode began and when it stopped, during functional acquisition; MRS data were available for a number of these subjects, having been acquired immediately prior to the functional acquisition. By correlating number of reported AVH episodes (which would indicate frequency of AVHs) with Glx levels from the same brain regions reported in Hjelmervik et al. (2020), we would have an extended replication of their findings.

Methods: 1H-MR spectroscopy was acquired with a GE 750 3 T scanner, using a PRESS sequence (TE=35ms) for data acquisitions, and LCModel for quantification. Subjects were 11 patients with an ICD-10 diagnosis of schizophrenia, 7 males and 4 females, mean age 27.8 years. The sample was a subset of a larger international sample for the study of brain markers of AVH. Presence of AVH episodes were identified from self-paced button-presses when voices started and stopped. Number of episodes were taken as a marker of frequency of hallucinatory experiences when in the scanner, and as such also a marker of severity of AVHs. The number of reported AVH episodes was correlated (using Spearman correlation) against Glx values quantified according to the Methods: in Hjelmervik et al. (2020).

Results: The Results: showed a positive correlation (r=0.46) for left auditory cortex Glx, contrasting a significant negative correlation (r=-0.78) for the midline anterior cingulate cortex, compatible both with predictions from the Hjelmervik et al. data (r=0.29 and r=-0.52 for

correlation between Glx and PANSS P3 for l-STG and m-ACC respectively [reported as unstandardized beta values]), and with an excitatory/inhibitory model.
Discussion: Although the sample size was quite small compared to the Hjelmervik et al. sample, the remarkable overlap in the direction of the correlations speak to a valid replication of the original findings. Thus, our combined studies point towards regional Glx increases and decreases as underlying previous findings of increased and decreased BOLD blood-flow changes in the same brain regions in hallucinating individuals.

T141. THE SMARTCUBE PLATFORM: USE OF PHENOTYPIC SCREENING IN MICE WITH MACHINE LEARNING TO IDENTIFY NOVEL ANTIPSYCHOTIC COMPOUNDS

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Background: SmartCube® is a phenotypic screening platform designed for the rapid evaluation of drug-like molecules in mice. This platform has resulted in the discovery, in partnership with Sunovion, of the novel antipsychotic candidate, SEP-363856 (Ulotaront), which is now in Phase III clinical studies.
Here we compare and contrast the mouse behavioral signatures obtained from SmartCube for reference antipsychotic compounds and other reference CNS drugs using analytical tools to map the chemical universe of therapeutic drugs and understand the relative position of novel drug candidates.

Methods: Mice are treated with test or reference compounds, administered intraperitoneal 15 min prior to the study. Mice are then placed in the SmartCube system, which runs through an automated configuration for 45 min involving several behavioral challenges. Behavior of the mice is monitored by high-resolution cameras in each plane, as well as a thermal camera and mechanical actuators. Behavioral features are identified using deep learning, and the overall behavioral activity is analyzed also using machine learning and compared against a library of several hundred behaviorally-active reference drugs and several thousand library compounds. The resulting analyses provides a probability score of similarity to known compounds and defined pharmacologies.
Results: Here we demonstrate how SmartCube can identify compounds with antipsychotic activity. Furthermore, the mouse behavioral features from SmartCube can be evaluated using a similarity approach to identify candidate drugs with novel mechanisms of action, such as those avoiding the dopamine D2 receptor. SmartCube can also support structure-activity relationship studies, allowing rapid testing of analogs to support identification of lead compounds.
We also demonstrate the power of this platform by exploring the different therapeutic potential of single isomers of racemic compounds.

Discussion: The SmartCube platform is uniquely positioned for target-agnostic polypharmacology drug discovery programs, such as those focused on treating schizophrenia. The platform has also demonstrated unique sensitivity to differential pharmacologic profiles due to minor 3-D changes to the drug candidate structure which can predict utility for multiple therapeutic indications.

T142. DOPAMINE D2 AND CANNABINOID CB1 RECEPTOR COMPLEXES IN THE PREFRONTAL CORTEX OF SUBJECTS WITH SCHIZOPHRENIA: A POST-MORTEM BRAIN STUDY

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Background: Dysregulation of dopamine D2 (D2R) and cannabinoid CB1 (CB1R) receptors may contribute to the pathophysiology of schizophrenia (SZ). While prior studies documented contrasting Results: regarding gene and/or protein expression levels of these G protein-coupled receptors (GPCRs), fewer studies focused on their functionality in SZ brains. GPCR activities largely rely on their ability to form oligomeric structures with other receptors, changing categorically their pharmacological features. The potential role of D2R and CB1R complexes in SZ brain has been barely studied. Using a well-characterized case-control post-mortem brain cohort, we addressed the hypothesis that D2R and CB1R complexes, rather than total protein expression, are altered in SZ prefrontal cortex.

Methods: Brain specimens from the dorsolateral prefrontal cortex (DLPFC; Brodmann's area 9) of subjects with SZ (n=27) and sex-, age-, and post-mortem interval-(PMI) matched controls (n=27) were obtained at autopsies performed in the Basque Institute of Legal Medicine. SZ cases were divided into antipsychotic-treated (AP+; n=20) and antipsychotic-free (AP–; n=7) groups, according to blood toxicological assessments at death. Cortical amounts of D2R and CB1R protomers (i.e. GPCR monomers) and complexes were resolved by conventional SDS- and blue native-(BNP) PAGE, respectively, followed by quantitative immunoblotting, using knockout-validated antibodies. Case-control datasets were compared by univariate paired t-tests. In GPCR oligomer analyses, the models were adjusted by the corresponding protomer amounts.

Results: The immunodensity of D2R protomers did not differ significantly between SZ cases and controls. In contrast, protomeric CB1R cortical amounts were significantly lower in SZ DLPFC (–24%, $p<0.01$), compared to those in control brains. Regarding antipsychotic treatment, CB1R downregulation reached significance in AP+ cases only, while D2R cortical expression was not influenced by the medication. In BNP experiments, native brain D2R were revealed as three sharp immunoreactive bands of approximately 700-, 800- and 1,000-kDa, whereas CB1R antibody detected a diffuse band mixture between 800- and 1,000-kDa, which was quantified as one single heterocomplex. Adjusting by total protomeric D2R amounts, cortical immunodensity of the 700-kDa D2R complex, but not that of 800- or 1,000-kDa species, was significantly lower in SZ subjects (–49%, $p<0.01$). When stratifying by toxicological data, AP+ cases displayed reduced levels of the 1,000-kDa D2R complex (-38%, $p<0.05$) compared with the corresponding matched

controls, while 700-kDa D2R amount was similarly reduced in both SZ groups. Controlling for total CB1R levels, no alterations in the CB1R complex were found in SZ brains, regardless of the antipsychotic treatment.
Discussion: The present Results: indicate that D2R ability to form specific receptor complexes is impaired in SZ brain. While the deficit in the 1,000-kDa complex might be attributable to antipsychotic medication, reduced 700-kDa D2R appears a SZ brain signature. Antipsychotic drugs may reduce cortical CB1R amounts, although no significant effects were observed in CB1R complex formation. Future studies will be needed to determine the subunit composition and stoichiometry of those complexes found altered in SZ brains, as they could be interesting targets for future drug design.

T143. A NOVEL TWO-INJECTION START REGIMEN WITH ARIPIPRAZOLE ONCE-MONTHLY: CASE-SERIES OF 33 CASES

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Background: The course of schizophrenia is characterized by multiple relapses, which can be associated with serious outcomes. Non-adherence to antipsychotic medications can also contribute to relapse. Long-acting injectable antipsychotics (LAIs) were shown to be effective in reducing relapses and hospitalizations compared to oral antipsychotics. In Quebec, the use of LAIs is recommended by experts as a first-line treatment of psychosis. Aripiprazole once-monthly (AOM) is a long-acting injectable antipsychotic indicated for the treatment of schizophrenia in adult patients, in the acute phase as well as maintenance therapy. AOM is also indicated in Canada as a maintenance monotherapy treatment for bipolar disorder 1 in adult patients. AOM can be initiated using a single IM injection of 400 mg in deltoid/gluteal muscle, with concomitant 10 mg to 20 mg oral aripiprazole for 14 days. Based on modeling and simulation study data, the treatment can also be initiated using a two-injection start, consisting of two injections of AOM 400 mg, administered at separate injection sites, along with one dose of 20 mg oral aripiprazole.
Methods: A total of 33 inpatients from two center, 22 at Douglas Mental Health University Institute and 11 at Institut Universitaire en Santé Mentale de Québec, were started with the two-injection start of AOM, between March and October 2021. The following variables were collected from extensive medical records review: demographic information, detailed information about AOM regimens prescribed (site of injections, oral and IM doses) and information about concomitant medication for akathisia and extrapyramidal symptoms.
Results: Patients were on average 34 years old [19-62] with 19 men and 14 women. Patients had different diagnoses: 13 schizoaffective disorders, 6 schizophrenia, 3 first-episode psychosis, 5 bipolar disorders, and 6 unspecified. Diagnoses were made according to DSM-5. Twenty-seven patients received two-injection of AOM 400 mg the same day at separate injection sites. Four patients received two-injection of AOM 300 mg the same day at separate injection sites. Two patients received the first injection of AOM on day 1 and the second injection on day 2. Most patients received their injections in one deltoid muscle and one gluteal muscle [24]. Four patients received two injections in both gluteal muscles and five patients in both deltoids. Regarding the 20 mg oral loading dose of aripiprazole, 17 patients received it, 10 patients refused the oral dose of 20 mg and 6 patients received a different dosage [15 mg,10 mg and 5 mg]. Out of the 33 cases,

all patients received at least one test dose of oral aripiprazole before starting AOM. We also collected data concerning the use of concomitant medication for the treatment of akathisia and extrapyramidal symptoms in the month following AOM two-injections. These data will be analyzed in December and included in the poster.
Discussion: Considering the high risk of non-adherence to treatment in schizophrenia, this new alternative regimen could be useful in reducing the risk of non-adherence compared to the other regimen of AOM which requires a 14-day oral intake. In our study, most patients accepted well the new regimen of AOM and receiving 2 injections the same day was not an issue. Our preliminary Results: show that the safety and tolerability of the alternative regimen of AOM seems to be comparable to the one-injection start regimen. Further studies are needed to establish the safety and efficacy of the two-injection start regimen.

T144. THE MUSCARINIC AGONIST XANOMELINE DEMONSTRATES STANDALONE ACTIVITY AND AUGMENTS CLINICAL ANTIPSYCHOTICS IN RODENT BEHAVIORAL MODELS OF PSYCHOSIS

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Background: Accumulating evidence indicates muscarinic acetylcholine receptor agonists exhibit antipsychotic properties. KarXT (xanomeline-trospium) is an investigational compound in phase 3 trials for treatment of schizophrenia. Xanomeline, the active compound of KarXT, is a centrally active M1 and M4 receptor agonist devoid of any direct dopamine receptor affinity. KarXT was associated with significant improvements in symptoms compared with placebo and was well tolerated in a 5-week, randomized, controlled, phase 2 clinical trial in schizophrenia (NCT03697252; PMID: 33626254). Given the unique mechanism of action of KarXT compared with existing antipsychotics, there is the possibility that xanomeline can augment the effects of other antipsychotics in patients with suboptimal response. Here, we test whether xanomeline coadministration can augment the effects of the antipsychotics risperidone (RIS) and aripiprazole (ARI) in standard preclinical models of antipsychotic activity.
Methods: The conditioned avoidance response (CAR) and psychostimulant-induced locomotor activity (LMA) assays are commonly used behavioral tests in rodents that have predictive validity for detecting antipsychotic activity. CAR assay: adult male C57BL/6J mice were first trained to avoid a foot-shock to a performance criterion of ≥85% avoidance responses. Dose response evaluations of xanomeline, RIS, and ARI were established, followed by experiments to evaluate the augmentation effects of threshold xanomeline doses with subtherapeutic doses of RIS and ARI. Additional studies assessed whether the muscarinic antagonist scopolamine reversed activity. In all CAR studies, drug agents were dosed 30 minutes before testing using a repeated-measures, counter-balanced experimental design. A satellite group of mice were assessed for plasma and brain exposures to determine if drug-drug interactions existed. LMA assay: agents that reverse enhanced LMA induced by NMDA antagonists (eg, ketamine, PCP, MK-801) in rodents commonly have atypical antipsychotic activity in the clinic. Using a between-subjects design, C57BL/6J mice received varying doses of xanomeline and RIS 30 minutes prior to a MK-801

challenge. Total distance traveled was recorded following MK-801 administration and analyzed by one-way ANOVA.
Results: Xanomeline showed similar dose-dependent CAR compared with the D2 receptor agents RIS and ARI without inducing escape failures, a proxy for extrapyramidal side effects. In combination studies with RIS and ARI, low-dose xanomeline significantly augmented the activity of both RIS and ARI vs the effects of these agents administered alone. The ability of scopolamine to fully block xanomeline but not RIS or ARI demonstrated that xanomeline's antipsychotic effects are mediated by muscarinic receptors, unlike RIS and ARI. In MK-801–evoked LMA, xanomeline and RIS dose dependently reduced hyperactivity and, when coadministered, significantly augmented activity vs either compound alone. The favorable augmentation effects of xanomeline were not a result of drug-drug interactions and altered drug concentration levels in plasma or brain.
Discussion: The muscarinic receptor agonist xanomeline is devoid of direct D2 affinity yet showed antipsychotic activity in multiple preclinical models of psychosis, which was demonstrated to be muscarinic-receptor dependent. Combined low doses of xanomeline with RIS and ARI significantly augmented CAR and attenuated MK-801–evoked hyperlocomotion vs the effects of each of the two antipsychotics alone. These data support further research evaluating the ability of xanomeline to augment the therapeutic effects of existing antipsychotic medications.

T145. HORMONES OF ADRENAL AXIS AS POTENTIAL BIOMARKERS OF THE ANTIPSYCHOTIC THERAPY EFFICACY IN PATIENTS WITH THE FIRST EPISODE OF SCHIZOPHRENIA

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Background: Introduction. Hypothalamic-pituitary-adrenal (HPA) axis is the very important system for the neurobiological investigation of the pathophysiological mechanisms of schizophrenia and the evaluation of the efficacy of the pharmacotherapy. There are hypothesis that investigation of the relation of the levels of cortisol (Cor) and dehydroepiandrosterone sulfate (DHEA-S) can be used for the prediction of the efficacy of the antipsychotic therapy in patients with schizophrenia.
Aim. Comparative investigation of the levels of Cor and DHEA-S in patients with the first episode of schizophrenia (FES) and chronic schizophrenia (Ch-SCH) in the dynamics of the antipsychotic therapy.

Methods: There were investigated 58 patients with FES, 34 patients with C-SCH (duration of the illness in average – 12.5 years) and 34 healthy volunteers (controls). All patients received olanzapine in average dose of 14.6 ± 6.6 mg/day. Investigation of hormonal parameters was conducted 3 times – at admission, on the 3-4th and 6-8th weeks of the therapy (the 1st, the 2 nd and 3rd stages) depending on the effectiveness of treatment. Cor and DHEA-S levels were measured using immune-enzyme method. Comparative analysis of the dynamics of Cor and DHEA-S levels was conducted separately in responders (R) and nonresponders (NR).
Results: The average levels of Cor in the FES patients (FES-R) exceeded the normative values on the all stages of investigation (the 1st – 732.8±64.0, the 2nd – 735.6±61.9 and the 3rd– 680.4±62.7 nmol/L). In the Ch-SCH-R patients the Cor levels were significantly higher ($p<0.01$) in

comparison with controls. A characteristic feature of the dynamics of cortisol in responders in both groups of patients is a decrease of this parameter towards the end of the therapy. In the non-responders of the both groups there revealed the fluctuation of the Cor levels on the all stages of investigation: FES-NR – 806.5±115.8; 622.6±63.7 and 660.7±672 nmol/L on the 1st, 2 nd and 3 rd stages, respectively; Ch-SCH-NR – 674.7±72.0, 718.6±50.4 and 653.3±36.5 nmol/L on the 1st, 2 nd and 3 rd stages, respectively.
There were no significant changes in the dynamics of the DHEA-S levels in the FES-R: 3.7±0.5, 3.7±0.4 and 3.6±0.4 μg/ml on the 1st, 2 nd and 3 rd stages, respectively. DHEA-S levels in the Ch-SCH-R patients did not change on the all stages of investigation. DHEA-S levels in the FES-R and Ch-SCH-R patients significantly differ from the controls. There were found the tendency to the increase of the DHEA-S levels in the FES-NR and Ch-SCH-NR patients

Discussion: Conclusion. We can suppose that the high DHEA-S levels in FES and Ch-SCH patients at admission and on the 3-4th weeks of the therapy can serve as the potential predictors of the efficacy of the olanzapine therapy.

T146. MATERNAL IMMUNE ACTIVATION AND MGLUR2 DEFICIENCY: A TWO-HIT MODEL MIMICKING COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA

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Background: Schizophrenia (SZ) is associated with complex interactions between genetic and non-genetic risk factors. Among the latter, viral infections during pregnancy were found to increase the risk of developing SZ later in the adulthood. Based on this observation, maternal immune activation (MIA) models have been broadly used to investigate both SZ pathology and novel pharmacological targets. In parallel, human post-mortem brain studies from our laboratory recently described lower expression of metabotropic glutamate receptor 2 (mGluR2) in the dorsolateral prefrontal cortex (DLPFC) of SZ subjects, an effect that might be exacerbated following treatment with antipsychotic drugs. First, this study aimed to investigate if MIA models recapitulate the abnormality of mGluR2 expression. A second aim was to develop a two-hit SZ murine model combining mGluR2 genetic deficiency with MIA, and characterize the potential SZ-like behavioral phenotypes.
Methods: To induce MIA, pregnant dams were injected with the viral-like antigen polyinosinic:polycytidylic acid (PIC) (5 mg/kg, i.p.) or saline at gestational day 9.5. Immune activation was verified by reduced rectal temperature 6 h post administration, reduced weight of pregnant dams and reduced litter size. Brain frontal cortices from adult offspring of PIC- and saline-administered dams (named PIC and saline mice, respectively) were dissected, and

immunoreactivity of key receptors, including mGluR2, was quantified by Western Blot. For the second goal, the same MIA procedure was applied to Grm2+/- pregnant dams, mated with Grm2+/- males. The SZ-like behavioral phenotype of adult mGluR2 wild-type (WT), heterozygous (HET) and knockout (KO) littermates, exposed to PIC or saline in utero, was evaluated in paradigms testing sensorimotor gating (prepulse inhibition, PPI), cognitive performance (novel object recognition test, NORT), locomotor activity (open-field test, OFT) and anxiety (OFT, and elevated plus maze, EPM).
Results: Compared to saline-exposed animals, PIC mice displayed lower cortical amounts of mGluR2, but not metabotropic glutamate receptor 3, cannabinoid CB1 or dopamine D2 receptors, which accounts for the specificity of mGluR2 downregulation following MIA. In mGluR2 deficient mice receiving PIC in utero, the inhibition of the PPI response did not differ from that in WT animals. The impact of genotype on cognitive function was noticed in NORT, as prenatal PIC exposure significantly lowered novel object exploration time in mGluR2 KO, but not WT or HET mice. Overall, mGluR2 deficiency was associated with reduced locomotor activity (total distance travelled and mean speed) in OFT. mGluR2 gene deletion was also associated with greater anxiety-like behavior in both OFT (e.g. fewer time spent in center) and EPM (e.g. fewer time spent in open arms) paradigms, although no genotype x MIA interactions were observed.
Discussion: Downregulated cortical mGluR2 expression in mice exposed to PIC in utero is consistent with prior findings in SZ human brain, supporting the validity of MIA model for studying the role of glutamatergic neurotransmission in SZ. Evaluation of SZ-associated phenotype shows cognitive impairment in PIC mice, with no alterations in either sensorimotor or anxiety-like phenotypes. The two-hit model, based on mGluR2 deficiency and MIA, displays greater cognitive impairment in NORT, while fails to diverge significantly from one-hit MIA model in all other studied paradigms. Larger sample size will be required to fully address the relevance of mGluR2 gene deletion combined with MIA in developing SZ-like phenotype in mice.

T147. METFORMIN FOR THE PREVENTION OF CLOZAPINE INDUCED WEIGHT GAIN: A RETROSPECTIVE CHART REVIEW STUDY

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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 (T2D). These problems are partially attributable to the use of second-generation antipsychotics (SGAs) that are associated with weight gain and other serious metabolic adverse effects. Concerningly, clozapine, which is the sole SGA with treatment superiority for refractory SCZ, carries the greatest metabolic liability of all SGAs. Furthermore, weight gain with this agent is most pronounced in the first few months after initiation. As such, there is an urgent need for safe and effective adjunctive pharmacological approaches to be implemented at the earliest stages of illness to ameliorate clozapine-induced weight gain. In this

chart review, we aimed to evaluate the effectiveness of adjunctive metformin in preventing weight gain in clozapine treated patients.

Methods: We conducted a retrospective chart review of patients newly initiated on clozapine through the assessment of patient data collected at Centre for Addiction and Mental Health (CAMH) in Toronto, Canada, from January 2014 to March 2021. A mixed model analysis with subjects as random effects was used for our primary outcome measures of body weight and body mass index (BMI) at 6 months after clozapine initiation. Time, group (clozapine + metformin vs. clozapine only) and the interaction between group and time, were included as predictor variables, while controlling for age, sex, T2D status, and smoking status. Secondary outcomes included proportion of individuals, by group, with ≥5% and ≥7% body weight change at 6 months, analyzed using chi-square tests and odds ratio (OR).

Results: Among 396 patients (males: 71.5%, mean age: 42.8 (SD = 15.2) years) initiated on clozapine, 69 (males: 68%, mean age: 49.1 (SD = 14.7) years) were already on metformin or prescribed it ≤3 months after clozapine initiation. A total of 44 patients had a diagnosis of T2D, 218 were tobacco smokers, and 243 had a baseline BMI ≥25 (overweight/obese). Mean clozapine dose was 286.4 mg/day (SD = 92.6) for the entire sample; the metformin group had a mean clozapine dose of 274.6 mg/day (SD = 83.3) and mean metformin dose of 1284.7 mg/day.

In this sample, the clozapine + metformin group demonstrated a lesser amount of weight gain over time (clozapine + metformin: -0.13 kg (SE = 1.19) vs. clozapine only: 3.03 (SE= 0.62); $F = 5.54$, $p = 0.020$). There was no significant difference in rates of ≥5% or ≥7% body weight gain between the two groups.

Discussion: In this retrospective cohort study, co-prescription of clozapine and metformin was associated with lesser weight gain at 6 months after initiation than being on clozapine alone. These findings provide evidence for the effectiveness of metformin in preventing clozapine induced weight gain that needs to be explored further using randomized controlled trials.

T148. SWITCHING FROM ONE TO THREE-MONTHLY PALIPERIDONE PALMITATE: A CROSS-SECTIONAL PATIENT SATISFACTION AND SAFETY SURVEY DURING THE COVID-19 PANDEMIC

Late-Breaking Poster

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Background: Patients with severe and enduring mental health conditions were advised by the National Health Service in the UK to limit contact during the Covid-19 pandemic due to their higher levels of clinical vulnerability. To help improve patient safety, mental health services encouraged the switch from Paliperidone Palmitate 1-monthly (PP1M) to Paliperidone Palmitate 3-monthly (PP3M) injections were appropriate. PP3M has been shown to be an equally effective and more practical [1] alternative to the PP1M, though, few studies have so far explored patients' experiences with switching. Therefore, the aim of the study was to assess their comparative satisfaction, perspectives and subjective feelings of safety following the change to the longer-acting formulation.

Methods: This cross-sectional survey was performed in a large mental health provider in London between May-June 2021 while the UK was still under Covid-19 restrictions. Two psychiatric doctors obtained verbal consent before administering the survey either face to face or over the phone. The four-item questionnaire explored satisfaction and perceived levels of safety (with the respondents rating to what extent they agreed or disagreed with the statements using a 5-point Likert scale) as well as enquiring about reported advantages and disadvantages as a result of the medication change (with participants selecting one or more options from a list). Additional demographic and clinical information of the study population were collected from the electronic records

Results: 44 patients (29 male and 15 female) receiving PP3M at the time of the survey agreed to take part. 88.7% of respondents strongly agreed or agreed that they were satisfied after switching from PP1M to PP3M, 6.8% neither agreed nor disagreed and only 4.5% disagreed. Similarly, the bulk of the respondents (93.1%) strongly agreed or agreed that they felt safer having their injection every 3 months instead of once monthly during the Covid-19 pandemic. 6.8% neither agreed nor disagreed but no one disagreed with this statement.

Respective questions on whether patients experienced any advantages or disadvantages as a result of the switch to the 3-monthly formulation allowed for multiple answers. Convenience (93.1%) was the most popular positive reply, followed by improved quality of life (59%), decreased stigma (40.9%), better adherence (29.5%) and improved tolerability (20.5%). While 6.8% said that they had not experienced any advantages, 93.1% declared that they had not encountered any disadvantages, with 4.5% reporting worsening or new side effects and 2.2% a relapse of symptoms.

Discussion: Study findings showed that the overall subjective experience of switching from monthly to three-monthly Paliperidone was very positive. Similar to two previous studies [2,3], the vast majority of patients favoured the change quoting convenience, quality of life and reduced discrimination as potential benefits. The importance of enhanced safety with less frequent medication administration under pandemic conditions was also highlighted. Shared and supported decision making should further inform clinical practice [4].

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T149. POLYPHARMACY AND CLOZAPINE-INDUCED HYPERSALIVATION: A CROSS-SECTIONAL EXPLORATORY STUDY

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Background: Clozapine-induced hypersalivation (CIH) is reported by about 30–80% of patients. We aimed to explore the effects of polypharmacy on CIH, particularly the combination with other antipsychotics, antidepressants or mood-stabilizers.

Methods: Sixty-three patients with severe mental disorders receiving clozapine were consecutively recruited at the Mental Health Care Centre from Mataró (Consorci Sanitari del Maresme, Spain). All participants were interviewed by a clinical psychiatrist. CIH was assessed with the Toronto Nocturnal Hypersalivation Scale (TNHS), with scores ranging from 0 (no hypersalivation) to 4 (very severe hypersalivation). Moderate or severe hypersalivation was recoded into a dichotomous variable using a cut-off score of 2. Current psychopharmacological treatment and doses were registered. The combination of antipsychotics was recoded into a categorical variable: none (clozapine on monotherapy), the addition of D2 antagonist, or addition of D2 agonist (aripiprazole). Antidepressants and mood-stabilizers were recoded into dichotomous variables. Logistic regression was used to explore the association between polypharmacy use and CIH while adjusting for age and sex. We further conducted a sensitivity analysis also adjusting clozapine doses. A p-value <0.05 was considered to be significant.

Results: The proportion of moderate to severe hypersalivation of the sample was 73%. Of all 63 patients, 35 (55.6%) received clozapine in monotherapy, 21(33.3%) also were taking D2 antagonists and 7 (11.1%) also received aripiprazole. In the logistic regression adjusted by age and sex, smoking (OR= 0.15, p= 0.023) was associated with reduced CIH whereas the combination of antipsychotic treatment with D2 antagonists (OR= 14.75, p= 0.009) but not D2 agonists (OR= 0.93, p= 0.941) was associated with CIH. In the sensitivity analysis, clozapine doses were not associated with CIH. In this analysis, similar effects were found for D2 antagonists (OR= 19.47, p= 0.008) and smoking (OR= 0.10, p= 0.011), and antidepressant use was also found to be significantly associated with reduced CIH (OR= 0.17, p= 0.037).

Discussion: Our study suggests that the combination of D2 antagonists is associated with greater hypersalivation in patients receiving clozapine. Antidepressant treatment and smoking are protective factors with a reduced prevalence of hypersalivation. The main limitation of our study is the cross-sectional design, which does not allow us to infer causality. Although we found an association between antipsychotic polypharmacy and CIH, it is also possible that a combination of antipsychotics could be used as a therapeutic strategy in patients with moderate or severe CIH (either for improving CIH or for reducing clozapine doses). Another limitation is the relatively small sample size, which limits the statistical power for conducting extended analyses of the combination of distinct antipsychotic drugs. Tobacco use could impact salivation through a reduction of clozapine levels due to the known effects of nicotine on the CYP1A2 enzyme since CYP1A2 is responsible for about 70% of clozapine's metabolism. The protective effect of antidepressant use could be explained by the association between some antidepressants and dry mouth. Further longitudinal studies are needed for testing the polypharmacy effects on CIH and to also explore the effects of smoking on CIH.

T150. PHARMACOLOGICAL CHARACTERIZATION OF THE NOVEL PHOSPHODIESTERASE-2 INHIBITOR BI 474121 ON TARGET ENGAGEMENT IN-VIVO AND IN ANIMAL MODELS RELATED TO COGNITIVE SYMPTOMS OF SCHIZOPHRENIA

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Background: Evidence from numerous clinical and preclinical studies has led to the hypothesis that impaired synaptic and neural network function related to NMDA receptor hypofunction plays an important role in cognitive impairment of schizophrenia. Second messenger pathways depending on cAMP and/or cGMP are key regulators of neural transmission and synaptic functions. Thus, specific cyclic nucleotide phosphodiesterases (PDEs) expressed in cognition relevant brain regions, such as PDE2, are considered interesting targets for cognition enhancement [1]. This study characterizes the potency and selectivity of the novel PDE2 inhibitor BI 474121 and its effects on cGMP increase in rodent brain and cerebrospinal fluid (CSF). In addition, BI 474121 was evaluated in two rodent cognition tasks addressing working memory or social recognition memory performance.

Methods: The molecular potency of BI 474121 for PDE2A was determined using cytosolic extracts of SF9 insect cells over-expressing full-length human enzyme employing fluorescence polarization for measuring cGMP or cAMP. Selectivity against other PDE and non-PDE targets was evaluated using fluorescence polarization or receptor binding assays. To show central target engagement, cGMP levels were determined in cognition relevant brain regions in mice (i.e. hippocampus and prefrontal cortex) and in CSF in rats via ELISA. Regarding cognition, BI 474121 was tested in the mouse T-maze spontaneous alternation test and in the social recognition test in naive rats.

Results: The IC50 value of BI 474121 on PDE2A was determined to be in the low nanomolar range using cAMP and cGMP as substrate, respectively. BI 474121 showed a >100-fold selectivity over other PDEs and non-PDE off-targets. The compound induced a dose-dependent increase of cGMP in mouse brain regions and in rat CSF. Regarding cognition, BI 474121 could reverse MK-801 induced memory deficits in the mouse T-maze and improved memory performance in the rat social recognition task addressing working memory and social recognition memory, respectively.

Discussion: The Results: of these studies demonstrate that BI 474121 is a potent and selective PDE2 inhibitor. Systemic administration of BI 474121 increased cGMP levels in the CSF and brain indicating functional target engagement, i.e. PDE2 inhibition, in the brain. This shows that cGMP levels in CSF can be used to assess PDE2 inhibition centrally, which might also be used to evaluate central target engagement in clinical trials. Confirming previous findings of other PDE2 inhibitors, 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.

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T151. SEX DIFFERENCES IN THE EMERGENCY TREATMENT OF SCHIZOPHRENIA OVER A 21-YEAR OBSERVATIONAL PERIOD

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Background: Patients suffering from schizophrenia are at high risk for admission and treatment in locked units. In this study, sex differences relating to the emergency treatment in schizophrenia patients over a 21-year observation period were investigated.
Methods: The current retrospective study was conducted at the Department of Psychiatry, Psychotherapy and Psychosomatics of the Medical University Innsbruck. All adult patients (n=845; 425 female, 420 male) suffering from schizophrenia who were admitted involuntarily to one of the acute psychiatric units in the years 1997, 2002, 2007, 2012 and 2017 were included in the study.
Results: In the years mentioned above, 590 schizophrenia patients (297 men and 293 women) admitted to the locked unit received psychiatric medication. Except the use of clozapine, significantly more frequently administered to men, no significant sex differences were found in the treatment with regard to acute therapy or choice of medication (antipsychotics and benzodiazepines) as well as in equivalent dose and type of application.
Discussion: As most treatment guidelines on schizophrenia do not include sex differences at all, it is not surprising that acute treatment is nearly the same in men and women. However, in times when individualized therapies gain more and more importance, sex differences should be part of new treatment concepts.

T152. ANTIPSYCHOTIC DRUGS AND THEIR EFFECTS ON COGNITIVE FUNCTION. SYSTEMATIC REVIEW, PAIRWISE AND NETWORK META-ANALYSIS

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Background: Schizophrenia is one of the most common mental illnesses worldwide. As schizophrenia usually starts in the second or third decade of life it leads to an enormous loss of productivity and very early disease-related premature retirements. Cognitive deficits are an independent, core part of the disorder, and they have been shown to be a strong, independent predictor of functional outcome and quality of life. Therefore, they are to an important extent responsible for the burden of disease. Moreover, as the disorder is often life-long many, if not most patients need to be treated continuously with antipsychotic drugs. Therefore, to find out which

antipsychotic is the best one in terms of cognitive function could substantially reduce burden of disease.
Methods: We are conducting a network-meta-analysis of randomized controlled trials (RCT) in patients with schizophrenia or schizophrenia-like psychoses. To identify eligible studies, we search the register of the Cochrane Schizophrenia group, the most comprehensive database of clinical trials in schizophrenia. RCTs comparing antipsychotic drugs with each other or placebo are included. We focus hereby on the clinically most important newer and older antipsychotic drugs – as identified by a survey of international schizophrenia experts. The primary outcome is cognitive functioning. As there is no consensus as to which cognitive domain is the most important one, we use the MATRICS composite score of the seven specific scores: speed of processing, verbal learning, working memory, reasoning and problem solving, visual learning, social cognition and attention/vigilance. We include only trials of at least 3 weeks in duration.
Results: We present our preliminary data at the conference.
Discussion: We expect that studies differ in their measurement of cognitive function as the MATRICS consensus is, however, relatively recent. This could be a major point of Discussion:.

T153. MRI NEUROMELANIN ACCUMULATION IN PATIENTS WITH TREATMENT-RESISTANT SCHIZOPHRENIA: A CROSS-SECTIONAL PILOT STUDY

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Background: Neuromelanin (NM) is a product of monoamine metabolism including dopamine (DA). NM-sensitive MRI sequences allow in vivo quantification of NM levels in the substantia nigra (SN). NM-MRI signal is thought to serve as a biomarker for SN dopamine neuron integrity, and in turn, striatal DA functioning. Increased striatal DA synthesis has been associated with response to first-line antipsychotics (FLR) in patients with schizophrenia, while normal striatal DA synthesis has been associated with treatment-resistant schizophrenia (TRS). As such, we hypothesized that FLR patients would show increased SN-NM levels and TRS would show normal SN-NM levels.
Methods: We enrolled TRS patients that had not responded to at least two antipsychotics and were receiving clozapine at the time of the study, patients with FLR, and healthy controls (HCs). SN-NM levels were measured using 3T MRI. Contrast-to-noise (CNR) was calculated as the relative signal intensity difference between SN and crus-cerebri. SN-CNR was compared between groups controlling for age and sex. Correlation coefficients were estimated between CNR and Positive and Negative Symptom Scale (PANSS) scores.
Results: 44 participants (TRS, n=13; FLR, n=11; HCs, n=20) completed the study. Overall group differences were found in SN-CNR ($p<0.01$, $\eta 2=0.22$). Specifically, FLR but not TRS showed

higher SN-CNR compared to HCs ($p<0.01$, Cohen's $d=1.34$). SN-CNR in the patient samples showed no associations with PANSS score.
Discussion: Our Results: suggest that SN-NM levels are elevated in FLR patients and similar to controls in TRS patients. Longitudinal studies are required to establish if SN-NM levels are a suitable biomarker to predict treatment response in schizophrenia.

T154. CLOZAPINE RECHALLENGE DESPITE PREVIOUS INDUCED NEUTROPENIA OR AGRANULOCYTOSIS USING COLONY-STIMULATING FACTOR: A SYSTEMATIC REVIEW

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Background: Clozapine is recognized as the most efficacious antipsychotic for treatment-resistant schizophrenia. Unfortunately, fear of neutropenia and agranulocytosis leads to its underutilization. Those hematological adverse events often lead to clozapine discontinuation, which may cause psychotic relapse and severely hinders recovery. Colony-stimulating factors (CSF) use to allow clozapine rechallenge or continuation despite neutropenia or agranulocytosis has been reported, but many unanswered questions remain. This review aimed to evaluate the efficacy and safety of this approach as well as to identify the optimal treatment regimen.
Methods: MEDLINE, Embase, PsycInfo and Web of Science databases were searched with a combination of the terms "clozapine" and "CSF" from inception date to July 21st, 2021. All screening and data extraction steps were realized independently by two reviewers, according to PRISMA 2020 systematic review guidance. Selected articles for the study had to report at least one case where clozapine rechallenge or continuation was allowed by CSF use after a previous neutropenia or agranulocytosis. Cases in oncologic settings were excluded. There were no language restrictions. CSF administration strategy was deemed successful if CLZ could be maintained at the end of follow-up, whether neutropenia or agranulocytosis episodes reoccurred during that span or not. Adverse events were also collected.
Results: 805 articles were retrieved from electronic searches, of which 30 were included in this review (27 case reports/series, 2 consecutive case series, 1 retrospective cohort study) for a total of 59 individual cases. Clozapine could be successfully rechallenged or continued with the use of CSF over an average follow-up period of 1.9 years in 76% of patients. There was a tendency towards higher success rates in case reports and series (n = 38 cases), compared with consecutive case series and the only retrospective cohort study (overall success rates of 84% and 60%, respectively, p-value = 0.065). Two CSF administration patterns were identified; as-needed and prophylactic. Both strategies were associated with the same efficacy, yielding respectively 81% and 80% success rates. No death nor severe hematological complications were reported, only mild and transient adverse events were described for a minority of the patients.
Discussion: Previous estimates of the efficacy of CSF use to allow CLZ rechallenge or treatment continuation despite neutropenia were 75 and 76%, based on 32 and 30 cases, respectively. These are in line with the result obtained herein, although the recent publication of consecutive case series has allowed us to highlight the importance of the publication bias inherent to case reports/series.

Although there was some evidence suggesting that the as-needed administration of CSF could be associated with better efficacy outcomes than the prophylactic strategy, this review seems to indicate that none of these 2 strategies is superior to the other. Still, when considering the costs associated with CSF use, an as-needed administration based on pre-specified thresholds seems more beneficial. While some elements still need to be addressed in more robust study designs, the use of CSF to allow either clozapine rechallenge or continuation in spite of blood dyscrasias appears to be a promising avenue for patients suffering from treatment-resistant schizophrenia. Perhaps the development of more strategies aimed at ensuring the safe use of clozapine despite rare, but serious adverse events, might lead to a more widespread use of this medication, which remains too often underutilized.

T155. EFFECTIVENESS AND SAFETY OF ANTIPSYCHOTIC DRUGS IN PATIENTS WITH SCHIZOPHRENIA INITIATING OR REINITIATING TREATMENT: RESULTS: OF A NATIONWIDE COHORT IN QUÉBEC (CANADA)

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Background: Over the past decade, new oral and long-acting injectable (LAI) antipsychotics (APs) have been introduced into the treatment options. Since then, LAI antipsychotics have shown their place as first-line treatment for schizophrenia at different stages of the disease, both in RCTs and observational studies. While the latest observational studies report data mainly from Scandinavia, a recent North American study provided complementary data to ensure representativeness across countries. However, this study was based on a cohort of veterans that may not represent appropriately the general population encountered in routine psychiatric care. Therefore, to assess the comparability of outcomes between national health care databases, we conducted an observational comparative effectiveness research study using a large longitudinal medico-administrative nationwide database from Quebec (Canada). The main objective of this study was to compare the effectiveness and safety of different APs (SGAs, newer oral, LAI SGAs, and FGAs) in patients with schizophrenia initiating or reinitiating an AP treatment.

Methods: This retrospective cohort study included medical-administrative information for patients with a diagnosis of SCZ living in Quebec (Canada), initiating or reinitiating at least one antipsychotic (AP) drug (with a clearance baseline period of 12 months without any APs). Effectiveness was defined in two ways: 1) by a reduced risk of hospitalization for mental disorder, and 2) by a reduced risk of hospitalization for mental disorder or AP discontinuation, two years after AP initiation or reinitiation. Safety was defined by a reduced risk of all-cause death and hospitalization for non-mental disorder, two years after AP initiation or reinitiation. Cox proportional hazard models were used to estimate the hazard ratios (HRs) of the events associated with the use of the different AP categories compared with oral olanzapine.

Results: The study cohort included 19,615 patients initiating or reinitiating an antipsychotic drug between January 2006 and December 2015. The Results: showed better effectiveness of LAI SGAs compared to oral olanzapine (HR 0.81, 95% CI 0.70-0.94, p=0.0061). Adding discontinuation to

the effectiveness criteria, clozapine (HR 0.36, 95% CI 0.30-0.42, p<0.0001) and LAI SGAs (HR 0.56, 95% CI 0.51-0.61, p<0.0001) were more effective than oral olanzapine, as opposed to oral FGAs (HR 1.36, 95% CI 1.27-1.46, p<0.0001) and LAI FGAs (HR 1.22, 95% CI 1.12-1.32, p<0.0001). Most APs were as safe as oral olanzapine, except for oral FGAs.
Discussion: This study represents, to our knowledge, the largest North American observational study, based on a nonveteran cohort, evaluating the effectiveness and safety of antipsychotic treatments in recent years. In summary, the effectiveness of LAI SGAs and clozapine appears to justify their use in new users and are as safe as a recognized treatment (oral olanzapine) in Quebec (Canada).

T156. IMPACHS: FEASIBILITY AND ACCEPTABILITY OF AN M-HEALTH SOLUTION INTEGRATED INTO ROUTINE CLINICAL TREATMENT FOR PSYCHOSIS

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Background: Cognitive behavior therapy for psychosis (CBTp) is effective and recommended in various national guidelines. However, the implementation of CBTp into clinical practice faces difficulties due to limited resources of the healthcare system, including extensive waiting-times for outpatient therapy, sparse options for support once therapy has ended, and a limited number of therapy sessions per patient. In the IMPACHS project, we examined the feasibility and acceptability of integrating a CBTp-based mobile solution covering monitoring, e-learning, and interventions into routine clinical care. We explored [1] whether patients are willing to use the solution as part of CBTp and continue to use it over an extended time-period; [2] whether symptom severity and trajectory preclude some patients from using the solution; and [3] whether clinicians support integrating solutions into face-to-face CBT.
Methods: The IMPACHS project aims to provide patients and clinicians with better access to relevant information and insights by facilitating the transfer of CBTp-intervention into patients' daily life, and data on wellbeing, symptoms, and behaviour from continuous patient monitoring into face-to-face CBTp. The solution consists of a Smartphone app for patients and a web interface for clinicians. The Smartphone app includes a psychoeducational manual, eight interactive e-learning-modules addressing relevant symptoms, experiences and difficulties associated with psychosis, individualised action plans, a trigger set-up, and self-assessment parameters.

In a non-controlled trial, we recruited 24 participants with psychosis (Female, n=14; age: M=28.21, range=18-50; 75% with a diagnosis of schizophrenia) in one German (n=8, participants) and two Danish (n=16) treatment sites. Participants could access the solution at any time during the six-month trial-related CBTp-treatment and up to 6 months thereafter. Solution usage was analysed, while acceptability of the solution amongst patients' was assessed via the User Version of the Mobile Application Rating Scale (uMARS), and clinicians' via an exit questionnaire that was developed for the IMPACHS trial at the end of the six-month access phase.

Results: We found that [1] the solution was widely accepted by patients and clinicians. Overall, patients rated the application as good (3.84/5). Information, functionality and aesthetics received the highest scores (4.24, 3.89, and 3.89 respectively/5) out of all assessed domains. On average, participants used the solution on 2.91 days/week, with more frequent usage in month one (M=4.25 days/week) than in later months (e.g., month five: M=2.10 days/week). The usage exceeded Results: from other self-guided applications (e.g., Torous et al., 2017: 10-14 interactions over 66 weeks); [2] patients with high baseline symptom levels or symptomatic deterioration did not seem to deter from using the solution ($-0.29 \leq r \leq -0.04$, all p's>0.10); and [3] clinicians reported frequent utilisation of the solution with beneficial effects (M=0.95, SD=0.23; -1=disrupted therapy, 0=no impact, 1=improved therapy), and none of the functions were reported as having a negative impact on therapy. On average, therapists used 4.95/8 functions when providing treatment, encouraged patients to use an average of 2.58/5 functions outside of therapy, and all supported the integration of the solution into face-to-face CBT.
Discussion: This study shows the feasibility of integrating an mHealth solution into long-term routine outpatient treatment settings. The intervention was relatively easy to implement, widely accepted by patients, and reported to facilitate treatment by clinicians. Future research through powered RCTs are needed to verify the self-reported positive impact of the app-supported therapy, and explore how variations in the solution usage are influenced by factors like patient characteristics, evolving nature of the therapy, and/or life events.

T157. PSYCHOLOGICAL AND PSYCHOSOCIAL INTERVENTIONS IN SCHIZOPHRENIA: WHICH ONES PREVENT PSYCHOTIC RELAPSE?

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Background: Preventing symptomatology recrudescence is of crucial importance in patients with schizophrenia. Psychological and psychosocial interventions can be used in combination with antipsychotics to prevent recurrence of psychotic episodes (relapse). Pairwise meta-analyses investigated single interventions such as psychoeducation or family therapy compared to standard care, so that no information is available on how these interventions compare to each other. However, many different interventions have been developed and investigated in clinical trials, and their comparative efficacy in the prevention of relapse is not known.
The methodology of network meta-analysis allows to compare two interventions, even if no clinical study compared them, thanks to the calculations of indirect comparisons. The aim of this

systematic review and network meta-analysis was to evaluate the efficacy, acceptability and tolerability of psychological interventions for the prevention of relapse in schizophrenia.

Methods: A systematic search was conducted in EMBASE, MEDLINE, PsycINFO, BIOSIS, Cochrane Library, WHO International Clinical Trials Registry Platform (ICTRP), ClinicalTrials.gov and Pubmed. Search Results: were independently screened by two reviewers in order to include randomized-controlled-trials (RCTs) that investigated psychosocial or psychological interventions aimed at preventing relapse in patients with schizophrenia. Primary outcome was relapse at one year. Relapse at 6 months and at more than one year were investigated as secondary time points for the primary outcome relapse. Data extraction was conducted by two reviewers independently, and inconsistencies resolved by Discussion: and by contacting study authors. Random-effects network meta-analysis were performed to calculate odds ratios (ORs) for binary outcomes and standardised mean-differences (SMDs) for continuous outcomes, with their 95% confidence intervals. Study protocol was a-priori registered in PROSPERO (CRD42019147884).

Results: After screening 28095 records by title and abstract and 3594 full-text articles for eligibility, 85 studies were included in the qualitative synthesis, of which 72 studies with 10364 participants had available data for the network meta-analysis. The included studies provided data about 20 different psychosocial and psychological interventions. Some psychological interventions reduced relapse more than treatment as usual at 1 year: Family interventions (OR 0.35, 95% CI 0.24-.52), relapse prevention programmes (OR 0.33, 0.14–0.79), cognitive behavioural therapy (OR 0.45, 0.27-0.75), family psychoeducation (OR 0.56, 0.39–0.82), integrated interventions (OR 0.62, 0.44-0.87), and patient psychoeducation (0.63, 0.42–0.94). In sensitivity and subgroup analyses the Results: for integrated intervention, patient psychoeducation and relapse prevention programmes show a variability in comparison to main analysis, with confidence intervals in six or more additional analysis including the possibility of no difference with treatment as usual. On the contrary, benefits in reducing the risk of relapse were robust after sensitivity and subgroup analysis for family interventions, family psychoeducation, and cognitive behavioral therapy.
Results: will be presented also for secondary time points relapse at 6 months and more than one year.

Discussion: Our results show that family interventions, family psychoeducation, and cognitive behavioral therapy are effective in preventing psychotic relapse at one year. These treatments should be the first psychosocial interventions to be considered in the long-term treatment for patients with schizophrenia.

T158. EXAMINING THE IMPACT OF EXERCISE, SLEEP, DIET AND SMOKING ON THE RISK AND OUTCOMES OF MENTAL ILLNESS: A META-REVIEW OF "LIFESTYLE PSYCHIATRY"

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Background: Health organisations and care services are increasingly addressing the role “lifestyle factors” (e.g. exercise, smoking, diet and sleep) in the prevention and treatment of mental health

conditions. However, the availability, quality and implications of the evidence around this topic is currently unclear.
Methods: A meta-review was conducted to aggregate and examine the overall evidence for the role of various lifestyle factors across a broad spectrum of mental health conditions. First, a systematic search was used to identify all 'top-tier' evidence for causal associations on this topic, including meta-analyses of prospective studies and randomized controlled trials, along with Mendelian randomization studies. Following this, data on how physical activity, tobacco consumption, diet, and sleep impacted on (i) the incidence / risk of mental illnesses, and (ii) the treatment outcomes in those receiving such interventions, was extracted and synthesised systematically.
Results: The search produced a total of 1,811 results, of which 41 met eligibility criteria. Among these, 11 articles focused on physical activity/exercise, 10 on sleep, 12 on dietary factors, and 15 on tobacco smoking.The meta-review aggregated findings from 29 meta-analyses of prospective/cohort studies, 12 Mendelian randomisation studies, two previous meta-reviews, and two separate meta-analyses of RCTs, examining the relations between these lifestyle factors with risk and outcomes of depression, anxiety, bipolar disorder, psychotic disorders and ADHD.
Discussion: The availability, strength, and implications of evidence varied across the lifestyle factors and the mental health conditions we examined. For instance, physical activity/exercise was found to have convergent evidence from multiple forms of top-tier evidence supporting this as a modifiable factor for reducing the risk of common and severe mental illness, and improving recovery in mental healthcare, whereas the evidence-base for causal other lifestyle factors (such as diet) was more nascent. Alongside this, there was a compelling body of emergent evidence examining the complex, bi-directional relations between other lifestyle factors, such as tobacco smoking and sleep, in the onset and outcomes of various mental health conditions. Implications/guidelines on these topics will be presented and discussed.

T159. ESTABLISHING A SPECIALISED OUTPATIENT CLINIC FOR GUIDED TAPERING OF ANTIPSYCHOTICS – DESCRIPTIVE CHARACTERISTICS OF REFERRED PATIENTS

Alexander Nøstdal*[1], Rikke Hilker[1], Jimmi Nielsen[1], Mette Ødegaard Nielsen[2]

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Background: Antipsychotics are effective at reducing psychotic symptoms, and most clinical guidelines recommend long-term treatment for patients diagnosed with schizophrenia. However, adverse effects to antipsychotic medication is common, and treatment is complicated by low adherence-rates over time. While the subject remains controversial, there is evidence indicating that a subgroup of patients might benefit from discontinuing antipsychotics. Consequently, tapering or discontinuation of antipsychotics under guidance by health care professionals is becoming increasingly common, and with funding from the Danish authorities in 2018, a specialised outpatient clinic for tapering antipsychotics was established at Mental Health Centre

Glostrup, Denmark. The main aim of this study is to explore the referred patients' motivation for discontinuing their antipsychotic medication.
Methods: Patients with schizophrenia were referred to the specialised outpatient clinic by public healthcare outpatient clinics and from general practitioners over a three-year period. Upon enrolment patients were requested to fill in an open-ended questionnaire regarding their motivation for discontinuing antipsychotic medication, and disclose previous experiences, if any. Symptom severity was rated using Positive and Negative Syndrome Scale (PANSS). Level of functioning was estimated with the Global Assessment of Function scale, and adverse effects was measured using Udvalget for Kliniske Undersøgelsers side effect rating scale (UKU).
Results: In the first three years, 88 patients (56% female, n=49) with schizophrenia were enrolled. Mean GAF score for the patients was 47 (31-82, SD 10.3). Based on PANSS-score (mean 64; 34-108; SD 16.2), the patients can be classified as well-treated with mild burden of symptoms. Symptomatic remission, defined by criteria proposed by Andreasen et al. 2005, was seen in 18 (21%) of the patients. On average use of antipsychotics were within recommended daily dose for maintenance treatment (mean Chlorpromazine-equivalents 393 mg, CI 323-462). The motivational questionnaire was filled in by 78 of the patients, and 54 (71%) listed adverse effects as their motivation for discontinuing, while clarification of need was the second-most common reason, listed by 22 (29%) of the patients. Other reasons were a hope to be normal or feeling stigmatized; worries about long-term effects; disagreeing with diagnosis; and insufficient symptom reduction. Side effect screening with UKU Side Effects Rating Scale showed weight gain, sexual dysfunction and cognitive side effects prominently reported. Out of the 42 (55%) patients who reported previous experience with discontinuation of antipsychotics, 23 (55%) admitted to relapse of symptoms.
Discussion: This is to our knowledge the first description of a treatment facility primarily focused on offering patients with schizophrenia structured and standardized tapering of their antipsychotic medication. The listed motivational factors for discontinuing antipsychotics, is in line with previous studies examining patients discontinuing on their own initiative and indicates that these patients may be willing to follow a guided tapering program, if given the option. The relative high proportion of patients who previously had experienced relapse after discontinuation attempts, indicates that these—often traumatic—experiences do not serve as a barrier for future attempts. The characterization of patients referred to this outpatient clinic, will offer valuable insight to colleagues facing patients seeking to discontinue their antipsychotic treatment, and potentially improve treatment alliances.

T160. VALUE OF SPECIALIZED CONSULTATIONS FOR INDIVIDUALS WITH SUSPECTED RECENT ONSET OF SCHIZOPHRENIA

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Background: Early diagnosis and treatment of new onset schizophrenia are associated with reduced morbidity and improved outcomes. We sought to determine the perceived value of a second opinion in a consult clinic specializing in new onset schizophrenia for individuals with suspected recent onset schizophrenia who were not were not receiving specialized care.

Methods: 121 consecutive in-depth consultations were performed in an academic medical center for individuals referred for a second opinion concerning recent onset of a schizophrenia-like disorder. Between 1 and 10 years after the consultation, parents of patients were questioned about the process and the value of the consultation. Interviews were completed for 79 of the 109 contactable parents.
Results: 85% of parents were very or moderately happy with the consultation experience, and 86% found the consultation to be very or moderately helpful, with nearly complete overlap between perceived helpfulness of, and happiness with, the consultation experience. 57% of parents found good or great value in clarifying the patient's diagnosis. 57% found good or great value in the pharmacological advice, and 60% found good or great value in the non-pharmacological advice, provided by the consultants. 75% of parents reported patient improvement following the consultation.
Discussion: Our Results: demonstrate that consultations are perceived as both positive and helpful experiences. Almost half of parents viewed the consultation as contributing to the long-term improvement of the patient's condition. Though there are a number of limitations to this study, the findings support the value of consultations in a specialty clinic for individuals thought to have recent onset of a schizophrenia-like disorder.

T161. IMPACT OF POSSIBLE TARDIVE DYSKINESIA ON PATIENTS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER: RESULTS: FROM THE RE-KINECT STUDY

Stanley N. Caroff[1], Andrew Cutler[2], Huda Shalhoub[3], William R. Lenderking[3], Chirag Shah*[4], Ericha Franey[4], Chuck Yonan[4]

[1]Corporal Michael J. Crescenz Veterans Affairs Medical Center and the Perelman School of Medicine, University of Pennsylvania, [2]SUNY Upstate Medical University, [3]Evidera, [4]Neurocrine Biosciences, Inc.

Background: Tardive dyskinesia (TD) is a persistent and potentially disabling movement disorder associated with prolonged exposure to antipsychotics and other dopamine receptor blocking agents. Using data from RE KINECT (NCT03062033), a real-world study of outpatients prescribed antipsychotics, this analysis was conducted to evaluate the impact of possible TD on patients with schizophrenia or schizoaffective disorder.
Methods: Adults with ≥3 months of lifetime exposure to antipsychotics and ≥1 psychiatric disorder were recruited. The presence of possible TD was based on clinicians' observation and assessment of abnormal involuntary movements in 4 body regions, rated as "none", "some", or "a lot". Assessments also included (but were not limited to) 3 patient-reported measures: impact of possible TD on 7 daily activities, rated as "none", "some", or "a lot"; Sheehan Disability Scale (SDS) total score (range, 0 [no impact] to 30 [extreme impact]) and domain scores for work/school, social life, and family/home life (range, 0 [no impact] to 10 [extreme impact]); and EuroQoL's 5-Dimension 5-Level questionnaire (EQ-5D-5L) utility index score (range, 0 [health state equivalent to death] to 1 [perfect health]) and visual analog scale (VAS: range, 0 [worst imaginable health] to 100 [best imaginable health]).
Results: Of 204 participants with clinician-confirmed possible TD, 111 (54.4%) had a diagnosis of schizophrenia or schizoaffective disorder. Baseline characteristics for this subgroup were as

follows: mean age (52.7 years); male (62.2%); White/Caucasian (62.2%); mean lifetime exposure to antipsychotics (19.5 years); and percentage currently taking ≥2 psychiatric medications (79.3%). Per clinician assessment, possible TD movements were most commonly found in the head/face (some=49.1%, a lot=20.9%) and upper extremities (some=48.6%, a lot=9.9%), followed by lower extremities (some=35.5%, a lot=8.2%) and neck/trunk (some=22.0%, a lot=5.5%). Approximately one-third (32.4%) of participants had severe movements (rating of "a lot") in any body region and 56.8% had ≥2 body regions impacted by abnormal movements. Over 30% of patients reported that abnormal involuntary movements had "some" or "a lot" of impact on their ability to talk (33.6%), be productive (33.6%), socialize (33.6%), and continue usual activities (32.7%). These Results: were consistent with mean SDS total and domain scores in the overall schizophrenia population, which were as follows: total (10.8); work/school (4.2); social life (3.7); family/home life (3.5). Mean scores for EQ-5D-5L utility index (0.74) and VAS health status (68.5) indicated substantial impact on health-related quality of life.
Discussion: In this real-world sample of outpatients with possible TD and a diagnosis of schizophrenia or schizoaffective disorder, abnormal involuntary movements were present throughout multiple body regions. A majority had possible TD symptoms in ≥2 body regions, and approximately one-third had "a lot" of severity in at least 1 body region. As reported by one-third of the patients, these possible TD movements had "some" or "a lot" of impact on daily activities, which was consistent with self-reported impairments on work/school, social life, and family/home life (SDS domains). Moreover, patients with schizophrenia or schizoaffective disorder reported that possible TD had substantial impact on health-related quality of life (EQ 5D-5L).

T162. THE IMPACT OF INTERNALIZED STIGMA AND RESIDUAL SYMPTOMS ON THE QUALITY OF LIFE IN PATIENTS LIVING WITH SCHIZOPHRENIA

Fabienne Post*[1], Christine Hörtnagl[1], Beatrice Frajo-Apor[1], Georg Kemmler[1], Silvia Pardeller[1], Alex Hofer[1]

[1]Medical University Innsbruck,

Background: Improving quality of life (QOL) is seen as an important objective in the treatment of schizophrenia and factors such as internalized stigma and the severity of symptoms are deemed relevant in this context.
Methods: Patients diagnosed with schizophrenia (according to ICD-10 criteria) aged between 18 and 65 years were recruited from our outpatient clinic. Next to collecting sociodemographic data, we also used the following scales in this cross-sectional study: the Positive and Negative Syndrome Scale (PANSS), the Internalized Stigma of Mental Illness (ISMI) Scale, and the Berliner Lebensqualitätsprofil (BELP), which is the German version of the Lancashire Quality of Life Profile.
Results: A total of 80 patients (47 males, 33 females) with a mean age of 43.0 ± 10.9 years participated in this study. The mean PANSS total score was 71.1 ±25.4, the mean ISMI score was 61.1 ± 14.7 (range: 29-116), and the BELP subscale overall QoL showed a mean score of 4.73 ± 1.17 (range 1-7). Statistical analysis showed a moderate correlation between QoL and internalized stigma (r=-0.468, correlation with general life satisfaction) and a weak correlation with the PANSS total score (r=-0.246, correlation with general life satisfaction). Multiple linear regression analysis showed that internalized stigma, but not residual symptoms of the disorder, negatively predicted QoL.

Discussion: Our results show that internalized stigma has a negative impact on quality of life, whereas residual symptoms play a secondary role. Accordingly, significant efforts should be made to reduce internalized stigma, and, ultimately, to improve quality of life.

T163. EXAMINING RELATIONSHIPS BETWEEN STATE AND TRAIT PSYCHOTIC SYMPTOMS AND QUALITY OF LIFE IN SCHIZOPHRENIA SPECTRUM DISORDERS

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Background: Positive and negative symptoms are core aspects of schizophrenia and have been shown to influence patient quality of life (QOL). Previous studies have largely focused on current or state symptoms, with limited work on the contributions of trait symptoms to QOL. This study sought to examine the relationship between both state and trait symptoms and objective and subjective QOL.
Methods: Fifty-three schizophrenia spectrum disorder patients and 47 healthy controls were recruited. State psychotic symptomatology was assessed using the Positive and Negative Syndrome Scale in the patients only. In all participants, trait symptoms were assessed using the Oxford-Liverpool Inventory of Feelings and Experiences, and QOL using Lehman's QOL Interview. Current depression was assessed using the Montgomery-Asberg Depression Rating Scale and neurocognition using the MATRICS Consensus Cognitive Battery.
Results: Hierarchical linear regression analyses, controlling for depression and neurocognition, revealed that negative state symptoms were related to objective QOL within the patients, while negative trait symptoms were associated with both objective and subjective QOL in patients and healthy controls. No relationships were observed with positive state or trait symptoms and either QOL measure. Post-hoc moderation analyses revealed that the directionality of relationships between negative trait symptoms and both objective and subjective QOL were similar in both patients and healthy controls.
Discussion: The findings suggest a degree of complexity in the associations between symptoms and QOL, with primacy for negative symptoms at both state and trait levels. The findings also highlight the need for a greater appreciation of trait symptoms, and how they may impact on wellbeing and functional prognoses post-diagnosis and during remission of state symptoms.

T164. SOCIODEMOGRAPHIC CHARACTERISTICS ASSOCIATED WITH PARENTHOOD AND INPATIENT ADMISSIONS AMONGST PATIENTS WITH A PSYCHOTIC DIAGNOSIS: A CROSS-SECTIONAL STUDY USING PATIENT CLINICAL RECORDS

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Background: The symptoms of psychosis and side-effects from anti-psychotic medication can affect patients' capacity to offer the consistent, responsive care required for healthy child development. Estimates of parenthood in individuals with psychosis range from 27% to 38%. The most recent UK study of parenthood estimates was conducted over 20 years ago, and should be updated.

When clients do have children, they can be reluctant to talk about them for fear of social services involvement, and mental health professionals can be hesitant to ask, meaning dependants are often invisible to services. This study assessed the following research questions: 1) What proportion of patients in secondary care with a psychotic diagnosis have children? and 2) What proportion of these patients have their children correctly recorded in their clinical notes?

Additionally, it is important to have a clear picture of the sociodemographic characteristics of patients with psychosis who are parents, and to know which parents are more likely to experience relapse in order to design effective interventions for these families. The final two research questions were: 3) What sociodemographic characteristics are associated with parenthood in this population? and 4) What characteristics are associated with inpatient stays for parents with a psychotic diagnosis?

Methods: This study used CRIS (Clinical Records Interactive Search), a database which contains over two million de-identified patient records, to search for patients with a diagnosis of non-affective or affective psychosis (F20-29, F31.2 or F31.5) within a UK NHS Trust.

Patients' notes were searched to see if any dependants had been recorded in the appropriate structured field. For the patients who did not have any dependants recorded in this manner, their non-structured fields were searched to determine if they had dependants who had not been recorded in the correct location.

The following variables were extracted from the structured fields of all participants: gender, date of birth, ethnicity, marital status, employment, accommodation, deprivation index, smoking status, ward stays and diagnosis. A binomial regression model was fit to identify the variables associated with parenthood.

A survival analysis was run for all parents who had experienced at least one ward stay. A cox proportional hazards model was fit to determine which variables were important in predicting a second ward stay.

Results: 1) 5178 patients with psychosis were included in this study and 38.8% were parents.

2) Out of the parents in the sample, only 67.2% of parents with dependant children had their children correctly recorded in the structured field of their clinical notes.

3) Patients were more likely to be a parent if they were female (OR = 2.17), an older age (OR = 1.04), had a higher socioeconomic status (OR = 1.05), renting (OR = 2.32) or owning (OR = 2.07) compared to being in supported living, married (OR = 7.60) or divorced (OR = 8.55) compared to being single. Patients were also more likely to be a parent if they were not White (British) and did not have an F20 schizophrenia diagnosis.

4) 1094 patients had at least one ward stay recorded. Of those, 599 had a second ward stay recorded and 495 did not. After applying a backwards stepwise algorithm, only marital status, diagnosis and smoking were included in the cox proportional hazards model. Parents who were married (HR = 0.74) or divorced (HR = 0.89) had a lower hazard for a second ward stay compared

to single parents. Those with an F31.2 or F31.5 diagnosis (HR = 1.40) had a higher hazard ratio when compared to patients with an F20 diagnosis. Patients who were current smokers had a higher hazard compared to non-smokers (HR = 1.19).

Discussion: Over one third of patients with psychosis were parents, which is very similar to the rates found in the most recent international estimate conducted in an Australian national survey. It is clear that not all NHS Trusts are recording dependants accurately. Policies in Norway, Sweden, and Australia now require that adult mental health services record the presence of children so that these families receive appropriate support. Policies in the UK must also reflect this need to accurately identify dependants in order for these families to receive appropriate support.

Many factors were associated with parenthood status. Women were more than twice as likely as men to be a parent. Most parents with psychosis have their first psychotic episode after becoming a parent. Since the age of onset is earlier in men, it may be than men with a psychotic diagnosis have fewer opportunities to meet a partner and have children.

Patients with affective symptoms (F23, F31.2, F31.5) were more likely than those with schizophrenia (F20) to have children, however they also had a higher risk of ward stays. Patients who were single were less likely to have children than patients who had ever been married, but it was these single patients who were at a higher risk of a second ward stay. Single mothers with psychosis have reported stress around coping with parenting tasks, and it could be that this lack of support is contributing to relapse. It may be that the parent patients who are single and experience affective symptoms are the ones who would benefit most from an intervention.

Poster Session II

12:00 p.m. - 2:00 p.m.

F1. SYMPTOMS OF PSYCHOSIS ARE DIFFERENTIALLY ASSOCIATED WITH ILLUSORY PERCEPTION IN THE HOLLOW MASK TASK

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Background: Patients suffering from schizophrenia are less susceptible to experiencing various visual illusions. For example, healthy participants perceive a hollow mask as a normal face, while patients with schizophrenia do not. This illusion originates from the prior expectation of human faces being convex, and it is driven by top-down signals that override the bottom-up stimulus characteristics. Thus, there is a mismatch of the concave face percept and the stored memory representation for faces being convex, and this phenomenon could be explained under the predictive coding account. However, symptoms like hallucinations and delusions may be the outcome of enhanced rather than weakened top-down predictive signaling (i.e. "strong" priors). Here, we examined susceptibility to the hollow mask illusion in schizophrenia patients(SZ), non-clinical voice-hearers(NCV) and healthy controls(HCs) and compared performance on the illusion task to that on a motion perception task that assays overreliance on prior information. As such, we sought to investigate the interplay between psychotic symptoms and the use of prior, top-down information versus bottom-up stimulus characteristics.

Methods: The hollow-mask task involves viewing the concave side of a human mask that has been painted to look like a normal face. Participants (30 HCs; 14 NCV; 48 SZ) were asked to stand at a distance of 2 meters and close one eye, swaying gently laterally while they view the mask. Every 12 seconds, participants were prompted to report whether they perceived the face to be concave or convex. The same participants also completed a motion perception task in which dots in a random dot kinetogram moved coherently in one direction, but on motion changed by 90°midway through the trial. Participants were asked to report the motion they perceived at the end of the trial. The apparent convexity of the mask was used as a measure of susceptibility to the illusion(weaker priors), while resistance to updating motion percept was indexed by proportion of responses centered around the initial motion direction (stronger priors/failure to update).

Results: Overall, patients experienced fewer illusions than HCs and NCV in the hollow mask task [$F(1,89)=7.03$, $p<0.001$, $\eta p2=.13$;mean percent convex reports(SD): SZ, 62.4(28.1); NCV, 68.4(24.7); HCs,80.5(17.5)]. In the patient group, resistance to illusion (More veridical perception) was associated with disorganized symptoms ($r= 0.32$,$p=0.03$), while increased reports of illusory percept was associated with hallucinations at a trend level($r=027$, $p=0.07$) and with delusions as measured by the Peters Delusions Inventory($r=0.28$, $p=0.05$). In the NCV group, susceptibility to illusions was associated with hallucinations ($r=0.56$, $r=0.04$). Interestingly, across both the HCs and NCV groups, propensity to perceive illusions was associated with our index of "strong" priors-proportion of responses centered around the initial motion direction in the motion task ($r=0.30$, $p=0.047$).

Discussion: In this exploratory analyses in an on-going study, we uncovered differential symptom correlates of the use of bottom-up evidence versus top-down priors in schizophrenia patients, non-

clinical voice-hearers and controls. The hollow-mask illusion, is interpreted as the result of a very strong prior ("faces are convex") overwhelming the visual evidence. Here, we demonstrate that the susceptibility to this illusion is associated with the failure to update sensory evidence in another task, as well as failure to update beliefs(delusions) and hallucinations, while resistance to the illusion in patients is associated with disorganized symptoms.

F2. USING POINT LIGHT DISPLAY STIMULI TO ASSESS GESTURE DEFICITS IN SCHIZOPHRENIA PATIENTS

Anastasia Pavlidou*[1], Victoria Chapellier[1], Lydia Maderthaner[1], Sofie van Känel[1], Sebastian Walther[1]

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Background: Gestures are visible bodily movements used with the intention to communicate. Schizophrenia patients often exhibit impairments when assessing pictures of hand gestures or video-recordings of real-life agents. Taking into account the dynamic nature of social communications, pictures of hand gestures offer minimal ecological validity, while video-recordings require the process of multiple verbal and nonverbal-cues (posture and gaze direction) that reflect several underlying socio-cognitive processes that go beyond gesture perception. Point-light displays (PLDs) depict biological-movements in the absence of any visual characteristics and are a great alternative in assessing gesture deficits. The current study explored the underlying socio-cognitive processes between static (pictures of hand gestures) and dynamic (PLDs) gesture representations, and their association with symptom severity, as well as, motor and cognitive modalities.

Methods: We included 39 stable schizophrenia outpatients and 27 age and gender matched controls. To assess gesture processing, both groups completed two tasks. The first task known as the Postural Knowledge Task (PKT) includes 20 pictures of a person performing a gesture. The limbs executing the gesture were missing and participants' task was to choose the correct gesture from three options provided. The second task included 40 videos of two PLDs interacting with each other. One PLD performed communicative gestures, while the other PLD imitated/followed these performed gestures. Participants had to indicate with a button press, which of the two PLDs was imitating/following the other. Additionally, symptom severity in patients was assessed using the Positive and Negative Syndrome Scale (PANSS), the Brief Negative Symptom Scale (BNSS) and the Thought and Language disorder (TALD) scale while motor, working memory and emotional perception abilities were assessed using the Neurological Evaluation Scale (NES), Digit Span Backwards (DSB), and the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) respectively.

Results: Schizophrenia patients performed worse in both the PKT ($F = 4.91$; $p < 0.05$) and PLD ($F = 5.25$; $p < 0.05$) tasks compared to controls. In addition, patients exhibited more motor symptoms ($X2=22.4$; p-value < 0.0001) and inferior emotional perception abilities than controls ($X2 > 6.36$; p-value < 0.01). In contrasts working memory abilities of patients was similar to controls ($X2 = 0.90$; p-value $= 0.34$). Poor performance in the PKT was associated with more symptoms within the blunted affect subdomain of the BNSS (tau = -0.25; p-value <0.05), while poor PLD performance was associated with the gesture expressive item (tau = -0.20; p-value

<0.05). In addition, poorer task performance in both tasks was associated with more motor symptoms in accordance to the NES scale (tau >-0.22; p-value < 0.06). Interestingly, the PLD task strongly correlated with the sensory integration subdomain of the NES (tau = -0.25; p-value <0.05) whereas, the PKT task strongly correlated with the motor coordination (tau = -0.27; p-value <0.05) and sequencing of motor acts domains (tau = -0.37; p-value <0.001). No other significant correlations were observed.

Discussion: Our Results: suggest that that gesture representations of static and dynamic stimuli are associated with distinct processes within the negative symptoms and motor domains in schizophrenia. Understanding the neural mechanisms associated with the processing of these stimuli will help in establishing novel therapeutic interventions necessary to improve social communication and social functioning in schizophrenia patients.

F3. EXAMINING THE CONSTRUCT VALIDITY OF A NEWLY DEVELOPED MEASURE OF INTERNALIZED STIGMA FOR INDIVIDUALS WITH PSYCHOSIS

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Background: Public stigma is defined as the endorsement of negative stereotypes, prejudice and discrimination towards a group by the general population. Internalized stigma occurs when an individual from the stigmatized group endorses and applies the negative stereotypes to themselves. Internalized stigma is associated with numerous negative outcomes for individuals with psychosis and plays a major role in the maintenance and severity of the disorder. Thus, a measure of internalized stigma for psychosis is necessary to examine the unique effects and points of intervention for individuals with psychosis. However, there is no validated measure for internalized stigma for psychosis. The goal of the current study was to examine the construct validity of the Self-Stigma Quadrant Measure (SSQM), a novel measure of internalized stigma in psychosis, and it's relationship with community functioning.

Methods: 121 participants, ages 17 to 67, were included in the following analyses. 97 participants had a diagnosis of a psychotic disorder and 24 participants were healthy controls. The SSQM is composed of four subscales; positive and negative beliefs of the self and of individuals with psychosis. Both positive and negative internalized stigma variables were calculated by subtracting psychosis beliefs from beliefs of the self and dividing by the sum of self and psychosis beliefs to determine the extent of internalization of stigmatizing beliefs. The Sheehan Disability Scale (SDS) and Specific Levels of Functioning (SLOF) were used to measure subjective and informant-rated overall functioning, respectively.

Results: There was a significant positive correlation between positive self and psychosis beliefs for the psychosis group ($r = .635$, $p<0.001$) and for healthy controls ($r = .462$, $p<0.05$). There was a significant positive correlation between negative self and psychosis beliefs for the psychosis group ($r = .635$, $p<0.001$) but not for healthy controls ($r=.250$, $p=0.239$). Moderation analyses showed that the participant group did not moderate the relationships between positive self and psychosis beliefs. There was a significant interaction between group and negative self-beliefs in predicting negative beliefs of psychosis ($F(1, 94) = 4.12$, $b= -0.45$, CI [-0.89, 0.01], $t= -2.03$, $p<0.05$), where negative self and psychosis beliefs were significantly correlated for individuals with psychosis ($b= 0.6739$, $p<0.001$) but not for healthy controls ($b=0.2228$, $p=0.2834$). A

correlation analysis showed that greater negative internalized stigma scores were associated with poorer subjective functioning (r= .35, p<0.05). There was no significant association between positive internalized stigma and subjective functioning (r =- .23, p= 0.124), informant-rated functioning (r= .06, p= .721), or between negative internalized stigma and informant-rated functioning (r= - .09, p= .573).
Discussion: The SSQM may be a valid new measure of internalized stigma that assesses multiple domains of internalized stigma in psychosis. Negative beliefs about psychosis were correlated with negative self-beliefs in individuals with psychosis and not for healthy controls. Furthermore, negative internalized stigma scores were significantly correlated with subjective functioning. It may be important to examine multiple facets of internalized stigma to understand the underlying causes stigma and inform of the development of more effective internalized stigma treatments.

F4. SOCIAL COGNITION AND GENDER IN PSYCHOSIS: A SYSTEMATIC REVIEW

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Background: Social cognition consists of several mental processes including emotion processing and recognition, theory of mind, attributional style, and social perception. Impairments in social cognition are present in psychosis and are already evident in first-episode psychosis. Gender differences have been found in social cognitive domains in different stages of psychosis, but current evidence shows inconsistent Results:.Since there is no consensus in the Results: to date, we believe analyzing the synthesis of the published evidence is of particular importance.
Methods: We aim to perform a systematic review of gender differences in social cognition in adults with psychotic spectrum disorders or a first-episode psychosis. To be included, studies must focus in social cognition or, at least, in one of its main domains – emotion processing, theory of mind, attributional style, and social perception. We conducted a preliminary database search in Pubmed and Psychinfo. We included three groups of search terms, referring to the study sample, sociodemographic variables, and outcomes. Three independent reviewers screened and selected the retrieved studies on the basis of their titles and abstracts. Full text assessment was conducted independently by three reviewers and three review collaborators. This project is registered in PROSPERO (CRD42020184657).
Results: We found 495 reports, from which 207 were included after the initial screening. After the full text review, we included a total of 61 articles. We will extract information about authorship, year of publication, sample sociodemographic characteristics, study design, outcomes, instruments applied to measure outcomes and main findings. We will evaluate the risk of bias using the NIH-NHLBI Study Quality Assessment Tools. We will complete the review and present the Results: at the SIRS 2022 Annual Congress.
Discussion: We believe this systematic review will offer a better understanding of how social cognition works in psychosis and whether men and women have different social cognitive functioning. This knowledge may help clarify whether tailored interventions regarding gender are needed in treatments for psychosis.

F5. INFLUENCE OF COGNITIVE FUNCTIONING ON THE MCT EFFICACY FOR THE IMPROVEMENT OF ATTRIBUTIONAL STYLE: A RECENT ONSET PSYCHOSIS STUDY

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Background: Cognitive dysfunctions are considered a common and disabling feature of psychotic spectrum disorders, reaching rates of 85% (Caponnetto et al., 2018). Although these deficits have showed associations with some cognitive biases, they have been considered separable constructs (Eisenacher and Zink, 2017). However, it may be possible that cognitive deficits may limit the efficacy of metacognitive interventions, being considered as a risk factor for poor metacognitive processes, such as attributional biases. In this sense, this study aims to analyse predictive capacity of baseline cognitive functioning regarding presence of attributional biases [Personalizing Bais (PB) and Externalizing Bias (EB)] after a metacognitive training programme was implemented.
Methods: A total of 63 patients experiencing a recent onset of psychosis were recruited in the setting of a randomized clinical trial (ID:NCT02340559) address to assess the efficacy of metacognitive training (MCT) (Ochoa et al., 2017). All patients had received MCT intervention and had been assessed in three time-points [baseline (T0), post-treatment (T1), and at 6 months follow-up (T2)] with a comprehensive battery of instruments including measure of socio-demographic and clinical variables, attributional style (IPSAQ) and cognitive functioning. A comparison means for repeated measures were carried out to know significant changes in relation to attributional style at post-treatment and at 6 months follow-up. Bivariate associations and multiple regression analysis were performed to analyse the capacity of baseline cognitive functioning to predict attributional biases at follow-up.
Results: The repeated measures analysis did not reveal significant mean differences in the attribution bias variables collected at the three time points (EB T0-T1: Mean T0=0.55; Mean T1=0.43; p=0.813) (EB T0-T2: Mean T0=0.58; Mean T2=1.62; p=0.111) (PB(+) T0-T1: Mean

T0=0.56; Mean T1=0.50; p=0.145) (PB(+) T0-T2: Mean T0=0.57; Mean T2=0.52; p=0.348) (PB(-) T0-T1: Mean T0=0.63; Mean T1=0.66; p=0.626) PB(-) T0-T2: Mean T0=0.61; Mean T2=0.64; p=0.627). Regression models revealed that some cognitive domains were predictors of attributional biases which are maintained at 6-months implementing MCT. Externalizing Bias (EB) were predicted by verbal memory domain at baseline (Beta= 0.520; t=3.103; p=0.004), showing scores below one standard deviation in all measures included in this domain. Verbal memory domain explained 31.4% of the overall self-serving bias variance. Personalizing Bias for negative events (PB-) was predicted by speed processing at baseline (Beta=0.423; t=2.148; p=0.041). This cognitive domain explained 26.7% of the total variance of the trend to attribute negative events rather to personal than to situational factors.
Discussion: MCT could see its effectiveness reduced in the presence of cognitive deficits prior to the intervention in people with recent onset of psychosis. Specifically, a low performance in verbal memory and processing speed domains previous at implementing MCT programme could interfere with the expected improvements in attributional style after this intervention. In this sense, cognitive remediation may promote the efficacy of MCT when used in combination due to its indirect impact on cognitive biases and on the capacity to evaluate and control our cognitive processes.

F6. DISENTANGLING THE INTERPLAY BETWEEN AUTISTIC SYMPTOMS, COGNITION, AND PRAGMATICS IN SCHIZOPHRENIA: A PATH ANALYSIS

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Background: Pragmatics, defined as the capacity to understand the speaker's meaning and to appropriately engage in a conversation, is widely affected in different clinical population, such as Autism Spectrum Disorder (ASD) and schizophrenia. Around 80% of patients with schizophrenia show a pragmatic impairment with negative impact on daily functioning.
Research tried to disentangle the relationship between pragmatic impairment and other domains typically disrupted in schizophrenia, such as Theory of Mind (ToM) and executive functions (EF), but results are still contrasting.

A field of recent interest concerns autistic symptoms (autistic-like symptoms that do not reaching diagnostic threshold for ASD), which have been found in a subgroup of patients with schizophrenia. Patients with autistic symptoms show more disrupted cognitive and sociocognitive abilities, suggesting that their co-occurrence would be associated with a 'double dose' of deficit. This hypothesis could also be extended to pragmatic impairment, given its presence in both schizophrenia and ASD. However, to date the effect of autistic symptoms on pragmatics is schizophrenia has not been investigated yet.

Thus, the aim of this study is to evaluate the interplay between autistic symptoms, ToM, EF, and pragmatic abilities.

Methods: 111 patients with schizophrenia were assessed for autistic symptoms (PANSS Autism Severity Score), ToM (Picture Sequencing Task), EF (Brief Assessment for Cognition in Schizophrenia), and pragmatics (Assessment of Pragmatic Abilities and Cognitive Substrates test). The interplay between variables was tested by means of different path analyses (firstly on global pragmatics, then on both pragmatic production and comprehension).

Results: In the first path analysis on global pragmatics, we found direct negative effects of autistic symptoms, ToM, and EF, and also indirect effects of autistic symptoms firstly through EF, then through EF and ToM. The path model showed a good fit ($\chi2$= 1.04, $\chi2$ test p-value= .30, CFI= .99, SRMR= .02, RMSEA= .02) and explained 35% of variance on global pragmatics.

In the second path analysis on both pragmatic production and comprehension, we found direct negative effects of both autistic symptoms and EF on pragmatic production, and direct negative effects of both autistic symptoms and ToM on pragmatic comprehension. As for indirect effects, autistic symptoms proved to affect pragmatic production thought EF, while the effect of autistic symptoms on pragmatic comprehension was mediated by EF and ToM. The path model showed a good fit ($\chi2$= 1.66, $\chi2$ test p-value= .43, CFI= 1, SRMR= .03, RMSEA= .00) and explained 17% of variance on pragmatic production and 30% of variance on pragmatic comprehension.

Discussion: Our Results: contribute to disentangle the relationship between cognitive and pragmatic abilities, highlighting that the effects of ToM and EF are differentiated according to specific pragmatic domains. Innovatively, our findings show that autistic symptoms have a main role, both direct and indirect, in negatively affecting different facets of pragmatics. These Results: confirms the hypothesis that the co-occurrence of schizophrenia and autistic symptoms could be associated with a 'double dose' of pragmatic deficit.

Our findings may help to reconcile the contrasting data on the relationship between pragmatics and both ToM and EF, also innovatively underlying the major role of autistic symptoms. Thus, our study suggests the need of further research on autistic symptoms in schizophrenia, as well as the necessity of better understanding the predictors of pragmatic abilities with consequent beneficial effects on functioning.

F7. PARANOIA IS ASSOCIATED WITH REDUCED SENSITIVITY TO PRECEDING CONTEXTUAL CUES DURING MNEMONIC DISCRIMINATION

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Background: Memory impairment is a core feature of psychosis, yet its mechanisms remain unclear. To adaptively move through the world, humans must balance two competing mnemonic processes: retrieval (i.e., accessing existing representations based on a reminder) and encoding (i.e., storing new information). While recent work has found an imbalance in retrieval versus encoding processes in subclinical paranoia, other studies show different patterns. To address these inconsistencies, we tested an alternate hypothesis: namely, that paranoia is associated with reduced sensitivity to contextual cues that adjudicate between retrieval and encoding modes of processing.

Methods: Guided by a preregistration (https://osf.io/wydvc), we administered a mnemonic discrimination task to 559 participants via Prolific (www.prolific.co). Following exclusions (including overall accuracy on the task, performance on attention checks, and response rates on critical test trials), this resulted in an unexcluded sample of 450 participants (achieving 86% power for the effect of interest). During this task, participants were shown a continuous stream of images which could be New (displayed for the first time), Old (identical to a previously displayed image), or Similar (only subtly different from a previously displayed image). For each image, participants indicated whether it was New, Old, or Similar using a keypress. In line with past work, we expected that participants would be more accurate at identifying Similar trials when they were preceded by New (versus Old) responses, consistent with the notion that the detection of novelty (versus familiarity) shifts the memory system away from a "retrieval mode" and towards an "encoding mode" of processing under which subtle differences are more likely to be detected. However, we expected that paranoia would be associated with a decrease in this novelty-induced performance boost. These hypotheses were tested using a mixed-effects logistic regression that modeled Similar trial performance (i.e., with 0 indicating an incorrect response; 1 a correct response) as a function of self-reported paranoia and preceding response type (e.g., Old or New).
Results: In line with our hypotheses, the logistic regression model revealed a statistically significant main effect of preceding response type, $z=-10.96$, $p<0.001$. The odds ratio for this effect was 0.71, 95% CI [0.67, 0.75], meaning that the odds of responding correctly to a Similar trial preceded by a response of "Old" was 0.71 times lower than that of a Similar trial preceded by a response of "New". This suggests that, overall, the detection of novelty conferred an advantage in identifying Similar trials. Critically, however, this model also revealed a statistically significant paranoia by preceding response type interaction effect, $z=2.49$, $p=0.013$. The odds ratio for this interaction term was 1.03, 95% CI [1.01, 1.05], indicating that for each unit increase in paranoia, the odds of responding correctly to a Similar trial preceded by a response of "Old" increased by 1.03 times relative to that of a Similar trial preceded by a response of "New". Put simply, this indicates that mnemonic discrimination among those higher in paranoia was less enhanced by the detection of novelty on a preceding trial.
Discussion: Rather than showing a systematic bias towards retrieval versus encoding processes, those higher in paranoia were instead less sensitive to the context created by a preceding response during mnemonic discrimination judgments. This suggests that paranoia-prone members of the general population may less readily use proximal cues to engage the competing hippocampal states thought to support retrieval (i.e., "pattern completion") versus encoding (i.e., "pattern separation"). This may fuel symptoms of paranoia by contributing to idiosyncratic interpretations that are out-of-sync with one's current context (e.g., retrieving paranoia-relevant representations in low-threat contexts).

F8. VOCATIONAL REHABILITATION AUGMENTED WITH COGNITIVE BEHAVIORAL THERAPY OR COGNITIVE REMEDIATION FOR INDIVIDUALS WITH SCHIZOPHRENIA: A 5-YEAR FOLLOW-UP STUDY

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Background: It is well documented that competitive work improves health and quality of life in people with severe mental illness (SMI) and that employment is a frequently stated goal. However, employment rates for this group remain low. Barriers to employment include illness-related factors such as neurocognitive impairments and psychotic symptoms, and external barriers e.g. stigma and welfare systems with high coverage and prolonged compensation. There is significant empirical support for the effect of vocational rehabilitation (VR) programs such as individual placement and support (IPS) in improving work outcome. Despite this, IPS may not always result in employment. Thus, augmenting IPS to address illness-related factors may optimize work outcomes. The Job management program (JUMP) study is a VR program in Norway for individuals with schizophrenia spectrum disorders in which VR was augmented with either cognitive remediation (CR) or elements from cognitive behavior therapy (CBT). The aim of this study is to explore 5-year follow-up registry data, specifically with regard to competitive employment outcome and predictors of competitive employment.

Methods: A total of 148 participants with schizophrenia spectrum disorders from six Norwegian counties received 10 months VR augmented with either CR (n = 64) or CBT (n = 84). Both competitive and sheltered workplaces were used in the process towards regular employment. Participants received the intervention by trained employment specialists, randomized to their catchment area twice a week over a 6-month period. Assessments were conducted at baseline, post intervention and 2-year follow-up. Data on employment status at 5-year follow-up was obtained by registry.

Results: At 5-year follow-up, 55.4 % were engaged in working activity, of whom 22.3 % worked competitively. A further 18.2 % had work placements in competitive workplaces. No statistical significant differences were observed in occupational outcome between CR and CBT for competitive employment, work placement or sheltered employment. However, the number of received intervention hours and competitive employment at 2-year follow-up emerged as significant predictors of competitive employment. IQ and intervention type in marginal favor of CBT were predictors on trend level.

Those competitively employed at 5-year follow-up displayed significantly higher IQ and GAF symptom scores compared to those who did not work competitively. Overall, there was also a significant difference indicating that those competitively employed at 5-year follow-up worked more hours per week at the end of the intervention period, and between the end of the intervention and 2-year follow-up

Discussion: To the best of our knowledge, this is the first study investigating competitive employment at 5-year follow-up for individuals with schizophrenia spectrum disorders. The current study identified that 55 % of the participants were in some form of employment five years after inclusion in the JUMP study and 22 % were competitively employed. This is slightly higher than at 2-year follow-up. Those who had worked the most early in the intervention period were also more likely to be employed at five-year follow-up. An important finding is that the amount of intervention provided was a key component for employment success. Participants working at 5-year follow up had, on average, received more intervention hours than those who were not

working. These findings add to existing evidence that individuals with schizophrenia spectrum disorders are able to both obtain and maintain competitive employment.

F9. METACOGNITION, SOCIAL COGNITION AND THE PSYCHOTIC CONTINUUM OVERTIME. PRELIMINARY FINDINGS OF THE SICILIAN GENETIC AND PSYCHOSIS (SGAP) FOLLOW-UP STUDY

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Background: Metacognitive bias, such as Jumping to conclusions (JTC), and social cognition impairment in the domain of emotion recognition are well-established features of psychosis, which are found at early stages of the disorder, at ultra-high-risk state, and in siblings of patients. Those biases are suggested as intermediate phenotypes of psychosis, thus they should be also found associated with core characteristics of the disorder in the general population. This study sought to test the association of jumping to conclusions and emotion recognition with subclinical psychotic symptoms and schizotypal traits in a sample of population-based controls, and testing these associations over a 8-year-follow-up period.
Methods: A sample of 15 population-based controls recruited from the SGAP case-control study were reassessed at 8-year-follow-up. Jumping to conclusions and Emotion recognition were measured at baseline using the Beads Task and the Degraded Facial Affect Recognition (DFAR) test respectively. Psychotic-like-experiences and schizotypy were assessed at baseline and 8-year-follow-up using CAPE and SIS-R. In STATA 15, non-parametric test Wilcoxon was used to test differences between the two measurements of CAPE and SIS-R dimensions over the two time points. Spearman correlation coefficient was estimated to test for association of baseline number of beads drawn (JTC) and DFAR scores with baseline and changing scores of CAPE and SIS-R.
Results: 7 males and 8 females participants, aged 39±12.2, were re-assessed after 7.8±1.2 years. CAPE scores differed between the 2 time points for total (0.8 vs. -0.5; z=2.3, p=0.02), negative (0.7 vs. -0.3; z=2.4, p=0.017) and depressive (0.8 vs. -0.4, z=2.6, p=0.009) scores, but not for positive dimension (p=0.33). No difference between baseline and follow-up were detected for both dimensions of SIS-R. Number of beads drawn positively correlated (correlation coefficients range 0.3 to 0.5) with SIS negative-disorganised, CAPE total, positive, negative, and depressive at baseline. A weak negative association was detected with SIS positive at baseline (r=-0.2). Moreover, the more the number of beads the lower the change scores at the negative dimensions (r=-0.6) of SIS and CAPE. DFAR total score at baseline positively correlated with both dimensions of SIS and CAPE negative at baseline (r=0.3), DFAR fearful score positively correlated with both dimensions of SIS (r=0.3), but negatively with CAPE positive (r=-0.3). Furthermore, DFAR angry positively correlated with negative dimensions of SIS (r=0.4) and CAPE (r=0.5). Change score at CAPE total negatively correlated with DFAR angry (r=-0.4) and positively with DFAR fearful (r=0.5), changes at CAPE negative negatively correlated with DFAR total (r=-0.5) and angry (r=-

0.6). Finally, DFAR fearful was negatively associated with SIS negative-disorganised change score (r=-0.4).
Discussion: Preliminary Results: suggest that schizotypal traits – as expected – are steady overtime, whereas subclinical psychotic experiences tend to decrease, especially for depressive and negative dimensions. In line with previous literature, jumping to conclusions and impaired recognition of negative emotions were associated with positive schizotypal traits and psychotic-like experiences. Interestingly, those biases are associated with changes of schizotypy and subclinical symptoms overtime, suggesting a potential predictive role for different trajectories even in non-clinical samples. Further research is warranted to investigate the role of metacognition and social cognition across the psychotic continuum overtime.

F10. NEUROBIOLOGICAL UNDERPINNINGS OF COGNITIVE SUBTYPES IN PSYCHOSES

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Background: Psychoses include patients with different characteristics, which may explain the lack of consistent replication of cerebral findings in disorders like schizophrenia and bipolar disorder. Studies aimed at identifying biotypes within psychoses, rather than comparing patients and healthy controls, may contribute to a better understanding of their underlying pathophysiological mechanisms, biomarkers definition, and the development of personalized treatments. In this line, recent studies support the identification of different patient's subgroups along the cognitive domain using cluster analysis. Our aim was to identify cognitive based subgroups within psychoses and to validate them assessing their relationship with demographic, clinical, and biological measurements. We hypothesized that subgroups characterized by different cognitive profiles would show differences in an array of biological data.
Methods: Cognitive data from 198 patients (127 with chronic schizophrenia, 42 first episodes of schizophrenia, and 29 with bipolar disorder) were analyzed by a K-means cluster approach. Cognition was assessed using the Brief Assessment of Cognition in Schizophrenia, also including percentage of perseverative errors in the Wisconsin Card Sorting Test. The resulting subgroups were compared on clinical variables, social cognition, modulation of electroencephalogram activity with a cognitive task, cortical thickness, functional networks of the electroencephalogram, and subcortical volumes. Data from 155 healthy controls were also included for further comparisons.
Results: The analysis yielded two subgroups based on their neurocognitive profile, including a severely altered group and a moderately altered group. The cognitive severely altered group was associated with higher illness duration and symptom scores, lower thalamus and hippocampus volume, lower frontal connectivity, and basal hypersynchrony in comparison to healthy controls and the cognitive moderately altered group. Both patients' subgroups showed lower cortical thickness and smaller functional connectivity modulation than healthy controls. Each diagnosis was represented in both clusters, although not evenly distributed.
Discussion: Our cluster analysis of cognitive data revealed a severely altered and a moderately altered subgroup across schizophrenia and bipolar disorder patients. The cognitive severely

impaired subgroup was associated with larger clinical, functional, and anatomical alterations compared to the moderately impaired subgroup. It is worth noting that subgroups did not group themselves based on diagnostic categories. This fact could help explaining the co-occurrence of functional and anatomical cerebral alterations in schizophrenia and bipolar disorder and the traditional lack of sensitivity and specificity to characterize these diagnoses. In conclusion, our Results: support the possibility of segregating at least two subgroups within de psychotic syndrome based on cognitive performance and with different biological underpinnings. Further studies in this line could help improving the definition of biomarkers and the development of personalized treatments for different psychotic subtypes.

F11. COGNITIVE PREDICTORS OF SOCIAL AND OCCUPATIONAL FUNCTION IN EARLY PSYCHOSIS: SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Many individuals with early psychosis experience impairments in social and occupational function. Identification of modifiable predictors of function such as cognitive performance has the potential to inform effective treatments. Our aim was to estimate the strength of the relationship between psychosocial function in early psychosis and different domains of cognitive and social cognitive performance.
Methods: We conducted a systematic review and meta-analysis of peer-reviewed, cross-sectional, and longitudinal studies examining cognitive predictors of psychosocial function. Literature searches
were conducted in PsycINFO, PubMed, and reference lists of relevant articles to identify studies for inclusion. Of the 2565 identified, 46 studies comprising 3767 participants met inclusion criteria. Separate meta-analyses were conducted for 9 cognitive domains. Pearson correlation values between cognitive variables and function were extracted.

Results: All cognitive domains were related to psychosocial function both cross sectionally and longitudinally. Importantly, these associations remained significant even after the effects of symptom severity, duration of untreated psychosis, and length of illness were accounted for. Overall, general cognitive ability and social cognition were most strongly associated with both concurrent and long-term function. Associations demonstrated medium effect sizes.
Discussion: These findings suggest that treatments targeting cognitive deficits, in particular those focusing on social cognition, are likely to be important for improving functional outcomes in early psychosis.

F12. ELUCIDATING ENVIRONMENTAL AND GENETIC IMPACT ON PSYCHOTIC-LIKE EXPERIENCES

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Background: Polygenic risk for schizophrenia as well as environmental factors like childhood trauma, urban-upbringing and neurodevelopmental factors are involved in the course and manifestation of the disorder. The interplay of those mediatory effects and their extent are still not fully understood.
Methods: We assessed polygenic risk score (PRS), childhood trauma, urban upbringing, cognitive capacity and psychotic-like experiences in a sample of 1419 healthy adolescents at the age of 19 taken from the cohort of the IMAGEN study. A multivariate mediation model testing the indirect effect of childhood trauma, urbanicity and cognitive capacity on the association between genetic risk for schizophrenia and psychotic-like experiences was calculated.
Results: We found a weak association between polygenic risk for schizophrenia and psychotic-like experiences. Childhood trauma showed a mediatory effect on the association between polygenic risk for schizophrenia and psychotic-like experience with the proportion mediated at 46% (bootstrapped 95% CI [30,59]), whereas urbanicity did not.
Discussion: This finding is crucial for the understanding of mental health problems in general and the implications for patients care as well as for political decisions on possible early intervention strategies.

F13. BEHAVIOURAL INDICATORS OF SUSCEPTIBILITY IN A RAT MODEL FOR SCHIZOPHRENIA

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Background: Exposure to infection in utero has been consistently linked with an elevated risk for neurodevelopmental disorders (NDDs) and other psychiatric illness including schizophrenia. Our group has developed a robust and reliable model of this risk in rats (maternal immune activation, MIA). As MIA does not elicit a 100% occurrence of NDDs, it is likely that it instead acts to prime adverse responses to postnatal stressors. We tested this two-hit theory using a model of material deprivation in early life to identify any synergistic effects on offspring behaviour with relevance to schizophrenia.
Methods: Female Wistar rats were time mated and injected i.p. with 10mg/kg of the viral mimetic poly(I:C) (Invitrogen, France) or vehicle (0.9% NaCl) on gestational day 15 to induce inflammation. Dams and litters were then reared in typical bedding conditions or with limited bedding and nesting (LBN). LBN litters were placed on a wire floor approx. 2.5cm above bedding material with the typical amount of nesting material from postnatal days 1-10. This resulted in four experimental groups: vehicle without stress, vehicle with stress, poly(I:C) without stress, and poly(I:C) with stress.
Litters were weighed on postnatal days 6, 10, and 14 to monitor body weight gain. Offspring of both sexes were tested on the elevated plus maze as juveniles or on a battery of behavioural tasks

(Novel Object Recognition [NOR], Open Field [OFT], Elevated Plus Maze [EPM]) in adolescence to monitor behavioural Results: of each insult individually or combined.

Results: Stressed offspring from vehicle-exposed litters and both poly(I:C) groups exhibited deficits in the NOR in adolescence. Vehicle-stress offspring still exhibited a familiarity preference, whereas both poly(I:C) groups had no preference for novel nor familiar items. Irrespective of prenatal treatment group, offspring exposed to postnatal stress exhibited significantly decreased time in the center of the open field, complemented by an increase in the time spent in the corners of the open field. Stressed male offspring also had a selective reduction in their locomotor behaviour, indicated through a reduction in the number of line crossings during testing.
In early adulthood (PD59-62), an interaction between offspring sex and stress status was identified for the amount of time spent in the closed arms, indicating reduced time for stressed females compared to all other treatments. We also noted a trend toward a sex*stress effect at this time point for the amount of time spent on the open arm.

Unbiased, two-step clustering Methods: identified three groups based on cognitive performance (D2). While the highest-performing cluster was made of approximately equal proportions of all four groups, the cluster of lowest performance only included offspring exposed to LBN, MIA, or both.

Discussion: Our findings illustrate a robust cognitive deficit elicited from both early-life stress as well as from prenatal inflammation. While there remains variability within each group, the use of unbiased grouping methods allows for better stratification in both the behaviour of the individual offspring and, potentially, the identification of molecular markers that may underpin the phenotype of relevance to NDDs as well as the intermediary "at-risk" phenotype.
Anxiety behaviours in both the OFT and EPM indicate a degree of sex-specificity. Some female offspring exhibited a resilience to the stressor in the OFT. Further, there is evidence of sex-specific reductions in anxiety behaviour in the EPM, suggesting a potential peripubertal adaptation of the glucocorticoid system in female offspring.

F14. COGNITIVE SCHEMAS IN POSITIVE AND NEGATIVE SCHIZOTYPY: A CROSS SECTIONAL DESIGN

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Background: Schizotypy is a set of traits associated with subthreshold psychotic-like experiences and is a potential precursor to the development of schizophrenia. The cognitive model of schizophrenia has provided valuable insights into the symptomology and treatment of this disorder, thus the application of this model to schizotypy is promising. Like in schizophrenia, schizotypal traits can be divided into positive and negative trait/symptom groups. Additionally, positive symptoms of schizophrenia (i.e., persecutory/referential thoughts) are thought to be associated with negative cognitive schemas about others, and negative symptoms with negative cognitive schemas about the self. Further, dysfunctional attitudes have also been shown to play an important role in the cognitive model as a potential mechanism for belief-maintenance. Negative cognitive

schemas and dysfunctional attitudes have yet to be fully empirically explored in schizotypy. The aim of the current study was to evaluate the relationships between schizotypal traits and types of cognitive schema, as well as whether these relationships are mediated by dysfunctional attitudes. Based on the cognitive model, primary hypotheses were that positive schizotypy would be positively related to negative schemas about other people, whereas negative schizotypy would be positively related to negative schemas about the self. Similarly, secondary hypotheses were that dysfunctional attitudes relating to self-performance would mediate the relationship between negative schizotypy and negative cognitive schemas about the self, while dysfunctional attitudes pertaining to approval by others would mediate the relationship between positive schizotypy and negative cognitive schemas about others.

Methods: In this cross-sectional study, 797 participants were recruited from a healthy sample and were given self-report scales including the Wisconsin Schizotypy Scales (WSS), the Brief Core Schema Scales (BCSS), and Dysfunctional Attitudes Scale Short Form (DAS-SF) divided using factor analysis by Cane (1986) into performance and approval-based attitudes. The BCSS has four subscales: negative self-schemas, positive self-schemas, negative other-schemas, and positive other-schemas. Primary analyses used two linear regressions for each positive and negative schizotypy in relation to all four subscales of the BCSS, while secondary analyses used two simple mediation analyses.

Results: Participants showed a representative demographic breakdown (Age= 16-77, M=32.21, SD=11.49; Gender= M=44.8%, F=54.6%). Positive schizotypy showed significant positive relationships with negative self-schemas (B=.117, se=.164, p=<.001), positive self-schemas (B=.060, se=.009, p=<.001), and negative other-schemas (B=.019, se=.007, p=<.001), but the relationship with positive other-schemas (B= -.016, se=.009, p=.07) was non-significant. Negative schizotypy showed significant relationships with negative self-schemas (B=.093, se=.012, p=<.001) and positive other-schemas (B=-.054, se=.010, p=<.001) but non-significant relationships with positive self-schemas (B=.010, se=.010, p=.319) negative other-schemas (B=.008, se=.008, p=.315). Dysfunctional attitudes about performance (B= .0163, CI95%=(.0070, .0264)) significantly mediated the relationship between negative self-schemas and negative schizotypy. Dysfunctional attitudes about approval by others (B= .0083, CI95%=(.0032, .0142)) significantly mediated the relationship between negative other-schemas and positive schizotypy.

Discussion: Evidence presented suggests that dysfunctional attitudes related to performance mediate the relationship between negative schizotypy and negative self-schemas and dysfunctional attitudes related to approval by others mediate the relationship between positive schizotypy and negative other-schemas. These findings support the application of the cognitive model of schizophrenia extending to schizotypy and point to potential underlying shared cognitive mechanisms of psychopathology. Implications of an extended cognitive model would bolster the conceptualization of schizotypy as a prodromal phase of psychosis and may highlight points of intervention and prevention.

F15. VIRTUAL REALITY FUNCTIONAL COGNITION ASSESSMENT IN PSYCHOSIS: VSTORE

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Background: Neurocognitive functions are characteristically impaired and strongly linked to functional outcomes in psychosis (Green at al, 2000). The importance of cognitive tests demonstrating a relationship to everyday functioning was emphasised by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) consensus conference (Green et al., 2004); and the Food and Drug Administration mandated the assessment of real-life functional change, alongside change in conventional cognitive performance (Buchanan et al., 2005). However, current measures do not fully meet these objectives. We developed an immersive virtual reality functional cognition assessment, VStore, to measure everyday functioning. The task is set in an ecologically valid minimarket environment, where participants are required to memorise and recall 12 grocery items; collect and pay for them at a self-checkout; and order a hot beverage from the coffee shop situated in the store. Previous findings showed that VStore has a similar construct to the MATRICS Consensus Cognitive Battery, tapping into cognitive domains impaired in psychosis (Porffy et al., 2021). In this study, the objective was to 1) establish VStore's sensitivity to classifying patients and thus provide a preliminary indication of its clinical utility, and 2) test whether it can predict outcomes on current standard functional capacity (FC) measures.
Methods: Twenty-six patients with a psychotic disorder (mean age = 40.7 ± 11.6 years, 6 female) and 26 age and gender matched healthy controls (mean age = 40.9 ± 11.6 years, 6 female) were recruited from South London. Both groups completed VStore and the Wechsler Abbreviated Scale of Intelligence (WASI) during a single study visit. In addition, patients' functional capacity was evaluated using the researcher-rated Global Assessment of Functioning (GAF) and Social and Occupational Functioning Assessment Scale (SOFAS), and the World Health Organization Disability Assessment Schedule II (WHODAS-II) self-report measure. The UCSD Performance-Based Skills Assessment Brief (UPSA-B) measuring communication and financial skills was also completed. VStore's sensitivity was tested using logistic regression. Clinical Status (1, 0) was entered as the dependent variable, and independent variables included main VStore performance outcomes: Clinical Status ~ Recall + Find + Select + Pay + Coffee. Youden's J statistic was used to establish the optimal threshold for sensitivity and specificity, and the area under the curve (AUC) and Akaike information criterion (AIC) were also calculated. Predictions of FC was assessed using linear regression: FC Score X ~ Recall + Find + Select + Pay + Coffee.
Results: Patients scored lower on the WASI (mean diff. = 23.1, $t = 7.464$, $p < .001$) and spent fewer years in education (mean diff. = 3.6, $t = 4.584$, $p < .001$) compared to controls. The logistic regression model predicting patient status achieved a sensitivity of 92.3% and specificity of 76.9% at the optimal threshold of 0.38, AUC = 88.9% AIC = 54.32. In addition, while VStore failed to predict functional outcomes as assessed by the WHODAS self-report measure and UPSA Communication sub-scale; models predicting the GAF ($F = 5.13$, $p = .003$, $R2 = .45$), SOFAS ($F = 4.30$, $p = .008$, $R2 = .40$), UPSA Finance ($F = 2.93$, $p = .033$, $R2 = .28$), and UPSA Total ($F = 2.66$, $p = .050$, $R2 = .24$) scores were statistically significant.
Discussion: These Results: show that VStore has a high sensitivity to determining patient status, supporting its utility in this disorder. In addition, VStore explains 24-45% of the variance in scores obtained from standard FC measures, indicating its suitability to evaluating everyday functioning. Further studies are needed to establish VStore's sensitivity to changes in functional cognition.

F16. CROSS-SECTIONAL ASSOCIATIONS BETWEEN ADAPTIVE FUNCTIONING AND SOCIAL COGNITIVE AND NEUROCOGNITIVE FUNCTIONS IN ADOLESCENTS WITH FIRST-EPISODE, EARLY-ONSET SCHIZOPHRENIA SPECTRUM DISORDERS

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Background: The functional prognosis of early-onset schizophrenia spectrum disorders (EOS) is heterogeneous: 60.1 % has a poor, 24.5% a moderate, and 15.4% a good outcome (Clemmensen et al., 2012). A substantial proportion of the variance of real-life functioning of young subjects with EOS is explained by processing speed, executive functions, social cognitive, and other cognitive functions (Hooper et al., 2010; Cervellione et al., 2007; Puig et al., 2012). The purpose of the current study was to further explore potential cross-sectional associations between adaptive functioning and cognitive functions in adolescents with first-episode EOS.

Methods: Adolescents (12-17 years of age) with EOS (N=59) and healthy controls (N=72) were characterized in terms of adaptive functioning (Vineland Adaptive Behavior Scale, Second Edition), neuro- and social cognition, positive symptoms, modified negative symptoms, and modified general symptoms. Multivariate analysis of variance followed by univariate analysis of variance assessed the between-group differences. Cognitive correlates of adaptive functioning to be included in the multivariate analyses were identified using bivariate analyses within the EOS group.

Results: Significant impairments in social- and neurocognitive functions and adaptive functioning were seen in the adolescents with EOS. Verbal working memory, visual memory, reaction time, processing speed, social cognition, and modified negative and general symptoms correlated significantly with the adaptive functioning. The multiple regression analysis revealed only verbal working memory as uniquely associated with adaptive functioning and this model explained 22.7 % of the variance of adaptive functioning. Verbal working memory associated significantly with adaptive functioning in the context of the significant general symptoms dimension and the non-significant modified negative dimension; this model explained 34.6 % of the variance of adaptive functioning.

Discussion: Adolescents with EOS show large impairments of adaptive functioning and moderate to large neuro- and social cognitive deficits. Verbal working memory is an important cognitive associate to concurrent adaptive functioning in the early illness phase. This suggests verbal working memory as a treatment target in future cognitive remediation trials to improve cognitive and adaptive functioning in adolescents with EOS.

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F17. PERINATAL EVENTS AND LIKELIHOOD OF PSYCHOTIC EXPERIENCES IN CHILDHOOD

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Background: There has been a long history of research on obstetric/gestational complications as risk factors for psychosis. A recent meta-analysis published in The Lancet (2020) found that certain complications such as maternal diabetes and fever were among the strongest perinatal predictors of subsequent psychotic disorder in the offspring (odds ratios >2.0). Our study investigated whether the total number of gestational complications were associated with psychotic symptoms in childhood (controlling for potential confounds). We also explored which, if any, specific gestational complication had the largest effect on psychotic symptoms.

Methods: The baseline data from the Adolescent Brain Cognitive Development (ABCD) study was used (mean age=9.9 years, SD=0.6; N=11,718). The study is a representative population-based cohort study of children in the United States. Parents completed a computerized Kiddie-Structured Assessment for Affective Disorders and Schizophrenia (KSADS 5). Children who met lifetime criteria for any psychotic symptom (hallucinations, delusions, associated symptom) or a diagnosis of Unspecified Schizophrenia Spectrum and Other Psychotic Disorder (F29) were classified as having psychotic symptoms (n=315). All others formed a control group (n=11,403). We used logistic mixed models (random effects for test site and family units) to test the effect of gestational complications (i.e. total number of complications; 0-13) on psychotic symptoms (1/0), controlling for sex, non-singleton birth, race/ethnicity, socioeconomic factors, familial psychiatric history and maternal substance-use during pregnancy (e.g. smoking).

Results: Gestational complications significantly increased the odds of psychotic symptoms in childhood (OR = 1.2, 95% CI = 1.1-1.3; p = .005). This means each additional complication was linked with a ~20% increase in the odds of symptoms. This effect was relatively unchanged by controlling for sex, non-singleton birth, race/ethnicity, socioeconomic factors, family history of mental illness/psychosis, parental history of mental illness/psychosis, and maternal substance-use during pregnancy.

Discussion: The robust effect of cumulative obstetric complication on psychotic symptoms is remarkable given the young age of participants at the time of assessment (age 9-10). The

independance of this effect from familial and parental mental health, as well as its independance from maternal substance-use during pregnancy, suggests that obstetric complications may be a partially modifiable risk factor in the development of psychosis. Limitations exist, particularly around the computerized (thus non-clinician led) version of the KSADS and to what extent it captures capture severity, persistence and distress around psychotic symptoms. At the very least, these findings are relevant to psychotic-like symptoms in children.

F18. SELF-COMPASSION, MINDFULNESS AND THEIR RELATIONSHIP TO DEPRESSION AND ANXIETY IN INDIVIDUALS DIAGNOSED WITH A PSYCHOTIC DISORDER

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Background: Self-compassion and mindfulness, constructs that have emerged from the contemplative traditions of the world, have been associated with positive psychological health, including lower levels of depression and anxiety in non-clinical populations. Depression and anxiety are common in psychotic disorders and contribute significantly to the overall burden of illness. This study sought to investigate the relationships among self-compassion, mindfulness, depression and anxiety in individuals diagnosed with a psychotic disorder. It was hypothesised that self-compassion and mindfulness would be negatively correlated with depression and anxiety in a sample of people diagnosed with a psychotic disorder.

Methods: 33 participants between the ages of 22 and 61 diagnosed with a primary psychotic disorder (DSM-5 criteria), were recruited from community mental health clinics in Halifax, Canada. Each participant completed the Self-Compassion Scale (SCS), Mindful Attention Awareness Scale (MAAS), Calgary Depression Scale for Schizophrenia (CDSS), and Beck Anxiety Inventory (BAI). Relationships among the scales were investigated using a series of Spearman correlations. Demographic variables were also collected. ρ represents the Spearman correlation coefficient and $p<0.05$ was considered statistically significant.

Results: Subjects were 67% male and 33% female. The mean age of participants was 40 years (SD 12.4). 52% of participants were diagnosed with schizophrenia, 42% with schizoaffective disorder and 6% psychosis not otherwise specified. The mean duration of illness was 12.35 years (SD 8.6) and mean number of hospitalisations due to psychosis was 4.5 (SD 3.5). Higher levels of self-compassion were associated with higher levels of mindfulness (ρ=0.71, p=0.00). Robust associations were found between self-compassion, anxiety and depression. Higher levels of self-compassion were associated with lower levels of anxiety (ρ=-0.70, p=0.00) and depression (ρ=-0.75, p=0.00). Various subscales of the SCS also correlated with anxiety and depression. The self-judgement SCS subscale was positively correlated with depression (ρ=0.56, p=.001) and anxiety (ρ=0.66, p=.00), whilst higher self-kindness was associated with lower depression (ρ=-.71, p=.00) and anxiety scores (ρ=-0.64, p=.00). The common humanity SCS subscale was negatively associated with depression scores (ρ=-0.45, p=.008). Higher levels of mindfulness were associated with lower levels of anxiety (ρ=-0.55, p=0.00) and depression (ρ=-0.47, p=0.00).

Discussion: Depression and anxiety can compromise recovery from psychosis. These data support the hypothesis and demonstrate that higher levels of self-compassion and mindfulness are related to lower levels of anxiety and depression in people diagnosed with a psychotic illness.

Interventions that enhance self-compassion and mindfulness, such as Mindfulness-Based Cognitive Therapy and Compassion Focused Therapy may be beneficial for those living with chronic psychotic disorders.

F19. LONELINESS AND SOCIAL SUPPORT IN YOUNG ADULTS WITH SUBCLINICAL PSYCHOTIC SYMPTOMS

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Background: Loneliness, a subjective experience that arises when one's desire for social relationships is not met, is one of the current public challenges, with a wide-reaching detrimental impact on mental health. Individuals with mental disorders such as anxiety and depressive disorders suffer from loneliness. However, individuals with psychotic disorders are particularly vulnerable, given the social problems they display. They often report poor social networks that are less interconnected and experience less social support. A systematic review has recently shown that in individuals with psychosis, loneliness may be influenced by factors such as increased depression and anxiety, poor social support, and more severe internalized stigma. Social problems often manifest themselves long before the first psychotic episode. Therefore, this study investigated loneliness and social networks in a community sample, linking the social measures to subclinical psychotic, depressive and anxiety symptoms. We predicted increased loneliness with higher psychopathology, especially with psychotic symptoms, and hypothesized that lower network density, less friends, less social support and increased stigma would moderate this association.

Methods: One hundred forty-four young adults, 46 male, mean age 21.6 (17-25 years) participated in this online study. Ego-centered networks were assessed, with the possibility of listing 10 connections. Network density was calculated as the number of unique links between these connections divided by the number of total possible links. Nature of the connection (partner, friend, classmate, neighbor) was asked and indicated. Psychopathology was assessed with CAPE for psychotic symptoms, and DASS-21 for depression, anxiety and stress. Loneliness was measured with RULS-8 and stigma with SSDS.

Results: Increased loneliness was associated with higher psychopathology, and this association was strongest for psychotic symptoms. Increased loneliness was associated with a smaller number of reported friends and with less social support, however not with network density or stigma. The number of friends decreased with increased psychotic, depressed and anxiety symptoms. Network density was not associated with symptoms, and increased support was only associated with lower psychotic symptoms. The association between loneliness and support was moderated by anxiety. The association between loneliness and psychotic symptoms was moderated by number of friends. Stigma was associated with psychotic symptoms, but did not moderate any of the associations.

Discussion: Mental health disorders are associated with increased loneliness. This study has shown that even in a subclinical community sample, loneliness is associated with increased symptoms. It is unclear whether increased symptoms lead to social withdrawal and loneliness, or whether loneliness increases symptoms. Either way, having friends and feeling supported is beneficial for mental health outcomes. Psychotic symptoms showed the strongest association, and

social support seems highly important for this pathology. Especially since psychotic symptoms inherently have social consequences, such as suspiciousness and withdrawal, and possible also because other people have less understanding for these symptoms (compared to anxiety and depression). The association with stigma suggests that individuals experience having symptoms as shameful and negative. Early detection of reduced social connectedness and embedding individuals with psychotic symptoms in a social supportive network may prevent the transition from subclinical to full-blown psychosis and increase mental health outcomes.

F20. THE EFFECT OF DEVELOPMENTAL TRAUMA ON MEMORY PROCESSING ACROSS THE PSYCHOSIS SPECTRUM: A SYSTEMATIC REVIEW AND META-ANALYSES

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Background: Developmental trauma increases the risk of psychosis. Memory impairments (such as working memory) have been consistently identified at both the onset of psychosis and within longitudinal studies of first-episode individuals (1). Impairments in episodic memory; a weakened ability to integrate incoming information, have been suggested in both psychosis and trauma models (2,3). Areas associated with memory performance, such as the hippocampus, have also shown structural and functional abnormalities in those with psychosis and PTSD (4,5). Therefore, one candidate mechanism underpinning the relationship between developmental trauma and psychosis is aberrant memory processing. We sought to systematically review studies measuring domains relevant to memory, including behavioural measures of memory function and brain areas key to memory processing. These impairments would be compared in those exposed to trauma with those not exposed to previous trauma in subgroups across the psychosis spectrum.

Methods: After pre-registering this study (PROSPERO REF: CRD42020221314), we systematically reviewed articles from EMBASE, PsycINFO, MEDLINE, OpenGrey, Google Scholar and PTSDpubs. We extracted data on domains of memory processing (like episodic and working memory) and hippocampal volume. Due to the heterogeneity of the studies, meta-analyses were conducted using multilevel random effect models to estimate effect sizes (Cohens d) and 95% confidence intervals.

Results: Of the 11,147 studies screened, 25 were included (10 cross-sectional, 12 case-control and 3 cohort studies; n=4085). Comparing trauma exposure vs non-exposure, exposure to trauma was associated with worse working memory (d=-.26, CI [-.04, -.47], p=.02) in people with psychosis. Working memory performance was worse in trauma-exposed individuals with first-episode psychosis (d=-.45, p<.01) and schizophrenia (d=-.20, p=.05), but not schizotypal disorder (d=-.55, p=.08). Episodic memory was worse in those exposed to trauma vs non-exposed across the psychosis spectrum (schizophrenia [d=-.15, p=.04], schizotypal disorder [d=-.98, p<.01], nonaffective psychosis [d=-.21, p<.01] and mixed phenotype psychosis [d=-.33, p<.01]). There was evidence that the FK506 gene variant reversed the association between trauma exposure and working memory (d=.16, p<.01) and episodic memory function (d=.11, p=.02) in those with psychosis. Survivors of sexual abuse with psychosis had significantly more intrusive memories than those without previous abuse (d=0.56, CI [0.03, 1.10], p=0.04). Regarding hippocampal

volume, trauma exposure was associated with reduced left hippocampal volume (d=-.40, CI [-.77, .03], p=.04).
Discussion: In this first meta-analyses to investigate the relationship between memory and trauma across the psychosis spectrum, we found that trauma exposure was associated with impairments in episodic and working memory across the psychosis spectrum. These findings suggests that memory may be a candidate mechanism involved in trauma-induced vulnerability to psychosis. Further work is needed to investigate these relationships and whether targeting the memory processing system is clinically effective in treating psychosis.

F21. NEUROCOGNITIVE AND SOCIOCOGNITIVE PROCESSES IN SCHIZOPHRENIA: ATTENTION AS A PREDICTOR OF INTENTION ATTRIBUTION

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Background: People with schizophrenia have shown deficits in social cognition processes, and these deficits are the most related to the functional outcome. Previous studies have considered neurocognition as necessary, but not sufficient to determine social cognition. Some neurocognitive processes have been reported as significant for social cognition (executive functions, memory, attention). The Theory of Mind (ToM) is the construct that defines the ability to infer emotions and intentions from others, which is a part of social cognition. Investigating the neurocognitive processes that are involved with social cognition is relevant to elucidate the neuropsychological processes in schizophrenia, and thus contribute to the development of more effective neuropsychological intervention strategies. The aim of this study is to identify neurocognitive and symptom influences in the ToM scores.
Methods: A neuropsychological assessment of 43 participants with a diagnosis of schizophrenia confirmed by the Structured Clinical Interview for DSM-5 (SCID-V) was conducted. The instruments used for the assessment were the Positive and Negative Syndrome Scale (PANSS) for dimensional assessment of symptoms, Wechsler Abbreviated Scale of Intelligence (WASI) to measure estimated intellectual functioning (eIQ), Psychological Battery for Attention Assessment (BAP), and Reading the Mind in the Eyes Test (RMET) to assess Theory of Mind. A multiple linear regression was conducted with Theory of Mind scores as dependent variable to assess the influence of attentional neurocognitive processes (BAP scores), symptoms (PANSS scores), age and intellectual quotient.
Results: After performing multiple linear regression, only attention was associated with RMET when controlled for eIQ, symptoms, sex and age. The Results: reveal attention as a significant predictor for ToM (β (SE), p = 0.450 (0.010), 0.007), in the model that includes estimated intellectual functioning (β (SE), p = 0.261 (0.060), 0.128), symptoms (β (SE), p = -0.037 (0.063), 0.812), male sex (β (SE), p = -2.259 (1.574), 0.161) and age (β (SE), p = -0.097 (0.060), 0.473). Regression analysis indicates Adjusted $R^2 = 0.405$, $F = 6.040$, $p < 0.001$.
Discussion: Neurocognition seems to be relevant to social cognition in schizophrenia, with the attention process associated with the Theory of Mind. Given this result, it is possible to suggest

that neuropsychological interventions oriented towards attentional processes, could contribute to the improvement in theory of mind performance and thus help in the functionality of people with schizophrenia.

F22. INTELLIGENCE TRAJECTORIES IN INDIVIDUALS AT ULTRA-HIGH RISK FOR PSYCHOSIS: AN 8-YEAR LONGITUDINAL ANALYSIS

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Background: Cognitive impairment is a well-documented predictor of transition to a full-threshold psychotic disorder amongst individuals at ultra-high risk (UHR) for psychosis. However, less is known about whether change in cognitive functioning differs between those who do and do not transition to a psychotic disorder. Studies to date have not examined trajectories in intelligence constructs (e.g. acquired knowledge and fluid intelligence), which have demonstrated marked impairments in individuals with schizophrenia.
Methods: This study aimed to examine intelligence trajectories using longitudinal data from three time points, spanning an average of eight years. Participants (N=139) at UHR for psychosis completed the Wechsler Abbreviated Scale of Intelligence (WASI) at each follow-up. Linear mixed-effects models mapped changes in WASI Full-scale IQ (FSIQ) and T-scores on Vocabulary, Similarities, Block Design, and Matrix Reasoning subtests.
Results: The sample showed stable and improving trajectories for FSIQ and all subtests, with no evidence of deterioration. There were no significant differences in trajectories between those who did and did not transition to psychosis and between individuals with good and poor functional outcomes. However, although not significant, the trajectories of the acquired knowledge subtests diverged between transitioned and non-transitioned individuals ($\beta=-0.12$, 95% CI [−0.29, 0.05] for Vocabulary and $\beta=-0.14$, 95% CI [−0.33, 0.05] for Similarities).
Discussion: We demonstrate that there is no evidence for deterioration in intelligence over a significant time frame in people identified as UHR for psychosis. However, there is a possible divergence in trajectory for some subtests between transitioned and non-transitioned individuals, suggesting a potential lag in developmental gains. As the small number of transitions may have limited our ability to detect subtle differences, future research with a larger sample size is needed.

F23. THE INFLUENCE OF GROUP PHYSICAL ACTIVITY ON EMPATHY, AFFECT AND STRESS IN INDIVIDUALS WITH SCHIZOPHRENIA SPECTRUM DISORDERS

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Background: There is evidence that physical exercise can reduce psychopathology and increase social functioning and social cognition in individuals with schizophrenia. Recent research also oberved a lack of empathy as part of social cognition in individuals with schizophrenia spectrum disorders (SSD). There are findings that a positive social setting can positively influence effects on empathy via endogenous oxytocin levels and that oxytocin is released through physical activity. The current study examined physical exercises in a group setting and its impact on empathy, affect and stress in individuals with a SSD.
Methods: Based on insight from preliminary studies and power calculations a cohort of 34 patients with a diagnosis of SSD was recruited at the Charité – Universitätsmedizin Berlin. Groups of up to six patients each underwent a supervised 20-minute guided physical activity session adapted to the needs of patients with SSD and focused on body tension and posture. Changes from baseline to post-intervention in empathy were measured as primary outcomes, and changes in affect and stress as secondary outcomes. Self- as well as rater-based psychometric questionnaires were used for the study. An ANCOVA design was performed to assess changes of the depicted outcomes while controlling for the severity of negative symptoms.
Results: Outcomes show that physical activity in a group setting significantly lead to a reduction of personal distress in the Interpersonal Reactivity Index (IRI) for empathy as well as to a significant reduction of general stress and symptom related stress. The patient group with high scores for negative symptoms experienced a larger reduction in general and symptom related stress. Additionally, a decrease of negative affect measured with the Positive and Negative Affect Scale (PANAS) was observed especially in the patient group with low negative symptoms.
Discussion: Findings provide a positive effect of physical exercises in a group setting for individuals with SSD. We could see a significant improvement in the condition of participants regarding stress and affect, after only a short intervention. Due to the ease of implementing group physical activities for individuals with a SSD, this therapy concept should be more integrated into the treatment. Future studies may explore physical activity as a therapeutic process by employing longer longitudinal designs. The inclusion of measurements of plasma oxytocin levels as a possible influencing factor is planned, as it has been shown that oxytocin levels correlate with empathy, are lowered in individuals with SSD and can be increased by physical activity.

F24. METABOLIC RISK IN EARLY-ONSET FIRST-EPISODE PSYCHOSIS: A 2-YEAR FOLLOW-UP STUDY

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Background: Patients with psychotic disorders show high risk of metabolic syndrome and cardiovascular disease, which are associated with 2-fold increased mortality rates relative the

general population. Some metabolic alterations could be present from the early phases of the disorder, even during the first episode of psychosis (FEP) and tend to progress over time. Young people with early-onset psychosis (i.e. onset of the first episode of psychosis before age 18; EOP) seem to be more sensitive to weight-related metabolic side effects than adult-onset cases. The aim of this work was to describe longitudinal anthropometric and metabolic changes during the first two years after a first episode of EOP and to identify putative predictors associated with weight gain during this period.

Methods: Longitudinal, naturalistic, 24-month prospective study including patients 8-18 years of age with a K-SADS confirmed diagnosis of a first episode of a psychotic disorder per DSM-IV-TR criteria with onset prior to 18 years of age and a group of healthy controls matched by age, sex, and socio-economic status. Anthropometric and metabolic parameters were evaluated at baseline and during a 24-month follow-up. Body mass index z scores (z-BMI) adjusted for age and sex were calculated. A categorical risk variable "At Risk for Adverse Health Outcome", defined as the presence of i) obesity or ii) overweight plus at least one related metabolic complication was also calculated. In the patient group, the association of demographic, premorbid, and clinical variables with 24-month longitudinal changes in BMI z-scores was tested using linear mixed model analyses.

Results: A sample of 112 patients with EOP (age 16.33 ± 1.49 years, 37.5% female) and 50 controls (age 14.54 ± 2.80 years, 44% female) was analyzed. At baseline patients showed significantly lower HDL cholesterol ($t = -3.44$, $p = .001$) and significantly higher triglyceride ($t = 2.33$, $p = 0.021$) levels than the control group. These differences remained significant in the 24-month follow-up visit ($t=-2.50$, $p=.014$ and $t=3.01$, $p=.003$, respectively). Patients showed a significantly greater increase in z-BMI than controls during the 24-month follow-up (0.71 ± 0.88 vs 0.01 ± 0.61, $t=4.82$, $p<.001$), with significantly higher BMI z-scores in patients than the controls in the 24-month visit (0.72 ± 1.41 vs 0.03 ± 1.10, $t=2.54$, $p=.013$). A significantly greater percentage of patients presented clinically significant weight gain during the 24-month follow-up (defined as an increase in z-BMI of ≥ 0.5; 57.7% vs 17.6%, $\chi^2 = 15.31$, $p<.001$). 22.9% of patients and 11.4% of controls were identified as being "At Risk for Adverse Health Outcome" in the 24-month follow-up visit ($\chi^2=2.06$, $p=0.151$). In the patient group, but not in the control group, increase in BMI z-scores was significantly associated with increase in HOMA-IR (Homeostatic Model Assessment of Insulin Resistance; $r=.389$, $p=.013$ and $r=.188$, $p=.329$, respectively). In the patient group, fully adjusted linear lineal mixed model analyses showed that higher scores in the academic subscale of the Premorbid Adjustment Scale in childhood, indicative of poor premorbid school performance before age 12 were associated with greater increase in BMI z-scores during follow-up ($F=5.60$, $p=.025$, explained variance: 0.18).

Discussion: This study suggests that some metabolic disturbances are present early during the illness course in EOP and that metabolic risk tends to increase during the first two years of follow-up due to clinically significant weight gain and an association between weight gain and an increased risk for insulin resistance. Consistent with previous studies in adult-onset samples, poor premorbid cognitive functioning may be associated with increased metabolic risk in first-episode early-onset psychosis. Identifying predictors of increased risk of metabolic complications in early-onset psychosis during the first years of the illness can facilitate the development of targeted preventive interventions and activities to improve prognosis.

F25. GENETIC AND STRUCTURAL BRAIN CORRELATES OF COGNITIVE SUBTYPES: A CLUSTER-BASED STUDY ACROSS YOUTH AT FAMILY RISK FOR SCHIZOPHRENIA AND BIPOLAR DISORDER

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Background: Cognitive impairment is a key feature of Schizophrenia (SZ) and Bipolar Disorder (BP) and an important determinant of psychosocial functioning. Severity across the two disorders is characterised by significant heterogeneity, which can be observed prior to illness onset and is considered to reflect different underlying disease trajectories. Cognition is amongst a number of potential transdiagnostic dimensions proposed as intermediate phenotypes, which are regarded as less complex compared to clinical constructs, such as SZ and BP, and more proximal to the underlying pathophysiology. We therefore grouped youth at family risk for SZ and BP based on cognitive function and examined the clinical, genetic and brain imaging correlates of cluster membership.

Methods: 160 participants, 32 offspring of patients with SZ (SZO), 59 offspring of patients with BP (BPO) and 69 offspring of healthy control parents (HCO), aged 6 to 17 years, underwent a clinical and cognitive assessment, genotyping and structural MRI. K-means clustering was used to group family risk participants based on measures of attention, processing speed, working memory, verbal memory, visual memory and executive function. Clusters were then compared in terms of cortical and subcortical brain measures as well as polygenic risk scores for SZ (PRS-SZ), for BP (PRS-BP) and for cognitive function (PRS-COG).

Results: Participants were grouped in three clusters, with intact, intermediate and impaired cognitive performance. Both family risk groups were represented in each of the clusters, yet not evenly, with a larger proportion of SZO in the impaired cluster but also a BPO representation. The intermediate and impaired clusters had lower total brain surface area compared to the intact cluster, with prominent localisation in temporal, parietal and frontal cortices. No between-cluster differences were identified in cortical thickness and subcortical brain volumes. The impaired cluster also had poorer psychosocial functioning and worse PRS-COG compared to the other two clusters and to HCO, while there was no significant between-cluster difference in terms of PRS-SZ and PRS-BP. PRS-COG predicted psychosocial functioning, yet this effect didn't appear to be mediated by an effect of PRS-COG on brain area.

Discussion: We for the first time employed a transdiagnostic risk approach and clustered youth at family risk for SZ and BP based on cognitive performance rather than parental diagnosis. Results:

supported a three-cluster solution, and similarly to what observed after illness onset, cognitive deficits of a similar magnitude were observed in both SZ and BP offspring, though in different proportions. This confirmed that more severe deficits are not specific to SZO but rather less frequent in BPO. The three clusters differed in terms of total brain surface area, with global findings reflecting significant differences in temporal, parietal and frontal regions. They also differed in terms PR-COG, which was significantly more disadvantageous in the impaired cluster, but not in terms of PRS-SZ or PRS-BP. Our Results: suggest that stratification based on cognition may help to elucidate the biological underpinnings of cognitive heterogeneity across SZ and BP risk.

F26. PERSISTENT CHILDHOOD AND ADOLESCENCE ANXIETY AND RISK FOR PSYCHOSIS: A LONGITUDINAL BIRTH COHORT STUDY

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Background: Persistent anxiety in childhood and adolescents could represent a novel treatment target for indicative prevention strategies for psychosis, potentially targeting activation of stress pathways, and secondary non-resolving inflammatory response. Here, we examined the association between persistent anxiety through childhood and adolescence with individuals who have psychotic experiences (PE) or who met criteria for a psychotic disorder (PD) at 24 years. We also investigated whether C-reactive protein (CRP) mediated any association.
Methods: Data from the ALSPAC cohort were available in 8242 children at 8 years, 7658 at 10 years, 6906 at 13 years, and 3889 at 24 years. The Development and Wellbeing Assessment (DAWBA) was administered to capture child and adolescent anxiety. We created a composite score of generalized anxiety at age 8, 10 and 13. Pes and PD were assessed at age 24, derived from the Psychosis-Like Symptom Interview. Additional features to meet criteria for PD were definite PEs not attributable to sleep or fever, having recurred regularly over previous 6 months, and being distressing or having a very negative impact. The mean of CRP at 9 and 15 years was used as mediator.
Results: We identified a group of individuals characterized by persistent high levels of anxiety, who were more to develop PEs (OR=2.02, 95% CI 1.26-3.23, p=0.003) and to meet criteria for PD at age 24 (OR=4.23, 95%CI=2.27-7.88, p<0.001). Finally, the mean of CRP at 9 and 15 years mediated the associations of persistent anxiety with PEs (bias-corrected estimate=-0.001, p=0.013) and PD at 24 years (bias-corrected estimate=0.001, p=0.003).
Discussion: Persistent high levels of anxiety through childhood and adolescence could be a risk factor for psychosis. Persistent anxiety is potentially related to subsequent psychosis via activation of stress hormones and non-resolving inflammation. These Results: contribute to the potential for preventative interventions in psychosis, with the novel target of early anxiety.

F27. NEUROCOGNITIVE DEVELOPMENT IN CHILDREN AT FAMILIAL HIGH-RISK OF SCHIZOPHRENIA OR BIPOLAR DISORDER – A FOUR-YEAR FOLLOW-UP STUDY IN PREADOLESCENCE. THE DANISH HIGH RISK AND RESILIENCE STUDY - VIA

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Background: Neurocognitive deficits across several domains are found in individuals with schizophrenia or bipolar disorder. These neurocognitive impairments have consistently been shown to have a profound impact on functional outcome, hence underscoring their clinical relevance. Research on first-degree relatives at familial high-risk of schizophrenia or bipolar disorder is a widely recognized study approach that offers a unique opportunity to investigate the etiology of the two disorders and identify early risk markers that precede illness onset. Evidence

from former familial high-risk studies suggests that offspring of individuals with schizophrenia or bipolar disorder exhibit the same pattern of neurocognitive impairments as adults diagnosed with the disorders, although with smaller magnitudes of impairments. There is, however, currently a lack of studies examining the developmental courses of specific neurocognitive functions during middle childhood. Therefore, the overall aim of the present study was to assess the development in neurocognitive functions from age 7 to age 11 in children at familial high-risk of schizophrenia (FHR-SZ) or bipolar disorder (FHR-BP) compared to population-based controls (PBC).
Methods: A total of 522 seven-year-old children were included at baseline in The Danish High Risk and Resilience Study, which is a prospective, longitudinal cohort study. Of these, 520 children (FHR-SZ n = 201, FHR-BP n = 119, PBC n = 200) underwent neurocognitive assessment. At four-year follow-up at age 11, 451 children (FHR-SZ n = 170, FHR-BP n = 103, PBC n = 178) were neurocognitively re-assessed. At both assessment points, children were examined with identical, validated neurocognitive tests covering general intelligence, processing speed, sustained attention, verbal and visuospatial memory, verbal fluency, set shifting, planning, and visual and verbal working memory. Multi-level mixed-effects linear regression models were applied to assess the development of neurocognitive functions from age 7 to age 11, and to assess between-groups differences at each assessment point.
Results: At age 7, age 11, or at both assessments, 520 children were neurocognitively assessed, and thus, included in the analyses. When correcting for multiple comparisons, we observed non-significantly different neurocognitive development from age 7 to age 11 across the three groups. At four-year follow-up, children at FHR-SZ were significantly impaired on seven of 24 neurocognitive measures compared to PBC. Compared with children at FHR-BP, children at FHR-SZ were significantly impaired on five of 24 measures. Children at FHR-BP and PBC did not differ significantly.
Discussion: Neurocognitive maturation is non-significantly different across children at FHR-SZ, FHR-BP, and PBC during middle childhood. Several neurocognitive impairments are detectable early in development in children at FHR-SZ and remain stable throughout middle childhood. Children at FHR-BP show neurocognitive functioning comparable to that of PBC at both age 7 and age 11. These findings indicate distinct neurodevelopmental pathways in children at FHR-SZ and FHR-BP with a more pronounced neurodevelopmental component in children at FHR-SZ. Such findings may have the potential to inform early intervention programs targeting cognitive impairments in children at FHR-SZ, since these impairments may be susceptible to remediation.

F28. SELECTION BIAS IN TRIALS OF PSYCHOTIC DISORDERS: EXPERIENCES FROM THE HAMLETT STUDY

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Background: Randomized controlled trials (RCTs) are considered the gold standard for assessing effectiveness of treatments. However, the generalizability of RCTs is limited. A factor contributing to non-generalizability is sampling bias, which is defined as non-random mechanisms causing members of the target population to be less likely included than others. It has been proposed to provide more in-depth data on the process of identifying possible participants before inclusion, as well as a description of participating centers and of the health care system in which the trial is carried out. The HAMLETT study (Handling Antipsychotic Medication Long-term Evaluation of Targeted Treatment) provides an instructive example of sampling processes. HAMLETT is an ongoing Dutch, multi-centre RCT investigating the effects of continuation versus early dose-reduction of antipsychotics after first-epiode remission. Here, we report on sources of sampling bias in HAMLETT.

Methods: HAMLETT includes participants who experienced a first psychotic episode, are remitted < 6 months, and use antipsychotics. Mandatory care or dangerous behavior during the psychotic episode are exclusion criteria. For this project, we assessed five potential sources of sampling bias: 1) Health care system in which the study is performed; 2) Participating centres; 3) Collaborating clinicians; 4) Screening process; 5) (non-)Consent.

Results: 1) Under the Dutch national healthcare system, all citizens have mandatory healthcare insurance, covering psychosis treatment. All citizens are associated with a general practitioner, through which access to specialized mental health care is provided. Sampling bias due to inaccessibility of mental health care is unlikely. 2) In HAMLETT, 26 mental health care institutes covering all major cities and provinces of the Netherlands participate, minimizing geographic sampling bias. 3) All professionals working in the participating institutes and involved in psychosis care have been extensively informed about the project. We found the screening process is critically influenced by opinions of local psychiatrists on reducing antipsychotics in general and per case, as well as the interpretation of exclusion criteria, i.e the 'dangerous behaviour' criterion. 4) Within each participating institute a 'dedicated includer' (often a psychiatric nurse) operating in collaboration with HAMLETT regularly checks eligibility of all patients with first episode psychosis. Identification is based on information provided by treating clinicians. Patients thus identified are considered eligible HAMLETT participants and the presence of in- and exclusion criteria are checked. Importantly, psychiatrists have the right to withhold consent to approach patients based on their personal professional judgment of the patients' suitability, apart from per-protocol criteria. 5) Finally, patients are contacted for information and subsequent informed consent.

2573 patients were considered as potentially eligible participants. Of those patients who were ultimately asked to consent, 40.9% agreed to participate in the study. Major sources for drop-out during the screening process were relapse of psychosis (16.5%), early discontinuation of antipsychotics (20.1%) and failure to establish contact with a potential participant (13.1%). Of all potential participants, 9.8% were eventually included in the study. Inclusion numbers between institutes: 35-1 (median 12).

Discussion: Of those subjects who were actually asked to participate some 40 percent agreed. We consider this a substantial number showing considerable willingness of patients to participate. Those who denied consent frequently reported objections against being randomized. Notwithstanding the success of the HAMLETT study to recruit participants relative to other dose reduction trials some 90% of the patients who were initially considered to be potential participants were not included in the HAMLETT study. Important sources of exclusion are the formal per-protocol criteria 'relapse of psychosis' and 'not using antipsychotics anymore' accounting for

some 37% of the drop-out during screening. We conclude that in- and exclusion criteria may profoundly influence the drop-out during screening and subsequently the validity of the findings. They should therefore be carefully assessed during study design and in any case should its influence on inclusion be reported.
We identified substantial variation in inclusion rates between institutes. Between institute variables greatly influences inclusion rates and may induce considerable bias in nationwide projects aimed to adequately represent the diversity of the patient population.

In spite of a high-quality study design considerable sampling bias seems to be an inevitable aspect of any RCT. We recommend that reporting factors that potentially affect sampling bias and thus generalizability becomes mandatory within CONSORT guidelines, with attention for characteristics of the healthcare system, inclusion numbers of participating centres, characteristics of professionals involved in the selection of eligible subjects, detailed screening process and an assessment of opinions toward research of patients requested to participate.

F29. CVL-231 AS A NOVEL POSITIVE ALLOSTERIC MODULATOR TARGETING M4 MUSCARINIC RECEPTORS: RESULTS: FROM A PHASE 1B TRIAL IN PATIENTS WITH SCHIZOPHRENIA

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Background: Previous studies have suggested that nonselective muscarinic receptor agonism can improve psychosis in schizophrenia; however, previously investigated agents were associated with gastrointestinal (GI) adverse events (AEs) likely related to peripheral muscarinic receptor nonselectivity.1,2 CVL-231 is a novel, highly selective, M4 muscarinic receptor positive allosteric modulator (PAM) in development for the treatment of schizophrenia. In Part A of a two-part, phase 1b, multiple-ascending dose trial (NCT04136873), no maximum tolerated dose was identified in participants with stable schizophrenia. Here, we describe the safety, tolerability, and pharmacodynamic (PD) Results: from Part B, the randomized, double-blind, placebo-controlled, parallel arm portion of the trial enrolling participants with acute schizophrenia.
Methods: Adult participants with a primary diagnosis of schizophrenia and a history of relapse and/or exacerbation of symptoms when not receiving antipsychotic treatment were eligible for Part B of the study if they were currently experiencing an acute exacerbation or relapse of symptoms within 2 months prior to screening. Additional eligibility criteria included a Positive and Negative Syndrome Scale (PANSS) score ≥80 and a Clinical Global Impressions Scale (CGI-S) score ≥4. Participants were randomized 1:1:1 to inpatient treatment with CVL-231 30 mg once daily (QD), CVL-231 20 mg twice daily (BID), or placebo for 6 weeks. Safety and tolerability were assessed using standard Methods:; extrapyramidal symptoms were assessed using clinical rating scales. PD

assessments included the change from baseline over time in the PANSS total score, PANSS subscale score, and the CGI-S score.
Results: Of 81 randomized and treated participants, AEs were reported by 29 (54%) receiving CVL-231 and 14 (52%) receiving placebo; headache was the most commonly reported AE (placebo, 26%; all CVL-231, 28%). Modest increases in supine blood pressure and heart rate observed with treatment initiation in the CVL-231 groups decreased over time, with no clinically meaningful difference vs placebo by end of treatment. Mean weight changes from baseline were similar across treatment groups. There was no indication of exacerbation of extrapyramidal symptoms. GI AEs occurred at a low frequency that was comparable across treatment groups (placebo, 15%; CVL-231 30 mg QD, 19%; CVL-231 20 mg BID, 7%). At week 6, patients treated with CVL-231 experienced significant reductions in PANSS total scores from baseline vs placebo at both the 30-mg QD dose (least squares mean [LSM] change from baseline, -19.5; difference vs placebo, -12.7; nominal p=0.023) and the 20-mg BID dose (LSM change from baseline, -17.9; difference vs placebo, -11.1; nominal p=0.047), with associated reductions across PANSS subscale scores. Clinically meaningful reductions in CGI-S were observed in both CVL-231 groups vs placebo at week 6, with significant LSM differences from placebo observed for the CVL-231 30-mg QD group (difference vs placebo, -0.89; nominal p=0.010). A greater proportion of participants receiving CVL-231 had ≥1-point improvement in CGI-S (30 mg QD, 59%; 20 mg BID, 56%) vs placebo (26%). Similar trends were observed with ≥2-point improvements in CGI-S with CVL-231 (30 mg QD, 30%; 20 mg BID, 26%) vs placebo (7%).
Discussion: These data support further investigation of the selective M4 muscarinic receptor PAM CVL-231 as a novel, once-daily treatment for schizophrenia without the need for titration and with an anticipated reduced side effect burden compared with currently available medications.

F30. ONE-YEAR REMISSION AND THE ROLE OF IMMUNOLOGICAL PARAMETERS AS PREDICTORS: A RANDOMISED TRIAL OF AMISULPRIDE, ARIPIPRAZOLE AND OLANZAPINE

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Background: The outcome of schizophrenia can be described in various ways. One of them is remission as described by the Remission in Schizophrenia Working group, based on the 6-month score of nine selected items from the Positive and Negative Symptom Scale. The role of the immune system in the course of schizophrenia is also gaining increasing interest. The aims of this study include the identification of the one-year remission rate using the remission criteria both with and without the time criterion. In addition, we aimed to find out if immunological parameters at baseline can predict the remission status at one year.
Methods: We used data from the BeSt InTro study, a 12-month prospective, randomized, rater-blind, head-to-head comparison of amisulpride, aripiprazole, and olanzapine. We had eight

assessment points and patients were recruited from three hospitals in Norway and one in Austria. We included patients having a diagnosis within the schizophrenia spectrum according to the ICD-10 diagnoses F20-29, excluding cases with the diagnosis F23 Brief psychotic disorder. Firstly, we identified the one-year remission status using the proposed symptom criteria, both with and without the time criterion of the absence of key psychotic symptoms for at least six months. We examined various demographic and clinical factors and their predictive value regarding remission status, by using t-test. We also measured various immunological parameters at all eight follow-up points: the cytokines interferon gamma, interleukin-1β, interleukin-2, interleukin-4, interleukin-6, interleukin-10, interleukin-12, interleukin-17A and tumor necrosis factor alpha, as well as the C-reactive protein (CRP). We then investigated if their baseline level could predict the one-year remission status.

Results: Data for 59 patients were available for analyses with the time criterion. We found that 17 (28.8%) were in remission at one year. The respective one-year remission rate without the time criterion was 55.1% (27/49 patients with data without the time criterion). None of the demographic parameters had a predictive value for remission at one year. We found that it was more probable to belong to the remission group for patients who had not tried any antipsychotic drugs previously ($p=0.003$) and for those with low negative PANSS subscores at baseline ($p=0.025$). When we analyzed the baseline values of the studied cytokines by a univariate t-test, none of them was significantly different between the two remission groups. This was also the case for CRP.

Discussion: The influence of the time criterion on the one-year remission rate is obvious. This underlines the need for a consensus on the remission criteria used in schizophrenia research, to make the outcome studies more comparable to each other. No prior use of antipsychotic drugs increased the probability of remitting at one year, a finding known from previous studies. High level of negative psychotic symptoms at baseline indicate non-remission at one year, which stresses the need for further research to increase treatment outcome for people with a high negative symptom load.

F31. EFFICACY AND TOLERABILITY OF CLOZAPINE IN AFRICAN-DESCENT PATIENTS: RESULTS: OF A SIX-MONTH, MULTINATIONAL OPEN-LABEL CLINICAL TRIAL

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Background: Although clozapine is the most effective antipsychotic for treatment-resistant schizophrenia, it is markedly underutilized, particularly in the African-American (AA) population. A major cause for clozapine underutilization in this population is low baseline absolute neutrophil counts (ANC), which are frequently secondary to Benign Ethnic Neutropenia (BEN). The AA population is at increased risk for BEN, because they have the Atypical Chemokine Receptor Gene -1 (Duffy null) "ACKR1-null" polymorphism, which leads to lower ANCs. Therefore, we conducted the current study to examine whether clozapine could be effectively and safely used in this population.
Methods: The study was a 6-month, open-label clinical trial of clozapine use in African-descent adult patients with schizophrenia spectrum disorders with or without the "ACKR1-null" genotype, conducted at two sites in the United States (Baltimore, MD; Washington, DC) and one in Lagos. Nigeria. We previously have reported ANC values by genotype, but here we report efficacy, plasma levels and side effects in this population. We evaluated psychiatric symptoms using the Brief Psychiatric Rating Scale (BPRS) and the Calgary Depression Rating Scale (CDS). Additionally, we measured extrapyramidal side effects (EPS), akathisia and tardive dyskinesia (TD) using the Simpson Angus Scale, Barnes Akathisia Scale, and the Abnormal Involuntary Movement Scale (AIMS), respectively. Genotype was determined using TaqManTM technology (Thermo Fisher Scientific, Waltham, MA USA).
Results: We enrolled 274 participants (150 US, 124 Lagos, Nigeria), of whom 227 (82.8%) completed 6 months of clozapine treatment. Forty-seven participants discontinued clozapine treatment: 14 from adverse events, 15 participant choice, 6 nonadherence, 2 lack of therapeutic response, and 10 lost to follow up/error/prescriber choice. There was one case of severe neutropenia (<500 cells/mm3) (0.36%). The mean stabilized dose was 271.9 ± 156.2 mg/day with a corresponding plasma level averaging between 300-350 ng/mL after week 8 in the study. There was a significant improvement in the total BPRS ($F=6.76$, df=6,237, $p<0.0001$) and the CDS ($F=2.98$, df=6,1117, $p=0.0068$) after 6 months. Overall, significant improvements were seen in positive symptoms and hostility on the BPRS, however, the Nigerian cohort had improvements in negative symptoms. Those with the ACKR1-null had significantly greater response in positive symptoms ($F=6.69$, df=1,226, $p=0.0103$) and hostility ($F=16.64$, df=1,236, $p<0.0001$) but no genotype by time interactions were noted. There was a significant decrease in akathisia, extrapyramidal side effects and tardive dyskinesia symptoms from baseline to endpoint. Rates of infection and fever were low, 2 cases of myocarditis were present (0.7%) and sialorrhea was the most common side effect (68%). Diastolic blood pressure, pulse and BMI significantly increased over time.
Discussion: To our knowledge, this is the largest prospective clozapine trial in African- descent patients. Severe neutropenia was very rare (0.36%), despite the expected occurrence of lower ANC and the high prevalence (80%) of the "ACKR1-null" polymorphism in this study. We observed a high retention rate while relatively low doses of clozapine were used. Significant improvements were noted in positive symptoms and hostility, while negative symptoms improved in the Nigerian cohort. Also, the genotype may play a role in clozapine response and more research is needed as this may serve as a responsive subgroup or biomarker for response. Clozapine is a safe and effective treatment option in African-descent patients with and without the "ACKR1-null" polymorphism, however this subgroup had the greatest clozapine benefit.

F32. REGIONAL DIFFERENCES IN NSA-16 FACTOR SCORES AT STUDY ENTRY. AN EXPLORATORY ANALYSIS

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Background: There is sparse literature delineating the impact of geography and culture on presentation of negative symptoms in clinical trials. The sixteen item version of the Negative Symptom Assessment (NSA-16) (Axelrod et al, 1993) is commonly utilized in clinical trials as a primary or a secondary outcome. In the current analysis we compared regional presentations of negative symptoms across using pooled baseline data from 5 clinical trials in subjects with prominent negative symptoms in schizophrenia.
Methods: Baseline NSA-16 data were obtained from 2,481 subjects. Given the countries of origin, 5 regions were defined (Asia; Eastern Europe, Western Europe, North America and South America). Individual NSA-16 factor scores were calculated using the Results: of factor analysis performed be Axelrod (Axelrod, 1993). For each factor separately we performed an analysis of variance (ANOVA) with post-hoc Bonferroni corrected head-to-head comparisons between individual regions.
Results: Significant regional differences were identified for every NSA-16 factor. The average Communication factor score was 12.5(SD = 3.2), with the lowest score that was significantly different from the remaining regions seen in Eastern Europe. The Emotion/affect factor score was 12.5 (SD=2.1) with North America and Eastern Europe having the lowest score. Both regions differed significantly from South America but not from the remaining regions. Social involvement factor score averaged to 13 points (SD=2.3) with Eastern Europe, North America and Western Europe having significantly lower scores compared to Asia and South America. The lowest score for the Motivation factor was found in Western Europe, significantly differing from both North and South America. The average Motivation score was 16.5 (SD = 2.7). Lastly, the average score for Retardation was estimated to 7.1 points (SD = 1.7). South America had the lowest scores, significantly different from all remaining regions, additionally Eastern Europe and North America had significantly lower scores than Asia.
Discussion: Our analyses identified significant regional differences in the severity of the individual NSA-16 factors at study entry. The differences were generally modest, and even in the most significant cases did not exceed a single point. Yet, summed together, they exceeded 2 points between some regions. With the exception of Retardation, subjects entering the trials in South America had one of the highest scores on all remaining factors. Similarly, subjects in Asia had constantly higher scores across all factors but Motivation. On the other hand, subjects entering in Eastern Europe had one of the lowest scores in all factors. One of the reasons for these differences could be explained by differences in symptom presentation or rather the 'visibility' of the symptoms against the reference heathy subject in their twenties. These observations are consistent with the notion that negative symptoms may be more apparent and therefore ratable in South America compared to say Eastern Europe. Other factors could contribute to the differences as well. For example, bias or measurement noise could have contributed to the differences. Additionally, one needs to assume differences between countries and most likely even between individual sites. Culturally sensitive rater training on the negative symptoms and continuous application of statistical data monitoring techniques should be employed in clinical trials to prevent and identify any worrisome differences between regions. Future analyses will assess whether change from baseline to endpoint differ between regions.

F33. BEHAVIORAL MAPPING OF PSYCHOMOTOR SLOWING IN SCHIZOPHRENIA

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Background: Psychomotor abnormalities are considered key features of schizophrenia and have been reported in every stage of the illness. One of these abnormalities is psychomotor slowing (PS), which affects up to 30 to 50% of patients with schizophrenia and which is associated with lower functioning, poorer treatment outcome, and higher cardiometabolic risks. However, PS in schizophrenia often goes unrecognized. Thus, we aimed at exploring motor behavior across multiple units of analysis in patients suffering from schizophrenia with and without PS and in healthy controls using expert-ratings, self-report questionnaires as well as objective instrumental measures. We also investigated the validity of these different measures compared to wrist actigraphy, which is the gold standard in PS evaluation.

Methods: We collected data on motor behavior of 56 slowed schizophrenia patients, 22 non-slowed schizophrenia patients and 42 healthy controls using two instrumental measures (i) wrist actigraphy, which assesses gross motor behavior for 24h and (ii) self-paced gait velocity using the GAITRite-carpet, in addition to (iii) an expert-rating using the motor items of the Salpêtrière Retardation Rating Scale (mSRRS) and (iv) a self-report, i.e. the International Physical Activity Questionnaire (IPAQ), which assesses activity levels during a week. We conducted a multivariate linear analysis using age as a covariate to compare the four motor measurements between the three groups (with PS, without PS and healthy controls). We also conducted partial correlation analyses between the four motor measurements in patients with PS controlling for age.

Results: There was a significant difference between groups on all four measures (mSRRS: $F(3) = 178.7$, $p < .001$; IPAQ: $F(3) = 5.4$, $p = .002$; actigraphy counts/day: $F(3) = 16.7$, $p < .001$; velocity m/s: $F(3) = 11.6$, $p < .001$). LSD post hoc analysis revealed that slowed patients had significantly lower activity levels and slower gait compared to non-slowed patients and healthy controls (all $p \leq .002$). Non-slowed patients and healthy controls did not differ regarding activity levels and gait velocity. The expert rating scale, mSRRS, indicated superior scores in slowed patients compared to the non-slowed patients and healthy controls, whereas the non-slowed patients also scored significantly higher than healthy controls (all $p < .001$). Finally, both the slowed and non-slowed patients reported less physical activity than healthy controls (all $p \leq .003$), however there was no significant difference between slowed and non-slowed patients ($p = .086$).

Spearman correlations within slowed patients indicated that activity levels measured by wrist actigraphy were highly correlated with mSRRS ($r = -.622$, $p < .001$), gait velocity ($r = .330$, $p = .014$) and IPAQ ($r = .309$, $p = .022$).

Discussion: Patients with psychomotor slowing had a unique set of motor measures spanning self-report, expert rating, and instrumental means. Actigraphy, the most sensitive measure was strongly associated with the expert ratings, self-report, and automated gait analysis. Thus, actigraphy might be a simple and effective tool aiding clinical routine assessment of PS severity.

F44. VALIDATION OF HUMAN FACTORS ENGINEERING FOR TV-46000, A LONG-ACTING SUBCUTANEOUS ANTIPSYCHOTIC (LASCA) AGENT CONTAINING RISPERIDONE IN A PREFILLED SYRINGE

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Background: The long-acting subcutaneous antipsychotic (LASCA) agent TV 46000 combines risperidone and an innovative, copolymer-based drug delivery technology in a suspension suitable for subcutaneous use. TV-46000 has demonstrated significantly prolonged time to impending relapse compared with placebo in patients with schizophrenia who underwent stabilization on oral risperidone. The TV-46000 prefilled syringe (PFS) combination product (including packaging, labeling, and instructions for use [IFU]) was developed and refined via human factors engineering. Several formative studies informed iterative design modifications. A simulated-use validation study was performed to evaluate tasks associated with use of the final drug-device combination product, with a focus on performance and knowledge of critical tasks.

Methods: All studies were conducted in environments that simulated healthcare settings. Healthcare professionals (HCPs; mental health nurses, psychiatrists, and retail pharmacists) selected TV-46000 doses based on simulated prescriptions and engaged in an injection scenario (ie, administering into an injection pad attached to a medical mannequin) to simulate first-time use of TV-46000. HCPs were not instructed to use the IFU, and use of the IFU was optional. Following these scenarios, HCP knowledge regarding storage, administration, and disposal procedures for the product was assessed through predetermined questions. HCP performance and knowledge were coded by trained moderators based on need for assistance, potential to cause harm, difficulty encountered, and accurate representation of real-world practices.

Results: Performance of critical tasks improved progressively throughout the studies, indicating that design changes – like including the addition of a syringe tag and quick tips regarding a critical use instruction – were effective. In the validation study, of the 23 participating HCPs (13 nurses, 4 psychiatrists, and 6 retail pharmacists), nearly all selected the appropriate dose of TV 46000 for each simulated prescription (prescription 1: 22/23; prescription 2: 23/23; prescription 3: 23/23). Most HCPs knew to administer TV-46000 subcutaneously (21/23), chose an appropriate injection site (abdomen or upper arm; 20/23), did not prematurely expel air from the PFS (17/23), and administered the entire dose by keeping the needle inserted for ≥2 seconds after pushing the plunger (17/23). All HCPs correctly placed the expended PFS into a sharps-disposal container (23/23), and most engaged the safety shield prior to disposal (19/23). A majority of HCPs moved the air bubble to the tip cap using the method outlined in the IFU (15/23), which is the only preparation step required prior to administration. The residual use-related risks have been reduced as far as possible through iterative user testing, cannot be reduced further, and are considered

acceptable in the context of the benefits of a long-acting medication that requires only a single administration once per month or once every 2 months.
Discussion: These Results: indicate HCPs were able to use the product successfully and had sufficient knowledge of critical tasks for the safe and effective use of the final TV-46000–PFS combination product in intended scenarios. Furthermore, compared with similar products, TV-46000 has only one preparation step (moving the air bubble to the tip cap) and does not require reconstitution, thereby reducing the opportunities for use errors.

F45. PREVENTION OF A FIRST PSYCHOTIC EPISODE THROUGH N-ACETYLCYSTEINE AND A SPECIALIZED PSYCHOTHERAPEUTIC INTERVENTION IN INDIVIDUALS AT HIGH RISK FOR PSYCHOSIS – A GERMAN MULTICENTER-STUDY

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Background: Prevention of a first psychotic episode in younger adults is an important pillar in early intervention for schizophrenia. In general, clinical high risk for psychosis (CHR) is often treated with low-doses of antipsychotic medication. Given that antipsychotic drugs bear strong side effects, however, and a considerable amount of patients fulfilling CHR criteria does not develop a psychotic episode, the search for compounds with fewer side effects holds high potential. Positive effects on various symptoms have been identified for well tolerated antioxidative substances as well as cognitive-behavioral interventions. In the present clinical trial our aim was to combine and compare the efficacy of both interventions.
Methods: In this multicentric double-blind randomized controlled trial (single-blind for the psychotherapeutic intervention) we employed a 2x2 factorial design to identify preventive effects of two interventions with (1) N-Acetyl-l-cysteine (NAC) and (2) integrated preventive psychological intervention (IPPI). N = 48 patients were recruited in nine facilities and followed a 26-week intervention period with a follow-up period of up to 12 months. Patients were randomly assigned to one of four arms (NAC vs. Placebo + IPPI vs. Stress management training). Primary endpoint was transition to psychosis after 18 months. Kaplan-Meier analysis and stratified Cox-regression were used to calculate survival-rate in both, treatment- and placebo-group. Social functioning and cognition were assessed as co-primary or secondary endpoints. Lastly, tolerability of the substance was assessed.
Results: The study was closed after a scheduled futility-analysis revealed insufficient statistical power due to lagging recruitment. Kaplan-Meier analysis showed n = 16 events for primary endpoints. There was a tendency towards better Results: for both interventions, however, no significant effects were found for either intervention. The occurrence of adverse events between

both groups did not differ significantly, which might indicate good tolerability among all patients. Analysis of secondary endpoints showed a strong tendency towards beneficial effects of NAC on social cognition.
Discussion: The Results: point towards usefulness of IPPI and NAC, however, they remain non-significant in light of the small sample size. Tolerability of NAC, however, could be established. As such, a follow-up trial employing a combination of IPPI and NAC might be beneficial and help find prevention strategies deviating from standard care with antipsychotic medication.

F46. THE POTENTIAL OF M1 AGONISTS TO TREAT COGNITIVE IMPAIRMENT: EVIDENCE FROM A PHASE 2 STUDY OF KARXT IN SCHIZOPHRENIA (EMERGENT-1)

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Background: The central cholinergic system plays a key role in cognition and has been the target of numerous drug development efforts, including cognitive impairment in Alzheimer's disease (AD) and schizophrenia. Acetylcholinesterase inhibitors are indicated for the treatment of cognitive impairment in AD, and development efforts have also directly targeted muscarinic acetycholine receptors, including M1, M4, or dual M1/M4 receptor agonists. In preclinical models, activation of M1 receptors enhance synaptic plasticity in both prefrontal and hippocampal circuits, whereas M4 receptor activators have potential antipsychotic effects and may also impact attention and memory. KarXT is an M1/M4 preferring central muscarinic agonist based on xanomeline. Xanomeline was previously shown to improve cognition in a Phase 2 trial in patients with AD and, in the recent phase 2 EMERGENT-1 trial, KarXT demonstrated meaningful reductions in the symptoms of schizophrenia compared with placebo. Here we present data from EMERGENT-1 (NCT03697252) on the impact of KarXT on cognition.
Methods: Cognitive performance was assessed using the Cogstate computerized cognitive battery in a randomized, double-blind, placebo-controlled, 5-week inpatient trial in patients (N=182) with schizophrenia experiencing acute psychosis. Participants (n=125) who had scores for all subtests of the Cogstate battery at baseline and endpoint were divided into 2 groups based on baseline cognitive impairment. Those performing >1 standard deviation below normative standards were designated as impaired and were compared to higher performing participants. Outliers with excessive variability in performance across subtests were identified by applying the 1.5 interquartile range rule for intraindividual variability (IIV). Analysis of covariance models assessed treatment effects for all completers and high and low impairment subgroups, with or without the removal of outliers. Linear regression was used to assess the relationship between cognitive performance and Positive and Negative Syndrome Scale (PANSS) scores.
Results: Among all participants, there was a nonsignificant treatment effect for KarXT (n=60) vs placebo (n=65), with greater improvement with KarXT (t=1.40, p=0.16, d=0.20). However, nearly half of all participants had low impairment and 8 subjects had excessive variability (IIV >2.4). Significant treatment effects were observed in the high impairment group, despite the smaller sample size (KarXT [n=23], placebo [n=37]; t=2.19, p=0.03, d=0.50), and in the entire sample

following outlier (n=8) removal (KarXT [n=54], placebo [n=63]; t=2.12, p=0.03, d=0.33). The relationship between cognitive improvement and change in PANSS total score was modest and consistent with prior Results: (β=0.29, P=0.002, R2=0.09).
Discussion: There was a significant benefit of KarXT compared with placebo, both when analyses were limited to impaired participants and those without with excessive baseline variability. In participants with higher cognitive impairments, KarXT was associated with larger treatment effects. Although these post hoc analyses must be interpreted with caution, the Results: presented here suggest that M1 and possibly M4 receptor agonists are a potential target for the treatment of cognitive impairment. Further development of KarXT and other similarly acting therapeutic agents for treatment of cognitive impairment in patients with schizophrenia seems warranted.

F47. THE EFFICACY OF TRANSCRANIAL MAGNETIC STIMULATION (TMS) FOR NEGATIVE SYMPTOMS IN SCHIZOPHRENIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Several trials have shown preliminary evidence for the efficacy of Transcranial Magnetic Stimulation (TMS) as a treatment for negative symptoms in schizophrenia. Here, we synthesize this literature in a systematic review and quantitative meta-analysis of double-blind randomized controlled trials of TMS in patients with schizophrenia.
Methods: MEDLINE, EMBASE, Web of Science, and PsycINFO were searched for sham-controlled, randomized trials of TMS among patients with schizophrenia. The standardized mean difference (SMD, Cohen's d) with 95% confidence intervals (CI) was calculated for each study (TMS vs. sham) and pooled across studies using an inverse variance random effects model.
Results: We identified 56 studies with a total of 2550 participants that were included in the meta-analysis. The pooled analysis showed statistically significant superiority of TMS (SMD=0.37, 95%CI: 0.23; 0.52, p-value <0.00001), corresponding to a number needed to treat of 5. Furthermore, stratified analyses suggested that TMS targeting the left dorsolateral prefrontal cortex, using a stimulation frequency >1 Hz, and a stimulation intensity at or above the motor threshold, was most efficacious. There was, however, substantial heterogeneity and high risk of bias among the included studies.
Discussion: TMS appears to be an efficacious treatment option for patients with schizophrenia suffering from negative symptoms, but the optimal TMS parameters have yet to be resolved.

F48. EFFICACY AND SAFETY OF BI 425809 IN PATIENTS WITH SCHIZOPHRENIA: CONNEX, A PHASE III RANDOMISED CONTROLLED TRIAL PROGRAMME

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Background: Cognitive impairment, a core feature of schizophrenia, is a major determinant of poor functional outcome in schizophrenia and no pharmacological treatments are currently available. Deficits in glutamatergic signalling play a key role in the neuropathology of schizophrenia, particularly in cognitive symptoms [1]. BI 425809, an inhibitor of glycine transporter-1, enhances N-methyl-D-aspartate receptor signalling in the brain by increasing synaptic levels of its co-agonist glycine [1]. A 12-week, Phase II, proof-of-clinical-concept trial (NCT02832037) that included 509 patients demonstrated BI 425809 was well tolerated and significantly improved cognition in patients with schizophrenia [2]. The Phase III CONNEX programme aims to confirm the efficacy, safety and tolerability of BI 425809 in improving cognition and functioning across a larger cohort of patients with schizophrenia.

Methods: The CONNEX programme consists of three replicate randomised, double-blind, placebo-controlled parallel group trials in patients diagnosed with schizophrenia (NCT04846868, NCT04846881, NCT04860830) on a stable phase of antipsychotic treatment. Each trial aims to recruit approximately 586 patients, 18–50 years old, treated with 1–2 antipsychotic medications (≥12 weeks on current drug and ≥35 days on current dose prior to treatment), who have functional impairment in day-to-day activities, and interact ≥1 hour per week with a designated study partner. Patients with cognitive impairment due to developmental, neurological, or other disorders, with a current DSM-5 diagnosis other than schizophrenia or receiving cognitive remediation therapy within 12 weeks prior to screening, will be excluded. Patients will be recruited from multiple centres across 32 countries in Asia, North and South America, and Europe, and randomised 1:1 to receive either BI 425809 10 mg (oral administration; n=293), or placebo (n=293) once daily over a 26-week period. The primary efficacy endpoint is change from baseline in overall composite T-score of the Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery (MCCB). The key secondary efficacy endpoints are change from baseline in total score on the Schizophrenia Cognition Rating Scale (SCoRS) and change from baseline in the adjusted total time in the Virtual Reality Functional Capacity Assessment Tool (VRFCAT). Long-term safety and tolerability data will be collected in an open-label safety extension study (CONNEX-X).

Results: The studies are currently recruiting (first patients enrolled Aug–Sept 2021), with completion expected in Q2 2024. As part of the presentation, an overview will be provided of the current study status, including any information relating to screening failures, and the experience of collecting these data as part of a large multi-country, multi-centre study.

Discussion: To date, most large, industry-sponsored studies testing various compounds to address cognitive function have failed to show proof-of-clinical-concept. Demonstration of efficacy of BI 425809 in treating cognitive impairment associated with schizophrenia in this Phase III programme would provide important insight into the role of glutamate in cognitive symptoms, that may also have relevance for other cognitive disorders. BI 425809 may represent the first efficacious medication for cognitive impairment associated with schizophrenia.

F49. DEVELOPING MULTIMODAL OUTCOME PREDICTION MODELS FOR PATIENTS IN CLINICAL HIGH-RISK STATES FOR PSYCHOSIS

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Background: Transition to psychosis and long-term functioning are both important outcomes for the Clinical High Risk for Psychosis (CHR) population. Predicting those who are most at risk of poor outcomes will allow earlier intervention and treatment. Several potential biomarkers and signatures have been suggested from sociodemographic, clinical, genetic, neuroimaging, cognitive and blood biomarker data, but many of these make for poor prediction models individually. Since psychotic disorders are governed by complex interactions between neurobiological, psychological and environmental factors with each conferring only a small increase in risk, combining these risk factors into one model may improve predictive accuracy. Novel machine learning techniques allow features from different modalities to be integrated into multimodal prediction models.
Large CHR datasets such as EU-GEI, PRONIA and NAPLS-2 provide large volumes of data for multimodal analysis. However, the complexity of the analysis is also significantly increased. Current multimodal prediction models use a variety of different modelling strategies and feature selection methods which makes replication challenging and risks introducing bias.

We propose two approaches for feature selection: a literature-based approach where only features strongly backed by literature are used, and a data-driven approach using all available data. Using the EU-GEI dataset, we will build multimodal models using these two approaches and compare their predictive ability. To our knowledge, this is the first time that literature-based and data-driven multimodal models will be compared in a CHR dataset.

Methods: The CHR sample (n=344) was taken from Workpackage 5 of the EU-GEI (EUropean network of national schizophrenia networks studying Gene-Environment Interactions) study. The transition rate was 19% (n=65). We will use the baseline clinical, sociodemographic, environmental, structural MRI, genetic, and cognitive data to build unimodal and multimodal machine learning models using NeuroMiner software. Outcomes are transition to psychosis as

measured by the CAAARMS and functional outcome as measured by the GAF one year after baseline.
For the preliminary results reported below, we use a data-driven approach to demonstrate our methodology with a subset of sociodemographic and clinical variables. The Support Vector Elastic Net algorithm was used to predict transition and Support Vector Regression to predict global functioning outcomes. A 5x5 cross-validation structure was used. Separate models were produced for the sociodemographic and clinical domains. These domains were then combined to produce a multimodal model using an ensemble-based data fusion approach. Model performances are measured by Balanced Accuracy (BAC), sensitivity and specificity.

Results: In our preliminary results, transition was predicted by clinical (BAC=58.6%) but not sociodemographic data (BAC 50%). The combined sociodemographic-clinical model predicted transition with a higher BAC (60.1%).
Global functioning was weakly predicted by clinical data (55.7%) but not sociodemographic data (BAC=46.7%). The combined model did not predict functioning (BAC=50.9%).

Discussion: Our preliminary Results: demonstrate how combining different data domains may improve prediction, even when the models alone do not predict. Including other data domains is likely to improve predictive ability if the other data domains provide additional information about the disorder. However, it is clear that this is not always the case, as seen in the results for functioning. It is our hope that comparing different multimodal approaches will guide future analysis in large psychosis datasets.

F50. 'MACHINE LEARNING-BASED IDENTIFICATION OF SUICIDE RISK IN SCHIZOPHRENIA BASED ON MULTI-LEVEL RESTING-STATE FMRI FEATURES'

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Background: Current research suggests that as much as 40% of all death causes among schizophrenia patients can be attributed to suicide. Thus, there is a vital need for objective and reliable Methods: to predict the suicide risk among schizophrenia patients based on biological measures that could also be considered neuromarkers of schizophrenia. Resting-state fMRI captures as much as 60-80% of brain total activity. Studies using resting-state fMRI demonstrated changes in the regions included in Default Mode Network (DMN), Salience Network (SN), and Sensorimotor Network (SMN) in schizophrenia patients. Recently, a growing number of machine learning (ML) algorithms were applied to resting-state fMRI data in order to make a prognostic evaluation and differential diagnosis. However, none of the studies focused on various ML classifiers based on rsfMRI data in order to discriminate between suicidal risk (SR) and non-suicidal risk (NSR) schizophrenia patients, and healthy controls (HC).
Methods: Fifty-nine participants including schizophrenia patients with (n=20) and without suicide risk (n=19), as well as age and gender-matched healthy controls (n=20) underwent 13 min resting-

state fMRI using a 3-T Siemens Skyra MR System. Anatomical images were obtained using sagittal 3D T1-weighted MPRAGE sequence with TR = 2,300 ms and TE = 3.9 ms.
Static and dynamic indexes of the amplitude of low-frequency fluctuation (ALFF), the fractional amplitude of low-frequency fluctuations (fALFF), regional homogeneity (ReHo) and functional connectivity (FC) were calculated. Then we the aforementioned indexes as input for five machine learning algorithms: Gradient boosting (GB), LASSO, Logistic Regression (LR), Random Forest (RF) and Support Vector Machine (SVM).

Results: Differences in rsfMRI measures: no differences were found among the three groups in static ALFF, fALFF, and ReHo. No significant differences were found in the case of temporal variability of ALFF, fALFF, or ReHo either. However, all three groups differed in FC among ventral DMN ($F = 19.02$; $p < 0.001$) and anterior SN ($F = 6.85$; $p = 0.001$), but not among dorsal DMN, posterior SN, or SMN. Temporal variability of FC demonstrated that all three groups were significantly different ($p<0.001$) in total FC variability measured with AAL and Power atlases. FC variability was significantly different between SR and NSR, between SR and HC, and between NSR and HC.
Classification results: three out of five variants of ML algorithm and rsfMRI measures turned out to be significant at $p < 0.05$. The best performance was reached for the LASSO applied to FC with an accuracy of 70% and AUROC of 0.76 ($p < 0.05$). The LR algorithm applied to dynamic ALFF with AAL atlas reached an accuracy of 65% and an AUROC of 0.75. (3) The GB algorithm applied to static fALFF with AAL atlas reached an accuracy of 65% and an AUROC of 0.74. It can be seen that AUROCs of the majority of variants were at chance level, even when accuracies were above 50%.

Discussion: The present study is the first and successful attempt to find rsfMRI features that allow detecting the risk of suicide of schizophrenia with the use of ML algorithms. Its Results: are in line with previous findings pointing to frontal and temporal brain regions alterations to be characteristic for suicide risk, and to studies that underscore the role of ACC, angular gyrus, precentral and postcentral gyrus in understanding suicidal behavior. Both ACC and PFC, responsible i.a. for anticipating the consequence of actions and inhibition of inappropriate behavior, are included in DMN and SN. Thus, our findings suggest that suicidal risk in schizophrenia can be seen on the level ofnDMN and SN functional connectivity alterations.

F51. SYMPTOM DIMENSION PROFILES IN PATIENTS WITH SCHIZOPHRENIA ARE ASSOCIATED WITH GENETIC RISK FOR THE DISORDER

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Background: Previous reports associated genetic risk for schizophrenia with inter-individual differences in symptom severity across patients. However, symptom severity varies over time, hindering the association between genetic risk and psychopathological dimensions. We hypothesized that multivariate dimension evaluations could be more stable over time and characterize patient clusters based on symptom patterns. We then associated the identified clusters with genetic risk for schizophrenia to address the role of genetic variation in clinical presentation of patients.

Methods: We assessed Positive And Negative Syndrome Scale (PANSS) in 1749 patients with schizophrenia of Caucasian ancestry from Bari (201), Brescia (121), Italian Network for Research on Psychosis (NIRP; blood sample: 276; saliva sample: 165), CATIE (270), Oslo (215), Munich (377) and Dublin (124) after at least 2 weeks of stable treatment with antipsychotics. Consistent with earlier studies, a two-fold cross-validated factorization approach identified five symptom factors, largely overlapping with positive, negative, mood, hostility, and cognitive domains. A K-means clustering of patients based on these factors identified four psychopathological clusters. CATIE longitudinal evaluations served to assess cluster membership stability over time measured in terms of Jaccard Index (JI = intersection/union of the clusters considered). We computed PGC2 individual polygenic risk score (SCZ-PRS) for non-PGC2 sites (Bari, Brescia, NIRP; N=762) and explored the association with clusters via ANCOVA. Finally, we computed a metanalytic logistic regression to discriminate patient clusters based on the SCZ-PRS across CATIE, Oslo, Munich, and Dublin sites (N=986) using PGC2 leave-site-out summary statistics.

Results: We identified 4 clusters of patients with 1) overall severe, 2) overall mild, 3) predominantly negative and 4) predominantly positive symptoms. Cluster membership was stable over time (cluster-1-JI[T3,T6, T9]: 0.4,0.27,0.20; cluster-2-JI[T3,T6, T9]: 0.4,0.36,0.29; cluster-3-JI[T3,T6, T9]: 0.58,0.48,0.39; cluster-4-JI[T3,T6, T9]: 0.35,0.21,0.24; all membership confirmation empirical-p[T3,T6,T9] < .05). For comparison, when considering membership to Positive or Negative symptoms quartiles (P and N scales of the PANSS), only the mildest and the most severe quartiles were confirmed after 6 and 9 months.

SCZ-PRS was significantly different between clusters (N=762, F[3,740]= 2.86, p=.036). Specifically, the predominantly positive cluster had lower SCZ-PRS than all others (N=762, F[1,742]=6.78, p=.009, Nagelkerke pseudo-R2=.012). We replicated this genetic association in the metanalysis of the European PGC2 sites (Oslo, Munich and Dublin) (estimated effect [90% CI]= -0.18[-0.33,-0.02], average Nagelkerke pseudo-R2=.016). However, the replication was not significant when including the American CATIE site in the metanalysis (estimated effect [90% CI]=-0.07[-0.30,0.15], average Nagelkerke pseudo-R2=.012).

Discussion: Multivariate clustering techniques applied to psychopathology provided a description of dimensional profiles relatively stable over 9 months and more consistent over time than PANSS dimension-based evaluations. Such clinical heterogeneity was associated with genetic heterogeneity within a European ancestry multi-site cohort but did not replicate into a cohort recruited outside Europe. The lack of replication in this site might reflect both population

stratification or clinical heterogeneity not captured by our clustering technique. Nonetheless, our findings suggests that the heterogeneous clinical presentation of patients with schizophrenia may reflect in part genetic heterogeneity.

F52. EARLY AND LATE ADMINISTRATION OF LONG-ACTING INJECTABLE ANTIPSYCHOTIC AGENTS AMONG PATIENTS WITH NEWLY DIAGNOSED SCHIZOPHRENIA: AN ANALYSIS OF A COMMERCIAL CLAIMS DATABASE

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Background: Long-acting injectable antipsychotic agents (LAIs) have demonstrated improved clinical effectiveness and adherence versus oral antipsychotic agents; however, LAIs are only used in a minority of individuals with schizophrenia (SCZ). Using a United States-based commercial claims database, this study evaluated treatment patterns and healthcare resource utilization (HCRU) and costs among patients with newly diagnosed SCZ treated with atypical LAIs early versus late after diagnosis.

Methods: Patients with newly diagnosed SCZ were identified using claims data from January 2013 and September 2019 from the IBM® MarketScan® Commercial and Medicare Supplemental databases. Key eligibility criteria included first diagnosis of SCZ in study period (index date), identification of first LAI administration, aged 18–40 years, no SCZ diagnosis and no LAI or oral antipsychotic claims during 12-month pre-index period, and continuous enrollment in the insurance plan from 12 months before index date through 12 months after first LAI administration (<30-day gaps allowed). Patients were grouped based on the timing of their first LAI administration: early (≤1 year after index date) versus late (>1 year after). Outcomes included proportion of patients with successful LAI implementation (≥90 days of continuous treatment with ≤7-day gaps), time to successful LAI implementation, proportion of patients with ≥1 SCZ-related hospitalization or emergency room (ER) visit prior to LAI initiation, and SCZ-related HCRU and costs ($2020 US) within 12 months after first LAI administration. All outcomes were examined descriptively.

Results: Of 1290 adult patients with SCZ and ≥1 LAI claim, 306 met eligibility criteria. Of these, 204 and 102 were in the early LAI and late LAI groups, respectively. Most patients were male (early, 77.0%; late, 82.4%); mean (SD) age was 23.3 (4.57) and 23.9 (5.90) years. The most frequently administered first LAIs were paliperidone (early, n=115 [56.4%]; late, n=59 [57.8%]), aripiprazole (n=46 [22.6%]; n=33 [32.4%]), risperidone (n=39 [19.1%]; n=8 [7.8%]), and olanzapine (n=4 [2.0%]; n=2 [2.0%]). Proportions of patients with successful LAI implementation were 53.9% and 48.0%. Median (IQR) times to successful LAI implementation were 177 (153)

and 184 (237) days. A higher proportion of patients in the late group experienced an SCZ-related hospitalization or ER visit prior to LAI initiation vs those in the early group (early, n=107 [52.5%]; late, n=75 [73.5%]). Mean (SD) SCZ-related HCRU and costs were lower in the early LAI group compared with the late group for ER visits (0.1 [0.5] vs 0.2 [0.7]; $140.50 [$661.25] vs $173.21 [$610.08]) and other outpatient visits (3.2 [9.1] vs 4.0 [12.9]; $1375.34 [$3774.01] vs $2373.01 [$8817.03]), and greater for office visits (4.3 [8.9] vs 3.7 [6.1]; $1219.86 [$4965.38] vs $1061.05 [$3972.94]). Antipsychotic prescription utilization (4.7 [7.2] vs 5.4 [7.5]) was lower in the early group vs the late group, while costs were comparable ($1375.34 [$3774.01] vs $1365.61 [$2538.26]); hospitalizations (0.2 [0.6] vs 0.2 [0.6]) were comparable between groups, while costs were lower ($3213.04 [$10,306.76] vs $4417.01 [$17,041.44]) in the early group compared with the late group. Mean (SD) total costs of SCZ-related healthcare after 1 year were $7088.91 ($13,753.61) and $9389.94 ($20,792.25).
Discussion: A greater proportion of patients with SCZ who received an LAI within 1 year of diagnosis achieved successful LAI implementation (53.9%) compared with those who received an LAI later than 1 year after diagnosis (48.0%). SCZ-related HCRU and costs among patients with early LAI administration was generally less than those with late LAI administration.

F53. USING COGNITIVE FEATURES TO DISTINGUISH FIRST EPISODE PSYCHOSIS PATIENTS, UNAFFECTED FAMILY MEMBERS AND HEALTHY CONTROLS: A GRAPH THEORETICAL APPROACH

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Background: Cognitive deficits are among the core features of schizophrenia. They are evident as early as in the first-episode and may also occur in the family members to some extent. However, the relationship between the cognitive features in schizophrenia patients, and how these relationships differ from their healthy family members and healthy controls without family history are not clear. Our aims in this study are (a)to generate cognitive graphs of the patients with first episode psychosis (FEP), healthy siblings and healthy controls without family history, based on Gaussian Markov random fields theory and (b) to examine whether these cognitive graphs can be to used to differentiate between individuals in the 3 groups.
Methods: The current study is part of an ongoing research study on FEPs at Istanbul Faculty of Medicine Psychotic Disorders Research Program, in collaboration with the University of Alberta. This study included 48 patients with FEP, 30 unaffected siblings and 35 age-, education- and gender-matched healthy controls without family history of psychiatric disorders. FEP subjects were recruited during a clinical stability period after the first psychotic episode. We assessed all siblings and healthy controls with SCID-I and included those who were not diagnosed with any psychiatric disorders. A cognitive test battery containing The Rey Auditory Verbal Learning Test, Stroop Test, Wisconsin Card Sorting Test, The Digit Span Test and Trail Making Test A/B was

applied to all subjects. Binary classifications were carried out by using cognitive features. We modeled the relationships among these cognitive features for the three different groups: FEP, siblings and healthy controls, using graphical LASSO (G-LASSO). Further, to estimate the classification capabilities of such cognitive graphs, we used 5-fold cross validation for 3 binary classification tasks: FEP vs healthy controls, FEP vs siblings and siblings vs healthy control. Here, we computed the likelihood of a test subject to each graph that was learned from the training split, and classified them to the group with higher likelihood.
Results: Using cognitive data, the learned G-LASSO model could discriminate between the individuals with FEP versus healthy controls with an average accuracy of 81.1%. With the same method, unaffected siblings vs healthy controls classification produced an average accuracy of 77.8%, and FEP and siblings classification produced an average accuracy of 63.2%. Trail Making B Test time appeared as a central node for all three groups. Cognitive graphs of both FEP and unaffected sibling groups had about three times more connections compared to those of healthy controls. Although FEP and unaffected siblings appeared to have a similar number of connections and 72.2% of these connections were shared between the two groups, 77.9% of the shared connections were stronger in unaffected sibling group compared to FEP.
Discussion: G-LASSO method can learn models that can effectively use cognitive graphs produced by using cognitive assessment scores to distinguish patients with FEP and their unaffected siblings versus healthy controls. At individual level, cognitive graphs of healthy siblings appear to be closer to that of FES patients than of healthy controls.

F54. BRAIN CONNECTIVITY ABNORMALITIES IN SCHIZOPHRENIA: A LONGITUDINAL STUDY

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Background: Schizophrenia is a mental illness, characterized by profound disruption in cognition and emotion. It affects about 1% of the population and is often described as a dysconnection syndrome1. The major symptoms of schizophrenia are traditionally divided into positive and negative symptoms. At the neural level, the mechanisms underlying schizophrenia are still unclear, but it is associated with altered dysregulations of neurotransmitters and dysfunctional network connectivity. Currently, the diagnosis, medication, and management of schizophrenia are based on subjective measures. There is, therefore, a critical need for objective quantification of clinical states, in particular based on measured brain activity. Although several quantitative measures of brain activity display significant differences between patients and control subjects, most of these studies use a single time point recording and compare distinct groups. Longitudinal studies of brain volume and neuropsychological functions in schizophrenia yield evidence for decline in those metrics, but relevant data about longitudinal changes of brain activity are still missing. To this end, we collected data from 10 subjects with schizophrenia during their hospitalization period. EEG data and clinical assessment of PANSS were collected across ~3 timepoints from admission to discharge.
Methods: Patients with schizophrenia were recruited from Sha'ar Menashe Mental Health Center immediately after hospitalization. Inclusive criteria were schizophrenia or psychosis diagnosis

according to DSM-V by a psychiatrist, ability to sign informed consent and willingness to participate in the study. Exclusion criteria were patients who were forced hospitalized. Participants signed an informed consent. The study was approved by the Helsinki ethical committee of Sha'ar Menashe Mental Health Center.
EEG was recorded at a few time points during the hospitalization period. At the recordings, participants were instructed not to move their head and not to fall asleep while seated in an upright position in two resting-state conditions: 5 min of Eyes Open, followed by 5 min with Eyes Closed. Data were collected using Cognionics quick-30, a wireless 30-channel system with dry electrodes. After each recording, PANSS (Positive and Negative Syndrome Scale, see appendix A) was filled by a psychiatrist, along with treatment information of the subject.

Preprocessing was done using implementation from the Matlab EEGLAB toolbox. Clean EEG data was filtered according to five frequency bands. Then, data was separated to windows (500 ms) and correlations were calculated for electrodes activity in each window. The final correlation matrix is an average of these correlation metrics. After calculating correlation, the matrix was unweighted. The binarization process was with a threshold corresponding to kappa of 0.04. Then we applied connectivity measures.

Results: We found a significant negative correlation between clinical assessment of schizophrenia (PANSS score) and small-worldness, a measure of functional connectivity. There was no evidence for correlation between spectral features and clinical assessment of schizophrenia.
Discussion: These preliminary findings indicate a connection between an EEG-based measure and the dynamics of clinical states in schizophrenia. Such measures could be used to better characterize the relationship between brain dynamics and clinical aspects of schizophrenia and lead to a more objective assessment.

F55. STRUCTURAL BRAIN-MRI BASED MULTI-SCALE STRATIFICATION TO QUANTIFY SOMATIC COMORBIDITIES IN PSYCHIATRIC DISORDERS

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Background: BrainAGE (brain age gap estimation) and BMIgap (Body mass index gap estimation) have established themselves as imaging-based biomarkers for brain aging and "global brain health". We created neuroanatomical BrainAGE and BMIgap models using machine learning analyses in two large, multi-site cohorts: IXI and PRONIA.
Methods: The BrainAGE pipeline was developed using grey matter (GM) maps, i.e., brain age estimates for each participant were derived from joint modeling of volumetric GM maps affinely registered GM maps, and GM density maps using the CAT12 pipeline. For model validation, we used external datasets of MUC healthy samples (N=327), schizophrenia patients (MUC SZ; N=155), patients with Clinical-High Risk (CHR; N=256), Recent Onset Psychosis (ROP; N=282), and Recent onset Depression (ROD; N=235) for all the analysis. The BMIgap pipeline was developed using volumetric grey matter maps (GMV) extracted using the VBM8 toolbox. We developed a regression model to measure the difference between neuroanatomically predicted and observed BMI (BMIgap) and a classification model to classify normal and obese individuals based on BMI using whole-brain grey matter volume data.
Results: Models with GM density maps (MAE/r: 4.4/0.9) showed better performance compared to volumetric GM maps (MAE/r: 5.0/0.88) and affinely registered GM maps (MAE/r: 5.0/0.88). Group-level analyses showed that BrainAGE was highest in MUC SZ (MUC SZ; N=155; mean(SD) BrainAGE = 5.8(±6.7) yrs) group, followed by PRONIA ROD (mean(SD) BrainAGE = -1.46(±4.6) yrs), CHR (mean(SD) BrainAGE= +0.93(±5.4) yrs), and the ROP (mean(SD) BrainAGE =+0.67(±6.9) yrs) groups. We also found significantly (F=111.95, p=1.16 x 10-23) higher BrainAGE scores (mean±SD: 5.8±6.6 years) in SZ compared to MUC HC. Similarly, the BMIgap regression model performed with an MAE of 3.3 BMI points (N=366, r/MAE=0.37/3.2; P<.001) during model discovery. We validated the model on external cohorts: remaining IXI PRONIA HC (N=426; BMIgap=3.9 (±2.5) yrs; r/MAE=0.12/4), MUC HC (N=366; BMIgap=3.4 (±3.2) yrs; r/MAE=0.27/4.1), MUC SZ (N=166; BMIgap=2.8(±3.8) yrs; r/MAE=0.47/3.9), PRONIA- ROP (N=76; BMIgap=2.4(±3); r/MAE=0.54/3.4), ROD (N=59; BMIgap=1.3(±4) yrs; r/MAE=0.37/3.6) and CHR (N=57; BMIgap=1.9(±3.2) yrs; r/MAE=0.37/3.2). The classification model identified the obese group with a balanced accuracy (BAC) of 64% during model discovery. The BAC varied 63.8-68% for different groups during model replication. We have also investigated the association between BrainAGE and BMIgap scores in the PRONIA disease cohorts (N=200) and found that they were inversely correlated (r=-0.2159, p= 0.002).

Discussion: We have detected significantly higher BrainAGE scores in SZ compared to HC, indicating significant accelerated brain structural aging in schizophrenia. Both studies will be essential in finding out important underlying signatures of somatic comorbidities associated with psychosis. So, the next step is to evaluate clinical, cognitive, and multi-OMICs batteries together with BrainAGE and BMIgap to identify biological signatures of somatic comorbidities and uncover associations between brain surrogates of obesity and accelerated brain aging.

F56. MULTIMODAL AI BASED FACIAL AND ACOUSTIC BIOMARKERS OF NEGATIVE SYMPTOMS IN SCHIZOPHRENIA

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Background: Many individuals with schizophrenia present with negative symptoms including abnormalities in vocal and facial expressions. One barrier in measuring negative symptoms is a reliance on clinician-rated assessments which can be subjective, insensitive to treatment change, require extensive training, lack regional and cultural adaptability, and have abstruse operational definitions. Novel conversational agents are equipped with artificial intelligence (AI) which are non-invasive and can accurately capture facial and speech movements. The aim of this study is to assess whether negative symptoms can be meaningfully measured using an AI audio-visual dialog system called Neurological Mental Health Screening Instrument (NEMSI) by comparing speech (e.g., prosody, rate, intelligibility, pausing duration) and video metrics (e.g., various facial movements) to clinician-rated negative symptoms assessments.
Methods: We assessed 21 inpatients (age 39.95 (SD=11.59)) with schizophrenia at a psychiatric facility in New York, NY. At the first visit, the sociodemographic and clinical questionnaire, PANSS, BNSS, CDSS, CGI-S, AIMS, SAS, BARS and NEMSI were administered. To assess reliability, the second visit occurred within one-week, was done by the same clinician, and included the same assessments plus the CGI-I. We assessed 9 healthy controls (age 42.11 (SD=12.18)) using the NEMSI assessment only. For NEMSI, participants interacted for 8 – 10 minutes with an avatar that provided a series of emotionally-ambiguous, valence-neutral reading tasks, an eyebrow raising task, an image description task, and a free speech task. Reliability, validity and internal consistency of NEMSI metrics and clinician-rated assessments were performed.
Results: ANOVA showed a significant difference ($p<0.05$) between patients and healthy controls for most NEMSI metrics. There were significant correlations ($p<0.05$) for: loudness of speech articulation with BNSS Total Score (r0.445); phonation of articulation loudness with alogia (r0.486); spontaneous speech articulation with PANSS negative symptoms (r0.506); internal silence with blunted affect (r0.440), avolition (r0.530) and alogia (r0.468); and speech duration with avolition (r0.530), anhedonia (r0.540), asociality (r0.548) and alogia (r0.431); speaking rate and blunted affect (r-0.459, $p<0.05$). Good reliability was observed between time 1 and 2 for NEMSI, BNSS and PANSS total scores (ICC>0.90) and good validity for BNSS total score, alogia, and avolition (Pearson $r\geq0.80$). Internal consistency of NEMSI was Cronbach α 0.86.

Discussion: Speech and facial AI technology showed significant correlations with clinician-rated assessments and could aid in rapid assessment of negative symptoms. NEMSI variables of articulation rate and lower facial movements have strong correlations to negative symptoms. NEMSI assessment showed good psychometric properties. The study is ongoing

F57. ACUTE STRESS EFFECTS ON PROBABILISTIC REVERSAL LEARNING IN HEALTHY PARTICIPANTS

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Background: Behavioral adaptation is a fundamental cognitive ability, which often goes awry in psychiatric disorders such as schizophrenia. These adaptive abilities can be measured using reversal learning paradigms requiring agents to adjust their reward learning to sudden changes in stimulus-action-outcome contingencies. Stressful situations have been found to alter flexibility of reward learning, but directionality of effects has been mixed across studies. Here, we used functional MRI (fMRI) informed by computational modeling in a within-subject design with healthy male human volunteers to investigate the effect of acute psychosocial stress on flexible behavioral adaptation.
Methods: Participants (n=28) underwent fMRI during a reversal learning task, once after the Trier Social Stress Test (TSST), a validated psychosocial stress induction method, and once after a control condition, in two separate sessions. Effects of stress on choice behavior were investigated using multilevel generalized linear models and a set of computational models describing different underlying learning processes. Computational models were fitted using a hierarchical Bayesian approach, and model-derived reward prediction errors (RPE) were used as regressors for fMRI analyses.
Results: We found that acute psychosocial stress only slightly increased correct response rates in our participants with high interinvididual variability. Model comparison revealed that double-update learning with stress-specific scaling of the inverse decision temperature parameter best explained the observed behavior under stress. On the neural level, RPE signals were represented in striatum and ventromedial prefrontal cortex (vmPFC). No whole-brain correctable effects of stress on RPE representations were found.
Discussion: Our study suggests that acute psychosocial stress does not alter neural representation of RPE and that interindividual variability on the behavioral level might be more related to use of choice values expressed in the temperature parameter.

F58. SECONDARY NEGATIVE SYMPTOMS IN OUTPATIENTS OF THE SCHIZOPHRENIA-BIPOLAR DISORDER SPECTRUM

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Background: Negative symptoms (NS) are a core feature of schizophrenia (SZ) and can also be measured in Bipolar-Disorder-I (BPD) patients. Secondary negative symptoms due to other psychotic symptoms or medication are frequently reported in clinical routine. Here, we aimed to characterize NS and potential sources of secondary NS in outpatients of the SZ-BPD spectrum.
Methods: We used open access data (Consortium for Neuropsychiatric Phenomics) including 50 outpatients with SZ and 49 with BPD. NS domains were assessed using SANS global scores for alogia, anhedonia, avolition and blunted affect. Positive symptoms (SAPS global scores), depressive (HAMD-28), manic symptoms (YMRS), and medication dose were additionally measured as potential source for secondary NS. Multiple regression analyses were applied to assess the association between negative symptom domains and potential source for secondary NS.
Results: Across the complete sample of SZ and BP, avolition and anhedonia were associated with bizarre behavior (beta=0,34; T=2,745; p<0,01, beta=0,555; T=5,168; p<0,01, respectively) and anhedonia also with depressive symptoms (beta=0,474; T=4,379; p<0,01). Similarly blunted affect and alogia were associated with bizarre behavior (beta=0,431; T=3,646; p<0,01, beta=0,406; T=3,397; p<0,01, respectively) and blunted affect additionally with depressive symptoms (beta=0,310; T=2,645; p=0,01). Group differences predicted only anhedonia (beta=-0,318; T=-2,099; p=0,039; SZ>BPD) and alogia (beta=-0,413; T=-2,460; p=0,016; SZ>BPD).
Discussion: Across SZ and BPD, subclinical positive symptoms of bizarre behavior relate trans-diagnostically to secondary NS in all four domains, while depression additionally contributes to secondary anhedonia and blunted affect. These findings suggest that secondary negative symptoms occur across the schizophrenia-bipolar spectrum and persist in outpatient sample.

F59. A META-ANALYSIS OF SEX DIFFERENCES IN SYMPTOMATOLOGY IN PEOPLE WITH PSYCHOSIS: STUDY PROTOCOL

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Background: Gender differences in symptomatology in people with psychosis have been studied extensively in last decades. Previous narrative reviews have shown some evidence of gender differences in depressive, negative and paranoid symptoms, but yielding inconclusive findings. These reviews are limited by not doing systematic searches nor performing quantitative synthesis of the evidence. Therefore, we aimed to systematically investigate if there are gender differences

in symptoms in people with psychosis. We describe the protocol for a systematic review and pairwise meta-analysis comparing a range of symptomatic outcome measures between men and women diagnosed with a psychotic spectrum disorder at different stages of the disorder (ultra-high risk for psychosis, early psychosis and established psychosis) in observational studies.
Methods: We will conduct systematic searches in PsychInfo, PubMed, Web of Science, Scopus and Dialnet to identify observational studies that compare gender differences or provide Results: separated by the gender of the participant in measures of symptomatology. Literature searches, study selection, data extraction, risk of bias assessment and outcome quality assessment will be undertaken by two independent reviewers. A series of pairwise meta-analyses will be conducted in R using random-effects models to assess the effect size of all outcome measures that are assessed in at least two studies.
Results: By beginning december 2021, the screening process has been performed. Currently two reviewers are doing the elegibility phase of the studies using the PICOPORTAL software. By this time, 36087 studies were identified in the first stage, and a total of 945 studies are being inspected for considering their final inclusion in the meta-analysis.
Discussion: No ethical issues are foreseen. The preliminary results from this study will be presented at the conference.

F60. COMPUTERIZED ADAPTIVE TESTING IN PSYCHOSIS: AN OPPORTUNITY FOR ESCALATING MEASUREMENT-BASED CARE

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Background: Time constraints and training requirements limit the use of measurement-based approaches in the routine clinical management of schizophrenia. Unlike regular assessments, Computerized Adaptive Testing (CAT) uses computational algorithms based on item response theory to match individual subjects with only the most relevant questions for them, reducing administration time and increasing measurement efficiency and scalability. However, CAT-based assessments in psychosis were lacking due to concerns about insight and the patient's ability to accurately report psychotic symptoms.
Methods: A computerized adaptive testing tool for psychosis (CAT-Psychosis), both a self-administered and rater-administered versions, were developed; an item bank was generated and calibrated from a sample of psychotic patients. An additional validation study was conducted in an independent sample of psychotic patients. The Scale of Unawareness of Mental Disorders

(SUMD) was administered to determine illness awareness. The Brief Psychiatric Rating Scale (BPRS) was administered to test convergent validity and chart diagnosis and the Structured Clinical Interview (SCID) was used to test discriminant validity.
Results: The development and calibration study included data from 649 psychotic patients. After development of the item bank, simulations that revealed a correlation of r=0.92 with the total 73 item bank score, using an average of 12 items. The subsequent validation study included an independent sample of an additional 160 psychotic patients and 40 healthy controls and showed that CAT-Psychosis possessed convergent validity against gold standard (clinician: r=0.690; 95% confidence Interval (95%CI): 0.610-0.757 vs BPRS; self-report: r=0.690; 95%CI: 0.609-0.756 vs. BPRS). Inter-rater (intra-class correlation coefficient (ICC)=0.733; 95%CI: 0.611-0.828) and test-retest reliability (clinician ICC=0.862; 95% CI: 0.767-0.922; self-report ICC=0.815; 95%CI: 0.741-0.871). Median length of the clinician-administered assessment was 5 minutes (min) (inter-quartile range (IQR): 3:23min-8:29min) and 1 minute, 20 seconds (IQR: 0:57min-2:09min) for the self-report, Additionally, 159 patients with a psychotic disorder who completed both CAT-Psychosis and SUMD were included in an additional secondary analysis aimed to elucidate the effects of insight on the accuracy of self-reported psychotic symptoms. For this subsample, CAT-Psychosis scores showed convergent validity with BPRS ratings ($r = 0.517$, 95% CI: 0.392–0.622, $p < .001$). Insight was found to moderate this correlation (= –0.511, $p = 0.005$), yet agreement between both measures remained statistically significant for both high ($r = 0.621$, 95% CI: 0.476–0.733, $p < 0.001$) and low insight patients ($r = 0.408$, 95% CI: 0.187–0.589, $p < 0.001$), while psychosis severity was comparable between these groups (for BPRS: $U = 3057$, $z = -0.129$, $p = 0.897$; disorganization: $U = 2986.5$, $z = -0.274$, $p = 0.784$, and for CAT-Psychosis: $U = 2800.5$, $z = -1.022$, $p = 0.307$). Lastly, CAT-Psychosis is able to reliably discriminate psychotic patients based on a lifetime diagnosis from healthy controls, both clinician (Area Under the ROC Curve (AUC)=0.965, 95%CI: 0.945-0.984) and self-report (AUC= 0.850, 95%CI: 0.807-0.894) versions.
Discussion: Computerized adaptive testing for psychosis provides valid severity ratings, even as a self-report, and can reliably discriminate psychotic patients from healthy controls, yielding a dramatic reduction in administration time. The availability of such a scalable, valid, quick and reliable self-administered instrument can be of enormous value for expanding measurement-based care into routine clinical practice.

F61. MEASURING AUTISM IN INDIVIDUALS WITH PSYCHOSIS: CROSS-SECTIONAL REPLICATION AND LONGITUDINAL EVALUATION OF THE PANSS-AUTISM-SEVERITY-SCORE

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Background: Autism and psychosis have been found to co-occur at elevated rates, with implications for clinical outcomes, functioning, and suicidality. In individuals with psychosis, this appears to be the case even if autistic traits do not reach diagnostic levels. The measurement of autistic traits in psychosis populations is complex and validated instruments do not exist. The PANSS-Autism-Severity-Score (PAUSS) is a measure of autism trait severity which is derived

from the PANSS. The PAUSS is gaining traction within the research field but has not yet been validated externally or longitudinally.
In the present study we aimed to replicate the analyses from the original PAUSS validation paper in a large cohort of individuals with schizophrenia spectrum disorders (SSD), to extend these analyses into SSD siblings, autistic individuals (ASC), and typical controls (TC), and to investigate the short and long-term stability of the PAUSS.

Methods: Participants were derived from the GROUP and SCOPE datasets, and consisted of 1449 SSD, 800 SSD siblings, 103 ASC, and 409 TC. Internal consistency between PAUSS items in SSD, ASD, siblings, and TC were investigated. PANSS score between PAUSS-Autistic and PAUSS-nonAutistic was compared. Within ASC participants, PAUSS scores were compared between ADOS subgroups, and intercorrelations between the PAUSS and the ADOS were examined. ROC curves investigated the use of the PAUSS to predict ASC diagnosis compared to TC. Finally, short (2 week) and long-term (3 and 6 year) test-retest reliability of the PAUSS in SSD was examined.
Results: Results: differed in important ways from the original analyses of the PAUSS. SSD individuals had the highest PAUSS scores (mean=14.54; SD=5.59), followed by ASC (13.85, 4.23), siblings (8.72, 1.83), and TC (8.30, 1.07). Cronbach's alpha was found to be acceptable for SSD ($\alpha = 0.76$), questionable for siblings (0.68), poor for ASC (0.58), and unacceptable for TC (0.30).
Based on suggested cutoffs, 1.4% of SSD participants met PAUSS-Autistic criteria (vs 12% in the original sample), with no ASC, siblings, or TC rated as PAUSS-Autistic. Study customized cutoffs resulted in 7.4% SSD and 1.9% ASC rated as PAUSS-Autistic. SSD PAUSS-Autistic participants were significantly more likely to be male and have higher scores on the PANSS total and subscales.

Within ASC participants, PAUSS scores were found to be significantly higher in the ADOS 'autism' subgroup compared to the ADOS 'autism spectrum' subgroup. PAUSS item intercorrelation with the ADOS was found to be high for two items, medium for one, and low for the remaining five items. ROC analysis indicated that a score of above 10 on the PAUSS distinguished between ASC compared to TC participants with an 88.3% sensitivity and 93.6% specificity.

Longitudinal analyses found that short term test-retest stability of the PAUSS was fair to good for all PAUSS items and total score. Long term test-retest stability was found to be poor for most PAUSS items but fair for the total PAUSS score.

Discussion: Although the PAUSS is growing in popularity as a measure of autism within psychosis, our Results: suggest that widespread use of the PAUSS is premature for several reasons. First, the cut-off proposed in the original PAUSS paper may need further refining. Second, the PAUSS does not appear appropriate for assessing autism in non-psychosis populations, with the low rate of PAUSS-Autistic in the ASC population, suggesting that the PAUSS may not accurately reflect autistic characteristics. Finally, the relative lack of long-term stability of the PAUSS is cause for concern and may suggest that the PAUSS is capturing psychotic symptoms rather than autistic traits.

F62. PHENOMENOLOGY AND GENETIC MODERATORS OF EXCESSIVE CHECKING AFTER ANTIPSYCHOTIC TREATMENT

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Background: A significant proportion of antipsychotic-treated schizophrenia patients develop de novo checking compulsions, a phenomenon that is yet to be understood. Informed by models of habit formation developed in the cognitive neurosciences, we hypothesised that excessive checking could be understood as the by-product of psychosis, promoted by clozapine's strong anti-serotoninergic action.
Methods: Using the anonymised electronic records of a cohort of 204 clozapine-treated patients, including longitudinal assessments of obsessive-compulsive symptoms (OCS) and psychosis (n=724 face-to-face assessments), we performed longitudinal multi-level mediation and multi-level moderation analyses to explore OCS' associations with psychosis and with patient genotype respectively.
Results: We found OCS to be common in clozapine-treated patients (54%), with checking being the most prevalent symptom. Mediation models showed psychosis severity to indirectly effect checking behaviour by inducing obsessions [0.08 (IC 0.05, 0.12); p<0.001). No direct effect of psychosis on checking was identified [-0.06 (IC -0.13, 0.02); p=0.145]. After psychosis remission, checking compulsion directly correlated with both clozapine plasma levels (r=0.33; p=0.005) and dose (r=0.30; p=0.010). The transition from psychosis to obsession and compulsion was moderated by glutamatergic genetic variants (GRIN2B). We also identified novel associations with the serotoninergic pathway (SLC6A4, HTR2A and HTR2C).
Discussion: Understanding the different phases of the complex transition from psychosis to compulsion may inform clinicians' therapeutic decisions.

F63. AUDITORY VERBAL HALLUCINATIONS AND CHILDHOOD TRAUMA SUBTYPES ACROSS THE PSYCHOSIS CONTINUUM: A CLUSTER ANALYSIS

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Background: A strong link between voice hearing experience and childhood trauma has been established. The aim of this study was to identify whether there were unique clusters of childhood trauma subtypes in a sample across the clinical spectrum of auditory verbal hallucinations (AVH) and to examine clinical and phenomenological features across these clusters.

Methods: Combining two independent international datasets (the Netherlands and Australia), childhood trauma subtypes were examined using hierarchical cluster analysis. Clinical and phenomenological characteristics were compared across emerging clusters using MANOVA and chi-squared analyses.
Results: The total sample (n=413) included 166 clinical individuals with a psychotic disorder and AVH, 122 non-clinical individuals with AVH and 125 non-clinical individuals without AVH. Three clusters emerged: 1) low trauma (n=299); 2) emotion-focused trauma (n=71); 3) multi-trauma (n=43). The three clusters differed significantly on their AVH ratings of amount of negative content, with trend-level effects for loudness, degree of negative content and degree of experienced distress. Furthermore, perceptions of voices being malevolent, benevolent and resistance towards voices differed significantly.
Discussion: The data revealed different types of childhood trauma had different relationships between clinical and phenomenological features of voice hearing experiences. Thus, implicating different mechanistic pathways and a need for tailored treatment approaches.

F64. CHILDHOOD TRAUMA RELATED TO TOBACCO SMOKING MEDIATED BY COGNITIVE CONTROL AND IMPULSIVENESS IN SEVERE MENTAL DISORDERS

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Background: People with severe mental disorders (SMDs) show an increased prevalence of tobacco smoking compared to the general population. Tobacco smoking and other adult adverse health behaviours have been associated with traumatic experiences in childhood. In the present study we investigated the relationship between childhood trauma and tobacco smoking in people with SMDs, including the possible mediating role of cognitive and personality characteristics, i.e. cognitive control, impulsiveness, affective lability and self-esteem.
Methods: Enrolled in the study were 908 participants with schizophrenia (SCZ, n=502) and bipolar (BD, n=406) spectrum disorders. Current tobacco smoking behaviour was assessed categorically (yes/no) as well as by intensity (average number of cigarettes, pipes, cigars per day),

and history of childhood trauma was assessed with the Childhood Trauma Questionnaire. Data on cognitive control (n=746), impulsiveness (n=369), affective lability (n=257), and self-esteem (n=681) were available in subsamples. Linear and logistic regressions were performed to examine the relationship between childhood trauma and tobacco smoking. Mediation analyses were conducted in PROCESS in subsamples. All analyses were run in SPSS and adjusted for age, sex, diagnostic group, and level of depression measured by Inventory of Depressive Symptomatology, Clinician-Rated (IDS-C).
Results: Experience of one or more subtypes of childhood trauma was significantly associated with smoking tobacco in SMDs (p=0.001). There were no significant associations between childhood trauma and intensity of tobacco smoking. Cognitive control and impulsiveness were significant mediators between childhood trauma and tobacco smoking.
Discussion: These findings indicate the experience of childhood trauma as a predisposing factor for tobacco smoking in SMDs. Cognitive control and impulsiveness were suggested as mediating mechanisms, indicating the importance of considering inhibition related self-regulatory aspects in efforts to improve health behaviour in individuals with SMDs and childhood trauma.

F65. CLUSTERING IS LESS LIKELY TO CAPTURE DISTINCT COGNITIVE SUBGROUPS ACROSS PSYCHOTIC AND AFFECTIVE ILLNESSES IN THE EARLY STAGE: NEW INSIGHTS FROM THE PRONIA STUDY

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Background: Deficits in processing speed and verbal learning, manifest in psychotic illness (Mesholam-Gately et al., 2009) and mood disorder (Snyder, 2013) whilst predicting transitioning to psychosis at clinical high risk (CHR; Cannon, 2016). Recent studies including our own identified cognitive subgroups in psychosis spectrum (Wenzel et al., 2020; Green et al., 2019), major depressive disorder (Martin et al. 2020) and in CHR (Haining et al., 2021) indicating marked heterogeneity in impairment. Brain structural and functional differences between cognitive subgroups in psychosis (Van Rheenen et al., 2018; Lewandowski et al., 2019) together with findings of transdiagnostic neurobiological patterns associated with cognitive deficits (Goodkind et al., 2015) encourage the existence of an intermediate transdiagnostic phenotype. However, a comprehensive design addressing these diagnoses simultaneously and in their early stages is lacking. In this study, we investigate transdiagnostic cognitive subgroups early in the course of affective and psychotic illness alongside individuals at CHR. In the second step, we characterize the subgroups with respect to symptoms and functioning and finally, validate them against structural and resting-state functional brain data.
Methods: We used a k means clustering approach on a total sample of 670 participants consisting of recent onset-psychosis (ROP) patients, recent onset depression (ROD) patients, CHR individuals and healthy controls (HC) recruited through the multi-site study PRONIA (Personalized Prognostic Tool for Early Psychosis Management, www.pronia.eu). Transdiagnostic cognitive subgroups were derived from eight neurocognitive domain scores corrected for sex, age,

education and site. Neurobiological differences between clusters were characterized using supervised machine learning. Results: were validated in the PRONIA validation sample (N=409). **Results:** We found an impaired cluster showing widespread neurocognitive impairment (p's < .001) accompanied by impaired premorbid intelligence (p < .001) and a spared cluster with preserved premorbid intelligence that performed cognitively comparable to HC. Neurocognitive and premorbid intelligence differences were observed across diagnoses, though functional and clinical differences between subgroups were mainly expressed in impaired ROP patients that showed reduced levels of functioning (p's < .05) and higher negative symptomatology (p < .01). We differentiated spared from impaired subgroup using brain volume and resting-state functional connectivity with a BAC of 59.1% (p < .01) and 57.7% (p < .01), respectively. Cluster differences for working memory, processing speed and attention as well as premorbid intelligence were most consistently replicated in the validation sample.
Discussion: In the current study we show that both patients with affective as well as psychotic illness cluster with CHR individuals and map onto two neurocognitive profiles. While different psychiatric illnesses seem to have spared and impaired cognitive subgroups in common, these are not necessarily accompanied by distinct functioning-, symptom- or brain patterns. As we only partially externally validate our Results: we assume that less distinct cognitive subtypes can be captured in the early stages of the illness. However, this could be the result of pronounced neurocognitive and functional heterogeneity across multiple sites that could not be entirely controlled for during our analysis. Future studies on large patient cohorts are needed to determine under which conditions clustering models may achieve better generalizability.

F66. WHEN VIRTUAL REALITY BECOMES REAL: CHARACTERISTICS OF FELT PRESENCE AMONG INDIVIDUALS AT HIGH RISK FOR PSYCHOSIS

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Background: When we sense that a friend is standing behind us, we might hear their voice, smell their scent, feel their warmth, and turn around and talk to them. These same sensations in the absence of a real person is called feeling of presence (FP) - one of the most common, yet underexplored hallucinations. Given FP's high prevalence in the schizophrenia spectrum and its association with psychosis-risk in healthy adults, it questions the dichotomous entities our clinical diagnostics mostly rely on. Instead of an all-or-nothing phenomenon, growing evidence indicates that psychotic symptoms are rather continuous, with 'psychotic' hallucinations distributed across the whole range from healthy to diagnosed individuals. In this context, FP's ubiquity can serve as a prime example to explore this continuum, while challenging the common classification in separate modalities, such as voice-hearing or visual hallucinations, and integrating the possible experiences of agency in hallucinatory phenomena. But so far, we know little about when its 'normality' ends and pathology begins. When does a FP become a symptom of psychosis - not until we speak to the FP? To elucidate this question, the current study explored the phenomenology of FP on the continuum from low to high psychosis risk in healthy adults.
Methods: The study was part of a larger online survey on FP distributed via e-mail and social media. Healthy adults (n = 211) completed the Prodromal Questionnaire-16 (Ising et al., 2012) and questions about the occurrence of FP. For participants with FP, yes/no questions on different

modalities (touch, sound, action, smell, location/space), as well interactive qualities such as social agency (the FP having influence over subject, the subject having influence over the FP) and communication with the FP were further assessed. In a within-group design, we compared psychosis risk among those who experienced FP in one or more of these characteristics.
Results: Apart from experiencing a FP in the first place (yes/no; $p < .001$), some characteristics of this FP were more related to psychosis risk than others. Specifically, within the group of participants who have experienced a FP, those whose FP could move ($p < .05$), talk or make sounds ($p < .05$) and be influenced by the participant ($< .05$) experienced a higher risk for psychosis. The number of reported characteristics was positively correlated with the frequency of an experienced FP ($r = .47$, $p < .001$). Furthermore, the more modalities of FP were reported, the higher psychosis risk was in participants ($r = .26$, $p = .004$).
Discussion: The overall number of reported characteristics were significantly related to a higher risk for psychosis in healthy adults, although not every sensory or social characteristic might seem to contribute equally. The richer the social and sensory characteristics of an individual's FP, therefore the closer to a 'real' experience of a presence, the higher the individual's risk was for psychosis. Moreover, a higher frequency of experienced FP was strongly related to a richer set of experienced modalities. Although cause and effects remain open, these Results: contribute the phenomenological understanding of FP in a continuum of low to high psychosis risk, as well as the growing focus on multi-modality in hallucination research.

F67. ASSOCIATION BETWEEN C-REACTIVE PROTEIN AND INFLAMMATORY INDEXES IN SCHIZOPHRENIA: AN EXPLORATORY STUDY

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Background: There is a rise of evidence supporting the existence of immune system abnormalities in schizophrenia. In order to study this feature, numerous immunological biomarkers have been used to define an inflammatory subgroup of schizophrenia and potentially lead to a more tailored treatment for these patients. C- reactive protein (CRP) levels have demonstrated a predictive value of worse clinical course and higher mortality in schizophrenia patients. In this line, inflammatory indexes (Neutrophil-Lymphocyte Ratio [NRL], Platelet-Lymphocyte Ratio [PLR] and Monocyte-Lymphocyte ratio [MLR]) are new, suitable for routine and reproducible markers of the systemic inflammatory response. Nevertheless, links between CRP and inflammatory indexes in schizophrenia petitions have not been previously studied. The aim of this study is to analyze the relationship between inflammatory biomarkers (CRP, NRL, PLR and MLR) in schizophrenia patients.
Methods: We identified patients with a primary diagnosis of schizophrenia (ICD-10 code: F20) aged 18 or older hospitalized in the Inpatient Psychiatric Department of Santa Maria Hospital (Lleida) from 1st January 2010 to 31st December 2019. A total of 753 (308 females, 325 males) aged 42,8 ± 12,9 years old were included in the study. Sociodemographic parameters where

collected. CRP and complete hemogram were collected from the protocol blood analysis at the time of admission. Inflammatory indexes (NLR, PLR and MLR) were calculated as the ratio of neutrophil, platelet and monocyte counts to lymphocyte count respectively. Statistical analyses were performed using IBM-SPSS v.23. Descriptive statistics was used to analyse the data. Normal distribution was evaluated using the Kolmogorov-Smirnov test. Correlation analysis was performed using Spearman correlation test.
Results: CRP correlates with NRL ($rs = 0.316$, $p < 0.001$), PLR ($rs = 0.132$, $p = 0.001$) and MLR ($rs = 0.271$, $p < 0.001$). Age was associated with CRP ($rs = 0.161$, $p < 0.001$), NRL ($rs = 0.267$, $p < 0.001$), PLR ($rs = 0.238$, $p = 0.001$) and MLR ($rs = 0.213$, $p < 0.001$). When stratifying by sex, CRP of female patients showed significant correlation with NRL ($rs = 0.300$, $p < 0.001$) and MLR ($rs = 0.230$, $p < 0.001$) but not with PLR ($rs = 0.114$, $p = 0.046$); CRP of male patients showed significant correlation with NRL ($rs = 0.337$, $p < 0.001$), PLR ($rs = 0.156$, $p = 0.005$) and MLR ($rs = 0.308$, $p < 0.001$).
Discussion: Altogether, our Results: showed that CRP is significantly but moderately associated with NRL and that the association with PLR and MLR is small. These associations remain significant for all indexes except for PLR in females. The four parameters studied showed a small association with age. This study suggests that NLR could serve as a potential predictive marker in schizophrenia.

F68. TRAIT ANXIETY MEDIATES THE RELATIONSHIP BETWEEN CHILDHOOD TRAUMA AND SYMPTOM DIMENSIONS IN EARLY PSYCHOSIS

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Background: Trait anxiety and neuroticism have been reported to be increased in patients with psychotic disorders and a history of childhood trauma. Previous studies also suggest that neuroticism mediates the relationship between childhood trauma and distress to auditory verbal hallucinations in non-clinical and clinical populations. The main aim of our study was to study the association between childhood trauma and distinct symptom dimensions and to explore whether trait anxiety could be a mediator of this relationship.
Methods: One hundred patients (aged 18-35 years, 35% women) with early psychosis (defined as a DSM-IV diagnosis of a psychotic disorder with less than 3 years of illness) and 58 healthy individuals were included. The clinical assessment was conducted when patients were clinically stable and treated at least with 4 weeks of antipsychotic treatment. The State-Trait Anxiety Inventory (STAI) was used to assess trait anxiety in all participants. The Childhood Trauma Questionnaire (CTQ) was used to assess a history of childhood trauma. The Positive and Negative Syndrome Scale (PANSS) and the Calgary Depression Rating Scale (CDSS) for Schizophrenia were used to assess symptoms. The PANSS was recoded in four factors considering a previous consensus: positive, negative, disorganized and excited symptoms. The CDSS was used for measuring depressive symptoms. Statistical analyses were conducted with SPSS v.24.0. T-test was used for comparing continuous measures between patients and healthy individuals. Spearman

correlation analysis was used for exploring association of trait anxiety, CTQ scores and symptoms. Mediation analyses were performed using the Process Macro in SPSS. CTQ scores were used as the independent variable. STAI trait subscore was used as the mediating factor. Five mediation analyses were performed, each analysis using one different dependent variable: positive, negative, disorganized, excited and depressive symptoms. All mediation analyses were adjusted for age and gender. Dependent variables were previously log-transformed (ln) for reducing skewness. Significant mediation effects were tested with bootstrapping.

Results: Patients with early psychosis showed higher trait anxiety (40.0 ± 11.6 vs 30.5 ± 5.8, $p<0.001$) and CTQ (25.6 ± 11.6 vs 14.1 ± 7.7, $p<0.001$) scores than healthy controls. In healthy individuals, trait anxiety was not associated with CTQ scores ($r= 0.25$, $p= 0.057$). In patients, trait anxiety was associated with CTQ scores ($r= 0.45$, $p<0.001$) and with positive ($r= 0.20$, $p= 0.020$), negative ($r= 0.18$, $p= 0.039$), disorganized (0.26, $p= 0.003$) and depressive ($r= 0.48$, $p<0.001$) symptoms but not excited symptoms ($r= 0.02$, $p= 0.799$). CTQ scores were associated with disorganized ($r= 0.21$, $p= 0.015$) and depressive ($r= 0.20$, $p= 0.024$) symptoms. Mediation analyses adjusted for age and gender showed that trait anxiety mediated the relationship between childhood trauma and positive, negative, disorganized and depressive symptoms.

Discussion: Our study replicates previous research reporting higher trait anxiety and childhood trauma in patients with early psychosis when compared to healthy individuals. As all patients were relatively stable and were treated for at least 4 weeks, the associations between childhood trauma, trait anxiety and symptoms could suggest the role of trait anxiety in the persistence of symptoms in the early stages of the psychotic illness. A limitation of our study is the cross-sectional design without including a longitudinal assessment of symptoms. Future studies need to explore whether trait anxiety is a mediating variable in the potential relationship between childhood trauma and lack of treatment response to antipsychotic treatment.

F69. LONGITUDINAL: EFFECTS OF DOSAGE AND ANTICHOLINERGIC BURDEN OF ANTIPSYCHOTICS ON HIPPOCAMPAL VOLUME AND VERBAL MEMORY IN FIRST-EPISODE PSYCHOSIS

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Background: Antipsychotics are commonly used to reduce symptoms of psychosis. However, they are not as effective in treating cognitive deficits and negative symptoms as they are in treating positive symptoms. Recent findings suggest that high doses and high anticholinergic burden of antipsychotics may actually contribute to verbal memory deficits and can be associated with hippocampal volume, with reduced volumes in areas with dense levels of dopamine receptors, such as in the dentate gyrus subfield. As part of a longitudinal study over an 18-month period with 4 time points, our objectives were to examine changes in verbal memory performance and hippocampal subfield volumes in patients versus controls over time and to determine the extent to which antipsychotic treatment may relate to changes over time. We hypothesized that patients would have poorer verbal memory performance and reduced hippocampal subfield volumes over time compared to controls. We also expected that dosage and anticholinergic burden would be

negatively associated with verbal memory performance and subfields with denser levels of dopamine receptors.
Methods: First-Episode Psychosis patients, followed by the PEPP-Montreal clinic (N = 74), and non-clinical controls (N = 53) completed a 3T MRI scan and a neurocognitive evaluation (CogState) at 3, 9, 12 and 18 months after admission.
Results: Generalized Estimating Equations (GEE) analysis revealed a significant group and time effect for verbal memory performance, for the right CA1 and left dentate gyrus subfield. Significant negative correlations were found between antipsychotic dosage and left CA1, left dentage gyrus, left fimbria and left hippocampus subfields volumes change over time. A significant negative correlation was found between anticholinergic burden and verbal memory performance change over time.
Discussion: As the relationship between antipsychotic treatment, brain volume and cognitive deficits remains poorly understood, this study could provide a better insight into the long-term effect of antipsychotics. More importantly, since cognitive deficits appear to be present in the early stages of the disease, it will be valuable to remind professionals of the potential long-term effects of medication on cognition in First-Episode Psychosis.

F70. EXPLORING THE MEDIATORY ROLES OF COGNITION AND INFLAMMATION IN THE ASSOCIATION BETWEEN SOCIOENVIRONMENTAL ADVERSITY AND PSYCHOTIC EXPERIENCES

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Background: Childhood socioenvironmental adversities, such as urbanicity, air pollution, neighborhood deprivation, and disorder, are well-documented risk factors for psychosis, including psychotic experiences during childhood and adolescence (e.g., hearing voices, paranoia). However, few studies have explored potential biomechanisms underlying this relationship. We investigated whether cognitive abilities (overall cognition, crystalized ability, fluid ability, working memory) and inflammatory markers (overall inflammation, CRP, IL-6, suPAR) mediate the relationship between socioenvironmental adversity during childhood and psychotic experiences during adolescence.
Methods: We used data from The Environmental-Risk (E-Risk) Longitudinal Twin Study, a longitudinal cohort of 2,232 children born in 1994-1995 in England and Wales and followed from birth to age 18. This population-based cohort represents the geographic and socioeconomic composition of UK households. Socioenvironmental adversities were measured from birth to age 10 using national statistics, air-quality models, consumer classifications, and interviews. Following exploratory factor analysis, socioenvironmental adversities were classified into social risk (defined by high deprivation, disorder and family disadvantage) and environmental risk (defined by high urbanicity and air pollution). Participants were privately interviewed at age 18

regarding thirteen psychotic experiences. Cognitive abilities were measured at age 12 using a short form of the Wechsler Intelligence Scale for Children-IV. Inflammatory markers were obtained from venous blood samples collected at age 18. We analysed data using linear and logistic regression and generalized structural equation models. Analyses were adjusted for sex, family psychiatric history, parental education, and polygenic risk for schizophrenia, educational attainment, and cognitive performance. We also calculated E-values to estimate unmeasured confounding.

Results: At age 18, 51% of participants were female, and 30.2% had one or more psychotic experience since age 12. After controlling for covariates, we found strong evidence for main associations of social risk with all cognitive abilities, overall inflammation and suPAR; and of environmental risk with crystalized ability. In turn we found strong evidence for associations of overall cognitive ability, crystalized ability, and overall inflammation with psychotic experiences. However, we found evidence only for crystalized ability as a mediator of the relationship between social risk and psychotic experiences, explaining ~16% of the association (total effect OR=1.34, 95% CI=1.18-1.52; indirect effect OR=1.05, 95% CI=1.01-1.09). E-values for this model were relatively large, increasing our confidence in the associations.

Discussion: Cognition, particularly crystalized ability, may partly mediate the relationship between childhood socioenvironmental adversity and adolescent psychotic experiences. This is in keeping with the neurodevelopmental model of psychosis and the causal role that neurocognition plays in psychosis. We found little evidence for inflammation as a mediator, despite this being the most commonly proposed mechanisms for how air pollution could affect mental health. If causal, interventions to enhance cognitive development among children living in disadvantaged settings could buffer them against developing psychosis.

F71. ASSOCIATION BETWEEN GUT MICROBIOME FEATURES AND COGNITIVE IMPAIRMENT IN EARLY PSYCHOSIS

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Background: Cognitive impairment manifests in up to 70% of patients with psychotic disorders, and represents a major barrier for functional recovery and a current unmet therapeutic need.

Specific gut microbiome abnormalities, namely reduced levels of anti-inflammatory butyrate-producing bacteria have been associated with the severity of cognitive impairment in dementia and autism, two disorders that share pathophysiological features with psychosis. The oral administration of these bacteria can reverse cognitive impairments in animal models of these disorders.

Recent meta-analytic evidence showed depletion of anti-inflammatory butyrate-producing bacteria in patients with psychosis. However, no study to date has investigated the association with cognitive impairment in these patients.

Here we provide the first study testing this association in early psychosis, where findings are less biased by long-term exposure to medications and chronicity.

Methods: We conducted a cross-sectional investigation of the gut microbiome and cognitive functions in 27 first episode psychosis patients (FEP) and 25 healthy controls. Gut microbiome compositions, diversity and community structure were obtained from stool samples using 16S rRNA sequencing of the V4 regions. Cognition was assessed with the brief assessment of cognition in schizophrenia (BACS).
One-way ANOVA was used for between-group comparisons of gut microbiome compositional and diversity measures. The Chao1 index was used as a measure of within-individual diversity (alpha diversity). The first three axes of principal coordinate analysis of the beta diversity (between sample distances; Weighted and Unweighted UniFrac metrics) were extracted to represent between-individual differences in overall microbiome composition. Linear regression analysis was used to evaluate the association between gut microbiome compositional and diversity measures and cognitive functions in FEP. Analyses were FDR-corrected and adjusted for obesity, diet, length of antipsychotic exposure, sociodemographic and technical covariates.

Results: FEP and controls did not show significant differences in terms of BMI, diet, and sociodemographic measures. FEP scored significantly lower than healthy controls in all BACS cognitive domains.
At the time of writing, gut microbiome analysis is available on a subgroup of FEP (N=18) and controls (N=15). Final analysis on the whole sample will be presented at the conference meeting.

No significant differences were found in alpha and beta-diversity measures between patients and controls. Compared to controls, FEP showed lower levels of the butyrate-producing bacteria Dorea, Akkermansia, and Roseburia.

Within FEP, we found: (i) a significant association between reduced alpha diversity and performances on the symbol coding (β = -0.66; P=0.03) and the tower of London tests (β = -0.32; P=0.04) of the BACS; (ii) a significant association between reduced levels of Akkermansia (β = -0.46; P=0.03) and Dorea (β = -0.37; P=0.03) and poor performances on the symbol coding test of the BACS.

Discussion: Albeit obtained from a small sample of FEP and controls, here we provide the first evidence on the association between specific gut microbiome features and cognitive performances in psychotic disorders. Reduced gut microbiome diversity and depletion of anti-inflammatory butyrate producing bacteria (such as Dorea, Akkermansia, and Roseburia) were associated with the severity of impairment in executive functions.
These findings need to be validated in larger cohorts of patients with psychosis, but they represent a first significant attempt to identify a novel target of intervention in area of clinical unmet need.

F72. INFLAMMATORY MARKERS IN PATIENTS WITH RECENT ONSET PSYCHOSIS: SUBGROUPS AND RELATION TO CLINICAL PHENOTYPE

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Background: People with early psychosis present with heterogenic phenotypes and varying degrees of functional impairment, whereby different pathogenic pathways are implicated. One potential pathway that is associated with psychosis is inflammation. However, findings with single inflammatory mediators and markers lack consistency, which may have hampered progress in this field. Identifying clusters of co-varying inflammatory mediators and markers within recent-onset psychosis and determining whether these subgroup(s) are associated with clinical phenotype could help the field forward.
Methods: In a cross-sectional study of 131 well-phenotyped young adults with recent onset psychosis, we performed cluster analysis based on 12 inflammatory analytes in EDTA plasma. After identification of clusters, associations were explored with baseline characteristics and severity of symptoms.
Results: We found two distinct clusters with relatively more females. One cluster (n=33, 25%) showed both elevated pro- and anti-inflammatory cytokines, indicating chronic low-grade inflammation. Individuals in this cluster remarkably smoked less tobacco but did not differ on clinical characteristics. The second cluster (n= 22 , 17%) showed a different pattern with higher MMP9 and IL-1beta levels, but lower levels for all other analytes.
Discussion: The cluster analyses indicate that inflammation may play a role in a substantial subgroup of patients with recent onset psychoses, whereby clinical characteristics cannot distinguish those subgroups. Identification of an inflammatory subgroup could provide a basis for personalised anti-inflammatory treatment as therapeutic option. Further research is necessary to validate this cluster approach and whether membership to a cluster affects illness course.

F73. ENDOCANNABINOID SYSTEM AND WEIGHT IN CLOZAPINE SCHIZOPHRENIA PATIENTS

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Background: Schizophrenia has a complex pathophysiology and etiology, which is not yet clearly defined. The currently most accepted hypothesis based on dysfunction in dopaminergic neurotransmission (1,2) has clear limitations. Currently, other neurotransmitters have been studied in addition to dopamine. Recent evidence points to the possible involvement of the endocannabinoid system (ECS) in schizophrenia (3,4). ECS regulates a number of physiological functions through the modulation of other neurotransmitters in the brain (5). It is a neuromodulatory system involved centrally and peripherally in the regulation of several pathophysiological processes (6).
Experimental studies in animals, healthy volunteers and patients with schizophrenia suggest a dysregulation of ECS in patients with schizophrenia (7,8). In parallel, growing evidence indicates that ECS also acts on appetite control, fat accumulation in adipocytes and on reducing energy expenditure through the action on glucose and lipid metabolism (9,10). Preliminary evidence links the weight gain often seen in patients with schizophrenia to ECS (11,12).

Methods: The patients were recruited from the outpatient clinic of the Psychosis Group of LIM-27 at the Institute of Psychiatry – HCFMUSP. The controls came from the screening for research of UHR individuals in the same clinic. The presence of mental disorders was excluded after performing the Structured Clinical Interview for DSM-IV axis I Disorders by a qualified and trained professional. The study was approved by the ethics committee and the subjects signed a consent form.
Socio-demographic characteristics in relation to gender, age, medication use and cannabis use were collected. Weight and height were measured to calculate the BMI based on standardized formulas. The PANSS scale was applied to patients with schizophrenia.

By measuring the proteins and metabolites involved in ECS pathways in peripheral blood, the analytes AEA (anandamide) and 2-AG were quantified by tandem mass spectrometry coupled to a liquid chromatograph.

Statistical analyzes were performed using the SPSS program. The value of the confidence interval adopted was 95%, with a value of $p<0.05$.

Results: Firstly we observed that the age of patients is higher and BMI had no significant difference between groups. Males prevail in the group with schizophrenia and are a minority among controls. The use of cannabis is more prevalent among patients, being rare in the other group.
For individuals in the three groups, quantification of AEA and 2-AG by mass spectrometry was performed. AEA had a non-normal distribution, whereas the distribution of 2-AG was normal, after performing the Shapiro-Wilk normality test. Thus, we used ANOVA to compare means of 2-AG and Kruskal-Wallis for AEA data. Values of $p=0.935$ were found for AEA and $p=0.485$ for 2-AG. Therefore, it is suggested that there is no significant difference between patients with schizophrenia and controls in these ECs, regardless of the use or not of clozapine.

There was also no correlation between BMI and anandamide or 2-AG levels, either in patients with or without clozapine, or in controls, analyzed separately or together.

However, differences were found between cannabis users. Those who report lifetime use of cannabis have lower 2-AG values ($p=0.015$). After controlling for weight, the result was maintained. For both controls and patients with schizophrenia analyzed separately or together, those who do not use cannabis have higher 2-AG values. It is thus possible to understand the use of cannabis as a determinant of 2-AG values.

A GLM model was performed to relate the data with the dependent variable, 2-AG, including group (clozapine, non-clozapine, control), use of cannabis and BMI. In this model, cannabis use remained the only factor that statistically influences 2-AG levels.

Discussion: Among the three groups, there was no significant difference in ECs levels related to the use of clozapine or other antipsychotic. To our knowledge, this is the first study considering clozapine modulation in peripheral ECs. Increased AEA levels were observed in the peripheral blood of treated individuals with schizophrenia (16,19). The similarity of ECs levels in patients and controls in our study can be related to the use medication and clinical stability.
We found lower values of peripheral 2-AG in individuals with cannabis use, with no significant difference regarding AEA. Contrary to our data, Morgan et al., 2013, found an increase in 2-AG levels relative to controls in heavy cannabis users. Sempio et al., 2021, corroborated these findings

and also demonstrated an increase in AEA levels. Cannabis use influence anandamide levels more consistently than 2-AG in current literature (20-23).

Regarding weight and BMI, we found similar values between patients and controls, different from what was expected. The issue of overweight, common to the total study sample has a complex and multifactorial origin (24).

Limitations of the present study include a relatively small sample size and the assessment of cannabis use according to the patients' self-reports. The relationship between peripheral findings and CNS are still uncertain and, although suggestive of similarities with central markers, they must be more robustly validated.

F74. FULL RECOVERY AND SELF-EFFICACY IN FIRST-EPISODE SCHIZOPHRENIA: THE OSR COHORT AT 10-YEAR FOLLOW-UP

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Background: Self-efficacy is commonly referred to as the expectation that one can effectively cope with and master situations through one's own personal efforts. Still, little is known about its influence on recovery rates in first-episode schizophrenia (FES). To our best knowledge, the Oslo Schizophrenia Recovery Study (OSR) is the only longitudinal study that investigates the relationship between trajectories of self-efficacy and full recovery in FES, using a comprehensive and strict definition of full recovery. As well as tracking the development of self-efficacy, we identify the time point during the 10-year follow-up period when participants meet criteria for remission and full recovery. The objective of the present study is to identify the proportion of individuals with FES reaching full recovery after ten years, and to investigate if there are significant differences in self-efficacy development among recovered and non-recovered participants. It has been proposed that the first two years of illness are critical for long-term outcome. Thus, a further differentiation between early full recovery (recovery during the first two years of follow-up) and late full recovery (recovery after the first two years of follow-up) was made, with an aim to investigate whether there exist different trajectories between those participants who show early full recovery versus those who recover later in the course of the illness.

Methods: 28 FES-patients are interviewed and assessed yearly according to a comprehensive and strict criterion of full recovery. Self-Efficacy is measured according to the General Perceived Self-Efficacy scale (GSE). The present study includes data from all twelve follow-ups over ten years. Both descriptive statistics and multilevel modelling were used to investigate the research questions.

Results: At ten-year follow-up, 79 % of the participants were retained. 59% of the patients fulfilled the criteria for full recovery, with a total of 63,5% being fully/partly recovered. 50% of the fully recovered participants were not on antipsychotic medication.

Choosing the overall best linear mixed model, there was a significantly larger increase in self-efficacy among the recovered than the non-recovered group. However, adding a Time x Group

interaction parameter did not significantly improve the model fit, indicating no differences in trajectory growth over ten years. The Results: from our second analysis, including three recovery groups, consistently showed a non-significant effect of the late full recovery group.

Discussion: The findings of the present study show that the rate of recovered participants steadily increases during the ten year-follow up, from 16 % (two-year follow-up) to 59% (ten-year follow-up). These findings indicate that a larger proportion of FES patients reaching full recovery than earlier expected. Second, the Results: highlight self-efficacy as a factor associated with increased recovery in FES, adding to the small literature on improvement among these patients. Third, even though self-efficacy may be harder to achieve in the context of a serious mental illness, it nonetheless appears to be a viable treatment goal with implications regarding a brighter and more positive outlook for the majority of FES patients. It is likely that our non-significant result of the late full recovery group represents limitations of the sample-size, and that the differentiation into late and early recovery still might be a meaningful subdivision in first-episode schizophrenia.

F75. SIDE EFFECTS ON A FIRST PSYCHOTIC EPISODE SAMPLE: INFLUENCE OF AGE AND GENDER

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Background: Antipsychotics are the first line treatment for acute psychotic symptoms and are widely used as maintenance medication for psychotic disorders. They are proven for positive and affective symptomatology, and partially for negative symptoms (Miyamoto et al, 2012). Nevertheless, both short-term and long-term treatments carry a side effect burden, frequently ignored or not assessed in a transversal way (M. Nose 2012). The medication used during a first psychotic episode (FEP) can determine a large part of the adherence and beliefs around medication (M. Lambert, 2004) and thus the clinical evolution of the person being treated (Gilmer et al, 2004). Different studies show that, regardless of the drug profile, there are other variables that affect and relate to this side effect burden, such as sociodemographic variables like age or gender (Trude Seselie Jahr Iversen et al, 2018). The Results: according to the types of side effects concerning those variables are not clear and should be further investigated in prospective studies.
The aims of the present study were: a) to study the prevalence of side effects in a FEP sample and b) to assess how age and gender influence the presence and perception of drugs side effects

Methods: 85 FEP (62 men and 23 women) who belong to Mental Health Parc Sanitari Sant Joan de Déu (for adults) and Hospital Sant Joan de Déu (for children and adolescents) were recruited.

The Side Effect Rating Scale (UKU) was administered to assess the side effect of the antipsychotic medication and sociodemographic data was also collected. The assessment took place 3 months after the patient's hospital admission. The statistical analysis was carried out through frequencies and percentages and to assess gender and age differences in side effects, we used the Chi-Square test and the Pearson correlation, respectively.

Results: The most prevalent side effects in our FEP sample at the 3 months follow-up were: Asthenia/lassitude (67.9%), the sleepiness/sedation (57.1%), the emotional indifference (51.2%) and weight gain (67.9%).

Taking into account gender, the Results: showed that women had more severity in the side effects related to asthenia/lassitude (X2=12.135; p=.007), nausea/vomiting (X2=8.309; p=.040), and constipation (X2=11.569; p=.021).

According to age, the older the sample, the more presence of: sleepines/sedation (r=.282; p=.009), depression (r=.240; p=.027), acatisia (r=.295; p=.007), weight loss (r=.300; p=.006) and amenorrea (r=.361; p=.036). The youngest the sample, the more increased duration of sleep (r=.215; p=.048).

Discussion: Age and gender need to be taken into account when prescribing antipsychotic medication, highlighting the importance of the psychic and autonomic side effects to improve the perception and the interference of these effects on the patient's quality of life.

F76. ANATOMICAL INTEGRITY OF WHITE MATTER LANGUAGE PATHWAYS AND SEMANTIC COGNITION DEFICIENCIES IN EARLY PSYCHOSIS

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Background: Semantic processing anomalies, clinically found within formal thought disorders (FTD) and delusional phenomena, are a core feature of psychosis. In a retrospective diffusion tensor imaging (DTI) study we recently highlighted the importance of the integrity of the ventral language stream in semantic processing deficits in schizophrenia spectrum disorders: axial diffusivity of the left inferior fronto-occipital fasciculus (IFOF) was inversely correlated with semantic processing impairments ($r=-0.579$, $p<0.0001$) – a finding that was replicated in an independent sample. However, the retrospective nature and the pooling of different aspects of semantic cognition limit the interpretation of these study. In a prospective study we thus investigate the white matter integrity of the ventral language stream with regard to specific aspects of semantic cognition (semantic representation and control) in early psychosis (EP) patients. We hypothesize in EP, a correlation of the integrity of the ventral language stream with semantic processing deficits. More specifically we hypothesize a correlation of the direct ventral pathway - IFOF) - with semantic control, on the one hand, and of the indirect ventral pathway - inferior longitudinal fasciculus (ILF) and uncinate fasciculus (UF) - with semantic representation, on the other hand.

Methods: DTI combined with probabilistic fiber tractography as well as different semantic representation and control tasks (such as the DO80 Picture Naming Test and the Camel and Cactus Test respectively) are applied in EP patients and healthy controls. For the ventral language stream, we assess the ILF and UF in addition to the IFOF. Since not associated to semantic cognition, the arcuate fasciculus and corticospinal tract are used as control tracts. The relationship between

representation and control elements of semantic cognition and tract integrity will be analyzed separately and with regard to both hemispheres.
Results: Based on our previous finding of a negative association between semantic impairments and axial diffusivity of the left IFOF (r = -0.564), we expect to achieve a substantial part of the targeted sample size until spring 2022 and will be able to present preliminary Results: of the data analysis at the SIRS Conference in April 2022.
Discussion: This work will provide potential new insights into the detailed structural anatomy of semantic processing disorders in schizophrenia.

F77. A PRELIMINARY LOOK AT HOW COORDINATED SPECIALTY CARE MAY DECREASE CONVERSION AND INCREASE FUNCTIONING IN INDIVIDUALS AT CLINICAL HIGH-RISK FOR DEVELOPING PSYCHOSIS

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Background: Clinical high-risk for psychosis (CHR-P) is an emerging field with limited established evidence-based treatment. The PeaceHealth Lane County Early Assessment and Support Alliance (EASA) program in Eugene, Oregon aims to establish guidelines and evidence for effective clinical practice for youth at clinical high-risk for developing psychosis. PeaceHealth began offering first episode psychosis treatment in 2010 through RA1SE (Recovery After Initial Schizophrenia Episode), which utilized the NAVIGATE program. RA1SE demonstrated that Coordinated Specialty Care (CSC) models can be effective in treating first episode patients compared to usual care. In 2018, PeaceHealth EASA received a Substance Abuse and Mental Health Services Administration (SAMHSA) grant to offer CHR-P services. Over the past three years, the PeaceHealth CHR-P program worked to clarify screening and assessment processes, adapt existing interventions, develop tools for assessing level of care, and measure outcomes. These outcomes are presented here.
Methods: Screening criteria: age 12-24 and meet criteria for Attenuated Psychosis-Risk Syndrome using the Structured Interview for Psychosis-Risk Syndrome (SIPS).
Assessments: The SIPS and Global Functioning: Social and Role Scales are administered quarterly. National Outcome Measurement System (NOMS) is administered at program entrance, and every 6-months.

Interventions: medication management., individual therapy using Cognitive Behavioral Therapy for CHR-P, family psychoeducation and therapy, occupational therapy, vocational/educational counseling and peer support. Services are offered in the office, in the community, in the home and via telemedicine, depending on participant need and preference. Level of care is determined using the Participant Engagement Framework (PEF) developed by the program. The PEF assesses acuity of symptoms and barriers to treatment. All cases are reviewed weekly by the team and individual case consultations occur at least bi-monthly.

Results: In a 6-month follow up assessment with 48 CHR-P clients, comparing baseline and follow up using the National Outcomes Measurement System (NOMS) improvements were reported in

overall health (61%), school/work (71%), overall daily functioning (42%), no serious psychological distress (52%), and no significant decrease in feeling connected socially (3%) and with the community (8%) despite Covid-19. Overall, 97% reported satisfaction with care. Global Function Scales improvements were also demonstrated in higher Role functioning scores (32%) and Social functioning scores (28%). Only 58 % fully completed the program and/or completed transition of care. Loss of contact was experienced at 17%, and 12% discharged for other reasons. Clients who experienced their first episode and were transferred to the First Episode of Psychosis (FEP) program was 12%.

Discussion: Based on these preliminary results, there is benefit to offering coordinated-specialty care to the CHR-P population. Participants in the interdisciplinary program experienced improvements in daily functioning and engage successfully in their social and role activities while minimizing the impact of the attenuated psychosis-risk syndrome symptoms. The Results: also demonstrate a lower conversion rate to first episode of psychosis compared with current expected outcome at about 35% based on the North American Prodrome Longitudinal Study (Addington et al., 2015).

A first episode coordinated specialty care program was successfully modified and adapted for CHR-P treatment through offering CBT for CHR-P in individual therapy rather that the Navigate curriculum. We developed age additional age-appropriate hand outs and activities for younger, pre-teen program participants. We also developed a tool for assessing level of care specific to the CHR-P population, the Participant Engagement Framework (PEF)

Limitations to the Results: include lack of a control group to compare treatment as usual versus the coordinated-specialty care, lack of follow up data for certain participants due loss of contact and/or early termination from the program, and changes in interventions over time. The Results: presented here also compared only the baseline to 6-month follow up data and would benefit from comparing data to additional follow-up outcomes over the two-year program period.

Recommendations for further research include completing a comparison study with program intervention and treatment as usual. Recommendations for further CHR-P program advancement include creating a manual of treatment guidelines to appropriately adapt interventions to the developmental and clinical needs of this younger age group; and finding efficient ways to implement CHR-P programs to existing First Episode Programs across the country.

Addington, J. et al (2015). North American Prodrome Longitudinal Study (NAPLS 2): The Prodromal Symptoms. The Journal of nervous and mental disease, 203(5), 328–335.

F78. SPEECH ILLUSIONS PREDICT OUTCOMES IN INDIVIDUALS AT-RISK OF PSYCHOSIS

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Background: Hallucination-proneness is associated with an increased risk of developing psychosis. Hence, experimentally captured speech illusions may predict the trajectory of psychosis and could be used as a marker for psychosis risk.
Methods: 344 CHR participants and 67 healthy controls (HC) were recruited as part of the EU-GEI study. At baseline, we assessed whether participants heard speech in white noise (speech illusion) and whether participants felt uncertain about the affective valence of the speech illusion. Whether CHR participants transitioned to psychosis or not (CHR-transition vs CHR non-transition), remitted from their CHR status or not (CHR-remit vs CHR non-remit), and score on the Global Assessment of Functioning scale was assessed at 1 and 2-year follow-up. We also analysed performance within a signal detection theory (SDT) framework. We used logistic and linear regression analyses to assess tested whether performance predicted clinical or functional outcomes, respectively.
Results: We observed group differences in the number of participants that heard a speech illusion they felt uncertain about (HC vs CHR: 36% vs 51%, p=0.03; CHR-remit vs CHR non-remit: 47% vs 76%, p=0.01). In CHR participants, hearing uncertain speech illusions at baseline predicted both functioning 1 year later (p=.02, B=-5.22, SE=2.23) and remission 2 years later (p=.01, OR=5.66). For the SDT analysis, performance was worse in participants who did not remit 2 years later compared to participants who did remit (t=-2.05, p=.04). The amount of certainty needed to make a decision on the task (c) differed between remitters and non-remitters (t=-2.35, p=.02), and this parameter predicted remission two years later (p=.04, OR=.25)
Discussion: Our Results: indicate that performance on the white noise task predicts remission status and functional outcome 1-2 years later. This may represent a useful marker to predict outcomes in CHR individuals.

F79. WHITE MATTER ABNORMALITIES IN CLINICAL HIGH-RISK STATE AND RECENT-ONSET PSYCHOSIS

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Background: Decreased fractional anisotropy of cellular tissue (FA-t) and increased free-water fractional volume (FW) derived from diffusion MRI (dMRI) represent replicated findings in individuals with psychosis and were also found in individuals at clinical high-risk (CHR), even though less consistently. FA-t reductions were found across disease progression, whereas FW increases were suggested to be linked with acute immune response that occurs close to psychosis onset. The Personalized Prognostic Tools for Early Psychosis Management (PRONIA) study recruited healthy controls (HC), individuals at CHR and individuals with recent-onset psychosis (ROP). This enables the direct comparison between CHR and ROP groups to better understand temporal occurrences of FA-t and FW abnormalities. We also tested for association of FA-t and FW with the duration of psychosis and at-risk status. In all analyses we accounted for sex-specific vulnerability.

Methods: N=207 individuals with ROP (91F/116M), N=183 CHR individuals (95F/88M) and N=297 HC (178F/119M) were recruited across seven sites. dMRI were pre-processed, harmonized, and co-registered to create averaged values for diffusion metrics (FA-t and FW) across 23 white matter regions of interests (ROIs). We investigated differences in diffusion metrics between ROP or CHR individuals and HC and group-sex interactions using linear models. Separate models were tested for each ROI using age (linear and quadratic effects) as nuisance covariates. Next, we modelled a normative trajectory in HC using a linear model of sex- and age-related differences of diffusion metrics. We then applied the normative trajectory model to CHR and ROP to obtain subject-specific residuals. Using these residuals, we investigated group differences and association with the duration of psychosis and at-risk status for ROP or CHR. We also tested for sex effects on these associations.

Results: Individuals with ROP showed significantly lower FA-t in 5/23 ROIs (pFDR<.025) and higher FW in the inferior fronto-occipital fasciculus (pFDR<.011) compared to HC. FW also showed significant group-sex interaction, where higher FW in ROP was driven by male individuals in 3/23 ROIs (pFDR<.010). CHR individuals showed significantly lower FW in the posterior thalamic radiation compared to HC but no differences in FA-t. Similar to ROP there was a significant group-sex interaction with higher FW in CHR males (in 4/23 ROIs; pFDR<.024).

Directly compared to CHR, ROP showed significantly lower FA-t and higher FW in the genu of the corpus callosum (pFDR<.042). In CHR, higher FW was associated with a shorter duration of CHR status in females (5/23 ROIs, pFDR<.040) but not in male CHR. No association with the duration of psychosis was found in ROP.

Discussion: Our Results: replicate previous findings in ROP and extend them to CHR. Interestingly, we found sex-specific FW increase driven by males in both groups. For females,

FW-increases were higher closer to symptoms onset followed by a reduction of FW with the duration of CHR, which could indicate habituation, treatment response or neuroprotective factors following an acute response. However, this hypothesis needs further testing in longitudinal studies.

F80. PROINFLAMMATORY BIOMARKERS PRESENT DURING ADOLESCENT FIRST EPISODE PSYCHOSIS: PREDICTORS FOR COGNITIVE IMPAIRMENT

Late-Breaking Poster

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Background: Regulation of the inflammatory response in Early Onset Psychosis (EOP) has emerged as a novel target in the search for pathophysiological mechanisms of psychotic disorders (Yao and Keshavan, 2011; Meyer, 2011; Meyer et al., 2011; Müller and Schwarz, 2008; Fan et al., 2007). Due to a deregulation, there is a higher inflammation response in both the peripheral and central nervous system from early onset psychosis (Leza et al., 2015). Objective: The current study was designed to assess the differences in proinflammatory cytokine levels in EOP subjects at the time of the first episode of psychosis compared to controls and the relationships between such proinflammatory biomarkers (MCP-1, TNF-α, and IL-6) at baseline and cognitive performance of attention, working memory, learning and executive function cognitive domains at baseline and at the two-year follow-up evaluation.

Methods: Data from a total 25 EOP subjects and 18 controls from the Longitudinal Study of First Episode of Early Onset Psychosis conducted at the Hospital General Universitario Gregorio Marañón were retrieved for this purpose. Peripheral blood samples were collected, and a comprehensive neuropsychological evaluation was conducted by means of a standardized cognitive battery, including measures of; Attention (Conners Continuous Performance Test II, CPTii, WAIS III / WISC-R digit span, Stroop words and Stroop colors, trail making test part A), Working Memory (WAIS III / WISC-R digits backwards, WAIS III / WISC-R letters and numbers, trial making test part B), Learning and Memory (Verbal Learning Test, Total of F responses, Total of A responses, Total of S responses) and Executive Function (WAIS III / WISC-R letter and number, trial making test ratio =TMT-B1 / TMT-A1, Wisconsin Card Sorting) Test,WCST

number total of errors, WCST preserved errors, WCST correct responses, and WCST number of categories completed, Stroop interference, Verbal Fluency Test Total Score, COWAT animals). Mann-Whitney U Test were used for comparisons between groups on levels of inflammatory biomarkers. Multiple Linear Regression models were built to examine the predictive value of baseline biomarkers on cognition over the first two years of psychosis.
Results: EOP subjects showed significantly higher levels of TNF-α than the control subjects ($U=214.50$, $p < 0.05$) at the time of the first episode of psychosis. For EOP subjects, at the time of the first evaluation, proinflammatory biomarker MCP-1 at the baseline evaluation was negatively associated with executive function performance ($B= 0.002$, $p = 0.034$) explaining a significant amount (14.89%) of variance at baseline, as well as with the attentional cognitive domain ($B= .0001$, $p = .034$), explaining 7.5% of variance at baseline.
Discussion: Thus, MCP-1 levels at the time of the first episode of psychosis, could serve as a predictor for cognitive performance outcomes, notably of on executive function and attention performance at the first contact with psychiatric services.

F81. SYNTACTIC NETWORK ANALYSIS IN SCHIZOPHRENIA-SPECTRUM DISORDERS

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Background: Language anomalies are a hallmark feature of schizophrenia spectrum-disorders (SSD). Network analysis has allowed the detection of language disturbances in SSD based on words' co-occurrence. In the present study, we propose to use network analysis to examine grammatical relations in SSD and healthy controls, using 'syntactic networks'. In such syntactic networks, words and syntactic categories are represented as nodes, and edges corresponding to the syntactic relations between them. We aim to explore differences in syntactic networks between patients with SSD and healthy controls, and assess their relationship with sociodemographic factors, psychotic symptoms, and cognitive functioning. Moreover, we aim to evaluate whether the quantification of syntactic network measures has diagnostic value.
Methods: During a semi-structured interview on neutral topics, we collected speech samples from 63 patients with SSD and 63 healthy controls. In order to quantify syntactic relations, each utterance was converted into its syntactic representation, namely a parse tree. Subsequently, the parse trees were modeled as directed networks in Cytoscape, and analyzed for local and global network measures. Thirteen network measures were compared between groups using multivariate analysis of covariance (MANCOVA), controlling for age, gender, and education. Correlations with psychotic symptoms (Positive and Negative Syndrome Scale; PANSS) and cognitive functioning (Brief Assessment of Cognition in Schizophrenia; BACS) were computed. The network features were fed into a random forest classifier with twenty-leave-out cross validation to assess the classification power of the model.
Results: Patients with SSD and healthy controls significantly differed on most syntactic network measures. Relative to controls, patients showed a lower number of nodes, edges and leaves, lower degree, decreased stress centrality, higher characteristic path length, and higher diameter (all

p<.001). The MANCOVA revealed that gender had a significant effect on syntactic network measures (F(12,109) = 2.006, Pillai's trace = 0.181, p = .030), and there was a significant interaction between gender and group (F(12,109) = 2.427, Pillai's trace = 0.211, p = .008), as the anomalies in syntactic relations were most pronounced in the women with SSD. No main effects of age or education were found. PANSS negative scores and global cognition were associated with several network measures. Post-hoc correlation analyses revealed that these network measures were significantly associated with working memory, information processing speed, attention, and executive function. The machine learning classifier distinguished patients with SSD from controls with a sensitivity of 76% and a specificity of 73% based on syntactic network measures. The model reached a sensitivity and specificity of 80% when trained on the female set separately.
Discussion: Examining syntactic relations from a network perspective revealed significant differences between patients with SSD and healthy controls, especially in women. Syntactic networks of patients with SSD are significantly smaller, less connected and less centralized compared to controls', presenting a linear rather than hierarchical organization. These measures are associated with negative symptoms and cognition, and can be understood in light of existing linguistic theories. Syntactic network measures provide a clinically meaningful way to quantify syntax and form an important addition to the broader literature on the development of a speech biomarker for SSD.

F82. THE ASSOCIATION OF PLASMA INFLAMMATORY MARKERS WITH OMEGA-3 FATTY ACIDS AND THEIR MEDIATING ROLE IN PSYCHOTIC SYMPTOMS AND FUNCTIONING: AN ANALYSIS OF THE NEURAPRO CLINICAL TRIAL

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Background: There is increasing evidence that dysregulation of polyunsaturated fatty acids (FAs) mediated membrane function plays a role in the pathophysiology of schizophrenia. Even though preclinical findings have supported the anti-inflammatory properties of omega-3 FAs on brain health, their biological roles as anti-inflammatory agents and their therapeutic role on clinical symptoms of psychosis risk are not well understood. In the current study, we investigated the relationship of erythrocyte omega-3 FAs with plasma immune markers in a clinical high risk for

psychosis (CHR) sample. In addition, a mediation analysis was performed to examine whether previously reported associations between omega-3 FAs and clinical outcomes were mediated via plasma immune markers.
Methods: Clinical outcomes for CHR participants in the NEURAPRO clinical trial were measured using the Brief Psychiatric Rating Scale (BPRS), Schedule for the Scale of Assessment of Negative Symptoms (SANS) and Social and Occupational Functioning Assessment Scale (SOFAS) scales. The erythrocyte omega-3 index [eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA)] and plasma concentrations of inflammatory markers were quantified at baseline (n = 268) and 6-month follow-up (n = 146) by gas chromatography and multiplex immunoassay, respectively.
Results: In linear regression models, the baseline plasma concentrations of Interleukin (IL)-15, Intercellular adhesion molecule (ICAM)-1 and Vascular cell adhesion molecule (VCAM)-1 were negatively associated with baseline omega-3 index. In addition, 6-month change in IL-12p40 and TNF-α showed a negative association with change in omega-3 index. In longitudinal analyses, the baseline and 6-month change in omega-3 index was negatively associated with VCAM-1 and TNF-α respectively at follow-up. Mediation analyses provided little evidence for mediating effects of plasma immune markers on the relationship between omega-3 FAs and clinical outcomes (psychotic symptoms and functioning) in CHR participants.
Discussion: Our Results: indicate a predominantly anti-inflammatory relationship of omega-3 FAs on plasma inflammatory status in CHR individuals, but this did not appear to convey clinical benefits at 6 month and 12-month follow-up. Both immune and non-immune biological effects of omega-3 FAs would be resourceful in understanding the clinical benefits of omega-3 FAs in CHR population.

F83. LONGITUDINAL CHANGES IN DELAYED VERBAL MEMORY AND TRANSITION TO PSYCHOSIS FROM THE CLINICAL HIGH-RISK STATE

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Background: Robust deficits in verbal memory and verbal fluency are evident in the early stages of psychosis development among people at clinical high-risk for psychosis (CHR). Reviews of cross-sectional studies have suggested a potential neurocognitive decline prior to or over the transition to psychosis. However, this has been debated as follow-up studies of CHR cohorts have not consistently found evidence for a decline. A better understanding of the course of

neurocognition in CHR individuals, and particularly over illness onset for those who transition to psychosis (CHR-T), may inform early intervention strategies in this population. Using data from a large, multi-national study, the aim of the present paper was to examine longitudinal changes in neurocognition of CHR individuals and its association with functioning and remission from the clinical high-risk state.

Methods: The EU-GEI study recruited CHR individuals from 11 psychosis early detection centres across Europe, Australia, and Brazil. Longitudinal, multi-modal data was collected for CHR individuals and a healthy control group (HC) at up to four timepoints (baseline, six months, 12 months, and 24 months). The final sample consisted of 319 CHR and 60 HC who had completed at least one measure of cognition. Cognition was measured by verbal memory (immediate and delayed recall) and verbal fluency (semantic and phonemic) performance. Most CHR participants were not on antipsychotic medication at first assessment (90.9%). Given the multi-level structure, we applied linear mixed models to determine differences in the cognitive trajectories of CHR compared HC, as well as CHR-T compared to CHR-NT individuals. We also examined whether changes in cognition were associated with functioning or remission status over time in CHR individuals.

Results: For CHR versus HC comparisons, we found significant effects of group status on immediate recall ($p<.001$), delayed recall ($p=.007$), semantic fluency ($p<.001$) and phonemic fluency ($p<.001$) performance at two-year follow-up. However, we did not observe differences in the cognitive trajectories of CHR and HC groups during the follow-up period (all $p>.05$). Among CHR participants, transition to psychosis was associated with delayed recall at two years ($p=.002$). Furthermore, trajectories of delayed recall performance over the study period significantly differed between CHR-T and CHR-NT groups ($p=.013$). In line with our previous findings, we found a main effect of immediate recall on both functioning and remission among CHR, yet Results: revealed trend level significance for immediate recall x time interaction effects ($p=.08$ to $.09$).

Discussion: Results: were consistent with evidence of verbal memory and verbal fluency deficits among CHR individuals compared to healthy controls, but the course of neurocognition did not differ between the two groups. Therefore, our Results: do not provide support for a generalised cognitive decline in the CHR state. On the other hand, CHR-T and CHR-NT participants showed distinct trajectories of delayed verbal memory performance over the course of follow-up. Findings indicate that the verbal memory domain may be an important target for early interventions aimed to improve cognitive deficits.

F84. ETEROGENEITY OF THE IMMUNE SIGNATURE OF SCHIZOPHRENIA AND ASSOCIATION TO BRAIN STRUCTURE: A SEMI-SUPERVISED MACHINE LEARNING APPROACH

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Background: Immune dysfunction is implicated in the aetiology of schizophrenia with elevation of interleukin (IL)-6 and CRP detected in the periphery and causality suggested in studies using mendelian randomisation. However not all patients with schizophrenia show evidence of inflammation and individual markers show heterogeneity of evidence across different studies. This may be the result of a more complex immune signature in schizophrenia than is currently seen in traditional clustering or subgroup analyses with relatively small samples. There is a need for identification of inflammation subgroups in large sample sizes using advanced clustering techniques with testing of generalizability in external datasets.
Methods: We used HYDRA (HeterogeneitY through DiscRiminant Analysis), a semi-supervised machine learning approach that generates a convex polytope formed by combination of multiple linear max-margin classifiers to separate patients (n=467) from healthy controls (HC) (n=600) and assess disease-related heterogeneity, in a schizophrenia dataset (Australia Schizophrenia Research Bank (ASRB)). HYDRA was trained using a repeated hold-out cross-validation strategy (i.e., 1000 repetitions with 80% of the data for training in each repetition) on cytokine data in the ASRB sample. Adjusted Rand Index (ARI) was used to measure cluster stability and permutation testing was employed to assess the cluster solution's statistical significance. Immunological profile, GMV alterations, and neurocognitive deficits were explored in the identified clusters. The Benefit of Minocycline on negative symptoms of schizophrenia in patients with recent-onset psychosis (BENEMIN) dataset was used as an external dataset to assess the clustering solution performance in a younger sample with less medication exposure.
Results: The optimal clustering solution revealed five main clusters (Cluster 1, Low inflammation: n=142, Cluster 2, elevated CRP: n=121, Cluster 3, elevated Il-6 and IL-8: n=82, Cluster 4: elevated IFN-γ, n=80, and Cluster 5, elevated IL-10: n=32, ARI: 0.573. When compared to healthy controls all clusters showed hippocampal and temporal GMV loss. The IL-6 and IL-8 inflammation cluster showed the most widespread GMV loss and was the only cluster to include anterior cingulate GMV loss. The low inflammation and the IFN-γ cluster showed bilateral pallidal and precentral gyrus GMV increases respectively. The IFN-γ cluster showed the least GMV loss and neurocognitive decline. The low inflammation, CRP, IFN-γ, and IL-10 clusters were detected in the BENEMIN replication dataset.
Discussion: We identified subgroups of schizophrenia with differential expression of immune dysfunction each associated with a distinct neuroanatomical signature. This may suggest that there are multiple inflammatory pathways to schizophrenia, with IL-6 related classical inflammation showing the most widespread GMV loss and a specific anterior cingulate signature. Identification of such subgroups have the potential to inform targets for targeted novel treatments in schizophrenia.

F85. AUTOMATED SPEECH MARKERS CAN IDENTIFY HIGH SCHIZOTYPY TRAITS

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Background: Psychotic disorders are increasingly recognized as having characteristics that may manifest continuously across the general population. Measures of psychometric schizotypy may capture trait-like vulnerabilities across a continuum from health to psychotic experiences. Recent studies have used natural language processing and network analysis to assess speech in people with psychotic disorders and clinical high-risk states. These automated measures of speech aim to operationalize formal thought disorder, a key symptom associated with poorer clinical outcomes and reduced socio-occupational functioning. Importantly, it is thus far unclear how they manifest in the general population with respect to psychometric schizotypy.
This study used 20 automated measures of speech connectivity and semantic coherence to characterize speech from individuals recruited from the general population who had either low or high psychometric schizotypy. We used machine learning to test whether these features can discriminate individuals with high schizotypy based on 8-minutes-long, online collected speech recordings.

Methods: Online recorded speech samples from a picture description test were collected from the general population (N = 482, women =59%) using online recruitment (Prolific) and speech assessment (Gorilla.sc). Participants were aged between 18 and 40 years old (Mage = 28.7), spoke English as a first language and did not have a history of psychiatric or neurological disorders. Psychometric schizotypy was measured by the Schizotypal Personality Questionnaire (SPQ) and recoded into binary high-low groups, resulting in a sample where 18% of participants were found to have "high" scores. Speech was transcribed and vectors for each sentence were calculated based on word embeddings from the word2vec model pre-trained Google News and non-semantic speech network analysis was conducted resulting in 20 features including semantic coherence, and connectivity measures. An independent sample T-test was conducted to test for group differences in these measures. After SMOTE oversampling and random undersampling to create a balanced training sample, two supervised machine learning approaches, logistic linear regression, and Extra Trees classifier were applied to test the classification performance of the features, then logistic regression was applied on the whole dataset to explore feature influence.

Results: Tangentiality, on topic, number of sentences, number of words, a median of the number of edges, a median of the largest connected component of the speech measures showed significant group differences. Using train-test split approach, our logistic linear regression model could classify individuals with 0. 74 accuracy (precision = 0.94/0.36; recall= 0.74/0.77) while Extra Trees classifier could classify individuals with 0.82 accuracy (precision = 0.90/0.45; recall= 0.88/0.50). Applied to the whole dataset, logistic regression could successfully distinguish high and low schizotypy in 83% of cases (0.96 specificity, 0.36 sensitivity). Number of words, number of sentences were the significant independent variables in the model; "on topic" coherence measure, loop of two nodes, and repeated edges speech connectivity features had effect on the trend level.

Discussion: Some speech patterns that characterize psychotic disorders like less coherent and less wordy speech appear to be present in individuals with high schizotypy. Automatedly assessable speech features can discriminate between people with high and low schizotypy at a high level of accuracy. Although further improvements are needed in the classification power of speech feature-based models, findings suggest that by further refinement and wider involvement of coherence and connectedness-related markers, there is a potential to identify high schizotypy via automated, online, few-minutes long speech assessment.

F86. COMBINING ACOUSTIC AND SEMANTIC SPEECH MARKERS IMPROVES DIAGNOSTIC CLASSIFICATION OF SCHIZOPHRENIA-SPECTRUM DISORDERS

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Background: Speech is a promising marker to aid diagnosis of schizophrenia-spectrum disorders, as it closely reflects symptoms like thought disorder and negative symptoms. Previous approaches made use of different feature domains of speech for diagnostic classification, including measures of coherence (semantic) and form (acoustic) features. However, an examination of the added value of each domain when they are combined is lacking as of yet. Here, we investigate these domains (i.e. acoustic and semantic) separately and in combination.
Methods: Using a semi-structured interview with neutral topics, speech of 94 subjects with schizophrenia-spectrum disorder and 73 healthy control subjects was recorded. As explainability of models and the importance of individual features is a requirement for future clinical applications, we kept the number of features limited. Acoustic features were extracted using a standardized feature set, and transcribed interviews were used to assess semantic word similarity using a word2vec model. Separate random forest classifiers were trained on each feature domain. A third classifier was used to combine features from both domains. 10-fold cross-validation was used for each model.
Results: The random forest classifier achieved 81% accuracy in classifying schizophrenia-spectrum disorder and healthy control using features from the acoustic domain. For the semantic domain, the classifier reached an accuracy of 80%. Joining features from the domains, the combined classifier reached 85% accuracy, significantly improving on models trained on separate domains. For the combined classifier, top features were fragmented speech from the acoustic domain and variance of similarity from the semantic domain, both of which were the top features for their respective classifier.
Discussion: Both semantic and acoustic analyses of speech achieved ~80% accuracy in identifying schizophrenia-spectrum disorder and healthy control. We replicate earlier findings per domain, and additionally show that combining these features significantly improves classification performance. The feature importances from both domains in the combined classifier together with the improved performance indicate that the domains measure different and complementing aspects of speech in SSD. The current approach can in future easily be expanded with other linguistic features.

F87. INVESTIGATING TRANSDIAGNOSTIC INFLAMMATORY SUBGROUPS IN PSYCHIATRIC DISORDERS AND PSYCHOTIC EXPERIENCES BASED ON PERIPHERAL BIOMARKERS

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Background: Meta-analyses indicate that individuals with psychiatric disorders, such as psychotic disorders and depressive disorder, exhibit altered concentrations of peripheral inflammatory markers including IL-6, TNF-α, and CRP. It has been suggested that clinical trials of anti-inflammatory therapies for psychiatric disorders should target subgroups of patients with an increased inflammatory profile.

In this study, we tested the hypothesis that different subgroups of individuals with psychiatric disorders exist transdiagnostically, which can be distinguished by inflammatory biomarker signatures. As a secondary aim we investigated, using the same method, the presence of subgroups within individuals with psychotic experiences based on their inflammatory biomarker profile.

Methods: This study was a nested case-control study within the ALSPAC cohort at age 24. We measured the concentrations of ten inflammatory markers (IL-6, IL-8, IL-10, TNF-α, IFNγ, sICAM-1, sVCAM-1, A2M and suPAR) in the plasma of 380 participants with psychotic disorder, depressive disorder or generalised anxiety disorder and 399 controls without psychiatric symptoms. We employed a semi-supervised clustering algorithm, which has the potential to discriminate multiple clusters of psychiatric disorder cases from controls and find inflammatory subgroups specific to psychiatric disorders. For the secondary aim we repeated the analysis in a cohort of 203 individuals with psychotic experiences (including individuals with psychotic disorder) and the same 399 controls.

Results: Clustering solutions obtained for the participants with psychiatric disorders were unstable and did not explain the inflammatory marker data better than a Gaussian distribution ($p = 0.911$). There was weak evidence for three inflammatory subtypes within the psychotic experiences group (mean Adjusted Rand Index (ARI) = 0.40 +/- 0.01). Permutation analysis indicated the stability of the clustering solution performed better than chance (mean ARI = 0.33 +/- 0.05; $p < 0.001$), and the clusters explained the inflammatory marker data better than a Gaussian distribution ($p < 0.001$). Cluster 1 exhibited increased levels of the chronic inflammatory marker (suPAR) while Cluster 2 exhibited increased levels of acute and chronic inflammatory biomarkers. Participants in Cluster 3 showed lower levels of inflammatory markers.

Discussion: Our study did not find evidence for transdiagnostic subgroups of psychiatric disorders based on their inflammatory biomarker profile, when controls were used as a reference population. There was some evidence for three inflammatory subtypes among participants with psychotic experiences, and therefore we recommend that inflammatory subgroups within the psychosis spectrum phenotype are investigated further. These Results: may be useful in the planning of future clinical trials of anti-inflammatory therapies for psychiatric disorders.

F88. THE IMPACT OF CUMULATIVE ENVIRONMENTAL RISK FACTORS IN CHILDREN, ADOLESCENTS AND ADULTS WITH A SCHIZOPHRENIA SPECTRUM DISORDER: A DANISH REGISTER STUDY

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Background: Numerous environmental factors have been shown to increase the risk of developing a schizophrenia spectrum disorder; however, the individual effects are small. Moreover, exposure to some of the identified environmental risk factors is relatively common, while the prevalence of schizophrenia is low. Only very few studies have examined multiple risk factors simultaneously and their independent and cumulative effects are therefore not well elucidated.
Methods: We performed a nationwide register-based case-control study including all individuals in Denmark with a first-time schizophrenia spectrum diagnosis in the Danish National Patient Registry from 1973 through 2018. A healthy control (HC) sample was matched 5:1 to patients on age, sex, and parental socioeconomic status (labour market affiliation, income, and years of education). The sample consisted of 29.149 patients and 136.387 HCs. From the Medical Birth Registry we included: Birth weight and length, gestational age, season of birth, population density of birth place, immigration status, paternal age, maternal smoking during pregnancy, and Apgar scores. We also included information on average school grades and cannabis use diagnoses from the registers.
Results: Maternal smoking [odds ratio (OR) = 1.39], advanced paternal age >45 [OR = 1.35], low birth weight <2500g [OR = 1.28], and population density of birthplace [OR = 1.06] were significant independent early risk factors for the development of a schizophrenia spectrum disorder. We also observed significantly lower average school grades in patients compared to HCs (5.4 vs 6.2), while only few individuals had received a cannabis diagnosis (1.6% of patients before their schizophrenia diagnosis, 0% of HCs). The mean age of illness onset for patients was 22.8 years old and ~20% of patients could be characterized as early-onset cases (before age 18). Only female gender [OR = 1.59], maternal smoking [OR = 0.89], and winter/spring birth [OR = 0.91] were significant predictors for having an early- compared to an adult onset. Finally, we observed a cumulative effect of early risk factors on age of illness onset with more risk exposures resulting in an earlier age of onset.
Discussion: Several early environmental factors independently increase the risk of developing a schizophrenia spectrum disorder, suggesting that multiple risk factors cumulate, leading to onset of symptoms once a critical threshold has been reached. Being female increased the risk of an early illness onset, which is associated with a worse prognosis. Additionally, our findings suggest that frequent environmental factors become a risk for an earlier illness onset when accumulated.

F89. THE NEEDS AND BARRIERS TO EXERCISE IN YOUNG PEOPLE WITH A FIRST EPISODE OF PSYCHOSIS: A QUALITATIVE STUDY

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Background: The literature has long described the benefits of exercise and sport in mental health care (Saxena, et al., 2005), and there is evidence that exercise and sport may have beneficial effects for the recovery of young people with a first episode of psychosis (Hallgren et al., 2018). Currently it is unclear which factors are most important for starting and maintaining sports participation in early psychosis, specifically with regards to sporting in the context of mental health care (psychomotor therapy) and maintaining sports in the community (e.g. football club). The aim of this qualitative study is to gain insight into what young people with a first episode of psychosis need to actively participate in sports and what possible barriers are for participation in sport.
Methods: Data collection will be collected from 15 participants through qualitative (semi-structured) interviews. Participants are diagnosed with a first psychotic episode, and are receiving care at the Early Intervention Psychosis (VIP) team in the northern part of the Netherlands. Data will be analyzed with Colaizzi's descriptive phenomenological method (Morrow, Rodriguez and King, 2015). The purpose of using this method is to uncover the genuine experience of the phenomenon that is being investigated (Turunen, Perälä and Meriläinen, 1994).
Results: This study is ongoing and data collection is currently taking place (75% of data has been collected). Results: will be presented at the conference.
Discussion: Findings of this study will contribute to gaining insight into what young people with a first episode of psychosis need during and just after a first episode of psychosis, with regards to participating in sports. This knowledge will form the basis for designing an innovative sports intervention for individuals with a first episode of psychosis with the aim of increasing the social participation.

F90. THE SAFETY AND EFFICACY OF PSYCHOSOCIAL ADHERENCE INTERVENTIONS IN YOUNG PEOPLE WITH EARLY PSYCHOSIS: A SYSTEMATIC REVIEW

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Background: The role of antipsychotic medication is supporting young people in their recovery from early psy-chosis is complex and controversial. It is common for young people, often given antipsychotic medication for the first time, to express a choice stop treatment potentially increasing the risk of relapse and admission to hospital. Our systematic review aimed to evaluate the safety and effectiveness of psychosocial interven-tions to enhance antipsychotic medication adherence in young people with early psychosis.
Methods: We reviewed randomized controlled trials (RCTs) of any psychosocial intervention explicitly de-signed to enhance adherence with antipsychotic medication in young people with early psychosis. Cochrane CENTRAL Register, Medline, Embase, PsychINFO and CINAHL were

searched on the 9th of July 2020 without time restriction. Studies were assessed for bias and quality using version 2 of the Cochrane risk of bias measure. Our initial search identified 3,020 documents.
Results: Following title and abstract and full-text screening, we were left with one published and un-published trial that met our inclusion criteria. Outcome data were available for one trial that tested a health dialogue intervention. Compared to the control intervention, health dialogue extended the time participants adhered to medication. Included trials were rated as having a high risk of bias.
Discussion: There is a paucity of evidence from high quality randomized controlled trials that establishes the safety and effectiveness of any type of psychosocial intervention to enhance medication adherence in young people with early psychosis. Further high-quality trials that are co-produced with ser-vice used are warranted.

F91. A ONE-YEAR NATURALISTIC COHORT STUDY FOLLOWING THE FIRST EPISODE OF PSYCHOSIS: TREATMENT OUTCOME, CLINICAL SYMPTOMATOLOGY AND PSYCHOSOCIAL AND OCCUPATIONAL FUNCTIONING IN THE PSYSCAN COHORT

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Background: Following the first presentation of an acute psychotic episode, outcomes vary from patients making a good recovery to cases suffering relapses repeatedly. Although the existing literature recognizes the importance of taking into account divergent factors like medication use, psychotherapeutic treatment, alcohol and substance use, methodological limitations have prevented past studies to take a broad approach by investigating the combination of these factors. The present study aimed to address this knowledge gap by painting a complete picture of one-year symptomatic and functional outcome in a large, international cohort of First Episode Psychosis (FEP) patients within a naturalistic follow-up design (PSYSCAN).
Methods: PSYSCAN is an international, longitudinal, multicenter study on the early stages of psychosis. The present work used data from the FEP cohort. Patients of 16–40 years of age, who had a first episode of psychosis as defined by a DSM-IV diagnosis of schizophrenia, schizoaffective disorder (depressive type) or schizophreniform disorder, were recruited at 16 institutions situated in Europe, Israel and Australia. Participants were followed up in a one-year, naturalistic, prospective design. Primary outcomes were the number of patients in symptomatic remission (1) and the number of patients who had functionally recovered (2) at one-year follow-up. Symptomatic remission was assessed according to the criteria described by Andreasen and colleagues (2005), except the time criterion. Remission status was based on the evaluation of symptoms in the past week; functional recovery was defined as a SOFAS score greater than 60 and the absence of any psychiatric hospitalizations since the previous assessment. Secondary outcomes included psychotic symptomatology (PANSS), depressive symptoms (HAM-D), psychosocial and occupational functioning (GAF and SOFAS), psychiatric hospitalizations, treatment characteristics and substance use involvement (WHO-ASSIST). To assess whether

proportions of category membership (e.g., remission and recovery status) change over time, generalized linear mixed models were performed using a binomial distribution and a logit link function. Continuous endpoints were analysed using linear mixed models.
Results: A significant effect of time was found on both remission status and recovery status ($p < .001$). The amount of patients in remission increased from 140 out of 301 patients (46.5%) at baseline to 144 out of 215 patients at 12-month follow-up (67.0%). A greater increase in recovery rates was observed, with 26 out of 302 patients (8.6%) being in recovery at baseline, to 114 out of 205 patients (55.6%) at month 12. Positive and negative psychotic symptoms, depressive symptoms and psychosocial and occupational functioning improved over time. In addition, a decrease in both the number of patients receiving inpatient treatment, and the number of patients receiving psychotherapeutic intervention was observed.
Discussion: The present study provides valuable insight in the general course of a broad range of clinical outcomes over a one-year period in a large group of FEP patients who are treated as usual in normal daily practice. The Results: support evidence of previous studies demonstrating a predominantly favourable one-year illness course in FEP patients at the early stage of the disease. It is recommended to create more consensus in the operational definition of outcomes like functional recovery, in order to enhance comparability between studies and move this area of research forward.

F92. COGNITIVE SUBGROUPS OF EARLY PSYCHOSIS DIFFER IN GLOBAL AND LOCAL BRAIN AGEING

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Background: Structural MRI data have been used to compare personalized estimates of brainAGE (i.e., deviation between neuroimaging-predicted and actual age) in patients with early psychosis (EP) and healthy controls (HC). These global brainAGE estimates suggest accelerated ageing in EP, but are not informative about potential regional differences. Additionally, prior research has not addressed the link between brain-ageing and cognitive function in EP. To address this gap, we used machine learning algorithms to identify subgroups of patients with EP based on their cognitive profile and then applied a deep learning algorithm to assess regional patterns of brain-ageing in each subgroup compared to healthy individuals.
Methods: Cognitive and T1-weighted structural neuroimaging data from the Human Connectome Project-Young Adults (HCP-YA) and the Early Psychosis (HCP-EP) studies were aggregated to yield a total sample of 1181 HC (mean age [SD] = 28.6 [3.87]; 46.7% male) and 126 patients with EP (mean age [SD] = 22.7 [3.37]; 69.8% male). Cognitive measures from the NIH Toolbox and the Penn Emotion Recognition Task were available for 84 patients and were submitted to K-means clustering implemented with the NbClust package in R. Subsequently, global and local brainAGE were computed from the neuroimaging data using the procedures developed and validated by Popescu and colleagues (https://githubmemory.com/repo/SebastianPopescu/U-NET-for-LocalBrainAge-prediction).

Results: K-means clustering identified two clusters of patients with EP: a cognitively impaired cluster (n=66) and a cognitively spared cluster (n=18), with the former, but not the latter, showing impairment across all cognitive domains compared to HC. Compared to HC, global brainAGE was significantly higher in the cognitively impaired cluster only ($P<0.001$) who also showed increased local brainAGE across the entire brain ($P<0.05$ with family-wise corrected cluster-size threshold). By contrast, the cognitively spared cluster had comparable global brainAGE to HC and evidence of mildly accelerated ageing localized to the prefrontal cortex (only at $P<0.001$, uncorrected).
Discussion: These findings suggest that in patients with EP cognitive impairment and accelerated brain ageing are linked and highlight the importance of parsing cognitive heterogeneity in EP and the value of spatially fine-grained estimates of brain-ageing.

F93. PROBLEM GAMBLING AMONG PEOPLE WITH FIRST-EPISODE PSYCHOSIS: STUDY PROTOCOL FOR A MULTICENTRE PROSPECTIVE COHORT STUDY

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Background: Risk factors for problem gambling (PBG) (e.g. personality and substance use disorders) are frequent in people with psychotic disorders, but this comorbidity has received little attention. Indeed, only one study has examined this comorbidity in first-episode psychosis (FEP), a subset of individuals even more vulnerable to PBG given their young age and the over-representation of men. Some evidence also suggests that the widely used antipsychotic aripiprazole (ARI) might be strongly associated with PBG. Given that PBG significantly hinders recovery, a better understanding of this comorbidity is essential.
Main objectives of this present study are to identify PBG risk factors among people with FEP and to quantify its incidence. Secondary objectives are to determine PBG characteristics specific to this population, establish PBG consequences on psychotic disorders evolution and document the efficacy of PBG treatments. Hypotheses are that ARI use, a history of gambling, personality and substance use disorders are all associated with an increased risk of PBG, that this latter exacerbates the psychotic disorder and that actual treatment approaches are inadequate.

Methods: This prospective multicentre cohort study is ongoing since November 1st, 2019, in 2 FEP programs (Quebec, Montreal), with patient enrollment running until November 1st, 2022. These 2 clinics admit together 180 patients annually, followed for 3 years on average (expected n = 540). There are no exclusion criteria; all patients between the ages of 18 and 35 with a diagnosis of FEP admitted to the 2 clinics will be included and followed until May 1st, 2023. The primary outcome is the occurrence of PBG during follow-up, defined by a DSM-5 diagnosis of gambling disorder by the psychiatrist. A screening tool for PBG has been developed by our research team and internationally renowned collaborators and implemented at both clinics as part of the systematic clinical follow-up. A blinded and prospective data collection is also ongoing using patients' medical files. The main objective will be answered using Cox proportional hazard models.

Results: A total of over 300 patients have been admitted at both clinics since the beginning of the study. They are aged 23.1 years old on average and they are mostly Caucasian (60%) men (70%). Main psychiatric diagnoses are unspecified psychosis (55%), followed by schizophrenia (21%). Many of the patients (56%) have at least one psychiatric comorbidity; the most common one being substance use disorder (36%). Most patients (55%) have been hospitalized in psychiatric units at least once and mean Clinical Global Impression-Severity score is 4.2. Antipsychotics are prescribed for 85% of the patients, with a minority (14%) receiving ≥ 2 antipsychotics and one-third of the patients are receiving ARI. One patient out of 4 reports having gambled in the 12 months prior to admission, only 3% have done so online. About a third of these gamblers (31%) have spent more than 100$ during that 1-year period, mainly on lotteries and card games. Two patients were classified as problem gamblers, including one with a formal DSM-5 diagnosis of gambling disorder.
Discussion: These preliminary Results: suggest that, although many patients with FEP report gambling, PBG is rare at admission in FEP clinics. This should be interpreted in light of the impact that the COVID-19 pandemic has had on gambling; many gamblers have stopped completely, while others have significantly reduced their gambling habits. In addition, the available data also suggest that FEP gamblers seem to prefer playing in-person activities, which could be seen as a way to overcome the social isolation they suffer. In any case, these findings underscore the need to incorporate routine PBG screening into clinical practice to better support these patients towards recovery.

F94. FAMILY AGGREGATION OF THE INTELLIGENCE QUOTIENT: UNDERSTANDING ITS ROLE IN FIRST EPISODE OF PSYCHOSIS

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Background: The familiality (or familial aggregation) of a trait indicates the degree of resemblance among family members. The familiality of intelligence quotient (IQ) might be associated with the diversity of manifestations in first episode of psychosis (FEP). This study aimed to explore whether IQ familiality is related to premorbid, clinical and neurocognitive characteristics in FEP patients.
Methods: FEP patients (n= 127) and their first-degree relatives (143 parents and 97 siblings) participated in this study. The individual IQ of these subjects was estimated using the WAIS vocabulary subtest. Then, for each family, the intra-family resemblance score (IRS) was calculated as an index of IQ familiality. Families with IRS<0 were referred to as "discordant" since scores below zero suggest low familiality. Families with IRS>0 were denominated "concordant" because scores above zero indicate high familiality. Based on the patients' premorbid IQ and their familial IRS, patients were subdivided using K-means cluster analysis.
Results: Cluster1 "Low IQ discordant" (n= 33): FEP patients with a low premorbid IQ (M=80) whose families had heterogeneous IQ (IRS= -5.62). On average, these patients deviated 13.06 points from their family-IQ. These patients showed a statistically significant worse premorbid

adjustment in childhood, and a trend toward a worse premorbid adjustment in early adolescence. They had significantly higher disability scores at baseline. Their neurocognitive performance was the most impaired of all patients.
Cluster 2 "Average IQ discordant" (n= 13): FEP patients with an average premorbid IQ (M= 96.53) belonging to families with heterogeneous IQ (IRS= -10.09). These patients deviated significantly more than others from their relatives since their premorbid IQ was 14 points below their family-IQ. Compared to the cluster "low IQ discordant", patients in this cluster had a better premorbid adjustment in childhood. They showed a marked deficit in attention.

Cluster 3 "Average IQ concordant" (n= 52): FEP patients with an average premorbid IQ (M=98.55) that resembled their family-IQ (IRS=3.42). They had a significantly better premorbid adjustment in childhood and lower disability scores at baseline compared to other clusters. Although it did not reach statistical significance, they had better baseline global functioning than the rest.

Cluster 4 "High IQ concordant" (n= 29): FEP patients with a high premorbid IQ (M=111.89) that closely resembled their family-IQ (IRS=5.73). They completed more years of education and had a better premorbid adjustment in childhood than cluster "low IQ discordant". This cluster had the lowest level of neurocognitive impairment among all patients.

Discussion: FEP patients with low premorbid IQ and low IQ familiality showed more unfavourable premorbid characteristics than patients whose IQ resembled their relatives. The relationship between deviation from the family-IQ and poor premorbid childhood adjustment supports the neurodevelopmental hypothesis of schizophrenia.

F95. PERSISTENT NEGATIVE SYMPTOMS IN FIRST EPISODE SCHIZOPHRENIA: LONGITUDINAL COURSE AND TREATMENT RESPONSE FROM A 2-YEAR FOLLOW-UP STUDY

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Background: Persistent Negative Symptoms (PNS) affect real-world functioning already at the onset of schizophrenia. Longitudinal studies on beneficial effects of psychosocial treatments for PNS in First Episode Schizophrenia (FES) are still relatively scarce. The aims of the current study were: (1) to evaluate the longitudinal stability of PNS in young FES individuals along a 2-year follow-up period, and (2) to examine any relevant association of PNS with the specialized treatment components of an Italian "Early Intervention in Psychosis" (EIP) program across the follow-up.
Methods: 133 FES subjects (aged 12-35 years) completed the Positive And Negative Syndrome Scale (PANSS) and the Global Assessment of Functioning (GAF). In accordance with specific international PNS criteria, we dichotomized FES individuals with and without PNS. In the FES group with PNS, a multiple linear regression analysis was conducted to examine relevant

associations between longitudinal PNS levels and the specialized treatment components of our EIP protocol.
Results: Twenty (15%) FES participants met the PNS criteria. At baseline, PNS levels had relevant positive correlations with functioning decline and PANSS total score. Across the 2-years follow-up period, FES subjects with PNS showed a significant decrease in PNS levels. This reduction was specifically related to the number of individual psychotherapy and case management sessions delivered during our follow-up (together with a shorter DUP).
Discussion: PNS are clinically relevant in a minority of FES individuals. Their clinical severity decreases over time, together with the delivery of specific, patient-tailored psychosocial interventions.

F96. DOES PPIOID USE DISORDER SHARE GENETIC ARCHITECTURE WITH SCHIZOPHRENIA, BIPOLAR DISORDER, AND MAJOR DEPRESSIVE DISORDER?

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Background: Opioid use disorder (OUD) is a severe substance use disorder that causes substantial morbidity and mortality worldwide, with some countries more affected, such as the US with the opioid crisis. In 2016 the prevalence of persons with OUD were estimated at 26.8 million worldwide. The prevalence is lower than for other substance use disorders but contributes a large part of the disease burden due to deaths by overdoses, which has increased during the COVID-19 pandemic. An increased risk of nonmedical opioid use has been found for patients with already diagnosed severe mental disorders, with hazard ratios (HR) ranging from, adjusted HR = 2.2 [95% CI = 1.9–2.6] to 3.1 [95% CI = 2.4–4.0]. On the other hand, an increased risk of developing severe mental disorders for patients with already existing nonmedical opioid use has similarly been found ranging from adjusted HR = 2.8 [95% CI = 2.2–3.6] to 3.6 [95% CI = 2.6–4.9]. Current research has shown genetic correlations between substance use disorders and severe mental disorders, but genomic overlap and architecture remains, in large, uncharacterized. In this study we aimed to increase discovery of genetic risk factors shared between the psychiatric disorders schizophrenia (SCZ), bipolar disorder (BD), major depression (MD) and OUD.
Methods: Here, we applied the conditional and conjunctional false discovery rate (cond/conjFDR) approach to large genome wide association studies (GWAS) of OUD (n = 15 756), SCZ (n = 69

369), BD (n = 41 917) and MD (n = 246 363) to increase discovery of overlapping genomic loci. We functionally characterized the identified loci with FUMA.
Results: We observed genetic enrichment for OUD conditioned on associations with SCZ, BD, MD and vice versa, suggesting polygenic overlap. Applying the conjFDR method we identified genetic loci shared between OUD and SCZ (n = 3), OUD and BD (n = 1) and OUD and MDD (n = 8) at conjFDR < 0.01. Of theses there are 9 loci novel for OUD. We observed a mixed direction of effects showing a complex relationship between the traits. Functional analyses remains to be completed.
Discussion: Our findings provide new insights into the shared genetic architecture of schizophrenia, bipolar disorder, major depression and opioid use disorder, by identifying overlapping genomic risk loci with mixed effect directions.

F97. THE IMPACT OF SOCIOECONOMIC STATUS IN THE POLYGENIC RISK OF PSYCHOSIS AND ITS PSYCHIATRIC COMORBIDITIES: EVIDENCE OF ASSORTATIVE MATING AND PARTICIPATION BIAS IN UK BIOBANK

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Background: Socioeconomic status (SES) has major implications in the risk of psychosis and psychotic illnesses. Large-scale genome-wide investigations demonstrated that the polygenic architecture of psychiatric traits and disorders can be affected by assortative mating (AM; i.e., the tendency for people to choose mates phenotypically similar to themselves than would be expected by chance) and factors affecting the structure of the cohorts investigated such as participation bias. However, it is not clear whether AM and population structure are due to the association of socioeconomic factors with psychopathology. Here, we investigated whether SES association with the polygenic risk for psychosis and its psychiatric comorbidities influence the presence of AM and participation bias in the UK Biobank (UKB).
Methods: Psychiatric and behavioral outcomes in UKB were evaluated using the online mental health questionnaire (MHQ). This included a comprehensive assessment of psychosis and psychotic illnesses together with several other psychiatric traits such as mental distress, depression, self-harm, traumatic events, and substance use, among others. Leveraging genome-wide information available for 136,284 unrelated UKB participants that were assessed with the MHQ, we identified traits with significant SNP-heritability ($z>4$). We quantified AM as the within-person correlation (θ) between polygenic scores calculated from SNPs on odd- and even-numbered chromosomes for psychosis and its psychiatric comorbidities in 243,476 UKB unrelated participants that were not assessed with the MHQ and participation bias. To verify whether the evidence of AM and participation bias was due to SES-related factors, we conducted a conditional analysis to remove SES effects i.e., household income (the combined gross income of all members of a household) and the Townsend deprivation index (i.e., a measure of material deprivation including unemployment, non-car ownership, non-home ownership, and household overcrowding) from the polygenic predictors and re-estimate the presence of AM.
Results: We found significant evidence of AM in the polygenic risk of psychotic illness other than schizophrenia (θ=0.26%). We then conducted two parallel analyses removing the effect of SES

from the psychosis polygenic risk considering household income and the Townsend deprivation index. After conditioning for these SES-related variables, we observed a strong reduction of the AM evidence when controlling for the Townsend deprivation index (θ=0.008%) while a negligible change was observed when controlling for household income (θ=0.24%). In addition to psychosis, we observed that other 37 psychiatric traits showed significant evidence of AM. These include several mental health outcomes known to be associated with psychosis: ever taken cannabis (θ=0.62%), panic attacks (θ=0.36%), obsessive-compulsive disorder (θ=0.06%), and ever self-harmed (θ=0.17%). Similar to psychosis, some traits showed a reduction in AM evidence after controlling for SES-related variables, e.g., frequency of drinking alcohol (original θ=0.63%; θ after conditioning for household income and Townsend deprivation index=0.31%). Also, we found that controlling for SES induced a negative estimate of AM (θ<0; e.g., felt loved as a child; original θ=0.19%; θ after controlling for household income and Townsend deprivation index θ=-0.12%). These findings highlight the effect of AM and demonstrate how SES may have influenced the participation of UKB-enrolled individuals in the MHQ assessment.
Discussion: The present study demonstrated that the AM observed among individuals presenting psychotic symptoms can be due to material deprivation in certain population groups. These findings have important research and social implications. From a research perspective, our study highlights that SES variables are an important factor that should be accurately modeled when investigating the polygenic architecture of psychosis in the general population. From a social perspective, our Results: highlight that material deprivation is likely a major driver in the life of individuals experiencing psychotic symptoms. Beyond our focus on psychosis, we found that SES significantly affected the participation in the mental health assessment of individuals enrolled in the UKB cohort. This participation bias is likely affecting mental health studies that are leveraging UKB resources.

F98. DNA METHYLATION IN 22Q11.2 DELETION SYNDROME AND RISK TO DEVELOP SCHIZOPHRENIA

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Background: Schizophrenia (SCZ) is a severe psychiatric disorder resulting from complex interactions between genetic and environmental factors. One of the highest genetic risk factors is 22q11.2 deletion. 25% of 22q11.2 deletion syndrome (22q11.2DS) individuals will develop SCZ in their lifetime. Some monozygotic twins with 22q11.2 deletion are discordant for SCZ. Therefore, we hypothesized that environmental factors such as stress increase the risk of SCZ through epigenetics.
Methods: We explored the DNA methylation in nine 22q11.2DS patients affected by SCZ compared to five 22q11.2DS patients without SCZ. One pair of discordant twins was included. Besides, 30 mice models were included and separated into four groups: wildtype mice (WT), mice

carrying a genetic risk factor Df(h22q11)/+ (G), WT mice exposed to stress (E), and Df(h22q11)/+ mice exposed to stress (GxE). Then blood samples from humans and prefrontal cortex samples from mice were sequenced by RRBS, which covered 6 million and 2 million CpGs, respectively. Differentially methylated probes (DMPs) and regions (DMRs) were detected by methylKit and DMRfinder, respectively. GO biological processes and pathways were enriched to the corresponding genes of DMPs and DMRs. We also compared these genes with SCZ GWAS, EWAS, TWAS, and differentially expressed genes to check the consistency with publications.
Results: A total of 3,895 DMPs and 1,562 DMRs (FDR<0.05 and methylation change (Δm) >25%) were significant in 22q11.2DS carriers with or without SCZ, corresponding to 3,773 unique genes. These genes were highly expressed in the brain and significantly enriched in SCZ GWAS hits (adjusted.p=9.64e-07). The most significant pathways were neuroactive ligand-receptor interaction, calcium, and focal adhesion. Meanwhile, 10,076 DMPs and 167 DMRs (Δm >50%) were identified in twins. For the mice, we checked the stress influence on transgenic mice and wildtype mice separately. In transgenic mice, 3,509 DMPs and 2,075 DMRs were identified. 253 of 1,579 genes were shared with humans.
Finally, TOP genes were selected by including at least 2 DMPs in their promoters or containing the DMRs with more than 10 CpGs. Of these, 34 protein-coding genes were overlapped in humans and mice results. These genes were notably involved in neural and synaptic function, glutamatergic and dopamine signaling, cAMP signaling pathways, and regulation of gene expression. Disease-gene association analysis revealed that 12 of them have been associated with SCZ.

Discussion: These Results: support the hypothesis that stress might play a significant role in the emergence of SCZ among 22q11.2DS carriers and identified potential genes involved in the associated pathophysiology. If replicated, these findings could lead to the identification of biomarkers for early diagnosis in 22q11.2DS carriers and new therapeutic strategies.

F99. THE GENETIC STRUCTURE OF PSYCHOSIS, MANIA, AND DEPRESSION

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Background: Genome-wide association studies have yielded important insights into the etiology of, and predictive biomarkers for, psychiatric illnesses. However, the utility of polygenic risk scores is limited by the high genetic correlations between diagnoses—for instance, the genetic correlation between schizophrenia and bipolar disorder is 0.68, meaning the schizophrenia PRS predicts bipolar disorder, and vice versa (Mullins et al., 2021). The high correlations among PRSs for psychiatric disorders could be explained genetic risk for transdiagnostic symptom dimensions, such as positive psychotic symptoms, that can be observed across diagnoses (Allardyce et al., 2017; Bigdeli et al., 2017; Wiste et al., 2014). If this hypothesis is true, genetic correlations among symptoms of psychotic disorders should be lower than genetic correlations among the disorders themselves. These analyses report the genetic correlations among symptoms of psychotic disorders, including elevated mood, reduced need for sleep, impulsivity, hallucinations, delusions, low mood, anhedonia, and suicidality, in a large (N=25,106) cross-sectional cohort of individuals with and without psychotic disorders (Pato et al., 2013).

Methods: Data are drawn from the Genomic Psychiatry Cohort, a cohort of individuals with schizophrenia (N=9,553), bipolar disorder (N=3,544, of whom 2,552 report psychotic symptoms), and controls (N=12,280). DNA was extracted from peripheral lymphocytes and genotyped on a number of different platforms, data from which were individually cleaned, merged across platforms, and cleaned again. Standard quality control procedures were performed to exclude SNPs with minor allele frequency <5%, genotyping failure >5%, Hardy-Weinberg equilibrium p<10-50, mismatch between recorded and genotyped sex, as well as related individuals ($\hat{\pi}$>.1875, equivalent to removing second-degree relationships). This resulted in a total of 21,319 individuals with 111,123 high-quality overlapping markers for analysis. Genomic data analysis was performed using Plink 1.9 and 2.0 (Purcell et al., 2007). Genetic correlations were calculated using BOLT-REML (Loh et al., 2018).
Results: All symptoms were heritable. SNP-based heritability estimates ranged from 0.08, for low mood and anhedonia, to 0.16, for hallucinations and delusions. Patterns of genetic correlations revealed three transdiagnostic symptom dimensions, one of positive psychotic symptoms, one of manic symptoms, and one of depressive symptoms. Genetic correlations among symptoms within the same dimension ranged from rg of 0.83 to 0.97. Genetic correlations across dimensions were significantly lower, ranging from 0.43 to 0.66.
Discussion: Despite significant clinical heterogeneity within diagnostic categories, schizophrenia and bipolar disorder are comprised of relatively homogeneous genetic risk for three symptom dimensions. Positive psychotic symptoms, mania, and depression have non-trivial SNP-based heritability estimates. Between-dimension genetic correlations were much lower, although moderate in size, consistent with some elements of genetic risk being shared among mood and psychotic disorders, and some genetic risk being specific to positive psychotic, manic, and depressive symptom dimensions. Genetic risk for positive psychotic symptoms, which can be observed in both schizophrenia and bipolar disorder, may explain the high genetic correlation between these two diagnoses. A limitation of this research is the lack of data on negative symptoms, a prominent feature of schizophrenia but not bipolar disorder. Genetic correlations between symptom dimensions are significantly lower than correlations between diagnostic categories, suggesting that symptom-based GWAS may improve the precision of genetic prediction in new samples. Future research will test this hypothesis in longitudinal data.

F100. IMPACT OF POLYGENIC RISK FOR SCHIZOPHRENIA ON CARDIAC STRUCTURE AND FUNCTION IN 32,966 PARTICIPANTS FROM THE UK BIOBANK

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Background: Schizophrenia is associated with an excess mortality of approximately 15 years, with cardiovascular disease (CVD) a major contributing factor. The mortality gap between individuals with schizophrenia and the general population is growing, suggesting a need for improved understanding of the factors underlying CVD in this group.
Recent evidence suggests that schizophrenia may be a multi-system disorder, with metabolic, immune, and hypothalamic-pituitary-adrenal axis alterations observed in antipsychotic naïve patients at the beginning of psychotic illness. Studies employing cardiac magnetic resonance

imaging have observed alterations in cardiac structure and function in people with schizophrenia even in the absence of metabolic disease; these changes are suggestive of a diffuse myocardial fibro-inflammatory process. Schizophrenia is a polygenic disease. Polygenic risk for schizophrenia in the general population is associated with increased risk for a variety of physical health conditions. Moreover, mendelian randomization has suggested that liability to schizophrenia in the general population causally increases risk of heart failure. However, it is not known if alterations in cardiac structure and function in schizophrenia have a genetic association.

Therefore, using data from the UK Biobank, we planned to explore the relationship between polygenic risk for schizophrenia in the general population and cardiac structure and function as assessed using cardiac MRI.

Methods: Participants from the UK Biobank with complete genetic and cardiac data (assessed using cardiac MRI) for parameters assessing left ventricular size and function were selected; where appropriate, cardiac phenotypes were indexed to body surface area. As such, cardiac parameters examined were: indexed left ventricular end systolic volume (LVESVi), indexed left ventricular end diastolic volume (LVEDVi), indexed left ventricular stroke volume (LVSV), left ventricular ejection fraction (LVEF), and cardiac index. Polygenic risk scores were derived using the most recent Psychiatric Genomics Consortium GWAS of schizophrenia. Linear regression was used to determine whether PRS-SCZ was significantly associated with cardiac phenotypes for each participant. The regression model included age, sex, genotype array, and 6 principal components as covariates. Standardised regression coefficients were calculated, alongside False Discovery Rate (FDR) adjusted P-values (PFDR) across the 5 cardiac phenotypes.
Results: The sample analysed included 32,966 individuals (male/female = 15922/17044; mean age at time of CMR scan = 55.01 years, SD = 7.38 years). We observed significant negative associations between polygenic risk score for schizophrenia (PRS-SCZ) and both LVESVi (beta= -0.15; PFDR = 0.0021) and LVEDVi (beta= -0.19; PFDR = 0.0198). Furthermore, we observed a positive relationship between PRS-SCZ and LVEF (beta= 0.08; PFDR = 0.0198). A positive relationship between PRS-SCZ and LV index (beta= 0.05; p = 0.0483) did not survive FDR adjustment (PFDR = 0.0604). We did not observe a significant relationship between PRS-SCZ and LVSVi (beta= 0.04; PFDR = 0.3512).
Discussion: These Results: suggest that alterations in cardiac structure and function in people with schizophrenia are partly influenced by genetic variants. Characterising the genetic pathways implicated may lead to novel therapeutic avenues to reduce cardiovascular disease burden in this patient group.

F101. DEVELOPING A SMOKING CESSATION INTERVENTION FOR PEOPLE WITH SEVERE MENTAL ILLNESS IN THE NETHERLANDS: A DELPHI STUDY

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Background: People with severe mental illness (SMI), such as schizophrenia spectrum or psychotic disorders, are affected more often by tobacco addiction compared to the general

population. They also have more difficulties to overcome addiction, manifested in more quit attempts and relapses, thus widening health inequalities between the general and psychiatric population. Explanation models for the high prevalence of smoking in this patient group are many and not mutually exclusive. They include shared genetic, environmental and social risk factors (e.g. genetic proneness to addiction, parents who smoke, a social surrounding accepting or even promoting smoking), as well as maladaptive coping mechanisms with stress. The self-medication hypothesis often used to explain the high prevalence has no clear evidence base. Misattribution of the effects of smoking is more likely to account for the alleged benefits experienced by smoking.
While there is a clear need, there is still limited evidence on the implementation and effectiveness of smoking cessation interventions for people with SMI in outpatient treatment. The objective of this qualitative study was to reach expert consensus on the core components of a smoking cessation intervention for patients treated by Flexible Assertive Community Treatment (FACT) in the Netherlands. FACT teams are multidisciplinary teams that offer long-term psychological treatment and care to people with SMI. We will carry out a randomised controlled trial (RCT) in FACT teams further examining the intervention.

Methods: We carried out a modified Delphi study between December 2020 and February 2021 to reach a consensus on three core components (1. behavioural counselling; 2. pharmacological treatment, 3. peer support) of the intervention. The Delphi panel comprised five experts with different professional Background:s recruited through the researchers' professional networks: one psychiatrist/post-doc researcher, two mental health nurse specialists, one senior consultant for tobacco regulation in mental health care, one expert-by-experience. Based on current literature, a first intervention concept was proposed. The panel critically examined the evolving concept in three iterative rounds of each 90 mins, by responding to a total of 9 open questions before the first round, 14 open questions before the second round, and 12 open questions before the last one.
After the final round, the panel received a definitive version of the intervention. The panel reached an eventual consensus through negotiation, taking into consideration the expected effectiveness of the component, needs of clients, treatment possibilities of clinical staff and practical conditions for implementation in psychiatric institutions.

All rounds were held online via videoconferencing software Zoom. Responses were recorded, transcribed verbatim, pseudonymised and thematically analysed with MAXQDA software. We obtained consent to recordings beforehand from all participants. Participants received monetary compensation of 1100 euros in total.

Results: Overall, Results: yielded that behavioural counselling should focus on preparation for smoking cessation, guidance, relapse normalisation and prevention. Behavioural counselling based on cognitive behavioural therapy and motivational interviewing will be delivered in groups, with optional individual counselling. An emphasis on the normalisation of relapse could reinforce a flexible approach to smoking cessation and reduce fear of failure.
Pharmacological treatment consisting of nicotine replacement therapy (NRT), Varenicline or Bupropion, under the supervision of a psychiatrist, was strongly recommended as it can increase chances of success in quitting. NRT and Varenicline are the first choices since Bupropion has more side effects and interactions with certain anti-depressants and anti-psychotics. The panel agreed on integrating peer support, led by an expert-by-experience, as a regular part of the intervention (1x per week), thus fostering emotional and practical support among patients. Co-additions, such as cannabis use disorder, need to be considered and incorporated into the intervention if indicated.

Clinical staff's motivation to support smoking cessation was considered essential for implementation. In each ambulatory team, two mental health care professionals need to participate in preparatory training and will play a central role in delivering the intervention.

Discussion: This study has provided insight into expert opinions on the core components of a smoking cessation intervention for people with SMI in Dutch outpatient settings and implementation strategies. Future Delphi studies on similar matters should include more patients currently in treatment. Results: were used for the development of a comprehensive smoking cessation program. The portrait of the complex interplay of physical, psychological and social factors can endorse a holistic approach to treatment in mental health care and improve the quality of care. Consensus on many aspects of the intervention was reached. Yet, implementation in realistic settings might still hold new challenges (to be assessed in RCT).

For more details on the intervention design, see http://kismetstudie.nl/.

F102. INVESTIGATING THE DEVELOPMENT OF CORONARY ARTERY DISEASE IN PATIENTS WITH SCHIZOPHRENIA USING CARDIAC CT

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Background: Patients with schizophrenia have a reduced life expectancy of 15-20 years, with cardiovascular disease being the most frequent cause of death. The degree of coronary artery disease is reflected by the quantity of coronary artery calcification. CT scan is the most used imaging technique to detect and quantify the amount of coronary artery calcium (CAC), using the Agatston scoring system as the golden standard.
Previous cross-sectional studies found no difference when comparing CAC in patients with schizophrenia to the general population. This study aimed to investigate the progression of CAC in a longitudinal study. We hypothesized that patients with schizophrenia have a more rapid arteriosclerosis progression compared to the general population.

Methods: In a longitudinal study, 163 patients with schizophrenia were examined at baseline and at the 2-4-year follow-up using cardiac CT and CAC score was measured. The progression of CAC from baseline to follow-up was compared to the general population using boxplot, and linear regression was used to investigate correlation with risk factors.
Results: Data is currently being processed and the Results: will be presented at the conference.
Discussion: Valid risk factors for CVD and models investigating changes in these in patients with schizophrenia is needed to possibly minimize the gap in life expectancy.

F103. DEINSTITUTIONALIZATION AND THE IMPACT OF ANTIPSYCHOTICS VERSUS POLICY CHANGE

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Background: Deinstitutionalization in American psychiatry refers to the depopulation of state mental hospital population in the 1950s where it decreased to a fifth of its size in over three decades. It involved a massive shift from inpatient to outpatient services and is often associated with the introduction of chlorpromazine in 1954. Because chlorpromazine was purported to impact specific diagnostic groups (schizophrenia) and important policy changes regarding federal welfare programs may have affected specific age groups, the present study uses interrupted time series analysis to assess diagnoses-specific and age-specific population changes of US state mental hospitals between 1954 and 1966. This study presents novel findings on the US state mental hospital depopulation of patients with schizophrenia and of elderly patients.
Methods: Using state mental hospital population data from the US Census Bureau, analyses of population movement of 9 diagnostic categories, 7 age groups, and lastly of each age group within each diagnostic category were carried out. Population movement was analyzed using an interrupted time series design to assess the effect of an intervention and does so by comparing the intercept and slope parameters for a pre-intervention time series with a post-intervention time series. The intervention in this case is policy changes in 1961 because there is reason to believe it is an important year: it marks the first significant decline in admissions and readmissions in 25 years and the publication of the Joint Report Action for Mental Health which strongly advocated for the downsizing of state mental hospitals. Moreover, it was one year after the Kerr-Mills Act was passed which authorized the first federal medical assistance program for the aged thereby providing federal funds to states for the provision of community-based care of the elderly. The slope and intercept of the time series regressions was assessed for the two time periods of 1954 to 1961 and 1961 to 1966 for the following analyses:
a) Population movement of 9 diagnostic categories (schizophrenia, alcoholism, personality disorder, mental deficiency, manic depressive disorder, psychoneuroses, cerebral aterio-sclerosis, syphilis, and senile brain disorder) using resident count and first admissions by state

b) Population movement of 7 age groups (under 24, 25 to 34, 35 to 44, 45 to 54, 55 to 64, 65 to 74 and over 75) using resident count by state and first admissions for the US total

c) Population movement of each age group within each diagnostic category for US total.

Results: The resident count of patients with schizophrenia did not significantly decline between 1954 and 1961 and declined between 1961 to 1964. First admissions for this group were increasing pre-1961, and post-1961 continued to increase but at a slower rate indicating that this post-1961 decline in resident count was due to an increase in discharges.
The pre-1961 decline in resident count occurred among patients aged 25 to 54 and the post-1961 decline occurred among patients over 35. Based on this a separate analysis on older patients was carried out: before 1961, patients below 55 significantly declined and patients 55 and above significantly increased. After 1961, patients below 55 showed no significant change and patients 55 and above significantly declined.

Lastly, before 1961, all age groups below 55 show variation in resident count i.e. the resident count for some diagnoses were increasing, decreasing or not significant. However, before 1961, all age groups above 55 showed a consistent increase in resident count (across diagnoses). After 1961, all age groups below 44 continued to show variation i.e. some diagnoses were increasing, decreasing

or not significance. However, all age groups above 44 consistently decrease in resident count across diagnoses. In examining the age makeup of patients with schizophrenia, we observe that pre-1961 the resident count increased for the youngest and oldest age groups (<24 and >55) and post-1961 all age groups (except <24) significantly declined. Patients with schizophrenia aged 55 and over was significantly increasing pre-1961, significantly decreasing post-1961 and the post-1961 decline in the resident count of schizophrenia was due to a decline in the resident count of older (>55) patients with schizophrenia.

Discussion: The resident count of patients with schizophrenia did not significantly decline between 1954 and 1961 and significantly declined after 1961 indicating that the post-1954 depopulation of this group was influenced by factors other than the pharmacological efficacy of antipsychotics. The observed trend of a national pre-1961 increase and post-1961 decline in the aged 55 and over population along with the finding that this shift in population movement by age occurred regardless of diagnoses strongly implicates the role of policy change, such as the 1960 Kerr-Mills Act which allowed states to transfer elderly patients out of state hospitals into federally assisted community settings. This study finds that 1961 marks important shifts in the composition of the patients being depopulated namely the discharge of elderly patients regardless of diagnoses and indicate that welfare policy changes had a substantial role in the deinstitutionalization movement.

F104. ASSOCIATION OF GESTATIONAL AND EARLY POST-NATAL TRIMESTER VARIABILITY IN MEAN ENVIRONMENTAL SUNSHINE HOURS IN A SCHIZOPHRENIA SAMPLE - PRELIMINARY FINDINGS

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Background: Studies have shown associations between perinatal light variability with case register incidence rates and of vitamin D deficiency in schizophrenia. Early post-natal solar insolation level has also been positively associated with age of onset in bipolar disorder ((Bauer et al; 2015; J. of Psychiatric Research; 64; 1-8). We investigated a hypothesis (Quested DJ. 1996 - Med. Hypotheses. Mar;46(3):233-8) that perinatal variation in environmental light (EL) exposure could be associated with the condition, in a model incorporating familial risk and gender, and present here the preliminary outcome of the environmental component analysis.
Methods: Schizophrenic patients (n=89) were diagnosed according to SADS-L. A healthy control version of the instrument was used for the comparator group (n=174). Information recorded included place and date of birth, family psychiatric history (FPH) with pedigree information as well as personal history and anthropomorphic measures. The study was ethically approved by OxREC, Committee A, reference O 03.017. Measures of perinatal environmental light (EL)

exposure were divided into 3 pre-natal trimesters and 4 post-natal trimesters. Sunshine EL exposure was calculated from MET Office UK data in:- 1) a summary dataset of monthly sunshine hours per day grouped by trimesters, following a statistical analysis plan; 2) the above dataset as a difference from the 63 year historic means for England and Wales, or Scotland, of monthly sunshine means subtracted from the individual's data. 3) A 'proportional' dataset analysed as a ratio of the difference calculated in '2' above, over the historic means. Logistic regression was used to estimate the effect on EL on schizophrenia risk by fitting a three way interaction term with gender and FPH.

Results: In dataset 1) monthly means in the trimester groupings showed a statistically significant effect of EL on the risk of schizophrenia in a three way interaction with gender and FPH in the second gestational trimester and the first post-natal trimester ($p=0.0137$ and 0.0367 respectively), time periods of greater cerebral mass increase; Analysis 2) - showed a significant first pre-natal trimester 2-way interaction for EL and FPH and a third pre-natal trimester 2-way interaction for EL and gender, ($p=0.0308$ and 0.0095 respectively); in analysis 3) - the derived ratios from differences over the historic means in pre-natal trimesters one and three show a similar pattern of significance to analysis 2 above.

Discussion: The above findings are suggestive of an association between EL and risk for schizophrenia by an interaction with gender and family history. This finding is limited by the sample size as well as an assumption that geographical relocation did not occur during the analysed phases of gestational and post-natal development. The association reported here will therefore need to be investigated in further studies with larger sample sizes.

F105. ETHNIC AND MIGRANT GROUP VARIATIONS IN CARE AND TREATMENT FOR PSYCHOSIS

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Background: Ethnic and migrant variation in treatment for psychosis have been frequently reported in studies from the Global North. Despite this, there has been no literature review to date on such inequalities. To address this gap, we conducted a systematic review of the literature on this topic to investigate the extent of ethnic/migrant variation in psychosis care and treatment.

Methods: In this systematic review, we sought to identify all studies which published data on ethnic and/or migrant variation in psychosis care and treatment available in English language, between 1996-2021. This period was consistent with the establishment and growth of Early Intervention in Psychosis [EIP] care as the gold standard for psychosis treatment. We followed PRISMA-P guidelines and prospectively registered the review protocol on PROSPERO.

We defined inclusion criteria as studies which: 1) pertained to non-organic psychosis in clinical settings; 2) involved patients aged 14-65 years; 3) presented Results: on psychosis care or treatment stratified by ethnic group and/or migration status; 4) were published between January 1996 to December 2021.

We defined our search term and extracted data for psychosis care or treatment, if the treatment was aligned to one of the following 8 domains: 1) Cognitive Behavioural Therapy for psychosis (CBTp); 2) family interventions; 3) clozapine treatment in non-responders; 4) supported

employment and education programmes; 5) physical health assessments; 6) interventions relevant to physical health; 7) carer-focussed education and support programmes; and, 8) any other treatment measure (e.g. atypical vs typical antipsychotics, type of service engagement i.e. inpatient, outpatient, secure setting).

We will search the following databases: Medline Ovid SP, PsycInfo, Web of Science and CINAHL. Search Results: will be exported, de-duplicated and stored in EndNote prior to title, abstract and full text screening by 2 researchers, with discrepancies resolved by consensus. Bibliographic searches of included studies and author contact for potentially missed work will be conducted. We will assess study quality of included papers using the Newcastle-Ottawa scale prior to data extraction.

A narrative synthesis following ESRC Guidance on the conduct of narrative synthesis in systematic reviews will be performed. Where sufficient data is available (N≥5 data points), we will use random-effects meta-analysis to pool estimates of variation in psychosis care or treatment by ethnic group or migrant status. Small study effects will be assessed via funnel plots and a modified Egger's test.

Results: Results: will be reported in accordance to PRISMA guidelines and presented at the congress. We expect to find a pattern of poorer psychosis treatment for ethnic minority and migrant group in studies, however do not predict homogeneity in treatment trends within ethnic/migrant groups.

Discussion: The findings from the paper will be discussed at the congress. Demonstration of ethnic or migrant variation in treatment for psychosis would allow clinical service providers and policymakers to reduce institutional inequalities in access to gold standard care.

F106. THE ENDURING GAP IN EDUCATIONAL ATTAINMENT IN SCHIZOPHRENIA ACCORDING TO THE LAST 50 YEARS OF PUBLISHED RESEARCH: A META-ANALYSIS

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Background: Educational attainment is associated with well-being and health. Unfortunately, patients with schizophrenia achieve lower levels of education, and the reason for this is likely multifactorial. People who later develop psychosis are known to have lower premorbid academic performance. The onset of the disorder itself after the first episode might also cause difficulties for a person's education. Symptoms (including cognitive deficits), medication, comorbidities, the time demands of participating in clinical care, or stigma, might all have a role in preventing patients from successfully going back to education after a psychotic episode.
Several effective interventions have been designed to ameliorate this. Promoting a prompt return to education after the onset of the disorder is an important goal of early intervention, as recommended by many guidelines. The importance of returning to education has been highlighted by at least two international calls for action in this area. Moreover, people with psychosis regard education as central to their process of recovery, ranking it more important than symptomatic remission.

However, the magnitude of the education gap in schizophrenia and changes over time are unclear. To shed light on these questions, we systematically reviewed the published literature of the last 50 years to reconstruct the trajectories of educational attainment in patients and if reported, on their healthy comparator controls.

Methods: We systematically reviewed the published literature from the last 50 years, including all studies reporting years of education in patients, with or without healthy controls. We estimated the birth date of the participants from their mean age and publication date, and meta-analyzed these data, focusing on educational attainment, the education gap and changes over time.
Results: We included 3,321 studies reporting on 318,632 patients alongside 138,675 healthy controls. We found that patients' educational attainment increased over time mirroring the controls'. However, the difference in educational attainment between patients and controls, namely 19 months less for patients, remained unchanged throughout the decades. The magnitude of this gap is equivalent to the educational gains after three generations in high-income countries, or an odds ratio of 2.6 for not graduating from high school versus controls. This stable gap was consistently seen across high-income economies. The gap was smaller in low- and middle-income countries, but increased as participants approached the educational attainment levels of high-income countries.
Discussion: Patients with schizophrenia have faced persistent inequality in educational attainment in the last century, despite recent advances in psychosocial and pharmacological treatment. Reducing this gap should become a priority to improve functional outcomes among people living with schizophrenia.

F107. A LONGITUDINAL THREE-WAVE NETWORK ANALYSIS OF COVID-19'S IMPACT ON SCHIZOTYPAL TRAITS, DEPRESSION, AND LONELINESS

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Background: Two years on and the novel coronavirus (COVID-19) pandemic is still negatively impacting the livelihoods of many individuals globally. While the quest to study how the pandemic has and continues to impact people's mental health is still on-going, fewer studies have investigated how paranoia/schizotypal traits may or may not have increased during this time of uncertainty. We know from existing longitudinal studies that early childhood life stressors predict psychosis (Varese et al., 2012) and schizotypal traits and externalising problems (Wong and Raine, 2019) in adulthood. However, whether the global pandemic has the same impact has been less examined.

Numerous psychological studies since the beginning of the COVID19 pandemic research have reported poor mental health in key sub-groups (e.g., keyworkers/BAME) and populations across countries. These studies focus on prevalence rates and account for Background: confounders, but most do not control for comorbid mental health variables and are limited to short, time-lagged designs that do not inform the stability and longer-term impacts of COVID post-lockdown restrictions. However, a handful of studies have addressed this comorbidity issue using network analysis, which maps all relationships between variables relative to other variables in the whole network – yet still, the narrow focus on mental health variables (anxiety/depression/loneliness) and not psychotic-like experiences is limited (Hung et al., 2020; Jia et al., 2020).

This study applies network analysis to test the relationship between paranoia/schizotypy and psychopathology across time. Understanding how mental health variables relate to paranoia/schizotypal traits during the pandemic may inform how resources should be directed to help individuals and develop targeted interventions in the future. We hypothesize that paranoia/schizotypal traits will be positively related to internalising/externalising problems across ages and gender. However, stronger networks will be found between constructs earlier on in the pandemic, compared to later on in the pandemic when lockdown restrictions begin to ease.

Methods: Participants (M=36.4, SD=13.53; range=18–89 years) from Wave 1 (N=1559; April-July 2020), Wave 2 (N=1000; October 2020-January 2021) and Wave 3 (N=744; April-July 2021) of the UCL-Penn Global COVID Study (Wong et al., 2020; https://osf.io/fe8q7/) completed a 30-minute online survey on the study website (GlobalCOVIDStudy.com). This convenience sample is not representative of the population and are from the countries with N >50 (UK, Greece, Italy, USA, HK). The survey assessed participant's Background: variables, levels of schizotypy, paranoia, anxiety, depression, aggression, loneliness and stress. Complete data on all variables of interest were used in our network analyses (in R) which were compared across ages (=<35 years, >=35 years) and gender.

Results: All variables were positively related in the expected way, such that higher levels of paranoia/schizotypy were associated with poorer mental health, specifically with levels of loneliness (Wave 1). For age, network structures were not different (M=0.10, p=0.58) but a network invariance test by age suggests stronger connections in the older (S=0.63, p=0.02) than the younger group. In terms of gender, both network structures (M=.08, p=.95) and connections (S=.02, p=.95) were not significant. However, schizotypal traits did show a decreased over the 12-month period of the study, while levels of self-perceived loneliness remained stable over time. Further cross-sectional and longitudinal relationships will be reported.
Discussion: This longitudinal network analysis study demonstrated that general psychopathology, particularly loneliness, was strongly associated with paranoia/schizotypal traits, though this did not differ by gender or time (wave 1 and 2). Contrary to prediction, network strengths were stronger in older than in younger individuals, suggesting strong inter-node network connections. Longitudinal analyses of Wave 3 are underway and will be available by the conference. Our study relies on self-report which may have inflated observed relationships, but this is the first COVID study examining the mental health-schizotypy relationship longitudinally.

F108. COMORBIDITIES AND MORTALITY IN PSYCHIATRIC PATIENTS: A BRAZILIAN COHORT STUDY

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Background: Mental disorders are often associated with one or more comorbidities and lead to even more aggravating physical consequences for the patient's health. The prevalence of chronic diseases, such as cancer, heart disease, obesity, diabetes mellitus and chronic obstructive pulmonary disease, in psychiatric patients from emerging countries varies from 46% in Africa, 37% in Asia, and 27% in America (Daré et al. BMC Public Health, 2019, 19:304). Given the relevance of updated estimates for low- and middle-income countries, our aim was to study the impact of comorbidities on premature mortality in Brazilian psychiatric patients.
Methods: A retrospective cohort of patients admitted to public mental health hospitals of the Ribeirão Preto catchment area (São Paulo state, Brazil) between January 1st, 2012, and December 31st, 2016, with vital status and causes of death until December 31st, 2016, was assembled. Admission diagnoses included psychoactive substance use disorders (40.3%; ICD-10 F10-F19), mood disorders (25.0%; ICD-10 F30-F39) and psychotic disorders (21.7%; ICD-10 F20-F29). Dates and causes of the death were obtained from the SEADE Foundation (state data analysis system of São Paulo). The observed number of deaths was compared with age- and sex-specific rates of deaths in the general population. Mortality rate (MR), age-sex-standardized mortality ratio (SMR), and years of life lost were computed. Cox's proportional hazards regression models were used to estimate risk of death associated with comorbidities (breathing problems, systemic arterial hypertension, stroke, convulsion, diabetes mellitus, infectious diseases and head trauma).

Results: Of 3,459 patients admitted (59.8% male), 148 died (62.2% male). The mean follow-up time was 27.6 months (standard deviation 16.8 months), 74.8% of the sample had no record of comorbidity at admission, 18.4% had one comorbidity, and 6.8% two or more comorbidities. Twenty-five per cent of patients died from unnatural causes, such as suicide (9.5%; ICD-10 X60-X84), accidents (8.1%; ICD-10 V01-X59), and assault (7.4%; ICD-10 X85-Y09). The overall MR was 1,800 (95% CI: 1,530-2,110) / 100,000 person-year. The SMR's were 3.0 (95% CI: 2.4-3.6) among men and 2.4 (95% CI: 1.8-3.1) among women. Having one comorbidity (adjusted hazard ratio (aHR) = 2.5 95% CI: 1.6-4.0) and two or more comorbidities (aHR = 4.3 95% CI: 2.5-7.4) significantly increased the mortality risk compared to patients without comorbidity. Stroke (aHR = 4.3 95% CI: 1.7-10.9), breathing problems (aHR = 4.3 95% CI: 2.0-9.3), convulsion (aHR = 3.2 95% CI: 1.9-5.5), infectious diseases (aHR = 2.6 95% CI: 1.2-5.6), diabetes mellitus (aHR = 2.5 95% CI: 1.5-4.4), and systemic arterial hypertension (aHR = 2.3 95% CI: 1.4-4.7) had the strongest associations with increased risk of death. Patients with one and two or more comorbidities died 26.6 and 28.5 years earlier on average than the rest of the population, respectively.
Discussion: Our study confirms that individuals with mental disorders associated with chronic diseases are at increased risk of premature mortality. The excess of mortality was observed in all the diagnostic groups, with a higher impact for psychoactive substance use disorders. These findings reinforce the need for effective care of chronic conditions in patients with mental disorders admitted to psychiatric beds.

F109. ANTIPSYCHOTIC DISCONTINUATION IN PEOPLE WITH FIRST EPISODE PSYCHOSIS (FEP): A LONGITUDINAL ANALYSIS OF ELECTRONIC HEALTH RECORD (EHR) DATA

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Background: Response and tolerability of antipsychotics vary between patients with FEP. Adverse side effects include sedation, weight gain, and extrapyramidal side effects. Randomised controlled trials are poorly representative of real-world populations as increased contact with study investigators may reduce the likelihood of antipsychotic discontinuation. We investigated the comparative discontinuation rates of antipsychotics in a large mental healthcare EHR dataset reflective of real-world clinical practice.
Methods: De-identified EHR data were obtained from the South London and Maudsley (SLaM) NHS Foundation Trust Biomedical Research Centre (BRC) Case Register. We obtained data from 2,309 adults with FEP receiving care from early intervention services between 1st April 2008 and 31st March 2019 using the Clinical Interactive Record Search (CRIS) tool. Data on start and stop dates of each antipsychotic prescribed to each patient were obtained. The period which a patient spent on an antipsychotic was defined as a treatment episode. We conducted a Cox (proportional hazards) regression using R to compare comparative rates of discontinuation between antipsychotics at treatment episode level, adjusted for the order in which the antipsychotics were prescribed. We included antipsychotics prescribed at least 5 times within the study population. Oral olanzapine (the most frequently prescribed antipsychotic – n=1,860) was set as the reference drug in our analysis.

Results: A total of 7,013 treatment episodes were included in the analysis. The rate of clozapine discontinuation (n=117) was almost half that of olanzapine (HR: 0.57, 95% CI: 0.43 to 0.76, p <0.001). The rate of discontinuation for paliperidone monthly long-acting injectable (PP1M – n=264) was also significantly less than olanzapine (HR: 0.83, 95% CI: 0.70 to 0.97, p = 0.021). Lurasidone (n=111) was the only antipsychotic that had a significantly greater rate of discontinuation than olanzapine (HR: 1.37, 1.08 to 1.75, p = 0.01). There were no significant differences in rates of discontinuation between olanzapine and any other antipsychotic. Antipsychotics which were prescribed later in patients' treatment trajectories had a greater rate of discontinuation, compared to earlier treatment episodes (HR: 1.06, 95% CI: 1.04 to 1.07, p < 0.001).

Discussion: We present one of the largest real-world studies examining antipsychotic discontinuation in FEP. We found that clozapine and PP1M had significantly lower rates of discontinuation and lurasidone a significantly greater rate of discontinuation than olanzapine. Later prescribed antipsychotics had a greater rate of discontinuation which could reflect difficulties in finding an effective/tolerable treatment for certain patients. Frequent monitoring and enhanced clinical support are likely to contribute to the lower discontinuation rate of clozapine. The lower discontinuation rate of PP1M suggests that LAI antipsychotics may support treatment adherence in FEP. However, we found no differences in discontinuation rates of other LAI antipsychotics and our findings are limited by the relatively small sample size of patients receiving LAIs.

F110. EPIC-FE. A DYNAMIC TOOL FOR BUILDING A LEARNING HEALTH NETWORK FOR FIRST EPISODE PSYCHOSIS PROGRAM IN FERRARA PROVINCE, ITALY: FROM DESIGN TO IMPLEMENTATION

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Background: A Learning Healthcare Network (LHN), according to the position of the Institute of Medicine, represents a key pathway towards value-based healthcare: it seeks to provide effective, high-quality care through constant improvement and innovation. In a LHN, data are routinely collected and made available to relevant stakeholders to drive research and healthcare in real-time. Our aim is to describe the implementation of EPIC-FE (Early Psychosis Implementation and Care in Ferrara) as the first LHN for a first-episode psychosis (FEP) Program built outside the USA, within a population-health framework. EPIC-FE will provide an innovative tool to monitor the implementation and outcomes of the ongoing FEP Program and correspondent local protocol (PDTA) in the province of Ferrara, Italy.

Methods: The study includes a retrospective as well as a prospective data collection. Participants are individuals with a diagnosis of affective and non-affective psychosis admitted to the FEP Program of the Ferrara public health agency (catchment: ~ 350,000) since January 2013. Participants have been offered a comprehensive multi-professional recovery-oriented program.

The FEP specialized team worked in the local community mental health center, following a decentralized model of care. The Hospital Institutional Review Board and the Ethical Committee approved the study in September 2021. A public-academic partnership has been contributing to the development and implementation of the study.
Results: Key indicators were redefined to measure: i) access to care (census of active patients and referrals, and duration of untreated psychosis); ii) implementation (frequency of interventions – e.g. CBT sessions, psychoeducation); ii) clinical outcomes (the HONOS scale was administered every 6 months for at least 2 years, hospitalizations, discharges, occupational status, physical health). Data were retrieved from electronic medical records (EMR), collateral information was provided by care managers, family, and patients. All data were entered in RedCap data manager. As of November 2021, the study has enrolled more than 120 individuals, with an average annual incidence of 15, mostly referred by the acute inpatient psychiatry unit. The LHN includes periodic data auditing, rigorous data reporting and sharing in the monthly meeting with care providers. This setting was used to discuss the challenges encountered by clinicians to implement the protocol (e.g. poor familiarity with the protocol, EMR, assessments, personnel turnover, and resources shortage). A tailored 4-hours workshop on FEP detection and treatment was thus offered to all mental health professionals; an additional 4-hour workshop on CBT for FEP techniques, and one on case management have been scheduled.
Discussion: A public-academic partnership has been implementing a LHN for first-episode psychosis in Ferrara. This strategy aims to provide clinicians, researchers, and local stakeholders a comprehensive tool to 1) implement the local protocol (PDTA) for FEP, according to the regional guidelines, 2) monitor in real-time the outcomes of the patient included in the program, 3) enable researchers to obtain and analyze real-world data, 4) strengthen the liaison between local health agencies and academia. Data regarding the implementation of the LHN in Ferrara will be presented and discussed.

F111. LONGITUDINAL ASSOCIATION BETWEEN NEIGHBOURHOOD-LEVEL SOCIAL CAPITAL AND INCIDENCE OF PSYCHOTIC DISORDERS: A COHORT STUDY OF 1.5M PEOPLE IN STOCKHOLM COUNTY, SWEDEN

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Background: Better neighbourhood-level social capital may be protective for people at risk of first episode psychosis, but longitudinal evidence is missing. We also do not know (i) whether this is specific to psychosis or extends to other forms of severe mental illness (SMI), or; (ii) whether these effects are protective for all groups equally, including people with and without a parental history of immigration. To investigate these issues, we used longitudinal cohort data from linked Swedish registers of 1.5m people living in Stockholm County, linked to prospectively-collected, population-based ratings of neighbourhood social capital.
Methods: All Swedish-born people living in Stockholm County between 2002-2016 while aged 14-64, were followed from earliest residency in Stockholm County after 14 years old until diagnosis of ICD-10 non-affective psychotic disorder (NAPD; F20-29), affective psychotic disorder (APD; F30/1.2, F32/3.3) or non-psychotic bipolar disorder (NP-BPD; F30/1.x except

APD codes), emigration from Stockholm County, 65th birthday, death, or 31 December 2016, whichever was sooner. We developed empirical estimates of neighbourhood social capital (political trust, welfare trust, personal trust) independently-rated in the Stockholm County Public Health (SPHC) survey (N=23,510) in 2002. Social capital domains were estimated using factor analysis and multiple imputation to handle missing survey data. We used directed acyclic graphs to guide confounder choice, which included age, sex, parental region-of-origin, parental history of severe mental illness, family disposable income quintile at cohort entry, deprivation quintile and population density quintile. We ran multilevel survival analyses with time-varying covariates for each social capital measure, deprivation and population density, to model exposure to area-level factors over follow-up. A priori interactions between each social capital measure and parental region-of-origin were tested.

Results: Our cohort included 1,467,128 participants, of whom 17,760 (1.2%) were diagnosed with SMI for the first time during follow-up. Compared with cohort participants, SPHC survey respondents were more likely to be of Swedish or European origin ($p<0.001$). In full multivariable models, a one standard deviation increase in neighbourhood-level personal trust was associated with reduced incidence of NAPD (hazard ratio (HR): 0.89; 95%CI: 0.83-0.95) and NP-BPD (HR: 0.92; 95%CI: 0.86-0.98), with a trend-level effect for APD (HR: 0.92; 95%CI: 0.83-1.01; $p=0.09$). For NAPD and NP-BPD there was strong evidence of effect modification by parental region-of-origin (both $p<0.001$); thus, neighbourhood-level personal trust appeared protective for participants of Swedish and European descent (i.e. NAPD: Swedish HR: 0.88, 95%CI: 0.82-0.95; European HR: 0.85, 95%CI: 0.74-0.97), but increased incidence for participants of North African and Middle Eastern (HR: 1.61; 95%CI: 1.17-2.02) and Sub-Saharan African (HR: 1.84; 1.09-3.09) descent. Political and welfare trust were not associated with NAPD or APD, although had a weak protective effect (HR: 0.88; 95%CI: 0.77-1.00; $p=0.05$) and risk-increasing effect (HR: 1.14; 95%CI: 1.02-1.28), respectively, on incidence of NP-BPD.

Discussion: Neighbourhood levels of personal trust – a form of bonding social capital, here disproportionately rated by people of Swedish and European descent – was longitudinally associated with protective effects against SMI, but only for these groups, and actually served to increase risk for those of African and Middle Eastern descent. These patterns reveal the highly context-dependent nature of designing area-level intervention strategies to improve SMI, and potentially unintended public health consequences.

F112. ASSOCIATIONS OF COMORBID SUBSTANCE USE DISORDERS WITH HEALTHCARE SERVICE UTILIZATION: A COHORT STUDY USING ELECTRONIC HEALTH RECORD DATA

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Background: Comorbid substance use disorders are associated with worse clinical outcomes in people with serious mental illness but less is known about their impact on mental healthcare service delivery. We investigated healthcare utilization in people with comorbid substance use disorders using a largescale electronic health record (EHR) dataset.

Methods: A retrospective cohort study was conducted on adults receiving mental healthcare from 25 U.S. providers with the following ICD-10 substance use disorder diagnoses: alcohol (F10*), opioid (F11*), cannabis (F12*), and cocaine (F14*) use disorders. Clinical Global Impression Severity (CGI-S) scores were analyzed at 6-12 months following the first recorded substance use disorder diagnosis (index date). Patients were assigned into the following three groups: schizophrenia and related disorders (F2*), mood disorders (F3*), and other mental disorders (not F2* or F3*). Data were obtained from the NeuroBlu platform, a HIPAA-compliant, trusted research environment that enables the analysis of de-identified EHR data through a cloud-based R analytics environment. Descriptive statistics were estimated on demographics and CGI-S at index date, emergency department (ED) visits within 12 months and CGI-S recorded at 6-12 months after index.
Results: A total of 20,988 patients with substance use disorders (F10* alcohol: 51.7%; F11* opioid: 27.7%; F12* cannabinoid: 14.9%; F14* cocaine: 5.8%) were included in the study with a mean age of 39 years and 58% male gender. F2* and F3* diagnoses were present in 8.4% and 47.2% of substance use disorder patients, respectively. F12* cannabis use disorders were most frequent in patients with F2* schizophrenia and related disorders (26.6% compared to 17.0% in F3* and 10.5% in other mental disorders). F2* and F3* patients were approximately 1 CGI-S point higher than patients with other mental disorders for both time points ($p< 0.001$). F2* and F3* patients had a two-to-five-fold greater risk of ED visit compared to controls ($p< 0.001$).
Discussion: Cannabis use was more frequent among patients with schizophrenia and related disorders consistent with its potential etiological role. Substance use disorder patients who had either schizophrenia and related or mood disorder diagnoses were significantly more likely to attend the ED within 12 months. This could indicate greater risk of substance overdose or mental health crisis among these groups. Dual diagnosis services could help to reduce the impact on healthcare utilization by ensuring that patients receive appropriate care for both substance use disorders and schizophrenia.

F113. TELOMERE LENGTH IS NOMINALLY ASSOCIATED WITH VERBAL LEARNING IN BIPOLAR DISORDER

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Background: The lifespan of people with severe mental disorders, including bipolar disorder, is shorter compared to the general population. Patients with bipolar disorder are also at an increased risk of developing somatic diseases that are typically associated with advanced chronological age, such as cardiovascular diseases, metabolic syndrome, immune dysregulation, and dementia. Recent studies indicate accelerated aging processes within this population. It is also well established in the literature that patients with bipolar disorder often perform poorer on cognitive tests compared to age-matched healthy individuals. However, how cognitive abnormalities may

be related to accelerated aging processes (i.e. shorter telomeres) within this group is yet to be established. Thus, this study will investigate the role of telomere length and cognitive functioning in patients with bipolar disorder. Since lithium may have a neuroprotective effect, we will adjust the analyses for lithium use, as well chronological age, sex, and ethnicity.
Methods: The study consisted of 647 participants (bipolar disorder [n = 246] and healthy controls [n = 401]) collected as part of the Norwegian NORMENT study. All participants underwent a standardized neuropsychological test battery, including working memory, executive functioning, processing speed, verbal memory, and verbal learning. Leucocyte telomere length was measured in blood and determined by quantitative real-time Polymerase Chain Reaction (qPCR). Telomere length was defined as the ratio telomere template to the amount of single-copy gene template with smaller numbers signifying shorter mean telomere length providing the single-copy ratio (T/S ratio). All analyses were adjusted for lithium use (Daily Defined Dose), chronological age, sex, and ethnicity. Linear regression analysis was applied to investigate the role of telomere length on cognitive functioning. Assumptions for regression analyses were checked and found satisfactory. All the analysis was performed in SPSS.
Results: Patients had shorter telomere lengths than healthy controls (ß=-0.13, p=0.003). Furthermore, within the patient group, a positive association was observed between verbal learning and telomere length (ß=0.14, p=0.026), as well as a trend between verbal memory and telomere length (ß=0.11, p=0.067). No relationship was observed between telomere length and the other cognitive domains (working memory, executive functioning, or processing speed, p>0.1).
Discussion: This study indicates that longer telomere lengths are nominally associated with higher verbal learning abilities in bipolar disorders. Thus, shorter telomere lengths observed in bipolar disorders may contribute to the pathophysiological mechanisms underlying cognitive abnormalities in this population.

F114. BRAINS IN A DISH! UTILISING INDUCED PLURIPOTENT STEM CELLS (IPSCS) TO INVESTIGATE INFLAMMATORY DYSFUNCTION IN SCHIZOPHRENIA

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Background: Schizophrenia (SCZ) is a severe and debilitating disease that affects over 20 million individuals worldwide. The mechanisms underpinning the pathophysiology of SCZ are largely unknown, with various genetic and epigenetic alterations contributing to the complexity of the disease. However, perturbations in immune activation,and neuroinflammation of the brain have been implicated with the development of SCZ, and the manifestation of specific symptom profiles. Contemporary evidence suggests that neuroinflammation and cytokine release that is present in SCZ may cause the subsequent activation of astrocytes, which become reactive and can engage in perturbed and damaging inflammatory processes. Induced Pluripotent Stem Cells (iPSCs) have emerged as a novel method for investigating mechanisms of disease, as these cells retain the genetic signature of the donor therefore replicating disease pathology in vitro, and give rise to multiple different cell types including brain cells. The current study aimed to characterise inflammatory perturbations in SCZ with focus on the potential role of ‘reactive astrocytes’, using iPSCs taken from patients with SCZ. Additionally, the metabolic profile of SCZ astrocytes was assessed to further characterise dysfunction in SCZ pathology.

Methods: iPSCs taken from a patient with SCZ and a healthy control were differentiated from iPSCs, through neural precursors and into mature astrocytes. Cell development was characterised by immunocytochemistry (ICC) conducted at iPSC, neural precursor, and astrocyte stages of differentiation. Flow cytometry was utilised to determine the inflammatory capacity of astrocytes 'at rest' and after stress, and differences in reactivity between SCZ and healthy controls. Cytokine production was assessed by secretion into spent media, via ELISA method. For experimental procedures, inflammatory stress was mimicked by short-term IL-1β exposure. Differences in astrocyte metabolism and extracellular flux was assessed by the Agilent SeaHorse XF Analyser.
Results: ICC analysis revealed the development of mature astrocytes for both SCZ and control conditions, through the expression of astrocyte specific proteins GFAP, ALDH1L1, and S100β. Significant changes in reactivity, inflammatory capacity, and metabolism were detected between SCZ and control iPSC-derived astrocytes. Flow cytometric analysis revealed a significant increase in IL-8 positive astrocytes in the SCZ condition when compared to controls, after short-term IL-1β ($p = <.05$). Further, SCZ iPSC-derived astrocytes displayed significantly lower oxygen consumption at baseline, and significantly lower glycolytic capacity ($p = <.05$).
Discussion: The Results: of this study indicate perturbations in astrocyte function within SCZ disease pathology, characterised by significant inflammation and impairments in energy metabolism. This suggests that in SCZ astrocytes may become reactive as a consequence of a neuroinflammatory microenvironment and contribute to neurodegeneration, as well as processes leading to manifestation of specific symptom profiles that are underpinned by inflammation.

F115. MATERNAL IMMUNE ACTIVATION IN LATE PREGNANCY INDUCES TRANSGENERATIONAL EFFECTS ON PREFRONTAL CORTEX STRUCTURE AND FUNCTION

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Background: Epidemiological studies have repeatedly implicated maternal immune activation (MIA) in the etiology of neuropsychiatric illnesses. Recent evidence suggests that the pathological consequences of MIA affect brain development and functions across multiple generations. It remains unknown, however, whether MIA in late pregnancy induces transgenerational effects on the prefrontal cortex, one of the main brain areas implicated in psychosis-related neuropsychiatric disorders.
Methods: To study transgenerational effects of MIA, we used an established mouse model of prenatal exposure to the viral mimetic poly(I:C). Pregnant C57BL6/N dams were treated with poly(I:C) (5 mg/kg, i.v.) or vehicle on gestation day 17 to yield first-generation (F1) offspring, which were then used to generate second generation of offspring (F2) with immune-exposed or control ancestors. A combination of cognitive testing and gene expression analyses was used to assess transgenerational effects of MIA on prefrontal cortex structures and functions.
Results: Gene expression analysis revealed that F1 and F2 offspring of MIA-exposed ancestors displayed abnormalities in GABAergic gene transcription in the prefrontal cortex, including alpha-

subunits of the GABA(A) receptor. These changes were accompanied by the presence of cognitive deficits that depend on the integrity of the prefrontal cortex, such as temporal order memory function (p's < 0.05; n = 8-10 per sex and group). These abnormalities were present in both the maternal and the paternal lineage of F2 offspring.
Discussion: These findings provide novel evidence for the hypothesis that MIA in late pregnancy can induce pathological effects across multiple generations. Our data highlight a novel role of the prefrontal GABAergic transcriptome in transgenerational disease transmission that go beyond classical genetic inheritance.

F116. IMPAIRMENT OF PREFRONTAL CORTICAL INTERNEURONS IN SCHIZOPHRENIA

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Background: Excitatory/inhibitory imbalance plays a major role in neuropsychiatric disorders such as schizophrenia (SCH). The prefrontal cortex had been studied extensively, yet there is no consensus on alterations regarding interneuronal composition in patients with SCH. In the last decades several independent workgroups observed both decreased and unchanged densities of parvalbumin (PV+) neurons and only one study reported the decreased density of calretinin (CR+) neurons in the Brodmann area 9 in SCH. It is highly important to take into account the individual variance and the challenging heterogeneity of schizophrenia; the inconsistent Results: might foreshadow the existence of a cellular/molecular schizophrenia spectrum. The current study is part of a project aiming to give a comprehensive view of all major interneuronal cell types of the dorsolateral prefrontal cortex (DLPFC) and their possible impairment is SCH.
Methods: Formalin-fixed tissue from 15 cases with SCH and 15 age- and gender matched control (CTR) cases obtained from the Netherlands Brain Bank, King's College Brain Bank and Oxford Brain Bank was immunohistochemically stained. We quantified CR+ and PV+
neurons in cortical columns after delineating cortical layers based on Nissl staining. Linear mixed models were applied for statistical evaluation of layerwise density values.

Results: Our Results: suggest layer-specific impairment of CR+ and PV+ interneurons in the DLPFC with layer 2 being the most affected. However, these changes were not present in all SCH cases, in fact several of them were closer to the CTR average.
Discussion: It is important to further study within-group differences as it may lead to the better understanding of schizophrenia. Cell types identified as impaired can be subjects of targeted experiments such as iPSC assays and organoid models, which hold the potential of revealing neurodevelopmental mechanisms underlying illness in postnatal life.

F117. A POTENTIAL ASSOCIATION BETWEEN GUT AND BRAIN IN SCHIZOPHRENIA SPECTRUM DISORDERS; LEAKY GUT MARKERS MIGHT BE RELATED TO DECREASED BRAIN VOLUME

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Background: Schizophrenia spectrum disorders (SSD) are associated with decreased brain volume, which is correlated to cognitive dysfunction. A leaky gut could be a potential route for brain volume loss, as it can increase peripheral and brain immune activity, negatively affecting brain homeostasis. Blood markers associated with gut permeability, including lipopolysaccharide binding protein (LBP) and soluble cluster of differentiation 14 (sCD14), have been associated with loss of brain volume in neurodegenerative disorders. This manuscript investigates if such associations may play a role in SSD.
Methods: We conducted a study in SSD patients (n=66) and healthy controls (HC) (n=39). We performed an MRI-scan, investigated symptom severity and cognition and assessed serum LBP and sCD14. We investigated associations between gut markers, intracranial volume, total brain volume, gray matter volume and white matter volume using linear regression. Group differences were assessed using ANOVA. Gut and brain markers were associated to symptom severity and cognitive function using a mediation analysis, with brain volume as mediator.
Results: (Preliminary) sCD14 nor LBP levels were increased in SSD compared to HC. We found an association between LBP and intracranial volume, total brain volume, gray matter volume and white matter volume, whereas sCD14 only associated with intracranial volume, in SSD and controls. Intracranial volume, total brain volume and gray matter volume were negatively associated with BACS but not PANSS scores. LBP and sCD14 were not associated with PANSS and BACS scores. Mediation analysis showed that an effect of brain volume on PANSS and BACS scores was not mediated by LBP or sCD14.
Discussion: This suggests that leaky gut may be associated to several brain measures, both in SSD patients and in controls. Replication is needed and future research should also assess how improvements in gut permeability might affect brain volume.

F118. ASSOCIATIONS BETWEEN SEVERE PSYCHIATRIC ILLNESSES, PRESYNAPTIC FUNCTIONALITY, AND BDNF, COMT AND MIR137 POLYMORPHISMS: A POSTMORTEM BRAIN, MULTI-SAMPLE STUDY

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Background: Synaptic abnormalities may be a common hub in severe mental illnesses, including schizophrenia (SCZ), bipolar disorder (BPD) and major depression (MDD). On the other hand, these disorders were associated with polymorphisms in the brain-derived neurotrophic factor (BDNF), catechol-O-methyltransferase (COMT), and/or micro-RNA 137 (MIR137) coding genes,

which in turn have important roles in synaptogenesis, neurotransmission, and synaptic protein homeostasis, respectively. Using a large postmortem brain case-control sample, we tested the hypothesis that abnormalities in the presynaptic SNARE (soluble N-ethylmaleimide-sensitive fusion protein attachment protein receptor) machinery could mediate the associations between BDNF, COMT and/or MIR137 risk variants and the corresponding severe mental illness.
Methods: Postmortem samples from the orbitofrontal cortex (OFC; Brodmann's area 10/47) of subjects with SCZ (n=70), BPD (n=34), and MDD (n=15), as well as sex-, age-, and postmortem interval-(PMI) matched controls (CTL, n=63) were obtained from the Stanley Foundation and the Macedonian/New York State Psychiatric Institute Brain Collection. Genotyping of select single nucleotide polymorphisms (SNPs) across the BDNF (11), COMT (9) and MIR137 (3) loci was performed by tetra-primer amplification refractory system (T-ARMS). Cortical amounts of eight presynaptic proteins were determined by ELISA, while SNARE PPIs were assessed by blue native-(BNP) PAGE followed by quantitative immunoblotting in the same postmortem OFC samples.
Results: We found no significant associations between SCZ and any of the studied SNPs. Interestingly, BDNF rs988748 (G) and rs7103411 (T) minor alleles were underrepresented in BPD ($p<0.0001$), while overrepresented in MDD ($p=0.001$) in a dose-dependent manner. Adjusting by sex, age and PMI, cortical amounts of vesicle-associated membrane protein (VAMP) were significantly lower in all three disorders, compared to controls ($p<0.05$). By contrast, SNARE PPIs were significantly increased in the same OFC samples from SCZ and MDD subjects ($p<0.01$). In turn, several synaptic proteins, including VAMP, were influenced by two particular COMT variants, rs737865 and rs2075507. Interestingly, greater density of SNARE PPIs was observed in the BDNF risk-allele carriers in BDP. Further logistic regression analyses showed that the effects of both SNPs (rs988748 and rs7103411) on BPD and MDD were indeed mediated by SNARE PPIs.
Discussion: While the present sample series is underpowered to perform genome association studies, the Results: suggest the possibility that BPD and MDD are respectively increased or decreased in carriers of two highly linked BDNF SNPs, rs988748 and rs7103411. Remarkably, these associations were mediated by a reduced (BPD) or increased (MDD) ability of the SNARE proteins to build functional complexes in cortical areas of the brain. Of note, dysregulation of SNARE PPIs may reflect synaptic dysfunction. COMT variants may also contribute to VAMP downregulation and synaptic dysfunction in MDD brains. While greater OFC amounts of SNARE PPIs were also associated with SCZ, larger numbers of samples will be needed to demonstrate whether the studied genes may contribute to presynaptic abnormalities and/or illness development.
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F119. 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 the 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 on 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 50 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 6 clozapine new starters have completed the study (3 currently active). Patients with chronic exposure to clozapine presented with a microbiome that is different from that of controls. Microbial diversity of chronic clozapine patients was significantly lower than that of controls, as indicated by the Shannon diversity index ($P=0.013$). The microbial community of chronic clozapine patients appeared to be more variable than that of controls, as measured by the Bray Curtis dissimilarity ($P=0.001$). No differences in taxonomic compositions were observed between chronic clozapine patients and controls. We speculate that due to our low number of patients and controls, we were unable to reach significance given the great variability of the microbial composition in patients with schizophrenia. Preliminary microbial analyses in patients starting clozapine ($n=4$) did not show anything significant differences across time.

Discussion: We have shown, employing two different cohorts of patients, that clozapine treatment likely impacts fecal microbiome composition significantly. The 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 gut microbiome composition, specifically Proteobacteria relative abundance. 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 treatment response and associated weight gain.

F120. COULD T REGULATORY CELLS HELP TO UNCOVER NOVEL NEUROIMMUNE MECHANISMS AND THERAPEUTIC TARGETS IN PSYCHOSIS?

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Background: There has been recent interest in neuroimmunology to restore T regulatory cells (Tregs) functional capacity to control systemic inflammation and glial dysfunction. Tregs (CD4+CD25+FoxP3+) are the guardians of immune homeostasis and limit inappropriate inflammation by maintaining balanced innate and adaptive immune systems and neuroimmune interactions between astrocytes and microglia. Breakdown of Treg homeostasis is associated with autoimmune disorders, obstetric complications, and cardio-metabolic diseases, some of which are comorbidities of psychosis. Low-dose methotrexate, which is known to restore Treg functional capacity, has recently been shown to have a significant antipsychotic effect. We proposed that Tregs may be hypofunctional in psychosis (PMID: 33713699), and this may be the missing link between low-grade inflammation and glial dysregulation. Here we review Treg studies in psychosis. We also discuss the interplay between Tregs and IL-6, the most consistently raised cytokine in psychosis, and suggest perspectives for novel mechanisms and personalised treatments.
Methods: We searched for articles using PubMed and included original Treg studies available in clinical psychosis. We also examined reference lists to find relevant studies.
Results: Out of eight studies, half found higher blood Treg percentages in medicated patients with schizophrenia compared to controls, with three concomitantly detecting greater percentages of activated T cells (CD3+CD25+) or Th17 (CD4+IL17A+). However, three studies identified lower percentages of blood Tregs in subgroups (around a third) of patients with schizophrenia, one including treatment-resistant patients. One study included a pooled sample of psychiatric patients (the largest proportion schizophrenia spectrum) and found a subgroup with lower but higher Treg percentages in the blood and cerebrospinal fluid, respectively. The only longitudinal study in drug-naïve first-episode psychosis reported that eight-week treatment with risperidone or olanzapine restored the lower blood Treg frequencies at baseline. One study found Tregs from chronic patients had impaired proliferative responses to in vitro stimulation with anti-CD3 and anti-CD28, with disinhibition of pro-inflammatory cytokines in culture supernatants (IL-6, IL-17A, IFN-γ, TNF-α). Four studies tested associations with symptom domains suggesting that low blood Tregs are correlated with worst symptomatology (global, negative, and cognitive symptoms).
Discussion: Although studies are few with important limitations, there is promising evidence suggesting that Tregs may be hypofunctional in psychosis. We propose that Tregs lose their homeostasis and suppressive ability due to direct (genetic) and/or indirect mechanisms (external cytokine milieu and others). Trans-signalling, the pro-inflammatory pathway of IL-6, in particular, suppresses the expression of transcriptional factor FoxP3, key for Treg development and immune-suppressive function, inducing pathogenic Th17 instead. In autoimmune diseases, IL-6 inhibition (e.g., tocilizumab) expands the proportion of functional Tregs in the blood of responders as soon as a month. More Treg studies in psychosis are needed to disentangle the mechanistic relevance of Tregs to low-grade inflammation, glial dysfunction, symptom severity, and the potential for personalised treatments, including repletion with Treg infusions. Ideally, future studies should be longitudinal including patients with primary negative/cognitive symptoms and target in vivo functional markers and in vitro co-culture assays to formally test Tregs suppressive ability.

Experimental medicine studies (e.g., using tocilizumab), assessing pre- and post-functionality of Tregs are awaited.

F121. DO COMPLEMENT AND COAGULATION PATHWAYS MEDIATE THE OMEGA-3 FATTY ACIDS ASSOCIATED CLINICAL RESPONSE IN EARLY PSYCHOSIS? A MASS SPECTROMETRY-BASED EXPLORATION OF PLASMA PROTEOME FROM THE NEURAPRO CLINICAL TRIAL

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Background: Preliminary evidence has shown that administration of omega-3 fatty acids (FAs) administration is beneficial in improving outcome at clinical high risk (CHR) for psychosis. However, the underlying biological mechanism in psychosis is currently not understood. In the current study, we used a mass-spectrometry based proteomic approach to explore omega-3 associated biological mechanisms of the subjects at CHR in relation to clinical response of CHR participants.

Methods: The study was carried out in a population of CHR participants (n=126) from the NEURAPRO clinical trial. We quantified the protein levels using a mass spectrometry-based data dependent approach at baseline and 6 months follow-up of plasma samples. Firstly, we performed a linear regression analysis to identify the plasma proteins that are associated with omega-3 FAs and used pathway analysis to explore the related biological pathways in CHR participants. Secondly, we evaluated the relationship of omega-3 FA associated proteins with clinical symptoms at 6 months follow-up. The positive symptom severity, functional symptoms and cognitive symptoms were measured at follow-up using the Positive Symptom Summery (PSS) score, Social and Occupational Functioning Assessment Scale (SOFAS) score and the Brief Assessment of

Cognition in Schizophrenia (BACS) score. Finally, we performed a mediation analysis to explore the biological mechanisms linking omega-3 FAs, complement proteins and clinical outcome.
Results: In linear regression analyses, change in omega-3 FAs were associated with 24 plasma proteins at follow-up that could be assigned to three major biological pathways namely the inflammatory pathway, hemostasis, and vesicle mediated transport. The complement cascade was found to be the top biological pathway enriched by the omega-3 associated proteins. Of these 24 proteins; two proteins (complement (C) 5 and S100A9) associated with PSS score; two proteins C5 and Apolipoprotein (APO) D associated significantly with SOFAS score; three proteins (Factor B, Complement C1QB, coagulation factor V); and three proteins of plasma lipoprotein assembly (APO E, APO D and APO CIII) associated significantly with BACS score at follow-up. Using mediation analysis, a significant total effect was found between change in omega-3 FAs with cognitive outcome at follow-up. Meanwhile, the complement and coagulation proteins expressed a significant longitudinal indirect (mediation) effect on omega-3 FA associated decrease in positive symptom score (PSS) and omega-3 FA related increase in cognitive (BACS) and functional scores (SOFAS) at follow-up.
Discussion: Our findings provide the first evidence for a biological longitudinal association of omega-3 FAs and complement and coagulation pathway proteins in the CHR. In addition, our findings provide novel insights into the mechanisms by which omega-3 FAs may improve outcome among the CHR population. The Results: suggest that the association of omega-3 FAs on psychotic, functional and cognitive symptoms is mediated longitudinally, at least in part, through the regulation of complement and coagulation pathway proteins.

F122. LONGITUDINAL GREY MATTER DEVELOPMENT ASSOCIATED WITH PSYCHOTIC EXPERIENCES IN YOUNG PEOPLE

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Background: Grey matter abnormalities are observed across the psychosis spectrum, with significant abnormalities demonstrated even in otherwise healthy individuals who report sub-threshold psychotic experiences (PE). Despite having no formal diagnosis, individuals with PE are at increased risk for psychosis and additional psychopathology. Investigation of the trajectory of these abnormalities in healthy adolescents reporting PE may provide insight into the neural mechanisms underlying psychotic symptoms, and also provides an opportunity to explore vulnerability for psychotic and non-psychotic psychopathology. Thus, the aims of this longitudinal study are to investigate PE related volumetric changes in young people.
Methods: 211 young people aged 11-13 participated in the initial Adolescent Brain Development study. PE classification was determined by expert consensus at each timepoint. Participants underwent neuroimaging at 3 timepoints, over 6 years. 76 participants with at least one scan were included in the final sample; 34 who met criteria for PE at least once across the timepoints, and 42 controls. Data from 20 bilateral regions of interest were extracted for Linear Mixed Effects analyses.
Results: Right hippocampal volume increased over time in the control group, with no increase in the PE group (FDR-corrected $p = 0.00352$). Right precentral volume was smaller in the PE group

regardless of time, although this did not survive correction. There were no significant effects of group or interaction in any other region.

Discussion: These findings further implicate hippocampal volumetric abnormalities in the pathophysiology underlying psychotic experiences. This data also supports the future investigation of the role of the motor cortex in psychosis symptomology. Furthermore, as suggested by previous studies in those at clinical high risk for psychosis and those with first episode psychosis, it is possible that these deficits may be a marker for later clinical outcomes.

F123. DYSCONNECTIVITY REVISITED: ABNORMAL TEMPORAL ORGANIZATION OF DYNAMIC FUNCTIONAL CONNECTIVITY IN PATIENTS WITH A FIRST EPISODE OF PSYCHOSIS

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Background: Abnormal functional connectivity between brain regions is a consistent finding in schizophrenia spectrum disorders; however, recent studies have highlighted that connectivity changes in time.

The objective of this study is to explore the temporal changes in functional connectivity, specifically to study the changes in the temporal order in which whole-brain organization states were visited in patients with psychosis compared to controls.

Methods: Two case-control studies, including in each sample a subgroup of patients and controls scanned a second time after treatment. This Binational study was performed in two tertiary centers in Chile and Mexico. The Chilean sample included 79 patients with a first-episode of psychosis and 83 healthy controls (gender matched). The Mexican sample (replication sample) included 21 antipsychotic-naïve first-episode psychosis patients and 15 healthy controls (gender and age matched).

Chilean site participants were scanned at baseline (patients having received antipsychotics for an average of 3 weeks) and after 12 weeks. Mexican site participants were scanned at baseline (when patients were antipsychotic-naïve) and after 4 weeks.

Characteristics of the temporal trajectories between whole-brain functional connectivity meta-states were examined via resting-state functional magnetic resonance imaging using elements of network science (graph analysis). We compared case-control differences and explored association with symptoms, cognition and antipsychotic doses.

Results: In our main analysis of 79 patients and 83 controls, we found that the temporal sequence in which patients' brain dynamics visited the different meta-states was more redundant and segregated ($P<.05$, corrected for multiple comparisons). Patients were less able than controls to reconfigure their network rapidly and explored the whole landscape of possible states in a less efficient way ($P<.05$, corrected for multiple comparisons). These changes were related to the dose of antipsychotic the patients were receiving, with higher doses slowing down the dynamics ($P<.05$, corrected for multiple comparisons). We also replicated the relationship with antipsychotic medication in the antipsychotic-naïve first-episode sample of 21 patients scanned before and after treatment.

Discussion: We conclude that psychosis is related to a temporal disorganization of the brain dynamics, leading to a slowing-down of the dynamics, which is associated to antipsychotic use. Higher antipsychotic doses were associated with more segregated and redundant trajectories.

F124. THE AGE OF VIOLENCE: MAPPING BRAIN AGE IN PSYCHOSIS AND PSYCHOPATHY

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Background: Based on epidemiological research, age is a strong predictor for antisocial behaviour in the general adult population and for violent offending in schizophrenia. The age of an individual can be predicted with high accuracy using brain scans and machine learning techniques, and the deviation between predicted and chronological age has been suggested to reflect general characteristics of brain health, likely relating partly to neurodevelopmental and aging-related processes and specific disease mechanisms. Higher brain age predicted by MRI has been demonstrated in patients with severe mental disorders including psychotic disorders. However, little is known about the brain's biological age in violent offenders with psychosis and the possible associations with psychopathy traits.
Methods: We estimated brain age in 782 males using T1-weighted MRI scans with 3 different models based on cortical area, thickness and subcortical volumes. The brain age models were first trained and tested on healthy controls (HC, n=586). Subsequently, the obtained brain age gaps (BAG; the difference between chronological and brain age) were compared between HC and age matched violent offenders with psychosis (violent-PSY, n=38), violent offenders without psychosis (violent non-PSY, n=20) and non-violent psychosis patients (non-violent PSY, n=138). We ran additional comparisons between BAGs of violent-PSY and non-violent PSY (controlled for psychosis symptoms). Psychopathy traits in the violence groups were measured with Psychopathy Checklist-revisited (PCL-R) and correlated with individual BAGs.
Results: We found significantly higher BAG in violent-PSY compared with HC (4.9 years, d=0.84) and in non-violent PSY compared with HC (2.7 years, d=0.98). No other pairwise comparisons yielded significant results. Total PCL-R scores as well as interpersonal-affective traits were negatively associated with BAG in violence groups.
Discussion: Our Results: revealed that BAG was larger for psychosis than violence traits. Additionally, the negative associations between BAG and psychopathy scores suggest lower brain age linked to psychopathy traits. These findings represent a proof-of-concept application of brain age prediction in severe mental disorders with a history of violence and psychopathy traits and need to be replicated in larger samples.

F125. BIOMARKERS IN TREATMENT RESISTANT PATIENTS WITH PSYCHOTIC DISORDER: A STUDY OF BRAIN, BLOOD AND CEREBROSPINAL FLUID

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Background: For several decades antipsychotic medication with dopamine antagonistic properties has been a cornerstone in the treatment of schizophrenia. However, not all patients with psychotic symptoms benefit from this treatment strategy. In around 30-40% of patients positive

symptoms persist despite treatment with antipsychotic medication. In this group of treatment resistant patients around 30-40% will respond to treatment with clozapine, whereas the remaining are defined as clozapine resistant patients.
Recent evidence points to changes in inflammatory biomarkers, disrupted blood brain barrier, structural and neurochemical brain changes in treatment resistant patients. Further knowledge about these putative biomarkers may help to stratify patients and develop novel therapeutics. In this study we aim to test the following hypotheses:

- Treatment resistant patients will show altered levels of glutamate in anterior cingulate cortex (ACC) and thalamus compared to patients who responded to first line treatment.
- Clozapine respondent patients will show more normalized levels of GABA and glutamate in ACC compared to clozapine resistant patients
- Clozapine resistant patients will have increased levels of inflammatory markers, increased permeability of the blood brain barrier and more pronounced white matter alterations.

Methods: Cross-sectional study of 135 patients with schizophrenia or other non-organic, chronic psychoses. Patients are divided into three subgroups based on their pharmacological response: 45 clozapine-responders being stable on clozapine for the last 8 weeks, 45 clozapine resistant patients and 45 patients respondent to first line antipsychotic treatment.
Treatment resistance is defined according to TRIPP-guidelines with persistent positive symptoms despite treatment with ≥2 antipsychotic drugs in sufficient dosage (≥600 mg clozapine equivalent) for a sufficient time (≥ 6 weeks). clozapine resistance is likewise having persistent psychotic symptoms , despite adequate clozapine treatment for at least 3 months with therapeutic plasma levels (>350 ng/mL) or a dosage of ≥400 mg.

Brain markers of treatment resistance are evaluated with magnetic resonance imaging including structural and neurochemical scans. Permeability of the blood-brain-barrier, and inflammatory markers are evaluated with cerebrospinal fluid and blood samples. Psychopathology and level of function are assessed with clinical rating scales.

Results: The study is currently recruiting patients and has enrolled 10 patients this far.
Discussion: We expect the data will contribute with significant insight to the different pathophysiological processes behind the treatment resistant subgroup of schizophrenia. This will subsequently allow better diagnostic procedures, individualized treatment strategies, and development of novel therapeutics.

F126. ELEVATED AND UNCOUPLED GLUTAMATE AND GLIAL BIOMARKERS IN PATIENTS WITH SCHIZOPHRENIA AND TREATMENT RESISTANT SCHIZOPHRENIA

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Background: Schizophrenia (SCZ) is a severe and chronic neuropsychiatric disorder that is often subcategorized into 3 treatment-response-subgroups: 1) Patients with improved positive symptom response (PSr) following conventional, non-clozapine, antipsychotic treatment (APT) (i.e., treatment responders; TR), 2) patients with improved-PSr solely to clozapine treatment (i.e., clozapine responders; ClzR+), and 3) patients with no or suboptimal improved-PSr to APTs, including clozapine treatment (i.e., clozapine resistant; ClzR-). Aberrant glutamate cycling and glial activity have long been postulated in SCZ and treatment-response-subgroups. Indeed, our group has previously reported 1) increased glutamate+glutamine (Glx) in the dorsal-anterior cingulate cortex (dACC) of ClzR-, and 2) elevated myo-Inositol (mI; glial biomarker) in the dACC of patients with SCZ compared to controls. In the present analysis, we explore the relationship between Glx and mI in the dACC of treatment-response-subgroups and controls.
Methods: Tissue-corrected 3T 1H-MRS data (PRESS,TE=35ms) from 89 SCZ (ClzR-=29, ClzR+=30, TR=30) and 49 controls, similar in age and sex, were used to quantify Glx and mI levels in the dACC. Cross-sectional groupwise mean differences were analyzed, and within-subject bivariate correlations were assessed.
Results: Glx levels were elevated in the dACC ($p=0.042$, $\eta2=0.059$) of ClzR- ($p=0.042$), and mI ($p<0.001$; $\eta2=0.202$) in ClzR- ($p<0.001$), ClzR+ ($p<0.001$) and TR ($p=0.036$), compared to controls. Glx and mI levels were coupled in the dACC of controls ($r=0.414$, $p=0.003$), but not ClzR- ($r=0.305$, $p=0.108$), ClzR+ ($r=0.272$, $p=0.146$), or TR ($r=0.207$, $p=0.272$).
Discussion: Decoupling of glutamate-glial biomarkers appears to be a defining pathophysiological mechanism of SCZ. This mechanism may prove a possible differentiating biomarker.

F127. CHARACTERIZATION OF CORTICAL THICKNESS DIFFERENCES IN THE HUMAN CONNECTOME FOR EARLY PSYCHOSIS STUDY

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Background: Psychotic disorders are characterized by structural changes in the brain, such as reduced cortical thickness. As there is a great deal of heterogeneity within and between DSM diagnoses of psychotic disorders, the psychiatric research field has begun to approach psychosis based on dimensions of mental and biological structure and function. Previous studies have reported cortical thinning in early-course schizophrenia compared to bipolar disorder and healthy

controls. However, these works typically separate groups by DSM diagnosis instead of viewing diagnoses of psychosis as a transdiagnostic clinical feature. Additionally, due to inconsistent findings in the literature, it is unclear whether these changes arise from primary illness factors, such as symptom severity, or from secondary effects, such as medication. To address these gaps and inconsistencies in the literature, this study utilizes high resolution imaging data drawn from the Human Connectome Project for Early Psychosis (HCP-EP; PIs: Shenton and Brier) to evaluate gray matter morphology in a transdiagnostic sample of individuals at the earliest stages of psychosis, as well as the relationship to antipsychotic intake, and other specific clinical features.
Methods: Participants included 159 individuals with early psychosis (EP) and 67 (HCs) from HCP-EP data. T1-weighted MR images were quality controlled and processed using FreeSurfer (v7). Cortical thickness was examined across 34 bilaterally represented regions of interest comprising the Desikan-Killiany atlas. Linear regressions were used to compare regional thickness values between EP and HC groups after controlling for age, sex, handedness, scanner (3 in total), and estimated total intracranial volume. Pearson correlations were used to assess the relationship between regional cortical thickness measures and current medication intake, defined as chlorpromazine equivalent (CPZ) doses. Secondary analyses examined relationships between cortical thickness and illness-related factors, including symptomatology, as assessed by the Positive and Negative Symptom Scale (PANSS) and diagnostic status (i.e., affective or nonaffective psychosis).
Results: Compared to HCs, EP subjects displayed significantly reduced cortical thickness in the left superior temporal (STG) ($F(7, 218) = 8.90$, $FDRp = 0.05$) and left middle temporal gyri (MTG) ($F(7,218) = 5.21$, $FDRp = 0.02$). Lower cortical thickness in both regions significantly covaried with higher current CPZ equivalent medication dosage in EP individuals (STG: $r(127)= -0.227$, $p = 0.009$, $r(127)= -0.310$, MTG: $p = 0.0003$). There was no significant relationship between cortical thickness in these two regions with PANSS total, positive, negative, cognition/disorganized thought scores, or the affective/nonaffective psychosis diagnosis after correction of multiple comparisons.
Discussion: Our analysis confirms prior reports of reduced cortical thickness in left-hemispheric temporal cortical regions. Crucially, these deficits were associated with current medication dose and not with illness-related factors, including symptoms or affective/nonaffective psychosis diagnosis. These findings, captured with high-quality imaging data raise important implications for understanding the early structural changes in the brain linked to presence psychosis and the effects of antipsychotic intake. Due to the large amount of data available from the HCP-EP study, we plan to analyze the relationship between cortical thickness and other factors like demographic and cognitive features, duration of illness, and medication type.

F128. COMMONLY REDUCED HIPPOCAMPAL GREY MATTER VOLUME IN PATIENTS WITH MAJOR DEPRESSION, BIPOLAR DISORDER AND SCHIZOPHRENIA SPECTRUM DISORDERS

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Background: Major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia spectrum disorder (SSD, schizophrenia and schizoaffective disorder) overlap in symptomatology, risk factors, genetics, and other biological measures. It remains unclear whether there are shared regional grey matter volume alterations across these disorders.
Methods: Grey matter volume (GMV, 3T magnetic resonance imaging) was compared between age and sex matched healthy controls (HC; n=110), DSM-IV-TR diagnosed MDD (n=110), BD (n=110), and SSD patients (n=110), drawn from a sample of N=1927. We applied a conjunction analysis to identify shared GMV alterations across the disorders. To identify potential origins of transdiagnostic GMV clusters, we associated them with early and current risk and protective factors, psychopathology, and neuropsychology, applying multiple regression models.
Results: Common to all diagnoses (vs. HC), we identified GMV reduction in the left hippocampus. This cluster was associated with stressful life events, the neuropsychology factor working memory/executive functioning, and with global assessment of functioning. Differential effects between groups were present in the bilateral frontal operculae and left insula, with volume variances across groups highly overlapping.
Discussion: Our study is the first with a large, matched, transdiagnostic sample to yield shared GMV alterations in the left hippocampus across the major mental disorders. The hippocampus is a central network hub, orchestrating a wide range of mental functions. Our findings underscore the need for a novel stratification of mental disorders, besides categorical diagnoses.

F129. EXECUTIVE FUNCTIONING AND CENTRALITY OF A PREFRONTO-STRIATAL NETWORK: IMPAIRED BRAIN-BEHAVIOR ASSOCIATION IN INDIVIDUALS AT CLINICAL RISK FOR PSYCHOSIS

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Background: Cognitive processing is associated with brain functional connectivity variation during resting state. Both cognition and functional connectivity are altered in chronic patients with psychosis (CPP, i.e., schizophrenia and bipolar disorder). Also individuals at clinical high risk for psychosis (CHR) show abnormal functional connectivity in brain regions involved in higher-level cognitive functions. However, extant evidence is mainly based on local, region-of-interest-based functional approaches. We aimed to assess the brain-behavior association between graph-based whole-brain functional connectivity and cognitive performance in several domains across healthy volunteers (HV), CPP and clinical high-risk for psychosis individuals (CHR). Considering the evidence that brain functional connectivity and neurochemistry are altered in psychosis even

before the onset of a chronic illness, we hypothesized shared brain-behavior abnormalities in CPP and CHR.
Methods: We enrolled 269 individuals: 117 HV used as a discovery cohort, and 87 HV, 43 CPP and 22 CHR, used for within-site validation. For external validation, we employed data from 331 subjects from the Philadelphia Neurodevelopmental Cohort (PNC) dataset: 45 with typical development (TD), 69 with a neurodevelopmental trajectory towards psychotic disorders (PSY), and 217 with a neurodevelopmental trajectory towards other psychiatric disorders (OD). Cognitive functions were assessed using Wisconsin Card Sorting Test (WCST), N-back task, Wechsler Memory Scale, Trail Making Test, Continuous Performance Test and Penn Conditional Exclusion Test (PCET; used in PNC as WCST equivalent). In the discovery phase, we calculated betweenness and degree centrality of 144 brain regions included in the Dosenbach atlas using GraphVar. We clustered the ROIs based on coordinates and graph-based indices into 25 short-range functional circuits. We then assessed which circuits were significantly associated ($p<0.05$) with cognitive performance in both HV cohorts. Finally, we tested the same association in CPP and CHR, and in each PNC group (external validation).
Results: In both HV cohorts, we found a positive correlation between the degree centrality of a right fronto-striatal circuit and the total errors at WCST (discovery HV: $r=0.331$; $pFDR=0.045$, validation HV: $r=0.267$; $p=0.007$). Conversely, when projecting the clustering solution on clinical groups, CPP and CHR showed a negative correlation between fronto-striatal degree centrality and WCST errors ($r=-0.370$; $p=0.019$ and $r=-0.595$; $p=0.007$, respectively). The projection of the circuits in the PNC groups revealed again a positive correlation between the degree centrality of the fronto-striatal circuit and the proportion of incorrect responses at PCET in TD ($r=0.307$; $p=0.023$). In PSY we observed a negative brain-behavior association in the same fronto-striatal circuit ($r=-0.204$; $p=0.049$), while no association was found in OD ($r=0.086$, $p=0.207$). In all samples, groups differed in terms of executive performance (all $p<0.05$), but not in degree centrality ($p>0.2$).
Discussion: A positive association between the degree centrality of a prefronto-striatal circuit and executive functioning in HV was reversed in CPP and CHR. PSY showed a brain-behavior association mirroring the one observed in both CPP and CHR. The observed negative association between fronto-striatal degree centrality and executive functions in clinical groups could reflect an early abnormality in the neurobiological substrate of cognition pre-dating onset of psychosis together with other alterations characterizing this condition, such as increased dopamine synthesis.

F130. THE ROLE OF THE CEREBELLUM DURING GESTURE PLANNING IN SCHIZOPHRENIA – AN FMRI STUDY

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Background: Gestures are an essential part of communication, as they support verbal communication and transmit information on their own. Patients with schizophrenia often exhibit gesture deficits, greatly affecting their communication skills and social functioning. Gestures rely on the coordinated interplay of motor- and speech-related brain regions, known as the ‘praxis

network'. Altered activation of the praxis network is often reported for schizophrenia patients. Here, we examined brain activation of schizophrenia patients and compared it to healthy controls during the planning of gestures.

Methods: We included 34 stable outpatients with schizophrenia spectrum disorders and 22 age and gender-matched healthy controls. Brain images were acquired using a 3T SIEMENS MAGNETOM Prisma. In an event related design, participants had to plan and execute 20 gestures: 10 meaningless (i.e. extend thumb and index finger) and 10 meaningful gestures (i.e. waving good-bye). In addition, a control condition included 10 neutral sentences (i.e. 'the weather is bad'), in which no gesture was required. The planning phase was visually cued with a triangle and the execution phase with a circle, both separated with inter-stimulus intervals. Instructions were presented as written commands. The total duration of the task was 7.5-12.5 minutes with each trial lasting 15-25 seconds. Gesture performance inside the scanner was compared between patients and controls using chi-square on accuracy percentage. In addition, brain activity during the gesture planning phase vs. control condition was examined for both patients and controls, using whole-brain voxel-wise one-sample and two-sample t-tests applying family-wise error correction.

Results: Gesture performance accuracy was poorer for schizophrenia patients (mean = 79.1%, SD = 19.0) compared to healthy controls (mean = 89.0%, SD = 9.4; X2 = 19.8, $p < .001$). Within-group contrasts of both groups during the planning phase of both meaningless and meaningful gestures vs. control condition indicated activations in the left praxis network, including the primary motor cortex, the left premotor cortex, and the left supplementary motor areas ($T < 7.03$, pFWE-corr $< .001$). Interestingly, between-group contrasts showed increased activation in patients compared to controls in the right cerebellum ($T = 5.08$, pFWE-corr $< .001$) for both meaningless and meaningful gestures vs. control sentences. In addition, between-group contrasts indicated increased activation in patients in the left prefrontal cortex (dlPFC; $T = 4.16$, pFWE-corr $= .034$) for only meaningless gestures vs. control sentences.

Discussion: During the planning of both meaningful and meaningless gestures, patients demonstrated increased activation of the cerebellum. Additionally, during the planning of only meaningless gestures, patients showed an increased activation in the dlPFC. The cerebellum is known to modulate motor control, cognition, and language, whereas the dlPFC plays an important role in motor planning, abstract reasoning, language, and executive functioning. The increased activation of both brain areas suggest that patients need to activate additional neuronal resources to successfully plan gestures compared to controls. These findings reveal the important role of the cerebellum and the dlPFC for nonverbal communication in patients with schizophrenia. We expect further group differences to appear, as more participants are included in the study.

F131. EVIDENCE FROM IMAGING RESILIENCE GENETICS FOR A PROTECTIVE MECHANISM AGAINST SCHIZOPHRENIA IN THE VENTRAL VISUAL PATHWAY

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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.
Discussion: 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 strengthening 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.

F132. RESTING-STATE EEG POWER AND P300 TASK-RELATED ACTIVITY MODULATION IN THE THETA BAND IN PATIENTS WITH SCHIZOPHRENIA

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Background: There is some consistency in the literature that patients with schizophrenia have increased EEG activity during the resting state, mainly in the low frequency bands. In addition, previous work by our group has provided evidence that there is a deficit in the modulation of bioelectrical activity during the performance of a P300 task in schizophrenia. The present work aims to study in this illness the relationship between basal hyperactivation and the altered ability to change or modulate cortical activity during a cognitive task. However, no study so far, to the best of our knowledge, has studied the association between resting-state activity and task-related modulation.
Methods: A sample of 100 patients with schizophrenia (including a subgroup of 30 first episodes) and 93 healthy controls underwent a dual EEG paradigm consisting of a resting state and an oddball task for elicitation of the P300 evoked potential. Cortical activity was collected throughout the scalp using 29-channel EEG equipment. The study measures were absolute power for resting-state; and spectral entropy (SE) and connectivity strength (CS) for P300-task data, whose modulation had been previously found to be altered in schizophrenia. Following the literature on P300 and our previous work, we focused our study on the theta frequency band.
Results: Our Results: showed an increase in resting state activity in the theta band and a reduced task-related modulation in patients with schizophrenia. We also found an inverse relationship between the amount of theta-band resting-state activity and modulation of task-related activity both in patients with schizophrenia and healthy controls.
Discussion: The Results: support the existence of a relationship between resting-state basal activity and its modulation during the performance of a cognitive task, and specifically the idea that a greater amount of resting resting-state synchrony in the theta band could hamper the modulation of signal regularity (quantified by SE) and activity density (measured by CS) during the P300 task performance. Since this association was found in both patients and controls, we may suggest the existence of a common mechanism and a possible ceiling effect in schizophrenia patients in relation to a decreased inhibitory function that limits their cortical reactivity to the task.

F133. IMPAIRED OBESITY AWARENESS MAY BE RELATED TO INTERHEMISPHERIC IMBALANCE IN THE POSTERIOR PARIETAL AREAS

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Background: The prevalence of obesity is higher in individuals with schizophrenia (40-60%) than the general population. Approximately 80% of overweight individuals fail to achieve sustained weight loss. Several factors may affect adherence to interventions, including impaired obesity awareness. Individuals with poor awareness may underestimate their weight, minimize the risks of obesity and decline or discontinue treatment. This novel study aims to evaluate the neuroanatomical model of impaired illness awareness (IA) in individuals with obesity using fMRI. Based on brain regions identified in other conditions including schizophrenia that feature impaired

IA, it is proposed that impaired IA may be related to interhemispheric imbalance, especially left hemisphere dominance in posterior parietal area (PPA) and the medial prefrontal cortex (mPFC).
Methods: Thus far, 15 individuals with a BMI of >30 kg/m2 have been recruited. Participants were categorized based on the Obesity Awareness Scale and Insight Scale (OASIS) as having intact or impaired IA (OASIS Average<7). All participants completed an fMRI IA task designed to confront participants with their condition. Non-parametric analyses were conducted to compare the brain activity, as measured by the BOLD response, in the PPA and mPFC to the IA task between the two groups.
Results: Preliminary Results: indicate that individuals with impaired IA (N=5) have higher left PPA activity compared to individuals with intact IA (N=10) during an illness awareness task ($p<0.05$ uncorr.).
Discussion: Identifying brain regions associated with obesity awareness may provide biomarkers for personalized and targeted interventions, such as non-invasive brain stimulation, which could impact treatment engagement and patient outcomes.

F134. RESTING STATE EEG ACTIVITY PREDICTS LEARNING DURING AUDITORY TRAINING IN PATIENTS WITH SCHIZOPHRENIA

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Background: Cognitive impairment is a major attribute of psychotic patients that directly correlate with poor social and work outcomes. Cognitive remediation (CR) is a non-pharmacological intervention whose main objective is to improve cognition, psychosocial functioning, and quality of life. Available evidence regarding the efficacy of CR shows a considerable variability in individual treatment response, which may undermine the effectiveness of CR in real-world settings. Several studies identified psychological, cognitive, and biological variables that predicts improvement following cognitive remediation interventions. The aim of this work was to identify neuroimaging predictors of cognitive improvement following CR.
Methods: We analyzed the data coming from 20 adult participants with a diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder or other psychotic disorders according to DSM-IV criteria (using SCID-5-CV) who underwent 10 hours of CR. At baseline, assessments of demographic and neurocognition functions were conducted. RestingsState electroencephalogram (rs-EEG) was measured before the intervention. Functional networks were estimated by computing the magnitude square coherence (MSC) and the cross correlation (CCOR) between the time series of all available cortical sources. A statistical model was used to form characteristic weighted and binary graphs. The introduced modulation was assessed primarily by network density, network degree and link level.
Results: We found linear correlation between rs-EEG beta band (12–30Hz) and best cognitive performance on measures of centrality (network degree and network density; $p < 0.05$, uncorrected), and inverse linear correlation between performance improvement and link levels in beta band between nodes E52 and E57 ($p < 0.05$, multiple comparison corrected).
Discussion: Our analysis identified new potentially tools that could be used to select patients that most stand to gain from CR and patients that instead would benefit more from a different treatment

approach. These findings enrich the understanding of functional connectivity networks, as it seems one of the first studies supporting the theory that resting state oscillations can predict cognitive enhancement. Finally, our Results: provide preliminary evidence for a future personalized medicine approach in which each patient would receive a different CR schedule based on their neural endophenotype.

F135. THE BENEFIT OF MACROANATOMICAL ALIGNMENT FOR FMRI VISUAL FIELD LOCALIZER DATA – IMPLICATIONS FOR THE STUDY OF VISUAL DYSFUNCTION IN SCHIZOPHRENIA

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Background: The visual system is highly relevant for cognitive processes such as attention and working memory. Hence, visual dysfunction can lead to higher-order cognitive deficits. Impairments in these systems are observed in several neuropsychiatric disorders, namely schizophrenia, bipolar disorder and ADHD. Additionally, perceptual processes, attention and working memory are part of the RDoC project. Therefore, mapping the visual system is crucial for a detailed study of its role in perceptual processing and generally in cognition.
Here, using visual field localizer paradigms and fMRI is a common approach to study local information processing of simple visual stimuli in early visual areas. However, high inter-individual macro-anatomical variability impedes such analyses at the group level. Therefore, we used the alternative method of cortex-based inter-subject alignment (CBA). We aimed to assess its benefits for a visual field localizer paradigm, which has so far not been evaluated.

Methods: 50 healthy participants underwent fMRI in a 3 T Siemens Trio scanner performing an attention-enhanced visual field localizer paradigm. The task consisted of a series of flickering black-and-white-colored round-shaped checkerboard stimuli (flicker frequency = 7.5 Hz). Checkerboard stimuli appeared randomly at one of four different locations (non-target trial) mapping an equivalent position in one of the four visual quadrants. Throughout the task a black, x-shaped fixation cross was displayed at the center of the screen which had to be fixated. During some trials, the two centrally located squares of the checkerboard changed their color to yellow (target trial). Participants had to indicate by button press the detection of a target. Target probability was 25 %. Data analysis in BrainVoyager 20.6 included standard data pre-processing, segmentation of the structural data and additionally, a multiscale curvature driven CBA. This was used to minimize inter-individual macro-anatomical variability. Subsequently, functional data were analyzed using a random-effects multi-subject general linear model.
Results: Group regions of interest (ROI) after CBA showed considerably increased spatial consistency and vertical symmetry. After CBA we further observed an increase in the probability

of activation overlap of up to 40 % for all visual quadrants. Additionally, after CBA the size of group ROIs for the lower visual hemifield was larger than for the upper.
Discussion: CBA noticeably decreased macroanatomical variability in early visual areas and ameliorated Results: of ROI analyses at the group level. It allowed us to reliably measure functional differences in visual hemifields mirroring previous findings from electrophysiological studies. Our findings provide clear evidence for the superiority of CBA over nonlinear volume-based alignment for the study of local information processing in early visual regions – in particular at the group-level. Therefore, this approach is of importance for the study of visual impairments in healthy populations but also in neuropsychiatric disorders like schizophrenia, which are characterized by increased interindividual macro-anatomical variability.

F136. LANGUAGE NETWORK SELF-INHIBITION AND SEMANTIC SIMILARITY IN FIRST-EPISODE SCHIZOPHRENIA PATIENTS: A COMPUTATIONAL-LINGUISTIC AND EFFECTIVE CONNECTIVITY APPROACH

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Background: A central and often persistent feature of schizophrenia is the disorganisation and impoverishment of language and related expressive behaviours. Recently, we observed higher semantic similarity in first-episode schizophrenia (FES) patients. In this study, we address the effective connectivity between two key nodes of the left lateralised word production system: Broca's inferior frontal gyrus (IFG) and the semantic hub at the ventral anterior temporal lobe (vATL)
Methods: Resting-state fMRI scans were collected for 60 participants (30 untreated first episode schizophrenia and 30 gender, age matched healthy controls). Speech samples were acquired from descriptions of 3 unambiguous pictures transcribed manually. The semantic distance (average similarity of words in the full text) between spoken words was measured with the Covington Vector semantic tool, a natural language processing tool based on GloVe. Repeated sampling from a restricted semantic space reduces semantic distance among words, resulting in lexical impoverishment. A spectral dynamic causal model (DCM) with Parametrical Empirical Bayes (PEB) was constructed with intrinsic self-inhibitory and extrinsic excitatory connections within the nodes . We estimated the parameters of a fully-connected model considering the semantic distance among spoken words as a covariate.
Results: Patients with schizophrenia chose words with reduced semantic distance (i.e., higher similarity) when describing the pictures, compared to the HC group, with very strong evidence against null hypothesis (Bayes Factor against null = 1623). Among patients with schizophrenia, increased semantic distance related to an increase in intrinsic inhibitory tone of the semantic hub (vATL) and Broca's area (IFG).
Discussion: Lexical impoverishment in schizophrenia relates to increased self-inhibition on Broca's inferior frontal gyrus and the semantic hub at the ventral anterior temporal lobe. The associated reduction in synaptic gain may relate to reduced precision of locally generated neural activity, forcing the choice of words that are already 'activated' in a lexical network. Higher local inhibitory tone may also prevent the 'release' required for disinhibition, making a brain region more dependent on extrinsically driven stimulatory processes. For our language network model, this

may mean that aberrant word sampling could be overcome in the presence of a supra-physiological top-down stimulation arriving at the vATL; this needs experimental verification during a speech production task.

F137. EFFECTS OF ANTIPSYCHOTIC MEDICATION ON FUNCTIONAL CONNECTIVITY IN MAJOR DEPRESSIVE DISORDER WITH PSYCHOTIC FEATURES: NEUROIMAGING FINDINGS IN THE CONTEXT OF A RANDOMIZED PLACEBO-CONTROLLED CLINICAL TRIAL

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Background: Olanzapine is associated with global and regional reductions in cortical thickness and other structural measures in major depressive disorder with psychotic features (MDDPsy). The effect of antipsychotic medication on resting state functional connectivity in MDDPsy is currently unknown. Based on our previous analyses of structural MRI, we hypothesized that, over time, longitudinal functional connectivity would differentially change in patients with remitted MDDPsy receiving olanzapine or placebo.

Methods: Participants in the STOP-PD II randomized placebo-controlled trial were treated to remission with sertraline and olanzapine before being randomized to sertraline plus either olanzapine or placebo. MRI scans were completed at the time of randomization and at study termination. We analyzed resting state fMRI in 58 participants with data of sufficient quality, controlling for age, sex, and site effects. Whole brain functional connectivity including cortical and subcortical regions was examined and graph metric analyses were first pursued followed by within and between network analyses.

Results: Analyses were confined to participants in remission (n = 32) to control for the effects of relapse. There was no significant effect of treatment-group for graph metrics (global efficiency, modularity, transitivity, clustering coefficient) at an uncorrected or FDR corrected level ($p < .05$). Similarly, there were no significant effects of treatment-group for within and between network functional connectivity that survived FDR correction. At an uncorrected level, functional connectivity between the secondary visual network and the rest of the brain was significant ($p = .0092$).

Analyses were also expanded to include the total sample. There were no significant treatment-group X time interactions for graph metrics at an uncorrected or FDR corrected level ($p < .05$). However, for within and between network functional connectivity, there was a significant treatment-group X time interaction for functional connectivity between the secondary visual network and the rest of the brain at an uncorrected ($p = .0004$) and FDR corrected ($p = .0112$)

level. When examined individually, neither treatment-group nor time were significant at an uncorrected or FDR corrected level.

Discussion: Overall, the lack of an effect of olanzapine versus placebo on functional connectivity among patients in remission suggests that the structural changes we reported previously may not be associated with functional connectivity changes in the graph metrics and resting state functional networks we examined. However, the significant treatment-group X time interaction suggests that there may be a relationship between effects of antipsychotic medication on functional connectivity and relapse or remission status.

F138. IMPAIRED NEURAL REPLAY OF INFERRED RELATIONSHIPS IN SCHIZOPHRENIA, AND THE RELATIONSHIP TO DMN ACTIVATION

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Background: An ability to build structured mental maps of the world underpins our capacity to imagine unobserved relationships between events or people. Inferences of this nature, when they go awry, are intimately related to symptoms of many psychiatric disorders, from worry about imagined futures in anxiety, to paranoia in psychosis. Preclinical studies show that such inferences are supported by sequential neural reactivations in hippocampus, which 'replay' previous experiences and 'join the dots' between related events. Replay occurs during resting (off-task) periods following new experiences, and coincide with periods of default mode network (DMN) activation. Multiple lines of evidence suggest a replay abnormality in schizophrenia, from neuroimaging studies in people with a diagnosis of schizophrenia (PScz) that report hippocampal hypermetabolism and DMN abnormalities, to genetic mouse models that show abnormalities in hippocampal replay and associated ripple activity. However, this hypothesis has not been tested in clinical samples owing to difficulties in detecting replay using conventional neuroimaging approaches. Here, we address this knowledge gap, leveraging analytic advances in magnetoencephalography (MEG) brain scanning to test the hypothesis of abnormal replay and replay-DMN coupling in PScz.

Methods: During MEG, we asked PScz (n = 28, 13 unmedicated) and control participants (n = 29, matched for demographic and educational variables) to complete a learning task in which they needed to infer sequential relationships between task pictures (e.g. A->B->C), by mentally reorganising visual experiences containing these objects (e.g. B->C and A->B) . After this learning task, participants completed an awake resting state MEG session. During this rest session, we measured the occurrence of spontaneous neural reactivations of task-state representations (A, B and C) using multivariate MEG decoding, and quantified whether such reactivations occurred in a manner that rapidly replayed the correctly inferred relationships between task pictures (i.e. A->B->C, replayed within 1 second) to a greater extent than 'non-specific' sequential reactivations (e.g. C->A), using a Temporally Delayed Linear Modelling analytic approach. We also quantified

whether replay events were temporally-coupled to DMN activation using a hidden Markov modelling (HMM) analytic approach.
Results: During the post-task rest session, control participants exhibited fast spontaneous neural reactivation (replay) of presented objects that replayed correctly inferred relationships. Replay events were coincident with increased high-frequency oscillatory power (120 – 150 Hz, 'ripple' band) in hippocampus. PScz showed both reduced replay ($F(1,52) = 8.08$, $P = 0.006$, mixed ANOVA) and augmented ripple power relative to controls ($t(51) = -2.6$, $P = 0.01$, two sample t-test), convergent with findings in genetic mouse models. These abnormalities were linked to impairments in behavioural acquisition and subsequent neural representation of task structure (measured using a Representational Similarity Analysis). Strikingly, PScz also showed a reduced coupling between replay onsets and DMN activation ($t(52) = 3.93$, FWE-corrected peak-level $P = 0.018$, non-parametric permutation test). This replay-DMN coupling deficit predicted a reduced stimulus-evoked DMN modulation in PScz ($r(52) = 0.39$, $P = 0.004$, Pearson's correlation), as well as a subsequent knowledge of the inferred sequences ($rho(52) = 0.31$, $P = 0.02$, Spearman's correlation).
Discussion: Together, our Results: represent the first quantification of offline neural replay in a clinical sample. They shed new light on the nature of off-task (resting) neural computation in schizophrenia, and its relationship to inference impairments. They represent an important translational bridge to preclinical genetic mouse models of schizophrenia. Furthermore, they enable a consilience between task-based and resting-state DMN literatures in the disorder, and highlight a mechanism whereby abnormal replay-DMN coupling might contribute to the generation of core symptoms.

F139. P100 IMPAIRMENT IN PATIENTS WITH SCHIZOPHRENIA AND VISUAL HALLUCINATIONS: AN ASSOCIATION WITH PREVIOUS RETINAL MEASUREMENTS

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Background: Deficits in the magnocellular visual system are reported in schizophrenia at the cortical level. However, recent studies showed retinal anomalies in this pathology, notably in patients with visual hallucinations (VH). These findings prompted us to explore in EEG the visual cortical processing in schizophrenia divided in two subgroups with and without history of VH. We also explored a possible link between the retina and visual cortex in these populations.
Methods: We recorded VEP in EEG during the projection of low or high spatial frequency gratings (LSF or HSF ; 0.5 or 15 cycles/degree respectively) presented statically (0Hz) or dynamically (8Hz) to isolate the activity of the magnocellular and parvocellular pathways. We analyzed the P100 amplitude and latency in 29 healthy controls (HC, n=29) and 21 patients with schizophrenia (SZ, n=21) divided in two subgroups with and without history of VH according to the PSAS : VH group (n = 9) and auditory hallucinations or no hallucinations group (AHNH, n = 12). We compare VEP to former Results: regarding retinal ganglion cells activity (N95) on the same sample (1) and visual cognition performances.

Results: Analysis showed a decreased P100 amplitude ($p<0.01$) and an increased P100 latency ($p<0.05$) in SZ than HC. Analysis reported main effects of SF and TF without group interaction. P100 latency was correlated with the VOSP object score and the N95 PERG latency (1) in SZ group. In subgroups, AHNH group showed a decreased P100 amplitude compared to both VH and HC ($p<0.05$) and VH group reported an increased P100 latency than HC ($p<0.05$). P100 latency was correlated with the VOSP object score and the N95 PERG latency (1) in the VH group. We found a partial mediation between P100 latency, N95 PERG latency and VOSP object score in VH group.
Discussion: P100 alterations in the schizophrenia group are consistent with the early visual cortical processing deficit in schizophrenia. Importantly, patients' results are not related to the magnocellular biased stimuli but seems to be associated with their previous retinal measurements. Indeed, although impaired P100 was found in all subgroups, the association between retinal and cortical anomalies is present only in VH, thus supporting the role of retina in VH. Coupled ERG-EEG studies are now required to clarify these findings.

F140. AGE-RELATED CHANGES IN GLUTAMATE IN THE PREFRONTAL CORTEX DURING NORMAL BRAIN DEVELOPMENT: A FRAMEWORK TO CHARACTERIZE GLUTAMATERGIC ABNORMALITIES IN PSYCHOSIS

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Background: Studying the neurobiological changes that precede the onset of psychotic disorders is essential to understand the etiology of these pathologies and develop effective treatments. In this regard, accumulating evidence has pointed to anomalous glutamatergic neurotransmission being involved in the underlying pathophysiology of psychosis, which is thought to be more pronounced before the outbreak of overt illness. This glutamatergic dysfunction is thought to be mediated by a dysfunction in NMDA receptors, which is believed to affect primarily parvalbumin positive neurons in the prefrontal cortex (PFC) and the hippocampus. As a consequence, inhibitory circuits are under-stimulated, which in turn Results: in increased levels of cortical glutamate. However, it is important to fully understand the normative patterns of glutamate levels over development before determining aberrant patterns of glutamatergic function. Although the psychosis usually has an onset during adolescence and early adulthood, previous investigations on the developmental

changes in glutamatergic metabolites have focused on adult population. For this purpose, the present study set out to explore the relationship between glutamate and Glx (glutamate + glutamine) levels in the PFC and the hippocampus and age and sex in the largest sample to date encompassing an age range range starting in childhood.
Methods: 84 healthy subjects (aged from 9 to 56 years-old, mean age 21.07) were recruited in the Hospital Clinic of Barcelona, 29 of which were evaluated longitudinally. Every subject at each timepoint underwent the acquisition of two magnetic resonance imaging sequences on a 3T scanner: a T1-weighted sequence and a magnetic resonance spectroscopy sequence (MRS) in two volumes of interest located in the PFC (2x2x2 cm^3) and the medial temporal lobe (3x2x2 cm^3). MRS data was processed employing LCModel, through which metabolite creatine-corrected metabolite ratios were obtained. Mixed linear models were conducted in R with metabolite as the dependent variable and sex and age and the interaction between them as fixed effects.
Results: Inspection of residuals for each model confirmed that concentration of glutamate and Glx for each of the VOIs followed a linear trajectory. There was a significant main effect of age (beta = -0.01, SE = 0.003, t = -3.3, p = 0.001), but not of sex on PFC glutamate levels, whereby glutamate levels in the PFC descended with age. No effect of age or sex was observed on PFC Glx concentration. None of these effects were observed for concentrations of glutamate or Glx in the medial temporal lobe.
Discussion: Along the lines of previous studies reporting an age-related decline in PFC glutamate, our study suggests that this decline already takes place during late childhood and adolescence. Glutamate in high concentrations is excitotoxic and it is believed to play an important role in synaptic pruning. This process, that has been reported to be anomalous in psychosis, develops during adolescence and entails the degeneration of dispensable synapses. Thus, it is coherent that this metabolite decreases with normal brain maturation. No effect of age or sex was found on medial temporal lobe metabolite levels. These findings provide insight into the developmental trajectory, starting at late childhood, of prefrontal and medial temporal lobe glutamate levels in healthy individuals, hence presenting a reference for future studies that analyze glutamatergic dysfunction preceeding and during the onset of the psychotic disorders.

F141. COMPLEMENT COMPONENT 4A PROTEIN LEVELS ARE NEGATIVELY RELATED TO MEDIAL ORBITOFRONTAL VOLUME IN SCHIZOPHRENIA SPECTRUM DISORDER PATIENTS

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Background: Due to its prominent place in large genetic studies, the complement system is suggested as a pathophysiological factor in schizophrenia-spectrum disorders (SSD). In particular, alleles associated with increased complement component 4A (C4A) expression also increase schizophrenia risk. Compared to healthy controls (HCs), brain tissue of individuals with SSD (combined n=196, Rey et al., 2020) display an over-expression of total C4. Preclinical studies show that this excessive C4A expression Results: in increased microglia-mediated synaptic pruning during postnatal development. This mechanism may account for the altered brain

morphology and cognitive symptoms observed in SSD. Previous studies mainly investigated predicted complement expression based on genotype. However, environmental factors also influence C4A gene expression. This study investigates C4A serum protein levels in association with brain morphology (i.e. cortical thickness and brain volumes) and cognition in SSD (n=66) and HC (n=40).

Methods: The study sample and data are part of the baseline measurements of a completed clinical trial (ClinicalTrails.gov:NCT01999309). Patients aged between 18-50 and diagnosed (295.x or 298.9) within 3 years prior to screening were included. HCs had no prior or family history with psychiatric disorders. C4A levels were determined using ELISA with a monoclonal antibody specific for C4A by Sanquin Diagnostic Services (Amsterdam, the Netherlands). C4A levels were log-transformed. Cortical volume and thickness were calculated based on T1 weighted images (3T) that were processed using FreeSurfer (version 6.0.1). Regions of interest (ROIs) included all regions from the Desikan-Killiany cortical atlas and FreeSurfer's subcortical atlas. All statistical tests were corrected for age, sex, BMI, and antipsychotic dose equivalent. The difference in C4A levels between groups was analysed using ANOVA. For every cognitive score (BACS composite and 6 sub-scores; n=7), ROI volume (n=103) and ROI thickness (n=70), a regression analysis was performed including covariates (handedness, total intracranial volume or mean cortical thickness), C4A level, group (SSD vs. HC), and C4A*Group interaction. All regression analyses were Bonferroni corrected (α=0.007, 4.9 x10-4, 7.1 x10-4, for cognition, volume, and thickness, respectively).

Results: The difference between SSD (374±219 μg/ml) and HCs (372±188 μg/ml) in serum C4A levels was not statistically significant ($F(1,100)=0.009$, $p=0.93$). Total grey matter volume and mean cortical thickness did not show a significant interaction effect of C4A*Group ($p>0.12$) or a main effect of C4A ($p>0.25$). None of the cognitive measures showed a significant interaction effect ($p>0.18$), but a trend-level positive main effect was found for C4A on executive functioning in both groups combined ($R2=0.06$, $\beta=0.25$, $p=0.009$). Only the left medial orbitofrontal volume (mOFC) showed a significant interaction effect ($R2=0.12$, $\beta=-0.72$, $p=2.6x10-6$). The relation between mOFC volume and C4A was negative for SSD ($\beta=-0.51$, 95%CI= [-0.85,-0.18]) and positive for HC ($\beta=0.82$, 95%CI=[0.40,1.24]). No main effect for C4A was observed in either of the volume and thickness analyses ($p>0.005$ and $p>0.003$).

Discussion: All main analyses did not show significant group differences in C4A or significant C4A*Group interactions in cognition or total grey matter volume and thickness. C4A was positively related to executive functioning in both groups combined on a trend-level. In addition, C4A was negatively related with mOFC volume in SSD, but a positively related in HC. These preliminary exploratory Results: suggest that peripheral levels of C4A may have a differential association with brain morphology in SSD compared to HC.

F142. MODELLING THE RELATIONSHIP OF AUTISTIC AND SCHIZOTYPAL TRAITS AND THEIR EFFECT ON HIPPOCAMPAL VOLUME AND BLOOD FLOW

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Background: Schizophrenia spectrum disorders (SSD) overlap in certain characteristics with autism spectrum disorder (ASD) and are diametrically opposed in others. This has been shown at the phenotype level, but may reflect inherent neurobiological predispositions. We analysed the overlap of subclinical autistic and psychosis spectrum characteristics and their association with brain structural and perfusion markers within the hippocampus, a central hub with transdiagnostic significance.
Methods: In two independent non-clinical German and French-Swiss cohorts (N=376, N=264), we assessed multiple schizotypy instruments and the autism spectrum quotient (AQ) and conducted correlation and principal component analyses to explore psychometric relationships and latent component structures. The first cohort partially provided hippocampal volume (n=318) and regional cerebral blood flow (rCBF) markers (n=348) to assess their association with positive schizotypy and autistic traits and their interactions using MANCOVAs and Response-Surface-Analysis.
Results: Autistic traits strongly overlapped with negative and disorganised and loaded diametrically to positive features of schizotypy, exhibiting comparable factor structures across samples and instruments. The positive schizotypy x AQ social skills interaction significantly explained hippocampal volume, especially in the head subfield ($p<0.026$, $d=0.26$-45), while rCBF was associated with the positive schizotypy x AQ attention to detail interaction in the hippocampal tail ($p<0.038$, $d=0.23$-31).
Discussion: Results: support a model of overlapping and opposed features of ASD and SSD, detectable across subclinical trait facets. Modelling this relationship on the level of neurobiological markers, we show that volume and rCBF are associated with the relative expression of ASD vs. SSD traits and establish a multimodal framework for the study of psychiatric co-morbidities.

F143. CENTRO-PARIETAL SLEEP SPINDLE ABNORMALITIES IN DRUG-NAïVE PATIENTS AT THE ONSET OF PSYCHOSIS

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Background: Sleep spindles are waxing and waning brain oscillations that define non-rapid eye movements (NREM) sleep stage 2. Evidence suggests their involvement in processes of declarative memory consolidation and learning. A decreased sleep spindle activity has been described in chronic Schizophrenia (SCZ) as well in early course patients; furthermore, recent studies have shown impaired spindle activity in first-degree relatives of SCZ patients, suggesting a link between spindle abnormalities and genetic vulnerability to SCZ. Impaired spindle activity may reflect functional abnormalities of the Thalamic Reticular Nucleus (TRN), which is involved in regulating attention and the processing of sensory information during wakefulness. Therefore, spindle abnormalities may have an important role in the cognitive symptoms observed in patients. In a recent study, decreased spindle duration and density were observed in First-Episode Psychosis (FEP) patients with some exposure to psychoactive treatments, and reduced spindle density correlated with the intensity of negative symptoms. However, clear evidence of altered spindle activity at illness onset has yet to be established in antipsychotic-naïve patients. In this study, we compared sleep spindle activity in drug-naïve FEP patients and healthy control subjects.

Methods: We recruited 20 drug-naïve, acutely ill FEP patients (M=13; mean age 22.5, SD 5.37) during their first hospitalization and 20 gender/age-matched healthy control (HC) subjects (M=13; mean age 22.25, SD 4.47, p=0.95). A 64-channel EEG system (BrainAmp, Brain Product GmbH, Gliching, Germany) was employed to record a whole night of sleep in each participant. FEP patients underwent sleep EEG during their first or second night in our inpatient unit and before any psychoactive treatment was administered. EEG data cleaning, sleep spindle detection, and sleep spindle parameter analysis were performed using customized algorithms. First, we analyzed the entire spindle frequency band (12-16 Hz); then a discrete analysis for slow (12-14 Hz) and fast (14-16 Hz) spindles was performed. Group differences in spindle parameters were assessed and a threshold-free cluster enhancement (TFCE) method was employed to account for multiple comparisons.
Results: We found no difference in spindle density (12-16 Hz) in FEP patients relative to HC. However, a significant decrease of mean spindle frequency was observed in FEP patients, compared to HC, in a large centro-parietal cluster of electrodes. Additional analysis for slow (12-13 Hz) and fast (14-16 Hz) spindles showed a significant increase of centro-parietal slow spindle density in FEP patients. Furthermore, in FEP, slow spindle density in centroparietal areas correlated with the severity of negative symptoms (p=0.0303; r=0.5255).
Discussion: Our data support the evidence of specific alterations in spindle activity in drug-naïve psychosis at illness onset. The increase of slow spindle density in the centro-parietal region, where fast spindles are physiologically predominant, suggests a global slowing of these oscillations in patients. Our data also suggest a correlation between negative symptoms and decreased slow spindle density in the early stage of psychosis.
Sleep spindle dysfunction may represent the earliest neural signature of thalamocortical system abnormalities in psychotic spectrum disorders, but further research is necessary to confirm our Results: in larger samples.

F144. LONGITUDINAL CORTICAL SURFACE AREA CHANGES IN ADOLESCENTS AT CLINICAL HIGH-RISK FOR PSYCHOSIS THAT DEVELOP A PSYCHOTIC DISORDER

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Background: Identifying biomarkers of transition to psychosis in individuals at clinical high risk for psychosis (CHR-P) is essential in order to understand the mechanisms underlying psychotic disorders and provide targeted interventions. Abnormalities in cortical surface area (CSA) have been consistently shown in CHR-P who transition to psychosis (CHR-P-P) compared to those who do not (CHR-P-NP). However, how CSA changes longitudinally in these subjects remain unclear, especially in younger individuals, in which changes in neurodevelopmental trajectories may confound cross sectional findings

Methods: One hundred and seven adolescents aged 11 to 17 years meeting SIPS/SOPS criteria for CHR-P and 102 healthy controls (HC) were included in this prospective, longitudinal, casecontrol study. During the 18-month follow-up period 25 individuals at CHR-P developed a psychotic disorder (23.4% transition rate). All participants underwent a comprehensive sociodemographic and clinical evaluation at baseline and 18 months. Neurological disease, head trauma history with loss of consciousness and previous or current psychotic disorder were exclusion criteria for the whole sample. High resolution T1-weighted images were acquired on a 3 Tesla Siemens scanner at Hospital Clinic Barcelona and on a 1.5 Tesla General Electric scanner at Hospital Sant Joan de Déu at baseline and at 18 months follow-up. Images were pre-processed employing the automated procedures and longitudinal pipeline implemented in FreeSurfer 6.0, cortical parcellation employed the Desikan-Killiany brain atlas. Regional CSA measurements were computed, and a mixed effect model was performed in order to identify age interactions between the three groups, including gender and scan as covariables. Significance was set al $p<.05$, corrected using the false discovery rate (FDR). An inter-site compatibility study showed high inter-site correlation coefficients ($r>.6$) for CSA measures, in a HC sample (N=9). The study was approved by the local Ethical Review Board

Results: A total of 313 scans were included in the analysis. There were no significant differences between CHR-P-P, CHR-P-NP and HC in gender (% females: 60.0% vs 67.1% vs 55.9%; $\chi 2=2.4$, $p=.302$) and age (15.3 ± 1.7 vs 15.3 ± 1.8 vs 15.8 ± 1.6; $F=2.2$, $p=.113$). There were no significant differences in chlorpromazine equivalent doses for antipsychotics at baseline between CHR-P-P and CHR-P-NP (58.6 mg/day vs 46.8 mg/day; $t=0.5$, $p=.623$).

No significant group by age interactions were found between all CHR-P and HC, nor between CHR-P-NP vs HC. A significant group by age interaction was found in the left lateral occipital (pFDR corr=.042), left precuneus (pFDR-corr=.025) and left superior parietal (pFDR-corr=.038) cortices between CHR-P-P and HC, and in the left precuneus (pFDR-corr=.030) and left superior parietal cortex (pFDR-corr=.030) in the CHR-P-P vs CHR-P-NP contrasts. In both cases CHR-P-P showed a greater age-related decrease in CSA than CHR-P-NP and HC.

Discussion: In our study individuals at CHR-P-P showed a greater CSA loss in parietal and occipital cortices as psychosis developed, which provides new insights on longitudinal CSA trajectories in individuals at CHR-P during adolescence. Smaller CSA in the parietal lobes have been reported in youth at familial risk for psychosis and in other regions in adolescents at CHR-P. Similarly, widespread CSA reductions have been reported in individuals with schizophrenia in larger samples. Further research is needed to better understand the trajectories of change in CSA prior to illness onset, and their relationship with other cortical measures.

F145. REASONS FOR DISCONTINUATION AND CONTINUATION OF ANTIPSYCHOTICS AND ITS PREDICTORS IN FIRST-EPISODE SCHIZOPHRENIA

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Background: Although discontinuation of antipsychotics increases the risk of psychotic relapse, many individuals with schizophrenia will taper or discontinue their antipsychotic medication. The literature is sparse on self-reported reasons for antipsychotic continuation and discontinuation in individuals with first-episode schizophrenia. Therefore, it is relevant to know about patients' reasons to discontinue or continue antipsychotics and what predicts these.
Methods: This is a prospective cohort study with a post hoc study design. Patients included were diagnosed with schizophrenia and part of the OPUS II trial. The OPUS II trial compares two years of early intervention treatment with five-year early intervention treatment for psychosis. Patients were assessed 19 months (baseline) and five years (follow-up) after treatment start in OPUS. Patient reasons for discontinuation or continuation of antipsychotics was assessed using RAD interview at follow-up. The reasons are described and clinical and social characteristics from baseline analyzed to find predictors of these reasons.
Results: Results: will be stated in the poster at the conference.
Discussion: Discussion: of the Results: will be stated in the poster at the conference.

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F146. EXPOSURE TO ANTIPSYCHOTIC MEDICATIONS AND COVID-19 MORTALITY 14 AND 30 DAYS AFTER HOSPITAL ADMISSION

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Background: There is evidence of a bidirectional association between COVID-19 disease and psychiatric disorders. Individuals with psychiatric disorders may have a worst prognosis and first-generation antipsychotics (FGA) and second-generation antipsychotic (SGA) may worsen the disease course.
Methods: In our study, we included all individuals with a laboratory-confirmed COVID-19 infection (PCR diagnosis) who were admitted to the University Hospital of Bologna between 1st March 2020 and 31st January 2021. Our main objective is to assess if exposure to psychotropic medications prior to hospitalization is associated with mortality at 14 and 30 days after admission. We also collected data about pre-existing psychiatric disorders and the use of psychotropic medications at the admission. Finally, we estimated cause-specific Hazard Ratios (HR) of mortality using weighted Cox regression models and adjusting sociodemographic (age, gender)

and clinically relevant variables (comorbidity, c-reactive protein levels, severity of disease at presentation, history of smoking).
Results: Out of a total of 1,201 hospitalized patients, 318 were prescribed psychotropic medications at the time of admission. Among these, 48 (4.0%) were taking an FGA and 63 (5.2%) an SGA. Exposure to FGA and SGA prior to hospitalization was associated with increased cause-specific HR of death at 14 and 30 days in adjusted models.
Discussion: Patients with COVID-19 infection exposed to FGA and SGA may have a higher risk of mortality, so psychotropic drugs, especially antipsychotics, should be prescribed with caution. People affected by severe mental illness have both medical and socioeconomic risk-factors for severe Sars-Cov-2 infection, morbidity and mortality, therefore they should be considered fragile patients within the COVID-19 vaccination campaign.

F147. LEVETIRACETAM ATTENUATES CHANGES RESEMBLING SCHIZOPHRENIA INDUCED BY ADOLESCENT STRESS IN RATS

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Background: Stress during adolescence acts as a major risk factor for the development of psychiatric disorders later in life. We previously found that adolescent stress caused, at adulthood, behavioral changes and enhanced ventral tegmental area (VTA) dopamine (DA) system activity, which were associated with dysregulation of the excitatory-inhibitory (E/I) balance in the ventral hippocampus (vHIP) Levetiracetam (LEV), an anticonvulsant drug, by regulating the release of neurotransmitters, including glutamate, via the inhibition of SV2A and modulating the activity of parvalbumin interneurons via Kv3.1 channels, is posited to ameliorate deficits in the E/I balance. We tested whether LEV attenuates the adolescent stress-induced behavioral changes, ventral hippocampus hyperactivity, and VTA DA system dysregulation in adult rats.
Methods: Male Sprague-Dawley rats were submitted to a combination of daily footshock (1.0 mA, 2 s, randomized every 60±20 s) for 10 days (adolescence: PND 31-40; adult: PND 61-70), and three restraint stress sessions (days PD31, 32 and 40), lasting 1h, right after the footshock session. At adulthood (PD62) animals were tested in the:elevated plus maze, light-dark box, social interaction test, novel object recognition test , and locomotor response to amphetamine. The in vivo electrophysiological activity of pyramidal neurons in the vHIP and dopamine neurons in the Ventral Tegmental Area (VTA) was also recorded. LEV (10 mg/kg, i.p.) was administered 30 min before each behavioral test or electrophysiology recordings.
Results: At adulthood, adolescent stress produced anxiety-like responses in the light-dark test, decreased social interaction, and impaired cognitive function in the novel-object recognition test. LEV reversed these changes. Adolescent stress did not change the locomotor response to amphetamine, but an increased locomotor response to amphetamine was found in LEV-treated stressed rats. LEV also reversed the increased number of spontaneously active VTA DA neurons and the enhanced firing rate of vHIP pyramidal neurons induced by adolescent stress.
Discussion: These findings suggest that LEV attenuates the adverse outcomes resembling schizophrenia caused by adolescent stress exposure. Financial support: Sao Paulo Research Foundation (FAPESP, 18/17597-3)

F148. NEUROPROTECTIVE EFFECT OF THE POSITIVE ALLOSTERIC MODULATOR OF THE MGLUR2 JNJ-46356479 IN HUMAN NEUROBLASTOMA CELL CULTURES

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Background: Current antipsychotics effectively control positive psychotic symptoms, mainly by blocking dopamine (DA) D2 receptors, but have little effect on negative and cognitive symptoms. Increased glutamate (GLU) release would trigger neurotoxicity leading to apoptosis and synaptic pruning involved in the pathophysiology of schizophrenia. New pharmacological strategies are being developed such as positive allosteric modulators (PAMs) of the metabotropic glutamate receptor 2 (mGluR2) that inhibit the presynaptic release of GLU. We aimed to evaluated, for the first time, the putative neuroprotective and antiapoptotic activity of JNJ in a human neuroblastoma cell line and compare it with the effect of clozapine (CLZ), as the reference clinical AP with apparent utility in managing negative symptoms.

Methods: We measured changes in cell viability, caspase-3 activity and cell death produced by CLZ and JNJ alone and in combination with a high DA or GLU concentration, as apoptosis inducers. Particularly, SK-N-SH cells were treated with CLZ or JNJ at 1, 10 and 25 μM, either alone or in combination with DA (100 or 200 μM) or GLU (80 or 160 mM). After 24 h and/or 48 h of incubation, cell viability and caspsase-3 activity was determined by use of alamarBlue® and a fluorimetric assay kit, respectively. We also used the Annexin V-FITC cell membrane labelling assay to detect the cell membrane translocation of phosphatidylserine (PS), as a marker of apoptosis and cell death. Flow cytometry measurement was performed to quantify alive, apoptotic and death cells.

Results: CLZ treatment resulted in a significant dose-dependent decrease in cell viability (5%-37%). However, the JNJ treatment did not affect cell viability and only a modest decrease (4%) was observed at the most detrimental condition (25 μM for 48h). Co-treatment with CLZ and, to a lesser extent, with JNJ enhanced DA toxicity as indicated by a dose-dependent decrease of cell viability (17%-45% and 9%-17%, respectively). With the same drug doses, cell cultures exposed to DA showed significantly higher viability when co-tretaed with JNJ than with CLZ. Co-treatment with CLZ, and not with JNJ, enhanced GLU toxicity.

While CLZ significantly increased caspase-3 activity in a dose-dependent way (49%-116%), JNJ treatment did not affect it. Co-treatment with CLZ enhanced the apoptotic effect of DA with a significant increase of caspase-3 activity (~60%) at the highest dose. In contrast, co-treatment with the highest JNJ dose reduced the apoptotic effect of DA (40%). Co-treatments with the highest doses of both CLZ and JNJ reduced caspase-3 activity (from 27% to 41%) compared to cells exposed only to GLU.

Regarding the annexin-V analysis, similar percentages of viable and dead cells were observed for CLZ and JNJ. However, there was a trend for JNJ to produce less cell death than the corresponding CLZ dose treatments. Compared to cells exposed to DA alone, co-treatments with CLZ or JNJ

showed reduced cell viability. However, while the CLZ treatment enhanced the GLU toxicity, deceasing viable cells and increasing cell death up to 20%, JNJ seemed to protect against it by increasing the number of viable cells and decreasing cell death.

Discussion: Our Results: demonstrate that JNJ-46356479 is not neurotoxic and attenuates the apoptosis, particularly the caspase-3 activation, induced by DA and GLU in neuroblastoma cell cultures. Its effects seem to be less neurotoxic and more neuroprotective than those observed with CLZ. More studies are needed to define the mechanisms of action of this GLU modulator and its potential to become a novel therapeutic agent for schizophrenia.

F149. EXPLORING THE DEFINITION OF RELAPSE IN SCHIZOPHRENIA: EQUIPERCENTILE LINKING AND DIAGNOSTIC TEST ACCURACY META-ANALYSIS

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Background: Symptom recurrence is common in the course of schizophrenia, and prevention of relapse is a major goal of maintenance treatment with antipsychotic drugs. However, definitions of relapse are inconsistent, often complex, involving multiple and alternative criteria, and with unclear clinical relevance. Therefore, clinical practice and research could be facilitated by a careful investigation of the definitions of relapse.

Methods: This is a secondary analysis of an individual-participant-data (IPD) meta-analysis investigating adverse events associated with antipsychotic discontinuation (PROSPERO-ID: CRD42021224350). In this analysis, we explored definitions of relapse in schizophrenia, since antipsychotic discontinuation could potentially lead to symptom recurrence and relapse. We searched the Yale Open Data Access (YODA) database for double-blind randomized-controlled trials (RCTs) investigating maintenance treatment with antipsychotics in stable patients with schizophrenia (any study definition was eligible). We used IPD on the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression (CGI) ratings at each timepoint (observed cases). First, PANSS and CGI ratings were compared using equipercentile linking. Second, definitions of relapse were constructed similar to previous RCTs (e.g., criteria used in Csernansky et al. 2002 and their modifications) using different cut-offs of PANSS total score change from baseline, as well as an increase in specific PANSS item scores. Using data from placebo-controlled trials, these definitions were compared with a reference definition based on CGI-Severity using diagnostic test accuracy meta-analyses.

Results: We identified seven studies with 2354 participants (5 studies were placebo-controlled) with a duration ranging from 25 weeks to 2 years. All but one of the studies used a maximum symptom score (PANSS total score <=70 or <=75) to include participants. At baseline, participants

were mildly ill with a mean CGI-S score of 3.1 and a mean PANSS total score of 59.2. The Results: of the equipercentile linking and diagnostic test accuracy meta-analysis will be presented.
Discussion: Results: from these analyses could further elucidate the clinical meaning of PANSS-based definitions of relapse and facilitate the development of clinically meaningful relapse definitions in schizophrenia.

F150. EFFICACY AND SAFETY OF CARIPRAZINE AUGMENTATION IN PATIENTS TREATED WITH CLOZAPINE: A PILOT STUDY

Late-Breaking Poster

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Background: Cariprazine, a novel antipsychotic drug is a partial agonist of dopamine D2/D3 receptors with preferential binding to the D3 receptor, that has shown clinical efficacy in patients with psychotic and mood disorders. The aim of this study, is to evaluate the efficacy and safety of the augmentation of clozapine with cariprazine in patients with sub-optimal treatment response.
Methods: Patients treated with clozapine and augmentation of cariprazine were prospectively included in this pilot study in a large mental health provider in London, UK. Demographic and clinical information of the study population were collected from the electronic records and PANNS scale administered at baseline and three months. Tolerability and discontinuation reasons where applicable were also recorded. The study was authorized by the local Audit Committee.
Results: Ten patients (4 men and 6 women) with a mean age of 36.1 years (range 26-45) were included. The majority (8/10) had a diagnosis of schizophrenic or schizoaffective disorder. Reasons for cariprazine initiation included inadequate treatment response, persistent negative symptoms and/or tolerability issues with previous augmentation options. Two patients discontinued treatment with cariprazine within the first 6 weeks due to restlessness and poor response. The remaining tolerated it well at a dose range between 3-6mg. There was a significant reduction in the mean total PANSS score from baseline to 3 months (from 45.8 to 27.6, $p<0.05$) and in the mean negative PANSS score (from 13.8 to 5.8, $p<0.05$) which correspond to a 40% and 58% score reduction respectively.
Discussion: This is the first study evaluating the effectiveness of clozapine augmentation and despite the small sample size, and the short period of follow-up, it provides preliminary evidence that this may be a safe and effective practice in patients failing to adequately respond to clozapine and/or not able to tolerate previous augmentation strategies.

F151. A CASE-CONTROL STUDY ABOUT TYPICAL AND ATYPICAL ANTIPSYCHOTICS EFFECT ON SARS-COV-2 IN PATIENTS UNDER TREATMENT FOR SEVERE MENTAL ILLNESSES

Late-Breaking Poster

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Background: Since the Severe Acute Respiratory Syndrome coronavirus type 2 (SARS-CoV-2) pandemic has sparked, the scientific community started investigating and searching possible treatments to prevent the infection or to decrease the disease severity. These treatments included the use of novel drugs and the off-label use of many commercialized drugs. It was supposed that inpatients with severe mental illnesses (SMI) could be at higher risk of developing the infection, as a consequence of their long stay in closed institutions, and the difficulty that SMI entails for compliance with prevention measures, like social distancing or mask wearing. Surprisingly, in Europe, a low proportion of patients with psychiatric disorders and SARS-CoV-2 disease have been reported. In Argentina, the SARS-CoV-2 units, located inside these closed hospitals and designed for inpatients testing positive, received few patients, and even fewer patients required to be transferred to more complex general hospitals because of the disease severity, though these patients usually had risk factors for an unfavorable course of disease. The aim of this study is to analyze if treatment with antipsychotics is associated with a protective effect for SARS-CoV-2 infection and/or with a better disease outcome.

Methods: A multicenter, analytic, case-control study was conducted. One hundred twenty-one cases (positives for SARS-CoV-2 test) and 121 controls (negatives for SARS-CoV-2) were included. The study was conducted since the first case was detected in each hospital and when no vaccines were available. Typical and atypical antipsychotics were included. We analyzed haloperidol, phenothiazines as a chemical group, clozapine, risperidone, olanzapine and quetiapine. To evaluate the possible association between the use of different antipsychotics and a positive diagnosis of SARS-CoV-2, logistic regression models were applied and the odds ratio and its 95% confidence interval (CI95%) were estimated. In the case of significant associations, the number needed to treat (NNT) was calculated and the relationship between the diagnosis and the daily dose of the antipsychotic was evaluated using logistic regression models. To compare the characteristics of the disease in patients with a positive diagnosis of SARS-CoV-2, the chi-square or Fisher's exact test was used for the qualitative variables and the t-student test for quantitative variables.

Results: Patients on haloperidol had 2 times more risk of infection compared to those who did not, and the risk decreased with increasing doses. Patients under treatment with clozapine had a 60% lower risk of infection than those without this drug, and this effect was independent of the dose. The absolute risk reduction in patients on clozapine was 22% and the number needed to treat (NNT) was 4.5. Also, patients under treatment with clozapine were 2 times less symptomatic than patients without clozapine. No significative differences were found in patients under treatment with other antipsychotics.

Discussion: Our main findings are that patients under treatment with haloperidol showed a risk of infection 2 times higher compared to those without this drug. This risk was dose-dependent, showing that higher doses of haloperidol were associated with a lower risk, although the higher doses under study (30 mg) were not enough to obtain a protective effect. Based on the in vitro

study conducted by Gordon et al. in which it was postulated that haloperidol could have antiviral properties, and analyzing the Results: of our clinical study, we could hypothesize that haloperidol could probably have antiviral effects at higher doses than those used for antipsychotic treatment, but more research is needed. Patients under treatment with clozapine had a protective effect against SARS-CoV-2 infection, and a more frequent asymptomatic course of the disease than those who were not under treatment with this drug, independently of the daily dose. Previous information about this finding is scarce and more studies are necessary to further analyze this finding and its possible mechanism.

F152. THE SIDE EFFECTS AND TOLERABILITY OF CANNABIDIOL (CBD): A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMISED CLINICAL TRIALS

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Background: Cannabidiol (CBD) is a potential treatment for psychosis, anxiety, addictions and several medical disorders. It has a reputation for having few adverse effects.
Methods: We conducted the first systematic review and meta-analysis of the adverse effects of CBD across all indications. Double-blind randomised placebo-controlled clinical trials which lasted for at least seven days were included in the study. Data on withdrawal, serious adverse events and adverse events were then extracted. We calculated odds ratios (ORs) with 95% confidence intervals using the Mantel–Haenszel method, and random-effects models were used to control for heterogeneity. Metaregression analyses of CBD dosage were conducted, and the risk of publication bias was tested using the Egger regression intercept method and visual inspection of funnel plots.
Results: Twelve trials contributed data from 803 participants to the meta-analysis. Compared with placebo, CBD was associated with an increased likelihood of withdrawal for any reason (OR 2.61, 95% CI: 1.38–4.96), withdrawal due to adverse events (OR 2.65, 95% CI: 1.04–6.80), any serious adverse event (OR 2.30, 95% CI: 1.18–4.48), serious adverse events related to abnormal liver function tests (OR 11.19, 95% CI: 2.09–60.02) or pneumonia (OR 5.37, 95% CI: 1.17–24.65), any adverse event (OR 1.55, 95% CI: 1.03–2.33), adverse events due to decreased appetite (OR 3.56, 95% CI: 1.94–6.53), diarrhoea (OR 2.61, 95% CI: 1.46–4.67), somnolence (OR 2.23, 95% CI: 1.07–4.64) and sedation (OR 4.21, 95% CI: 1.18–15.01). The likelihood of adverse events was related to the dose of CBD ($\beta = 0.0013$, $p = 0.0023$).
Associations with abnormal liver function tests, somnolence, sedation and pneumonia were limited to childhood epilepsy studies, where CBD may have interacted with other medications such as clobazam and sodium valproate. After excluding studies in childhood epilepsy, the only adverse outcome associated with CBD treatment was diarrhoea (OR 5.03, 95% CI: 1.44–17.61). The overall quality of studies included was high and the likelihood of publication bias was low.

Discussion: Data from clinical trials suggest that CBD is well tolerated and has relatively few serious adverse effects, however interactions with other medications should be monitored

carefully. Additional safety data from clinical trials outside of childhood epilepsy syndromes and from studies of over-the-counter CBD products are needed to assess whether the conclusions drawn from clinical trials can be applied more broadly.

F153. ACETYLCHOLINE AS A REGULATOR OF DOPAMINE PATHWAYS: RATIONALE FOR SELECTIVE MUSCARINIC AGONISTS AS CANDIDATES FOR ANTIPSYCHOTIC DRUG DEVELOPMENT

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Background: Clinical trials of muscarinic receptor agonists for schizophrenia are ongoing and, if successful, hold the potential to change the current therapeutic landscape away from reliance on direct dopamine (DA) D2 receptor antagonists.
Methods: A literature review was performed to find preclinical data on muscarinic acetylcholine receptor (mAChR) regulation of DA neural networks implicated in psychosis. The evidence gathered was used to develop hypotheses about the role of mAChR involvement in the regulation of psychosis pathways.
Results: Acetylcholine (ACh) plays an important regulatory role on the mesocorticolimbic DA pathway. The muscarinic agonists in development for psychotic disorders have preferential functional activity at M4 receptors, including dual functional activities at both M1 and M4 receptors. The observed antipsychotic efficacy of muscarinic receptor agonists is consistent with preclinical findings identifying M1 and M4 receptors as regulators of DA circuits associated with psychosis. A "bottom-up" hypothesis is based on ACh regulation of DA neurons in the mesocorticolimbic pathway. These DA neurons originate in the ventral tegmental area (VTA) and end at the nucleus accumbens (NAc). At both the VTA and NAc, the presence of ACh is an excitatory neurotransmitter for DA neurons. ACh-containing neurons are the main source of ACh release, and ACh in the synaptic spaces is excitatory for DA neurons. Presynaptic M4 receptors located on ACh-containing neurons are autoreceptors, such that activation of M4 receptors by ACh acts as a "brake" to inhibit further ACh release. An M4 receptor agonist would therefore decrease ACh release, which would reduce DA hyperactivity associated with psychosis through a "bottom-up" mechanism. A "top-down" hypothesis states that the role of M1 receptor agonists in antipsychotic activity involves M1 receptors on cortical GABAergic interneurons that terminate on cortical glutamatergic neurons. Activation of M1 receptors on GABA interneurons stimulates GABA release, which then dampens cortical excitatory glutamatergic pyramidal cells that terminate in the VTA. Stimulation of these M1 receptors by ACh (or an M1 agonist) may ultimately provide feedback inhibition for glutamatergic excitation of downstream targets, including midbrain DA neurons. Therefore, M1 receptor agonists may decrease top-down excitatory (glutamatergic) drive onto subcortical circuits.
Discussion: A growing body of evidence supports the development of muscarinic receptor agonists as potential treatments for schizophrenia and related psychotic disorders. Although the exact mechanism is unknown, ACh regulates DA signaling specifically within DA networks associated with psychosis. Muscarinic receptor agonists may represent a new therapeutic class that may extend beyond the limitations associated with direct DA D2-based antipsychotics.

F154. DOPAMINE D2 BINDING AFFINITY OF ANTIPSYCHOTIC MEDICATION PREDICTS RELAPSE WITHIN 12 MONTHS AFTER REMISSION FROM A FIRST EPISODE OF PSYCHOSIS

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Background: After a first episode of psychosis (FEP), 80% of patients experience one or more relapses after initial remission. Psychotic relapses are associated with poor outcome, functional deterioration, and increased risk of suicide. PET-studies and animal work indicate that dysfunctional striatal dopamine autoregulation may increase the risk for psychotic relapses after antipsychotic discontinuation.
According to the dopamine super-sensitivity hypothesis, dopamine dysregulation is provoked by antipsychotic medication use, with strong antagonist having the largest impact. To test this idea, we assessed whether dopamine D2 binding affinity of previously used antipsychotic medication, can predict relapse in the first year after initial remission of FEP.

Methods: In a longitudinal randomized controlled and cohort study on antipsychotic discontinuation (HAMLETT-OPHELIA), FEP patients are followed for 10 years after initial remission. Relapse within the first year after recovery from FEP was operationalized as a score of 4 and higher on any positive item of the Positive And Negative Symptom Scale (PANSS) or hospitalization for psychosis. Dopamine D2 binding affinity was assessed as Ki and based on the type of antipsychotic medication used during baseline (3-6 months after remission of FEP). At baseline, every participant used antipsychotic medication, and during the course of one year, many participants tapered off, while others continued antipsychotic medication.
Results: From 206 FEP patients, 89 (43%) experienced a psychotic relapse within the first year after remission. Using a logistic regression, we found that dopamine D2 binding affinity (Ki) significantly predicted relapse in the first year after recovery from FEP ($z=2.012$, $df=192$, $p=0.046$).
Discussion: Our Results: suggest that greater dopamine D2 receptor binding affinity by antipsychotic medication plays a role in relapse risk in FEP patients. As relapse prevention is crucial in this vulnerable group, these findings may play a role in the shared decision process of choosing optimal medication during a FEP.

F155. ADIPOSITY IN SCHIZOPHRENIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: The existence of a relationship between schizophrenia (SCZ), antipsychotic (AP) medication, and metabolic dysregulation is now well established. However, the effect of this relationship on peripheral adiposity is less well understood. Imaging techniques such as bioelectrical impedance analysis (BIA), dual energy X-ray absorptiometry (DXA), computed tomography (CT) and magnetic resonance imaging (MRI) have been used to explore this relationship. By synthesizing these findings, our review aims to determine the adiposity-related effects of illness and treatment among patients with SCZ spectrum disorders.
Methods: We searched Medline, EMBASE, PsychINFO and Scopus for all relevant articles from inception until February 2021. This was supplemented by searches in Google Scholar, ClinicalTrials.gov, and hand searching. Cross-sectional case-control studies and prospective longitudinal studies were included. Measures of adiposity including percent body fat (%BF), subcutaneous adipose tissue (SAT), and visceral adipose tissue (VAT) were analyzed as primary outcomes. For each outcome, data from individual studies were pooled in a random effects meta-analysis and a mean difference (MD) was calculated. Where possible, a sub-group analysis according to previous AP exposure (AP-naïve/AP-free vs. treated) was also conducted.
Results: Our search identified 29 articles that used imaging Methods: to quantify adiposity among patients with SCZ spectrum disorders; 19 studies compared patients with healthy controls, six examined changes in adiposity before and after AP treatment, and four conducted both kinds of comparisons. The Results: indicate that patients have greater %BF (MD = 3.09%; 95%CI: 0.75 to 5.44; p = 0.010), SAT (MD = 24.29 cm^2; 95%CI: 2.97 to 45.61; p = 0.03) and VAT (MD = 33.73 cm^2, 95%CI: 4.19 to 63.27; p = 0.03) compared to healthy controls. In addition, AP treatment was found to increase SAT (MD = 31.98 cm^2; 95%CI: 11.33 to 52.64; p = 0.002) and VAT (MD = 16.30 cm^2; 95%CI: 8.17 to 24.44; p < 0.0001) with no effect on %BF (MD = 1.73%; 95%CI: -1.41 to 4.86; p = 0.28). However, change in %BF was higher for AP-naïve/AP-free patients compared to previously treated patients.
Discussion: In this review, we found that patients with SCZ spectrum disorders have greater adiposity compared to healthy controls which is increased by AP treatment. Young, AP-naïve patients may be particularly susceptible to this effect. These findings highlight the need for increased monitoring and earlier treatment of metabolic dysfunction, including increased adiposity, in patients with SCZ spectrum disorders. Future studies should explore the effects of specific APs on adiposity and its relation to overall metabolic health.

F156. OUTCOMES AND CLINICAL IMPLICATIONS OF INTRANASAL INSULIN ON COGNITION AND BRAIN FUNCTION IN HUMANS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Aberrant brain insulin signaling has been posited to lie at the crossroads of metabolic and cognitive disorders. Impaired insulin signaling and insulin resistance are observed

across multiple patient populations. Intranasal insulin (INI) is a non-invasive approach that allows direct access to the brain while limiting systemic glucose uptake and peripheral side effects. After two decades of research, INI's pro-cognitive effects have been examined in cognitively unimpaired individuals and patients with Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI). However, there is a limited body of literature describing the efficacy of INI on cognition across multiple patient populations and healthy individuals, and even fewer articles comparing the types of cognitive measures used to assess the various domains of cognition in these studies. The objective of this systematic review and meta-analysis is to evaluate the effects of INI on cognition and brain function in diverse patient populations and healthy individuals.
Methods: We performed a systematic database search in OVID Medline, Embase, PsycINFO, CINAHL, CENTRAL, ClinicalTrials.gov, and ICTRP Search Portal. The inclusion criteria were as follows: (1) randomized controlled trials; (2) INI intervention; (3) all ages and populations; and (4) standardized cognitive outcomes. Random effects meta-analyses were used to examine cognitive outcomes.
Results: Thirty RCTs met inclusion criteria for this review and nineteen of these studies (pooled N = 1,186) were included in the quantitative meta-analysis. The population studies spanned from healthy individuals to patients with AD and MCI, major depressive disorder, bipolar disorder, and schizophrenia, among others. The median INI dose was 40 IU (range 40 to 160 IU). The median duration of treatment of INI was 8 weeks (range 2.5 to 16 weeks). Patients with AD treated with INI were more likely to show an improvement in global cognition (MD = 0.18, 95% CI: 0.13-0.22 p = < 0.00001, N = 8 studies). Healthy individuals were found to have improved verbal memory, specifically delayed recall (SMD = 0.79, 95% CI: 0.16-1.43 p = 0.01, N = 4 studies). No significant effects of INI on cognition were observed in other patient populations that were studied.
Discussion: This review demonstrates that INI may be associated with pro-cognitive benefits for verbal memory and global cognition. However, this effect may be limited to unique patient populations and healthy individuals. Further studies are required to better understand the neurobiological mechanisms and differences in etiology to dissect the intrinsic and extrinsic factors contributing to the treatment response of INI.

F157. LURASIDONE TREATMENT COUNTERACTS BEHAVIORAL AND FUNCTIONAL ALTERATIONS IN THE CHRONIC MILD STRESS MODEL: A KEY ROLE FOR THE PREFRONTAL CORTEX

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Background: Stress represents a critical risk factor for the development of different psychiatric disorders. Accordingly, exposure of adult rats to chronic stress represents a valuable tool to characterize the brain mechanisms that sustain pathologic alterations. In the present study, we used the chronic mild stress (CMS) model that produces different behavioral alterations, including anhedonia, a core domain in psychiatric disorders, to investigate the ability of the antipsychotic drug lurasidone to counteract the adverse effects produced by stress exposure.

Methods: Adult male Wistar rats were left undisturbed or exposed to the CMS paradigm, a well-established model of depression and emotional dysregulation. After two weeks of stress, both controls and CMS rats were randomly divided into two subgroups that received vehicle or lurasidone for five weeks while continuing stress exposure. Sucrose consumption was used to measure anhedonia. A sub-group of animals was also used to investigate the responsiveness to an acute challenge, as a proxy of emotional control, by exposing them to a 30 min-immobilization stress, whereas control rats were left undisturbed in their home cages. Statistical significance was ascertained by two-way ANOVA followed by Tukey's and Sidak's multiple comparison test, when appropriate. Significance was set at $p<0.05$

Results: CMS rats show a significant reduction in sucrose consumption (-46% after two weeks, $p<0.0001$). Lurasidone administration in CMS rats produced a gradual improvement of the anhedonic phenotype until complete normalization. Interestingly, after two weeks of treatment, lurasidone was already able to improve anhedonia in a sub-group of CMS rats (early responders, $p=0.006$ vs. CMS treated with vehicle). We found that rats that were early responders to lurasidone showed a significant up-regulation of activity-dependent genes (Arc, Zif268, and Npas4) in the prefrontal cortex. Moreover, when investigating the responsiveness to an acute challenge at the end of the 7-week period, we found that exposure of control animals to an acute stress was able to up-regulate Bdnf expression in the prefrontal cortex, a mechanism that was impaired in CMS rats but restored by chronic lurasidone administration. Furthermore, using RNA scope we were able to establish a role for parvalbumin and calcium calmodulin kinase II positive neurons in these mechanisms.

Discussion: The Results: of this study provide further support to the ability of lurasidone treatment in counteracting the alterations produced upon exposure to chronic stress. Moreover, our data suggest that the modulation of the prefrontal cortex represents an important mechanism for the responsiveness to lurasidone administration as well as for long-term adaptive changes that may ultimately promote resilience.

F158. THE METABOLIC ADVERSE EFFECTS OF ANTIPSYCHOTIC USE IN INDIVIDUALS WITH INTELLECTUAL AND/OR DEVELOPMENTAL DISABILITY (IDD): A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Individuals with intellectual and/or developmental disability (IDD) have elevated rates of co-morbid psychiatric disorders and often experience difficulties with emotional and behavioral regulation. This Results: in frequent co-prescription of antipsychotics. However, it is becoming increasingly apparent that antipsychotics (APs), particularly second-generation antipsychotics (SGAs), can cause undesirable outcomes including weight gain, diabetes, metabolic effects, and increased risk of mortality/cardiovascular events. Currently, there is a limited body of literature describing the metabolic adverse effects of APs in individuals with IDD across the

lifespan. This is significant considering their widespread use and their known propensity to cause metabolic adverse effects in individuals with severe mental illness.
Methods: We conducted a comprehensive search in MEDLINE, EMBASE, PsycINFO, Cochrane CENTRAL and CINAHL databases. Inclusion criteria included all randomized controlled trials (RCTs) that reported on weight with the use of first- or second-generation APs in individuals with a diagnosed IDD. Data on other metabolic parameters were also extracted. Meta-analyses of reported weight gain were completed based on prescribed antipsychotic; mean difference (MD) was calculated for continuous outcomes and odds ratio (OR) for dichotomous outcomes.
Results: Seventeen RCTs were included in the meta-analysis, with a total of 1357 patients across a variety of IDD's, including Autism Spectrum Disorder (ASD), Pervasive Developmental Disorder (PDD), Disruptive Behaviour Disorder (DBD), Conduct Disorder (CD), and Oppositional Defiant Disorder (ODD). Mean follow-up period was 10.8 weeks (range 6 to 24 weeks). Fourteen studies compared APs vs. Placebo (9 of these involved risperidone) and three studies used risperidone as an active control. Among the 17 studies, only two involved adults. SGA use was associated with significantly greater weight gain compared to placebo when reported as either a continuous or dichotomous outcome (Continuous: MD = 1.11 kg, [0.78, 1.43], $p<0.00001$, $I^2=57\%$, N=10; Dichotomous: 3.94, [2.15, 7.23], $p<0.00001$, $I^2=0$, N=9). Sub-group analysis revealed a significant effect of AP, with risperidone having the greatest effect size (continuous only). No significant difference in weight gain was observed when comparing risperidone (active control) to other APs, although the number of studies in the comparison was low. The reporting literature had insufficient data to meta-analyze the effects of APs on other metabolic outcomes.
Discussion: This review demonstrates that use of antipsychotics, and particularly risperidone, is associated with significant weight gain among patients across a variety of IDD diagnoses. Concerningly, most reported studies were in children and adolescents, which sets up an already extremely vulnerable population for adverse medical sequelae at an early age. SGA use irrefutably contributes to significantly higher risk of type 2 diabetes, metabolic syndrome, and cardiovascular disease in severe mental illness; therefore, similar attention should be given to these risks in patients with IDD. Further studies are required to better understand the effects of SGA use on other metabolic parameters.

F159. METABOLIC SIDE EFFECTS OF ANTIPSYCHOTIC DRUGS IN INDIVIDUALS WITH SCHIZOPHRENIA DURING MEDIUM- TO LONG-TERM TREATMENT: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Background: Antipsychotic drugs are pivotal in the pharmacological treatment of schizophrenia and are used to treat acute episodes and to prevent relapses. Unfortunately, antipsychotic drugs and especially the newer compounds cause metabolic side effects including weight gain and disturbances of the lipid and glucose metabolism. The aim of our systematic review and network

meta-analysis is to investigate how the different antipsychotic drugs differ in their metabolic side effect profile during medium- to long-term treatment of schizophrenia.
Methods: Systematic review and network meta-analysis (NMA).
Randomized controlled trials (RCTs) were included if they compared antipsychotics vs. placebo or antipsychotics vs. antipsychotics in individuals with schizophrenia or related disorders (such as schizophreniform or schizoaffective disorders) for more than 3 months.

The primary outcome was body weight in kg. Secondary outcomes were further metabolic parameters: fastening glucose, total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol and triglycerides.

To identify eligible studies, we searched the Cochrane Schizophrenia Group's Study-Based Register and checked studies included in previously published systematic reviews. Study selection and data extraction were performed independently by at least two reviewers. We conducted a random-effects NMA with a combination of Bayesian and frequentist Methods: to synthesize all evidence for the outcomes.

The protocol has been registered at the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42020175414).

Results: The literature search yielded 12690 references. After full-text screening 351 eligible studies were identified. Of these 139 studies reported on any metabolic outcome of interest. Thus we were able to analyze data for 35419 participants and 31 antipsychotics with a median study duration of 41 weeks. The median average age of study participants was 39 years and the median percentage of women was 36%.
111 studies reported on the primary outcome continuous weight gain comparing 29 antipsychotics in 66 comparisons with 29207 study participants. The mean differences in kg (95% Cis) compared to placebo ranged from -9.06 (-19.21 to 1.08 for fluspirilene LAI) and -2.46 (-5.13 to 0.20 for haloperidol LAI) to 4.33 (3.16 to 5.51 for cozapine oral) and 5.12 (2.04 to 8.20 for chlorpromazine oral). Antipsychotics which showed more weight gain compared to placebo were paliperidone oral and LAI, amisulpride oral, quetiapine oral, risperidone oral and LAI, sertindole oral and in a more pronounced way olanzapine oral and LAI, zotepine oral, clozapine oral and chlorpromazine oral. The data for pimozide oral and brexipiprazole oral were not clear. The other antipsychotics did not show more weight gain than placebo in our analysis.

Discussion: As antipsychotic drugs differ not much in efficacy the choice of antipsychotic medication should be informed by the side effect burden. The Results: of this systematic review and network meta-analysis could help to inform clinicians about the metabolic side-effects of antipsychotic drugs in medium- to long-term treatment in schizophrenia.

F160. OPTIMAL DOSES OF ANTIPSYCHOTICS FOR RELAPSE PREVENTION IN A NATION-WIDE COHORT OF PATIENTS WITH SCHIZOPHRENIA

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Background: Optimal doses of most antipsychotics in the maintenance treatment of schizophrenia are unknown. We aimed to study the risk of severe relapse indicated by re-hospitalization for different dose categories of 15 most frequently used antipsychotics in Finland.
Methods: We studied the risk of re-hospitalization (adjusted Hazard Ratio) associated with six dose categories (as time-varying dose, measured in defined daily dose, DDDs per day) of specific antipsychotic monotherapies in a nationwide cohort of persons diagnosed with schizophrenia (n=61,889, 1996–2017, median follow-up=15.3 years, IQR=7.9–22.0), using within-individual analyses to eliminate selection bias.
Results: Mean age of the cohort was 46.7 years (SD 16.0) and 50.3% (N=31,104) were men. Among the 15 most widely used antipsychotics, 13 had a U- or J-shaped dose-response curve, showing the lowest risks of relapse for doses of 0.6–<1.1 DDDs/day versus non-use of antipsychotics. The exceptions were oral perphenazine (aHR=0.72, 95% CI=0.68–0.76, <0.6 DDDs/day), and olanzapine-long-acting injectable (LAI) (aHR=0.17, 95%CI=0.11–0.25, 1.4–<1.6 DDDs/day), the latter of which had the lowest aHR of any antipsychotic. Certain risperidone and perphenazine doses <0.9 DDD/day were associated with 21%–45% lower risk of re-hospitalization (p<0.001) than the standard dose of 0.9–<1.1 DDD/day. High doses (>1.6 DDDs/day) of oral perphenazine (aHR=3.35, 95%CI=2.37–4.73, >48 mg/day), risperidone LAI (aHR=1.41, 95%CI=1.25–1.59), and oral risperidone (aHR=1.34, 95%CI=1.22–1.47, >8 mg/day) were associated with substantially higher risk of re-hospitalization than non-use of antipsychotics. Secondary between-individual analysis and sensitivity analyses confirmed the primary results. In the first-episode cohort, Results: for high-dose perhenazine (aHR=6.12, 95%CI=1.17–32.03), risperidone (aHR=2.00, 95%CI=1.46–2.73), and olanzapine LAI (aHR=0.07, 95%CI=0.03–0.19) were even more extreme than in the primary analysis.

Discussion: Our Results: suggest that olanzapine-LAI is highly effective in dose ranges >0.9 DDD/day, and especially at 1.4–<1.6 DDDs/day (405 mg/4 weeks) associated with substantially lower risk of re-hospitalization than any dose of any other antipsychotic. The current WHO DDD definitions appear to be clearly too high for perphenazine and somewhat too high for risperidone.

F161. NETWORK META-ANALYSIS OF COHORT STUDIES INVOLVING ORAL AND LONG-ACTING INJECTABLE ANTIPSYCHOTIC AGENTS: ADMINISTRATION FREQUENCY AND INCIDENCE RATE OR ODDS OF HOSPITALIZATION IN SCHIZOPHRENIA

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Background: For most patients, schizophrenia is a debilitating, life-long psychiatric disorder. The use of long-acting injectable antipsychotics agents (LAIs) over oral antipsychotic agents (OAs) has been associated with reductions in relapse, hospitalization, all-cause discontinuation, and mortality, all of which may contribute to decreased healthcare resource utilization. Although these benefits associated with the use of LAIs over OAs have been widely documented, the impact of administration frequency on clinical outcomes remains an active line of investigation. This study used network meta-analyses to assess the association between OA and LAI administration frequency and hospitalization outcomes in patients with schizophrenia.
Methods: Studies published between January 1, 2008, and July 31, 2020, with information on the adjusted incidence rate ratio (aIRR) or adjusted odds ratio (aOR) of hospitalization for different antipsychotic administration frequencies were identified in a targeted literature review of PubMed®, ClinicalTrials.gov, and Google Scholar. Included studies met the following criteria: (1) nonrandomized cohort study of patients with schizophrenia; (2) treatment with atypical LAIs or OAs; (3) reported aIRR and/or aOR of hospitalization. Data were extracted on key variables, including antipsychotic formulation and administration frequency, patient baseline characteristics, study design details, and adjusted hospitalization outcomes. A sensitivity analysis of the incidence rate of hospitalization excluding potentially overlapping patients across studies was performed to ensure the robustness of the results. Three sensitivity analyses of the odds of hospitalization were conducted to ensure the robustness of the results: grouped by antipsychotic agent, excluding potentially overlapping patients across studies, and including studies that reported unadjusted ORs.
Results: Altogether, 456 studies were reviewed. Nine studies reporting aIRRs of hospitalization across 3 antipsychotic administration frequencies met inclusion criteria (n=73,160; mean age=46.4 years; male=62.6%). Similarly, 9 studies reporting aORs of hospitalization across 3 antipsychotic administration frequencies met the inclusion criteria (n=43,977; mean age=46.1 years; male=66.5%). Once-daily OAs had a higher overall median incidence rate and odds of hospitalization than once-monthly LAIs (IRR [95% credible interval {CrI}]: 1.14 [1.03–1.27]; OR [95% CrI]: 1.65 [1.44–1.96]) and a similar overall incidence rate and odds of hospitalization to once-every-2-weeks LAIs (IRR: 0.93 [0.74–1.17]; OR: 1.14 [0.78–1.66]). The overall median incidence rate and odds of hospitalization were higher for once-every-2-weeks LAIs than once-monthly LAIs (IRR: 1.22 [1.00–1.51]; OR: 1.46 [1.04–2.07]). Results: were consistent across all sensitivity analyses.
Discussion: In cohort studies, which likely reflect real-world settings more closely than randomized controlled trials, once-monthly LAIs had the lowest incidence rate and odds of hospitalization compared with once-every-2-weeks LAIs and once-daily OAs.

F162. SWITCHING LONG-ACTING INJECTABLE ANTIPSYCHOTICS: HOW CAN WE DO IT?

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Background: Long-acting injectable (LAI) antipsychotics are broadly prescribed, for their many advantages comparing to oral formulations: increase of adherence, maintenance of stable drug

concentration and improvement of clinical outcomes. In clinical practice it is often necessary to switch between different LAI antipsychotics. Switching LAIs can prove to be challenging, as antipsychotics have very distinct pharmacodynamic and pharmacokinetic profiles, especially first-generation (FGAs) and second-generation antipsychotics (SGAs). Moreover, prolonged exposure to FGAs can induce changes in the dopaminergic receptor profile due to upregulation mechanisms, resulting in increased risk of clinical relapse or adverse events when switching to a SGA LAI.
Methods: Brief narrative review of the literature concerning antipsychotics, dose equivalents and switching/tapering Methods.
Results: Difficulties in switching LAI antipsychotics include pharmacological adverse events and disease relapse, as result of exposure to either excessive or inadequate drug concentrations. In the event of its occurrence, it is recommended to add the indicated oral medication.
Another concern is the upregulation of dopamine receptors (D2R), with an increase of total D2R density, particularly high-affinity state D2R. These mechanisms can lead to the occurrence of supersensitivity psychosis or movement disorders, like Tardive Dyskinesia. It appears that all antipsychotics, even SGAs, have potential to produce this effect.

There are few case reports describing antipsychotic withdrawal syndromes after switching from FGAs to SGAs. As SGAs have greater capability of blockade of other receptors, like 5-HT2A/2C receptors, their affinity to D2R is lower. Although SGAs show a lesser risk of adverse effects, there is a greater risk during the switch if receptors are upregulated. During this process, regular levels of dopamine can cause overstimulation of the sensitized receptors. Furthermore, if one of the LAI antipsychotic involved in the switch is Aripiprazole, a partial agonist of D2R, the effects may not be the expected if the other drug is a full D2R antagonist.

The upregulation of D2R could be indirectly detected: clinically, by an extrapyramidal symptoms' thorough examination; or analytically, by prolactin level follow-up, since both are expected to be altered when there is a high D2R occupancy.

It has been proposed that intermittent dosing regimens and the use of minimal efficacious dosage, with gradually lower doses (in a hyperbolic curve), could prevent this.

Discussion: Switching LAI antipsychotics is still a uncharted area in Psychiatry, with scarce studies developed. However, the analysis of literature, provides some strategies that can be adopted.
The assessment of extrapyramidal symptom and prolactin level evaluation could be helpful in predicting an upregulation of D2R, realizing if the patient is more prone to negative outcomes.

We hypothesize that, when switching directly from FGAs to SGAs, if there is upregulation of D2R, there is consequent risk of developing withdrawal symptoms. Regarding the tapering Methods: for antipsychotics described and our clinical experience, it would be important to establish a new method from switching FGAs and SGAs, particularly in LAI formulation. We propose a method for this process, that includes a cross titration, involving the coadministration of a progressive lower dose of the first antipsychotic while introducing the second one.

In conclusion, further studies and more standardized and evidence-based strategies for switching LAI, particularly between FGAs and SGAs, should be developed, since there is a need for an adequate guidance to optimize this strategy.

F163. ANTIPSYCHOTIC UTILIZATION TRAJECTORIES IN SCHIZOPHRENIA: A STATE SEQUENCE ANALYSIS APPROACH

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Background: State Sequence Analysis (SSA) is an innovative method to study longitudinal sequential data. Primarily used in social science, this approach aims to analyze and visualize life trajectories such as occupational status over time. This study aimed to apply this method to describe the utilization patterns of antipsychotic (AP) medications in patients with schizophrenia (SCZ), three years after initiating or reinitiating a given AP.

Methods: Based on medico-administrative information on patients living in Quebec (Canada), this retrospective cohort study included 6,444 patients with a previous diagnosis of SCZ initiating or reinitiating an AP medication between January 2012, and December 2014, with continuous coverage by the public drug insurance plan. Using the prescription drug database, which includes all community-dispensed drugs, a patient was considered exposed to the drug from the date(s) a prescription was claimed at a community pharmacy and for the time the drug was provided. Hence, for each day of follow-up (1092 days), the patient was either exposed to one of the chosen categories of APs, or to none, except for inpatient stays, as no information on drug treatment was available. This patient's sequence of AP exposure over time has been referred to as the "antipsychotic utilization trajectory" and was analyzed using SSA. This innovative approach provides useful visual information on the continuation and discontinuation patterns of use over time. As a complementary analysis, the following dichotomous indicators were also assessed: non-renewal of the first AP prescription; discontinuation of all AP treatments (with 30, 60, or 90 consecutive days without any AP treatment); and nonadherence defined as a proportion of days covered by an antipsychotic <80%.

Results: Clozapine and long-acting injectable (LAI) second-generation APs had the best 3-year continuation and discontinuation patterns among all other groups, including reduced switch of APs, whereas first-generation oral APs had the poorest patterns. These Results: were comparable in the incident and nonincident cohorts. Oral SGAs, except for clozapine, had a poorer pattern of continuation and discontinuation than LAI antipsychotics. Although no specific statistical measures, covariate adjustment, and tests were used for comparing the trajectories, the graphs from SSA revealed very similar Results: for treatment adherence and antipsychotics switching with respect to usual dichotomous indicators.

Discussion: This innovative method highlighted the impact of the AP chosen to initiate or reinitiate treatment in SCZ, which was identified as a key factor for long-term treatment continuation and discontinuation. This study provides an original method to examine longitudinal patterns of treatment utilization and may contribute to the study of the dynamic nature of treatment adherence in psychiatry and many other fields of medicine, as a complementary approach to the usual statistical analysis.

F164. COMPUTERISED COGNITIVE REMEDIATION DURING PSYCHOSIS: A PILOT STUDY EXAMINING NEUROCOGNITION AND NEURAL OSCILLATIONS

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Background: Schizophrenia is characterised by deficits in cognition and oscillatory activity, especially in the gamma-band range. Such impairments are already present during early illness stages, including in the clinical high-risk for psychosis (CHR-P) state and first-episode psychosis (FEP). Although cognitive remediation can alleviate cognitive deficits, improve functional outcomes and improve circuit deficits in schizophrenia patients, evidence for its effectiveness in CHR-P and FEP participants is limited. We sought to assess whether a computerised cognitive remediation intervention can improve neurocognition and enhance oscillatory brain activity in CHR-P and FEP participants.

Methods: Thirteen participants (n = 5 CHR-P; N = 8 FEP) underwent a 10-session computerised cognitive remediation programme (BrainHQ) comprised of visual exercises, 1 hour per day using a computer or laptop. Before and after the training, participants completed the Brief Assessment of Cognition in Schizophrenia (BACS) and magnetoencephalography (MEG) data were obtained during a visual grating task. In the visual task, participants had to press a button when a speed change was detected in a concentric inward moving visual grating stimulus. Oscillatory activity was examined in the 1-90 Hz frequency range at sensor- and source-level in analyses that were either time-locked to stimulus onset or to speed change onset, with a specific focus on gamma-band oscillations in visual cortex.

Results: We found significant improvements in BACS-measured cognition pre- to post- training in the domains of verbal memory (d = 1.43), motor speed (d = 0.68), attention and processing speed (d = 0.79) and BACS total score (d = 0.88). In the MEG stimulus-locked analysis, we found increased gamma-band power (~40-44 Hz) at sensor level 250 to 750ms after stimulus onset in frontal, motor and cingulate regions. In the speed change-locked analysis, we observed decreased gamma band power (~55-65Hz) at virtual channel level over occipital regions of interest, prior to the onset of the speed change. In particular, this effect appeared to be driven by early occipital regions. No behavioural effects were observed in visual task performance.

Discussion: Our findings suggest that neuroplasticity-based cognitive remediation can improve cognition, particularly verbal memory, as measured by the BACS. In addition to changes in higher cognition, we found that training was able to modulate gamma-band activity. Overall, our findings implicate improved attentional and motor-related processes in CHR-P and FEP participants following a 10-hour cognitive remediation intervention.

F165. PHYSICAL ACTIVITY AND COGNITIVE FUNCTIONING IN OLD ADULTS WITH SCHIZOPHRENIA

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Background: People with schizophrenia exhibit cognitive deficits compared to those in the healthy general population. The restorative effects of physical activity on cognition in other patient populations—through enhancing neuroplasticity—suggest that physical activity (PA) potentially is an effective behavioral treatment to enhance cognition in patients with schizophrenia. The purpose of this study is to explore the preliminary efficacy of PA, compared to a health education (HE) program, on cognitive outcomes in older adults with schizophrenia.

Methods: This prospective randomized trial implemented a 12-week home-based, telephone-delivered physical activity (PA) program (i.e., brisk walking, 30–45 minutes/day). Older adults (i.e., age ≥ 50 years) with schizophrenia meeting the eligibility criteria and consenting to participation were randomized for a controlled trial. All participants were given a wearable device to wear for one week to determine baseline daily PA. After this baseline data collection (T1), participants were randomly assigned to either the PA group or the HE group, based on gender and daily PA. Participants in the PA group used a pedometer as a self-monitoring tool and received weekly scheduled calls (10 min/session) from the research team to enhance skill development and confidence to initiate and maintain the recommended PA. Participants in the HE group were provided a weekly newsletter (written at a 6th-grade reading level to ensure comprehension) regarding caloric reduction. The neurocognitive functioning of the participants was measured with brain-derived neurotrophic factor (BDNF) and the MATRICS Consensus Cognitive Battery (MCCB). Norm-based T scores of MCCB (i.e., speed of processing, attention vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, social cognition, and composite score) were computed. Higher scores indicate better functioning. Data was collected before randomization (T1), the end of the 12-week program (T2), and the 12-week post-program (T3). Descriptive statistics, a Mann Whitney U test, and a Wilcoxon signed-rank test were used to analyze data.

Results: A total of 20 adults were recruited and randomized to either the PA group (n=11) or the HE group (n=9). Of the participants, 50% were Caucasian and the mean (SD) age was 61.33 (7.36) years. The finding indicated that there was a significant difference in attention vigilance between the HE group and the PA group at T2. The score of attention vigilance for the PA group was higher than the score for the HE group (U=14.50, P=0.045). Although the change did not last at T3 in the PA group, there was a trend to higher attention vigilance at T3 in the PA group than the HE group (p=0.059). The composite score of cognitive functioning exhibited an increased pattern in the PA group even though there were no significant differences. There were no statically significant differences in other areas of cognitive functioning and BDNF between the two groups at T2 or T3 respectively (ps>.05).

Discussion: The PA intervention shows promise in increasing cognitive functioning among older adults with schizophrenia. The physical activity intervention featured in this study can be implemented at home to improve cognitive functioning—especially among patients with schizophrenia. This finding warrants further investigation into the relationships between physical activity and cognitive functioning in larger sample sizes. Several limitations warrant considerations including small sample size, non-parametric statistics, and a short duration of physical activity.

F166. "CEREBRAL PHOTOBIOMODULATION FOR THE TREATMENT OF NEGATIVE SYMPTOMS OF SCHIZOPHRENIA: DOUBLE-BLIND, SHAM-CONTROLLED, CROSSOVER RANDOMIZED CLINICAL TRIAL WITH MAGNETIC RESONANCE SPECTROSCOPY"

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Background: Hypothesis: The negative symptoms of schizophrenia are associated with poor premorbid function and poor clinical outcomes. It has been suggested that negative symptoms are ''semi-independent'' of positive symptoms, as they increase over time in severity, stability, and prognostic weight. Although the antipsychotic medication is effective in managing the positive symptoms, usually the negative symptoms persist with such treatment. Some studies have been suggested that the dorsolateral prefrontal cortex (DLPFC) is involved in the pathophysiology of negative symptoms, reduced levels of metabolism in the prefrontal cortex in schizophrenic patients with or without medications, and seems to be not related with duration of the disorder and an inverse correlation of severity of negative symptoms and cerebral blood flow in the prefrontal cortex. Recent clinical trials demonstrated a possible role of the use of non-invasive neuromodulation (targeting the DLPFC), as TMS and tDCS, for the treatment of these symptoms. A new form of neuromodulation is emerging, called photobiomodulation (PBM), that uses Infrared light can activate mitochondria, which in turn stimulate second messenger systems, DNA transcription, and growth factors. Animal studies have shown that infrared PBM may reduce the size and severity of brain injury and stroke, as well as diminish damage and physiological symptoms in depression, posttraumatic stress disorder (PTSD), Parkinson's disease, and Alzheimer's disease. Human studies demonstrated that PBM can change Magnetic Resonance Spectroscopy. Besides, several clinical trials have demonstrated effects in the treatment of depression, traumatic brain injury, and PTSD. The use of this in schizophrenia has not been done. Aims: to evaluate the efficacy of PBM in patients with schizophrenia and prominent negative symptoms in a randomized, double-blind, sham-controlled trial. Primary aim: to compare the effects of active vs. sham PBM in patients with schizophrenia. Secondary aim: we hypothesize that active vs. sham PBM can positively impact Magnetic Resonance Spectroscopy of lactate levels in DLPFC.

Methods: As a pilot study, granted by the SIRS the 2020 Research Fund Awardee, we will enroll 30 adults (18-55 years) with schizophrenia. We are supposed to finish the study in January 2022 and present the Results: in SIRS meeting of the same year. It will be applied the scale PANSS (positive and negative symptom score) and the patients will have a minimum score of 20 points in the sum of negative subscale and stable antipsychotic medications (at least six weeks with the same dosage). Other drugs that can interfere with negative symptoms are not allowed. Exclusion criteria are other neuropsychiatric conditions; specific contra-indications to PBM; severe/life-threatening clinical conditions. The study will be a randomized, double-blind, crossover sham-controlled clinical trial in which volunteers will be recruited at the Clinical Hospital of the Medical School of the University of São Paulo. They will be allocated to start at one of the groups: active or sham stimulation. Participants will receive 10 sessions of active or sham PBM in 10 consecutive days,

and after this period the participants will change groups for more 10 sessions of sham or active PBM. A blinding scale will be applied to evaluators, applicators, and volunteers to see if blinding has been effective. Participants will be assessed by training psychiatrists. The main scales will be applied at week 0 (baseline), week 2 (endpoint), week 4, week 6 and week 12 (PANSS). Adverse effects will be assessed using a standardized questionnaire. Treatments were administered daily over a period of 2 weeks with a Light-Aid, continuous wave, 300 LED wavelength 850 nm) or with a placebo probe of the same appearance and display. The Proton Magnetic Resonance Imaging and Spectroscopy will be performed using spectrum was to the sum of four signals: choline, creatine, N-acetyl-aspartate, and the lactate double peak in DLPFC at baseline and at the end of the PBM session.
Results: As a pilot study, granted by the SIRS the 2020 Research Fund Awardee and intended to finish in January 2022, we will enroll 30 adults and we have already enrolled 24 volunteers so far. Here we have a subanalysis of the clinical data of the first 20 individuals of the study. We did not analyze the Results: of spectroscopy of magnetic resonance. We had enrolled 20 volunteers enrolled, 10 started in the active group and 10 in the sham group. We did not have any dropouts so far. In this analysis, we are blinded by the group until the end of the enrollment but at the time of the SIRS meeting, all the data will be analyzed without blinding. Both groups of the sequence of starting have similar clinical and demographic data: age (36 and 30 years old); negative PANSS (24.8 (3.1) and 24 (4.1)). total PANSS (78.2 (10.7) and (78.5 (7.2)) and others. The ANOVA for a crossover study showed significant treatment effect ($p=0.019$) and period effect ($p<0.00$) without carryover effect ($p=0.24$).
Discussion: This preliminary blinded data suggests clinical differences between the groups. At the time of the SIRS meeting, we will present the final unblinded both clinical and spectroscopy of the resonance magnetic data.

F167. THE IMPACT OF TELEMEDICINE ON SERIOUS MENTAL ILLNESS AND MOVEMENT DISORDERS: A LITERATURE REVIEW AND GAP ANALYSIS

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Background: Although telemedicine has been available for decades, the COVID-19 pandemic precipitated a rapid increase in utilization and widespread expansion of this model of care. While much has been reported about the ability of telemedicine to increase access to care, less is known about its impact on quality of care, cost of care, and health disparities, particularly for those living with serious mental illness (SMI) and movement disorders (MDs). The objective of this review is to report the findings of a systematic literature review and gap analysis of research on the screening, diagnosis, and treatment of SMI and MDs through telemedicine.
Methods: A search of the BIOSIS Previews®, Embase®, MEDLINE, and Northern Light Life Sciences Conference Abstracts databases was performed to identify peer-reviewed journal articles and conference abstracts published between January 1, 2011, and August 5, 2021. Eligible publications included SMI or MD as the primary or co-occurring condition, telemedicine as an intervention, and measurement of specified health care outcomes. Seven independent reviewers systematically reviewed titles and abstracts of eligible publications and extracted the following data points for analysis: therapeutic area, outcomes studied, Results: of analysis, timeframe in

relation to the COVID-19 pandemic, study design, telemedicine intervention type, location, US payer type, setting of care, and sociodemographics.
Results: One hundred and twelve studies (80 journal articles and 32 conference abstracts) made up the study network. MDs were investigated in 67 (59.8%) studies, whereas SMI was the focus of 45 (40.2%). Nearly half (49.1%) of the studies measured more than one health care outcome. Seventy-one (63.4%) studies measured acceptability of telemedicine and 22 (19.6%) measured utilization, while quality of care and cost of care were measured in 40 (35.7%) and 19 (17.0%) studies, respectively. Fifteen (13.4%) studies compared telemedicine head-to-head with in-person care alone. Nine (8.0%) studies evaluated, or offered commentary on, the impact of telemedicine on health disparities.
Discussion: Overall, the vast majority of telemedicine study outcomes measured convenience endpoints, such as access, acceptability, and utilization, rather than key metrics such as quality of care and health outcomes, costs, or health disparities. A greater percentage of research on telemedicine has been conducted in MD than SMI, though no abstracts that referenced tardive dyskinesia or drug-induced movement disorders were identified. A very limited number of direct comparisons have been conducted assessing the impact of telemedicine versus in-person care in persons living with MDs, and even fewer in SMI. Although abstracts in the analysis related to health disparities were limited, findings did not support the use of telemedicine to eliminate rural-urban differences in specialty mental health care. Collectively, these findings reveal a meaningful evidence gap related to the impact of telemedicine on key outcomes for persons living with SMI and MDs. Further exploration of these outcomes is critical to understanding the effectiveness, including benefits and limitations, of telemedicine compared to in-person care for these patient populations. Supported by Neurocrine Biosciences, Inc.

F168. REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION ON THE PREMOTOR CORTEX TO TREAT PSYCHOMOTOR SLOWING IN PSYCHOSIS – PRELIMINARY FINDINGS FROM A RANDOMIZED CONTROLLED TRIAL

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Background: Psychomotor slowing is a frequent and distressing problem in psychosis affecting gross and fine motor behavior. Currently, there are no effective treatment recommendations available. Neuroimaging studies suggest aberrant connectivity in the cerebral motor circuit and hyperactivity in the premotor cortex to contribute to psychomotor slowing. A pilot RCT demonstrated a clinical effect of three weeks of repetitive transcranial magnetic stimulation (rTMS) with 1 Hz over the supplementary motor area (SMA). Here, we report on a larger, confirmatory RCT using brain imaging and rTMS. We hypothesized beneficial effects of the 1Hz stimulation of the SMA on measures of psychomotor slowing.
Methods: In an ongoing randomized controlled trial, 88 patients with schizophrenia spectrum disorders with severe psychomotor slowing are randomized to one of four protocols over three weeks as add-on therapy: 1Hz inhibitory rTMS over the SMA, 50 Hz excitatory intermittent theta

burst stimulation over the SMA, placebo stimulation over the SMA, or no add-on treatment in a waiting group. Afterwards, the waiting group is receiving 1Hz stimulation for three weeks. Primary outcome is response (30% improvement from baseline) in the Salpêtrière Retardation Rating Scale (SRRS), secondary outcomes are SRRS course, catatonia severity measured with the Bush Francis Catatonia Rating Scale (BFCRS), and gait velocity from automated gait analysis. Raters were blind to treatment group. As of September 2021, 83% of the planned sample were enrolled. Here, we analyze the data of the unblinded waiting group during 3 weeks no treatment and subsequent 3 weeks rTMS. Repeated measures ANOVAs were performed with baseline, week 3 and week 6 as time-points.

Results: Currently, 18 patients were randomized to the waiting group, 5 of whom dropped out before study completion. After 3 weeks, 24% responded without treatment. Later, after 3 weeks of 1 Hz rTMS treatment, 69% responded. The SRRS scores declined following rTMS ($F = 18.8$, $df = 2$, $p < .001$). Mean scores SRRS baseline = 22.0, week 3 = 22.4, week 6 = 13.5. Likewise, BFCRS scores declined with treatment ($F = 8.3$, $df = 2$, $p = .002$). Mean scores BFCRS baseline = 3.8, week 3 = 5.9, week 6 = 2.1. Gait velocity demonstrated a non-significant increase at week 6 ($F = 2.6$, $df=2$, $p = .142$), with complete gait analysis data in $n = 8$. Mean gait velocity was 108 cm/s at baseline, 118 cm/s at week 3, and 120 cm/s at week 6.

Discussion: In general, the study intervention was well tolerated. As expected, we found little improvement (24%) over three weeks without specific treatment, while 69% responded following subsequent 3 weeks of 1Hz rTMS. Ratings of psychomotor slowing and catatonia decreased with rTMS treatment. In sum, our preliminary Results: suggest that rTMS may be beneficial, however, the final analysis of all interventions will be conducted once all patients completed study procedures.

F169. IMMERSIVE, MINDFULNESS-BASED VIRTUAL REALITY (VR) TO IMPROVE AGGRESSIVE BEHAVIORS IN AN INPATIENT SETTING: PILOT DATA

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Background: One of the most important issues in working with schizophrenia patients residing in a psychiatric institution is managing aggressive behaviors that are directed toward staff and other patients. Aggressive behavior in schizophrenia poses severe health and social consequences for which Mindfulness-Based Interventions (MBIs) have shown positive results. Although some studies have examined the use of Virtual Reality (VR) with psychiatric populations, none of these studies assessed interventions for aggression regulation. Given the positive Results: from intervention research in other psychiatric disorders using VR (e.g., PTSD), we suggest that MBI VR exposure can be used to stimulate psychological and behavioral aggressive responses and to test if patients can control aggressive behaviors as MBI VR may temporarily remove patients' view of the real world, which may assist in achieving a state of mindfulness more easily. The aim of this study is to examine the efficacy and feasibility of an audio-visual VR compared to an audio-only digital mindfulness intervention in inpatients with schizophrenia and aggression.

Methods: This is a randomized-controlled trial comparing a self-guided auditory mindfulness app 'Headspace' (HS-MM) to self-guided VR mindfulness 'TRIPP VR' presented as geometric images and fractals. The Excitement Component of the Positive and Negative Syndrome Scale (PANSS-EC), Oxford Mood Scale (OMS), State Trait Anxiety Index (STAI), number of aggressive incidents and PRNs were collected at baseline and endpoint (week 6). The Mobile Application Rating Scale (MARS) to assess feasibility was completed.
Results: 28 participants with schizophrenia (HS-MM n = 13, TRIPP-VR n = 15) were enrolled. Repeated measures ANOVA found a significant decrease in PANSS-EC for TRIPP-VR (baseline mean = 9.73 (±4.06); endpoint = 7.27 (±1.62), p =.01) with an effect-size of 0.80 (Cohen's d), and a decrease in PANSS Total Score (baseline mean = 73.60 (±13.84); endpoint = 63.33 (±13.00), p = 0.005) compared to HS-MM (PANSS-EC: baseline mean = 10.54 (±3.33); endpoint = 10.23 (±3.72); PANSS total: baseline mean = 75.69 (±9.65); endpoint = 72.62 (±12.67). A significant decrease was observed in number of aggressive episodes for TRIPP-VR (baseline mean = 4.09 (±4.75); endpoint = 3.11 (±4.04), p=0.023). Participants reported greater acceptability for TRIPP-VR than HS-MM (MARS ($p < 0.05$).
Discussion: Preliminary Results: suggest TRIPP-VR shows significant improvements in aggression over HS-MM. To the best of our knowledge this is the first study to examine the effectiveness of MBI VR on aggression in hospitalized schizophrenia inpatients. A fully powered double-blind randomized-controlled trial is underway.

F170. FACTORS IMPACTING ACCESS AND ENGAGEMENT OF COGNITIVE REMEDIATION THERAPY FOR PEOPLE WITH SCHIZOPHRENIA: A SYSTEMATIC REVIEW

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Background: Neurocognitive dysfunction is considered a core deficit in schizophrenia and has a significant impact on the daily functioning of individuals. The absence of effective pharmacology to treat cognitive symptoms in schizophrenia has contributed to a growing interest in psychosocial interventions that target neurocognition. The efficacy of cognitive remediation on neurocognitive functioning for individuals with schizophrenia has been demonstrated in clinical trials and meta-analyses. However, sizeable attrition rates are reported, with the reasons unknown. Furthermore, cognitive remediation is not part of routine mental health care.
Methods: We conducted a systematic review following PRISMA guidelines, to investigate factors that influence access and engagement of cognitive remediation for individuals with schizophrenia. We searched PubMed, Web of Science, and PsycINFO databases, identified 2645 records, and assessed 297 full-text articles for eligibility. We included 67 studies that reported data on access and engagement, and extracted quantitative and qualitative data.
Results: Our Results: show that cognitive remediation is mainly delivered in middle to high-income countries to outpatients on-site, with limited remote access. Drop-out rates ranged from 0 to 47.5% (median = 14.29%). Only a small number of studies explored differences between dropouts and completers (n = 5), and engagement factors (n = 13). Dropouts had higher negative symptomatology and baseline self-efficacy, and lower baseline neurocognitive functioning and

intrinsic motivation compared to completers. Positive associations were found between engagement and intrinsic motivation, self-efficacy, perceived usefulness of the programme, educational level, premorbid IQ, baseline neurocognitive functioning, some neurocognitive outcomes, and therapeutic alliance. In contrast, a negative association was found between engagement and subjective cognitive complaints. Qualitative Results: showed good acceptability with some areas for improvement (e.g., duration).
Discussion: Overall, access and engagement results are scarce and heterogeneous, which stresses the need for further investigation. Individuals with lower neurocognitive functioning, especially in attention and working memory, could be at higher risk for drop-out. Individuals with higher insight into their cognitive difficulties could also be at higher risk for drop-out, potentially because they would perceive themselves as less competent, inducing a lower perceived value of cognitive remediation. Clinicians should pay a particular attention to participants that are at higher risk for dropout and implement strategies to try to keep them interested and engaged. Future clinical trials should systematically explore attrition and related factors, as well as consumers' subjective experience of the programme. Access to cognitive remediation remains largely underinvestigated. Overall, the intervention is mostly delivered on-site to outpatients. Remote delivery and access at different illness stages should be further investigated. Determining influential factors of access and engagement will help improve the implementation and efficacy of cognitive remediation therapy, and thus the recovery of people with schizophrenia.

F171. THINKAPP: AN ONLINE INTERVENTION FOR YOUNG PEOPLE WITH FIRST EPISODE PSYCHOSIS. PRELIMINARY RESULTS: OF SYMPTOMATOLOGY, QUALITY OF LIFE AND FUNCTIONING

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Background: People with first episode psychosis (FEP) usually show cognitive impairments, reduced quality of life, functioning alterations, suicide, and social disability. Quality of life is related to residual psychopathology and poor effect of treatment and poor functioning is associated with different impairments such as cognitive impairments, social malfunction and a lesser rate of symptom remission. Interventions should encompass a comprehensive approach that delves into these functional and quality of life difficulties (Grant et al., 2017). However, most of the interventions are satisfactory in reducing symptoms, but do not address all the needs derived from this condition. Early interventions raise the possibility of preventing or reducing the consequences

that occur rapidly during the first years, which usually determine the course of the disease. In this context, online interventions can be a therapeutic complement to maintain the long-term effectiveness of psychosocial interventions that have already demonstrated their efficacy in the short and medium term and are an accessible and cost-effective option for delivering evidence-based interventions to this population (Firth, 2016). In addition, recent studies show its acceptability, efficacy, and feasibility through smartphones (Camacho, Levin and Torous, 2019). The objective of the study is to test the effectiveness of a mobile app–based intervention (Thinkapp) to improve quality of life, functioning and symptomatology in young people with FEP.

Methods: We included 17 patients with FEP, aged 14-30, recruited from Gregorio Marañón Hospital, Ramón y Cajal Hospital, Parc Sanitari Sant Joan de Déu and AMAFE Foundation in Spain. Patients received treatment as usual plus five modules of a psychological intervention through the mobile app (psychoeducation, recognition of symptoms and prevention of relapses, problem solving, mindfulness, and contact wall). The effectiveness of the intervention was assessed by means of a battery of clinical tests which comprised symptomatology, functioning, and quality of life at baseline, 3-month and 6-month follow-up. Symptomatology was assessed with the Positive and Negative Syndrome Scale (PANSS); quality of life was assessed with the World Health Organization Quality of life (WHOQOL-BREF) and with the EuroQoL-5 Dimension (EQ-5D); and functioning, with the Global Assessment of Functioning (GAF). We used the Wilcoxon test to analyse changes throughout time.

Results: : Of the 17 patients included, 12 completed the 3-month follow-up and 7 patients completed the 6-month follow-up. There were significant differences in PANSS positive ($p = 0.017$) between baseline [□ (SD) = 8.70 (3.46)] and 3-month follow-up [□ (SD) = 7.50 (1.00)]; in PANSS negative ($p = 0.010$) between baseline [□ (SD) = 10.82 (6.41)] and 3-months [□ (SD) = 8.67 (2.19)]; in PANSS general ($p = 0.031$) between baseline [□ (SD) = 19.76 (6.45)] and 3-months [□ (SD) = 19.00 (2.49)]; and in PANSS total scale ($p=0.005$), between baseline [□ (SD) = 40.23 (17.48)] and 3-months [□ (SD) = 34.00 (3.57)]. Between 3 and 6-month follow-up, there were significant Results: ($p = 0.041$) between PANSS total scale and 6-months [□ (SD) = 34.86 (3.13)]. No significant Results: were observed in functioning and quality of life.

Discussion: These preliminary Results: show that the use of a mobile app-based intervention. as a complement to usual treatment, may help in the reduction of symptoms in patients with FEP.

F172. "A SMOLDER OR A BURN?" BURNOUT, TURNOVER, AND TECHNOLOGY AND ORGANIZATION READINESS IN EARLY PSYCHOSIS (EP) CARE ACROSS CALIFORNIA (CA)

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Background: Early psychosis (EP) clinics are demanding environments typically, and during the pandemic, staff burnout and turnover reportedly were high. At COVID's start, there was a mass transition to telehealth, with most individuals/clinics providing these services for the first time. It is unclear what types of technology and organization readiness factors and clinic characteristics

were related to burnout and turnover, and how this may guide ongoing use of technology in EP settings.
Methods: As part of the California Collaborative Network to Promote Data Driven Care and Improve Outcomes in Early Psychosis (EPI-CAL), implementing a novel eHealth data collection and visualization platform, 156 EP staff from 18 EP CA clinics (university and community) completed baseline surveys (Oct. 2019-Oct. 2021). 119 EP staff completed a second set (Apr. 2020-Oct. 2021). Measures: eHealth Readiness (Individual [Indv], Environment [Env], Technology [Tech])—for most teams collected pre-COVID, Organizational Readiness for Change (ORC; Motivation for Change [MFC], Resources, Staff Attributes, Climate), Professional Quality of Life (ProQOL; Burnout, Compassion Satisfaction), and demographic and clinic characteristics. The ORC item, "Frequent staff turnover is a problem here," was also used. Multiple regression (MR): burnout, turnover, compassion satisfaction were dependent variables; ORC and eHealth scales were predictors. A subsample retrospectively provided two ProQOL ratings (last 30 days in-person; 30 days start of COVID) allowing for additional analysis. Differences between clinic settings are highlighted. Open-ended survey responses about burnout and wellness qualitatively assessed for themes to contextualize quantitative findings.
Results: eHealth and organization readiness were mostly adequate or positive. Burnout was rated low and compassion satisfaction was moderate. Turnover was neutral. When data were assessed by setting, compared to universities, community sites reported higher turnover patterns and lower MFC, but no differences in burnout. Within ORC subscales, community sites had more training needs (MFC), less adequate office space and internet (Resources), and less team cohesion (Climate). Personal commitment to eHealth (Indv) was lower for universities. Multiple regression, assessing setting type separately, showed distinct patterns predicting burnout, turnover, and compassion satisfaction. RM-ANOVA, with pre and post-COVID burnout controlling for ORC and eHealth, showed an interaction effect—community and university clinics' burnout varied over time. University staff had higher burnout pre-COVID and then dropped, while community staff showed little change. At the individual level, data and qualitative themes pointed to significant individual variability, many noting technology's contribution to burnout, while others had positive experiences (professionally and personally).
Discussion: Across CA EP clinics, though readiness was high and burnout low, compassion satisfaction was moderate. Further, it was evident university and community settings had unique needs. When assessing burnout, turnover, and satisfaction, individual and organization eHealth readiness, organization factors, like SA and climate, and individual variability need to be taken into account. Factors related to burnout likely preceded COVID and technology uptake at community sites, who showed little change. To ensure these clinics prosper and are sustainable, technology, organization, and training resources should be allocated as appropriate to support individual- and agency-level needs, as telehealth and technology use is here to stay. Moving forward, there are lessons to be learned from this major shift in technology uptake during COVID.

F173. INCIDENCE OF DIAGNOSED PSYCHOSIS BEFORE AND AFTER COVID-19 AMONG FINNISH ADOLESCENTS

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Background: It has been speculated that psychosis incidence would increase due to the COVID-19 pandemic, but studies have also shown a decrease in psychiatric services in the beginning of the pandemic. We aimed to study incidence of diagnosed psychosis among adolescents in nationwide specialized services, as young people could be particularly vulnerable of the effects of the pandemic. To contrast the findings to societal restriction measures, we examined separately the months in the beginning of the pandemic (March–May 2020) with restrictions and the following year (June 2020–May 2021) with fewer restrictions.
Methods: The source population was the total population of Finnish 13–17-year-olds between January 2017 and May 2021 (between 295,020 and 307,037 at risk per year). The primary outcome was register-based monthly numbers of incidence non-affective psychosis diagnoses (ICD-10 F20-F29) in specialized services. To estimate the trend- and seasonality-corrected expected numbers of incidence cases after the onset of the pandemic (March 2020), we fitted a negative binomial model to monthly data prior the pandemic (January 2017 – February 2020) and predicted the model to months after the onset of the pandemic. The observed counts between March 2020 and May 2021 were then compared to the corresponding expected counts.
Results: Between March and May 2020, the observed number of incidence cases with psychosis diagnosis in specialized services did not significantly differ from the expected counts (42 vs. 53, 95% confidence interval [CI] 34–72). Between June 2020 and May 2021, the observed and expected incidence counts did not differ either (222 vs. 226, 95% CI 143–308).
Discussion: The incidence diagnoses of psychosis among Finnish adolescents did not significantly change in the beginning of the COVID-19 pandemic during the tightest restrictions. During the following year when services operated with less restrictions, no significant changes in incidence diagnoses were not detected either.

F174. NEXT-OF-KIN EXPERIENCES OF PERSON-CENTERED INPATIENT CARE: RESULTS: FROM THE PERSON-CENTERED PSYCHOSIS CARE PROJECT

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Background: Next-of-kin are important in patients' recovery process. Although their involvement in the care process is considered valuable, next-of-kin report experiences of not being included or being dismissed in inpatient settings. Person-centered care (PCC), which emphasizes the patient's context and resources, including next-of-kin, could improve unsatisfactory conditions. In an attempt to improve psychosis inpatient care, an educational intervention with following implementation of PCC was conducted at four acute psychosis wards in a major Swedish city. Previous evaluations of patient outcomes of the project, Person-centered psychosis care (PCPC), suggested increased patient satisfaction. This study was set up to explore next-of-kins' experiences of inpatient care encounters following the implementation of PCPC.
Methods: Focus group participants were recruited among next-of-kin to consenting inpatients who participated in an evaluation of the PCPC project, 12 accepted participation. Most participants were parents, nine were female, and the mean age was 56 (range 26- 79 years). As five participants requested individual interview both individual and focus group interviews were conducted. A

semi-structured interview guide was used, covering next-of-kin's own experiences and views of the care delivered to their significant other during their last inpatient care episode. The interviews were recorded and transcribed verbatim. Thematic analysis is ongoing.
Results: Preliminary findings suggest two main themes, revolving around care environment and care quality. Finalized Results: will be presented.
Discussion: Findings from this study will shed light on next-of-kins' perceptions of inpatient care for persons with acute psychosis that incorporates a person-centered care approach. Previous and ongoing evaluations of the PCPC project suggest increased patient satisfaction and improvements in the care environment, including relations with next-of-kin. The result of this study will indicate whether similar positive experiences can be found among next-of-kin and what areas require further improvement. As most patients chose not to disclose contact information for next of kin, the number of participating next-of-kin was not large. Therefore, Results: must be interpreted with caution.

F175. IMPACT OF COVID-19 PANDEMIC OF SERIOUSLY MENTALLY ILL (SMI) AND NON-PSYCHIATRIC CONTROL SUBJECTS IN CLINICAL TRIALS

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Background: This study aimed to examine the impact of the COVID-19 pandemic on SMI patients, specifically relating to psychiatric morbidity, pandemic-induced stress, and ability to cope with pandemic-related precautionary measures, restrictions, and disruptions to daily life.
Methods: A cross-sectional, survey study of 287 clinical trial patients was conducted. This sample included non-psychiatric controls (n=149) and SMI patients (n=139) with a diagnosis of bipolar disorder, major depression, or schizophrenia, located at five clinical trial sites across the United States. A univariate analysis was performed to obtain general frequencies of the sample. Unpaired t-tests were used in comparing the groups on numerical variables, and an ANOVA was performed to identify differences when comparing 3 or more categories
Results: SMI patients were more likely to report wearing face masks, avoid large gatherings, and endorse the use of precautionary measures despite receiving a COVID-19 vaccine ($p < 0.001$). 70.3% (n=97) of all SMI patients reported experiencing at least one episode of worsening, 48% reported experiencing suicidal ideation, and 66% reported a need for increased mental health care due to COVID-19 distress. SMI patients reported higher levels of stress in comparison to the controls, with MDD patients having the highest levels of stress ($p < 0.001$).
Discussion: These findings demonstrate an increased vulnerability to symptom worsening in SMI patients during a pandemic and suggest the need to account for pandemic-induced psychological stress in clinical trials design, subject selection, and symptoms ratings.

F176. PATIENT VIOLENCE TOWARDS THEIR FAMILY CARERS: A QUALITATIVE EXPLORATION OF CARERS' EXPERIENCES IN PSYCHOSIS

Emilie Wildman*[1], Elizabeth Kuipers[2], Deirdre MacManus[3], Juliana Onwumere[2]

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Background: Compared to the general population, people living with schizophrenia spectrum disorders (SSD) are more likely to perpetrate acts of violence. When this happens, family members (informal carers) are most commonly the victims. However, family violence by people with SSD is often a taboo topic and largely neglected within public discourse, research and clinical domains. Consequently, our understanding of families' experiences and support needs are limited. This study sought to develop a detailed understanding of the subjective experiences, and impact, of patient violence on carers, and to explore carers' perceptions of the personal and professional support they have received.
Methods: Individual semi-structured interviews were held with family carers of adults with SSD and a history of violence towards their family carer. Interview data were subject to thematic analyses using NVivo software.
Results: Twenty-three UK based family carers that were predominately White British (83%) and female (83%) were interviewed. Key themes highlight a range of physical and mental injuries endured by carers following patient violence, and speak to carers' experiences of suffering, living in a constant state of hypervigilance, as well as social isolation in the context of shame, stigma, and an absence of professional and informal support.
Discussion: Family violence by people living with SSD can and does happen. Yet, too often, carers are left with no option but to continue supporting their relative in the absence of support, even in contexts where this compromises their own safety. The devastating impact of violence is far-reaching, across all levels of the family-system. The findings highlight the danger of neglecting family violence by people living with SSD in research and clinical fields.

F177. PEER SUPPORT AND RECOVERY – A RESEARCH PROGRAM IN REGION NORTH IN DENMARK

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Background: Peer support is a collaborative practice, where individuals are employed to make use of their personal experiences as mental health service users to support likeminded. Peer support has been recognized as an important facilitator of personal recovery. Recently, peer support workers have been employed in the Psychiatric Department in Region North in Denmark. Research with peer support have been conducted in the US and UK in health systems different from the Danish health system, therefore there is a need to explore and generate knowledge and insight on peer support and personal recovery from a Danish health care setting. This also supports the lack of a model for peer support in regard to education, function and implementation in Denmark.
Methods: The purpose of this research program is to explore and understand peer support and personal recovery from the perspectives of peer support workers, persons with psychosis and

health care professionals from F-ACT Teams and hospital wards in Region North in Denmark, and to draw inferences between the perspectives.
The overall design is an explorative design using quantitative and qualitative Methods: with innovative co-design workshops guided by participatory design core principles and consists of four work-packages that addresses the overall purpose.

Results: The Results: are expected to shed light over the benefits of peer support and to provide recommendations of how to promote a recovery-oriented culture in clinical practice in the treatment and care of persons with psychosis. Additionally, to argue for employment of peer support workers in every ward and outpatient clinic. Furthermore, to contribute to development of a model for peer support to implement in Denmark.
Discussion: The poster will present the research program in more details.

F178. SOCIAL DEAFFERENTATION AND THE RELATION BETWEEN LONELINESS AND HALLUCINATIONS

Sanne Brederoo*[1], Janna De Boer[2], Mascha Linszen[2], Renske Blom[3], Marieke Begemann[1], Iris E. C. Sommer[1]

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Background: The relation between loneliness and the occurrence of psychotic symptoms such as hallucinations is well-known and often replicated. The social deafferentation hypothesis (SDA) has been proposed as an explanatory mechanism of hallucinations, based on the theory that social withdrawal triggers the initial phase of schizophrenia. Support for the SDA can be found in studies showing that people with smaller social networks and fewer social interactions are more prone to experience hallucinations. However, in such studies it is difficult to disentangle cause and effect, as it is also known that people with psychotic experiences will become more socially isolated as a result from their symptoms. Therefore, a rigorous and more direct test of the SDA is needed. The current study forms such a test by assessing whether increased loneliness is associated with hallucinations that carry social meaning, rather than with hallucinations lacking any social connotation. We overcome confounding factors often associated with such research (e.g., social isolation as a result of a psychiatric disorder) by examining loneliness and hallucinations in a large non-clinical sample.
Methods: Using an online survey, we assessed the occurrence and phenomenology of hallucinations and loneliness in a sample of 6,331 adults from the general Dutch population (median age 35 yrs; 68% female). We used the Questionnaire for Psychotic Experiences (QPE) to examine auditory [AH], visual [VH], and tactile [TH] hallucinations, and the shortened De Jong Gierveld Loneliness Scale (DJGL-6) to assess degree of loneliness.
To ascertain that the expected relation between loneliness and hallucinations is present in our sample, binomial logistic regression was used to investigate the effect of loneliness severity on past month prevalence of AH, VH, and TH. We, furthermore, tested the SDA by examining the effect of loneliness severity on the presence of hallucinations that carry social meaning (e.g., hearing voices, seeing people, feeling touch, sensing a presence) versus hallucinations without social meaning (e.g., hearing music, seeing animals or objects, formication). Under the SDA,

increased loneliness is hypothesized to affect the occurrence of social hallucinations, but not non-social hallucinations.

Results: Our Results: show that the lonelier a participant indicated to feel, the more likely he or she was to experience an AH, VH, or TH in the past month (all p's < .001). In participants who had experienced hallucinations in the past month, some types of 'social' hallucinations were more often experienced with increasing loneliness. Specifically, the lonelier a participant reported to feel, the more likely he or she had been to hear voices ($p < .05$) or experience the feeling of being touched in the absence of others ($p < .05$). Conversely, the lonelier participants reported to feel, the less likely they were to experience the non-social hallucinations of hearing animal sounds ($p < .05$) or seeing patterns ($p < .05$). As expected, loneliness did not increase the prevalence of experiencing non-social hallucinations. The hypothesized increase in prevalence of seeing people or sensing a presence with increasing loneliness was absent in our sample ($p > .05$).

Discussion: In line with previous research, we show that increased loneliness is associated with a higher prevalence of hallucinations, in a dose response fashion and across perceptual modalities. Our Results: go further in showing that loneliness increases the chance of hearing voices or feeling touch, both of which carry social meaning. Hallucinations without social meaning were not more likely to be experienced with increasing loneliness. This forms a first direct confirmation of the SDA.

Poster Session III

11:45 a.m. - 1:45 p.m.

S1. NIGELLA SATIVA OIL IMPROVED MEMORY, REDUCED ANXIETY AND ATTENUATED PSYCHO-BEHAVIOURAL ENDOPHENOTYPES IN DIZOCILPINE (MK-801)-INDUCED BALB/C MICE MODELS OF SCHIZOPHRENIA

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Background: Schizophrenia is a psychotic disorder with unascertained aetiology, and characteristic positive, negative and cognitive symptoms. Despite years of research however, this ailment still lacks a holistic and side-effect-free therapy. To identify alternative drugs for this condition, this research investigated the anti-psychotic potentials of Nigella sativa oil (NSO) on the neurobehaviour of Dizocilpine-induced mice models of schizophrenia. Nigella sativa is a highly medicinal plant of midle-eastern origin, historically notable for its multi-therapeutic potentials and affirmed by modern science.

Methods: Sixty male albino mice were divided equally across five groups, namely, Control, DZ, NSDZ and DZNS. Elevated Plus Maze, (EPM), Novel Object Recognition (NOR) and Object Location tests (OLT) were conducted, and the animals were euthanised 24 hours after final administration.

Results: Dizocilpine induced schizophrenia-like symptoms, while Nigella sativa oil prevented and attenuated the expression of schizophrenic endophenotypes such as popping behaviour, impaired gait, anxiety, defective learning and recognition memory in schizophrenic BALB/c mice. It also reduced food intake and thus regressed weight gain significantly to 0.47%, -10.00% and -24.24% of initial body weights in the NS, NSDZ and DZNS groups respectively. NSO also increased the relative brain weights by 1.86% and 2.51% in NSDZ and DZNS groups respectively against the DZ group, while it improved recognition memory in the schizophrenic NSDZ and DZNS groups by 15.54% and 18.13% more than the DZ schizophrenic control.

Discussion: The anti-schizophrenic potential of Nigella sativa has thus been established by this study neurobehaviourally, particularly in anxiolysis, memory enhancement, and attenuation of psychotic explosive behaviours.

S2. NEGATIVE SYMPTOMS AND ANXIETY PREDICT LONELINESS IN PATIENTS WITH SCHIZOPHRENIA

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Background: Loneliness (i.e., `perceived social isolation´) can have critical health consequences. People with psychosis are particularly vulnerable to loneliness, with reports demonstrating loneliness in up to 80% of patients during a one-year period. Patients with negative symptoms and anxiety may be particularly vulnerable, as they are more prone to social withdrawal. Here, we aim

to test whether severity of negative symptoms and levels of anxiety contribute to feelings of loneliness in patients with schizophrenia.
Methods: We recruited 70 patients with schizophrenia at the University Hospital of Psychiatry and Psychotherapy in Bern, Switzerland. Current feelings of loneliness, objective and subjective ratings of negative symptoms, as well as state- and trait-levels of anxiety were assessed with the UCLA loneliness scale, the brief negative symptom scale (BNSS), the self-evaluation of negative symptoms scale (SNS), and the State-Trait Anxiety Inventory (STAI). Two two-stage hierarchical multiple regressions were performed, to independently assess the predictive capacity of subjective negative symptoms (regression one, stage one) and objective negative symptoms (regression two, stage one) on current levels of loneliness in patients, with state- and trait-levels of anxiety as additional predictors (stage two in both models).
Results: The first regression indicated that self-reported negative symptoms accounted for 31% of the variance in current feelings of loneliness, while trait-anxiety accounted for 10% of loneliness above and beyond negative symptoms. The second regression indicated that objective ratings of negative symptoms did not significantly account for variance in current feelings of loneliness, while trait-anxiety accounted for 30% of loneliness, when controlling for objective negative symptoms.
Discussion: Our Results: suggest that severity of negative symptoms and anxiety-levels significantly contribute to current feelings of loneliness in patients with schizophrenia. Interestingly, our Results: suggest that subjective rather than objective ratings of negative symptoms and trait- rather than state-anxiety most accurately predict current feelings of loneliness.

S3. INFLUENCE OF BDNF ON COGNITION IN RELATION TO RISK OF PSYCHOTIC TRANSITION

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Background: The ultra high-risk category refers to patients at the early stage of psychosis and is defined by the presence of subclinical symptoms. It has been estimated that 25% of these patients will develop a full-blown psychotic episode within 3 years. High-risk patients already suffer from cognitive difficulties. Many hypotheses have been proposed to explain the mechanisms, but to date, they are not fully understood. One of these hypotheses involves the Brain Derived Neurotrophic Factor (BDNF). Lowered BDNF levels are repeatedly found in schizophrenia and during the first episode of psychosis (FEP). This decreased level is correlated with cognitive functioning. In this exploratory study on a sample of young UHR patients, we hypothesize that (1)

before the psychotic transition, there are differences in the concentration of BDNF mRNA and its protein between converters and non-converters and that (2) these concentrations have an impact on cognitive functions with a different effect depending on the clinical outcome.
Methods: The patients were part of the ICAAR cohort. Individuals were categorised as "not at risk" or “at-risk" on the basis of CAARMS criteria. At-risk patients were followed for one year and classified as converters (C) when the CAARMS threshold for psychosis was reached and as non-converters (NC) when symptoms remained below this symptomatic threshold. We used clinical data from 135 patients for whom we had BDNF levels for 67 patients (26 C; 41 NC) and BDNF mRNA levels for 120 patients (39 C; 81NC). BDNF analysis was performed on serum using the ELISA technique and total BDNF mRNA was analyzed by qPCR from whole blood samples. Total intellectual quotient (IQ) was assessed by the WAIS III.
Results: Before psychotic transition, converters have a significantly higher level of BDNF mRNA expression than non-converters ($p=0.0008$). On the cognitive side, there was no difference between converters and non-converters before transition. In converters, we found a significant positive correlation between total IQ and BDNF ($r=0.47$; $p=0.017$). In non-converters, we found a significant negative correlation between total IQ and BDNF mRNA ($r=-0.23$; $p=0.039$). Finally, using multivariate linear regression taking into account the effect of age, gender, body mass index, CRP, cannabis use, chlorpromazine equivalent in case of antipsychotic treatment, positive and negative symptoms, we find a significant interaction between BDNF and clinical outcome ($p=0.020$) on IQ and between BDNF mRNA and clinical outcome ($p=0.013$) on IQ.
Discussion: The role of BDNF on IQ differs between future converters and non-converters. In converters, a higher level of BDNF would be beneficial for IQ, whereas the relationship seems to be the opposite in non-converters. If these Results: were to be confirmed, this difference might be linked to compensatory mechanisms in converters, to a difference in receptor expression (P75 or TrkB) or to a difference in the distribution of BDNF isoforms (ProBDNF and mBDNF). Making a distinction between these two isoforms or between receptors expression could be important in future studies as they have opposite effects. Further studies on a larger number of subjects are needed to confirm these preliminary Results: and define the role of BDNF in the pathophysiology of cognitive impairment and test its importance as a biomarker. A better understanding of these mechanisms could pave the way for personalized treatments.

S4. EVIDENCE FOR SPECIFICITY OF METAMEMORY IMPAIRMENT IN PSYCHOTIC ILLNESS

Rashina Seabury*[1], Tyrone Cannon[1]

[1]Yale University

Background: Metacognitive impairments related to memory performance have been hypothesized to contribute to the genesis and/or maintenance of positive symptoms of schizophrenia and related disorders. While metamemory impairment has been established as correlate of psychotic illness, the question remains whether this is a feature specific to schizophrenia or apparent among other psychiatric disorders, particularly those that share genetic overlap with schizophrenia and also similarly significantly impact psychosocial functioning.
Methods: In the present study, we used a verbal associative memory paradigm incorporating subject confidence ratings to examine differences in metamemory processes in three psychiatric samples: patients with schizophrenia or schizoaffective disorder ($n = 44$), euthymic patients with

bipolar disorder (n = 45), and individuals with attention deficit-hyperactivity disorder (n = 34), as well as a healthy control sample (n = 82).
Results: We found that confidence gap and knowledge corruption, both indices of metamemory, as well as the proportion of confident errors, significantly differed between diagnostic groups, with the schizophrenia group showing significant impairment in metamemory functioning compared with each of the others. Moreover, despite exhibiting a significant impairment in general verbal memory performance as measured by the California Verbal Learning Test, the bipolar group did not significantly differ in metamemory performance from the ADHD and healthy samples.
Discussion: This pattern suggests that metamemory impairment is specific to psychotic forms of illness among those examined here and that this deficit may be, at least partially, distinct from generally reduced memory performance in this respect.

S5. SOCIAL AND OCCUPATIONAL RECOVERY IN EARLY PSYCHOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF PSYCHOSOCIAL INTERVENTIONS

Emma Frawley*[1], Megan Cowman[2], Martin Lepage[3], Gary Donohoe[1]

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Background: Psychosis, even in its early stages, ranks highly among causes of disability worldwide, resulting in an increased focus on improved recovery of social and occupational functioning. This study aimed to provide an estimate of the effectiveness of psychosocial interventions for improving functioning in early psychosis. We also sought evidence of superiority between intervention approaches.
Methods: An electronic search was conducted using PubMed and PsycINFO to identify original articles reporting on trials of psychosocial interventions in early-stage psychosis, published up to December 2020 and is reported following PRISMA guidelines.
Data were extracted on social and occupational functioning outcomes from included studies. Relevant data extracted also included study and participant characteristics (nature of the intervention, intervention length, follow-up length, control condition, number of sessions, age, percent male, diagnoses, medication use, illness duration).

Pooled standardised difference in means (SMD – Cohen's d) were estimated with Comprehensive Meta- Analysis Software (CMA), Version 3. Separate analyses were conducted for five different intervention groups, and an overall summary analysis was conducted including all psychosocial intervention studies. For two intervention groups (supported employment and family-based interventions) only three studies were included in the meta-analysis, due to the small number of studies in each group these analyses should be considered exploratory. Subgroup analyses were performed to account for differences in effect size based on participant, intervention, and measurement characteristics.

Results: In total, 31 studies involving 2811 participants were included, focusing on: Cognitive Behavioural Therapy for Psychosis (CBTp), Family Based Therapy (FBT), Supported Employment, Cognitive Remediation (CRT), and Multi-Component psychosocial interventions.

Across interventions, improved function was observed (SMD=0.293; 95% CI 0.115 to 0.364, p<0.001).
A meta-analysis of the effects of CBT interventions on social and occupational function was non-significant based on a total of eight available studies (SMD=0.139, 95% CI [-0.021 – 0.299], p=0.089) (See Figure 2). Of note, four of these eight studies were based on UHR samples. Also noteworthy was that the largest of these studies – based on 'social-recovery orientated' CBT rather than a symptom orientated CBT, was the sole individual study associated with significant gains in psychosocial function (Fowler et al., 2018).

An insufficient number of family therapy studies (n=3) were available to calculate an effects size specifically for family interventions.

Similarly, there was an insufficient number of IPS-based studies from which to generate an intervention-specific effect size. However, as Figure 3 illustrates, the three studies included in our overall meta-analysis showed significant effects favouring the intervention groups.

The data from the 10 CRT studies were available for meta-analysis, allowing us to test the significance of this intervention separately. CRT was associated with modest but significant improvements in social and occupational function when compared to control conditions (SMD=0.301, 95% CI [0.004 – 0.599], p=0.047). Difference in effect sizes reported could not be easily understood in terms of differences in sample type (first episode/early psychosis groups versus UHR groups).

The data from the seven multi-component psychosocial studies were also available for meta-analysis. This group was also associated with modest but significant improvements in social and occupational functioning when compared to a control condition (SMD=0.452, 95% CI [0.061 – 0.843], p=0.023).

Discussion: Psychosocial interventions, particularly when provided as part of a multi-component intervention model and delivered in community-based settings are associated with significant improvements in social and occupational function. This review underscores the value of sensitively tracking and targeting psychosocial function as part of the standard provided by early intervention services.
In conclusion, the increased emphasis on the value of targeting and treating social and occupational function in the early treatment of psychosis appears to be well founded. As reviewed here, there is evidence that many, but not all, psychosocial interventions are associated with improvements in these areas. Providing these as part of multi-component interventions in community-based settings remains an important need for this cohort. Supporting the recent progress in increasing the availability of these interventions remains a key priority.

S6. THE ASSOCIATIONS AMONG POSITIVE SOCIAL APPRAISALS, SUSPICIOUSNESS, AND SOCIAL MOTIVATION DAILY LIFE AMONG PEOPLE WITH SCHIZOPHRENIA

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Background: Social motivation deficits (i.e., low drive to initiate and maintain social bonds) are pervasive and debilitating in people with schizophrenia (SZ). Although positive appraisals of social interactions (i.e., perceiving interactions as positive or rewarding) are associated with higher social motivation in the general population (Schoch, Nikitin, Freund, 2015), the extent to which this is also true within the daily lives of people with SZ is unknown. Additionally, because suspiciousness often leads to social avoidance within SZ, the association between positive social appraisals and social motivation in daily life may be dampened among those with higher suspiciousness.
Methods: In the context of a 60-day Ecological Momentary Intervention (EMI), 31 people with SZ completed brief, twice daily smartphone assessments of appraisals of recent social interactions (i.e., perceptions of one's competence, likability, and effort) and social motivation (i.e., willingness to interact with others, willingness to work towards a self-determined social goal). We examined whether higher levels of positive appraisal were associated with greater willingness to interact with others and greater motivation to work towards their social goal at the daily level. We also examined whether suspiciousness (based on the Brief Psychiatric Rating Scale [BPRS] at baseline) attenuated these associations.
Results: We found that higher levels of positive appraisals were related to greater willingness to work towards a social goal ($b = 0.42$, $SE = 0.07$; $p < 0.01$; 95% CI: 0.25-0.60) and, to a lesser extent, willingness to talk with others ($b = 0.14$, $SE = 0.09$; $p = 0.06$; 95% CI -0.006-0.289). Suspiciousness did not moderate these associations (b values < .0001).
Discussion: The findings suggest that positive social appraisals are contemporaneously related to motivation to pursue social goals, and are not moderated by levels of suspiciousness in the context of a structured digital intervention. Importantly, perceived positive outcomes of recent interactions could serve to motivate people to attend to their social goals, and thus may act as a target for interventions designed to improve social outcomes.

S7. READING BETWEEN THE DIAGNOSTIC LINES: SOCIAL COGNITION AND METHODOLOGY

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Background: Both schizophrenia spectrum disorders and autism spectrum disorders are characterized by impairments in social cognition. While the two groups can perform similarly on tests of Theory of Mind, emotion recognition and other similar assessments, it remains unclear where deficits converge and diverge. Recently, a number of meta-analyses and systematic reviews have called attention to the fact that Results: in this area are highly heterogenous. While efforts have been made to clarify the concept of social cognition and validate its inner domains, there continues to be discrepancies evident in the literature. In this review, we will investigate the methodology being used across these studies as well as inclusion criteria for patient groups. This is a crucial issue to analyze further due to the general confusion currently surrounding the area of social cognition and the ways in which we apply these concepts to transdiagnostic studies. If the future intention is to influence clinical practice and utilize similar social cognitive training across groups, it is imperative that we understand their underpinnings. This is only possible by utilizing sound methodology.

Methods: We conducted a systematic review of the literature using the search string: (schizophrenia and autism) AND "social cognition".
Results: A preliminary review of the literature suggests a lack of clarity in the concept of social cognition and how it relates to both schizophrenia and autism spectrum disorders. Many of these empirical studies vary drastically in what measures they use to asses "social cognition", a term which remains somewhat ill-defined. Some studies assess only Theory of Mind while others assess emotion recognition or emotional intelligence. And the measures used to assess these concepts can vary greatly. Some investigators attempt to generalize Results: from studies with patient populations that are either highly exclusive or mismatched. For example, high-functioning autism as compared to chronic schizophrenia, or inclusion criteria which allows for active substance abuse in the schizophrenia group but not in the autism group.
Discussion: Although there is evidence to suggest that common social cognition impairments can be seen in both schizophrenia spectrum and autism spectrum disorders, the nature of these impairments remains elusive. In studies that compare these disorders, methodology is unclear and variable.

S8. SUBJECTIVE COGNITION IN SCHIZOPHRENIA AND BIPOLAR DISORDER – AN INVESTIGATION OF GROUP DIFFERENCES AND ASSOCIATIONS WITH OBJECTIVE COGNITION AND CLINICAL FACTORS

Kristoffer Grimstad*[1], Håkon Sørensen[1], Christine Mohn[1], Linn Sofie Sæther[1], Ole A. Andreasen[1], Ingrid Melle[1], Merete Glenne Øie[2], Beathe Haatveit[1], Torill Ueland[1]

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Background: Cognitive dysfunction is a well-documented and prominent feature of both Schizophrenia (SZ) and Bipolar (BD) spectrum disorders. A less investigated phenomenon is the person's own experience of cognitive difficulties – the degree of subjective cognitive impairment. To our knowledge, no previous studies have directly compared subjective cognition in SZ and BD patients.
Methods: The psychometric properties of a novel measure of subjective cognition, the self-assessed cognitive complaints scale (SACCS), were investigated. Objective cognition was assessed using the MATRICS Consensus Cognitive Battery (MCCB). Subjective and objective cognition were compared between 91 SZ patients, 55 BD patients and 55 HC using analysis of variance (ANOVA). The relationship between subjective and objective cognition, as well as clinical variables were explored using Pearson´s correlation analyses. All participants were selected from the ongoing Thematically Organized Psychosis (TOP) study at the University of Oslo and Oslo University Hospital, and consisted of a subsample of participants that completed an assessment of subjective cognition.
Results: The SACCS showed adequate psychometric properties. The clinical groups reported significantly more cognitive complaints than HC. The clinical groups reported a similar degree of cognitive complaints. Compared to HC, SZ patients performed the worst, and BP patients at an intermediate level on most objective cognitive domains. There were no significant associations between subjective and objective cognition in any of the groups. Among SZ patients a small association was found between subjective cognition and insight into illness. However, the effect

did not survive Bonferroni correction. In BD patients moderate sized associations were found between subjective cognition and general psychopathology, depressive, manic and disorganized symptoms, as well as general functioning. After correcting for multiple testing only associations between general psychopathology and functioning remained statistically significant.
Discussion: Although SZ patients are significantly more cognitively impaired on most objective measures than BD patients, the two patient groups report similar levels of subjective cognitive complaints. Our Results: suggest that the expression of subjective cognition is associated with different clinical factors in SZ and BD. We argue that our findings underline the need for thorough cognitive assessment of patients with BD and SZ, and that subjective cognition constitutes an important clinical dimension that should be included.

S9. EXAMINING THE EFFICACY OF COMBINING COGNITIVE TRAINING AND NON-INVASIVE BRAIN STIMULATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Cognitive impairment is related to impaired everyday functioning in many people with psychiatric and neurological disorders. Cognitive training may help to overcome these impairments. An innovative treatment strategy is combining cognitive training with non-invasive brain stimulation (NIBS) to increase the learning effect of cognitive training. We conducted a transdiagnostic meta-analysis to investigate how effective this treatment combination is in improving cognition and minimizing associated problems people experience in daily life.
Methods: We performed a systematic search across electronic databases (Pubmed, MEDLINE, PsycInfo, and Web of Science), registries and reference lists. We integrated 653 effect sizes from 60 controlled studies in healthy and clinical populations (schizophrenia, mild cognitive impairment, Alzheimer's disease, HIV-related neurocognitive impairment, multiple sclerosis, Parkinson's disease, fibromyalgia, morbid obesity, ADHD, substance-use disorder) that tested the effects of combining NIBS with cognitive training compared to cognitive training alone or combined with sham stimulation. We investigated whether the treatment combination Results: in additional improvements in cognitive functioning, clinical symptoms, and everyday functioning at post-intervention and follow-up compared to cognitive training alone.
Results: Using random-effects meta-analyses with robust variance estimation, we found that global cognition ($g = 0.27$, 95% CI [0.15, 0.42], $p < .001$), working memory ($g = 0.15$, 95% CI [0.06, 0.24], $p = 0.002$), learning/memory ($g = 0.15$, 95% CI [0.03, 0.28], $p = .018$), and executive functioning ($g = 0.10$, 95% CI [0.01, 0.19], $p = 0.040$) improves significantly more when adding NIBS to cognitive training compared to cognitive training alone. Everyday functioning ($g = -0.165$, 95% CI [-0.33, -0.00], $p = 0.081$) and clinical outcomes ($g = -0.01$, 95% CI [-0.15, 0.13], $p = 0.894$) did not seem to benefit from the addition of NIBS to cognitive training. However, only 8 of 60 studies assessed functional outcomes. The Results: remained significant after excluding 22

studies that were considered at high risk of bias in selective outcome reporting, missing data, sequence generation, or allocation concealment (global cognition: g = 0.35, 95% CI [0.17, 0.53], p = .011; working memory: g = 0.17, 95% CI [0.06, 0.28], p = 0.007; learning/memory: g = 0.19, 95% CI [0.08, 0.30], p = .004; executive functioning: g = 0.13, 95% CI [0.02, 0.24], p = 0.034).
Discussion: In this meta-analysis, we found significantly better effects of cognitive training combined with NIBS on multiple cognitive outcome measures (global cognition, working memory, learning/memory, and executive functioning). All effects were small but significant. For clinical and functional outcome measures, we did not find any beneficial effects of the treatment combination compared to cognitive training only. Hence, the Results: indicate that combining CT with NIBS could be beneficial for cognitive outcomes. The clinical relevance is unclear since few studies assessed functional outcome; hence, we do not know whether the benefits transfer to everyday life. This review highlights common issues in cognitive training research: in most studies, essential elements of cognitive training that promote the transfer of cognitive improvement to everyday functioning (e.g., problem-solving strategies) are missing, few studies assessed functional outcomes and long-term effects, and cognitive outcomes are not always assessed with validated measures. Future studies should focus on assessing the clinical relevance of the treatment combination by (1) designing the cognitive training with a focus on improving everyday functioning, (2) adding functional outcome measures, (3) assessing long-term effects, and (4) using validated cognitive outcome measures.

S10. COROLLARY DISCHARGE ASSOCIATED WITH SACCADIC EYE MOVEMENTS IN INDIVIDUALS WITH SCHIZOPHRENIA AND BIPOLAR DISORDER WITH PSYCHOTIC FEATURES

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Background: Corollary discharge (CD) signals are ‘copies’ of motor signals that are sent to sensory areas of the brain and allow us to predict the consequences of impending actions. A match between the CD-guided sensory prediction and afferent sensory input associated with a movement engenders a sense of agency. But a failure to generate or use these predictions may cause the agency disturbances that characterize psychosis. Previous studies have suggested persons with schizophrenia have altered CD signaling associated with saccadic eye movements. In the current study, we examined whether findings of altered oculomotor CD signaling extend to persons diagnosed with bipolar disorder with psychotic features.
Methods: We used a double-step task to test oculomotor CD in samples of 44 persons with schizophrenia or schizoaffective disorder (SZ), 25 persons with bipolar disorder with psychotic features (BPP) and 39 healthy controls (HC). This task measures the degree to which CD informs successive eye movements, and our version comprised two trial types: retinal and extraretinal. In both conditions, two visual targets were presented sequentially and participants were asked to look at the targets (T1 and T2) in the order they appeared. The conditions differed in stimulus timing. In the extraretinal condition, targets were flashed in rapid succession, such that T2 was

extinguished by the time gaze had landed on T1. Thus, to accurately look at T2, participants had to rely on extraretinal information (i.e., CD). In the retinal condition, T2 was flashed once the participant was looking at T1, and retinal information could guide the saccade to T2. Multilevel modeling was used to examine the extent to which participants compensated for variability in the amplitude of the first saccade when generating the second saccade to T2, and whether this differed between groups. We predicted the amplitude of the second saccade from the expected saccade amplitude, condition, T1 hemifield, and group. We also examined group differences in the amplitude of the first saccade. Main and interaction effects involving group were followed by tests comparing groups to each other, and the combined psychosis group to HC.
Results: There was a main effect of group on amplitudes to both T1 ($d = 0.468$, $p=0.003$) and T2 ($d = 0.464$, $p=0.002$): SZ made smaller saccades than HC, whereas BPP did not differ from either group. Saccades were significantly shorter in the combined psychosis group compared to HC. There was a trend-level three-way interaction effect on the amplitude of the second saccade (S2) between group, condition and expected S2 amplitude ($d = 0.233$, $p = 0.07$). Follow-up tests revealed a blunted relationship between expected and actual amplitude of the second saccade in the combined psychosis group, but only in the extraretinal condition where an accurate second saccade relied on CD ($d = 0.283$, $p=0.027$). These data suggest a decreased ability to use CD to compensate for variability in the endpoint of the first saccade when generating the second saccade in individuals with psychosis.
Discussion: Persons with psychosis showed a decreased ability to use CD signals to inform successive eye movements when compared to HC. These data tentatively suggest that CD may be a transdiagnostic marker of psychosis.

S11. THE ASSOCIATION BETWEEN ATTACHMENT AND SOCIAL FUNCTIONING IN PATIENTS WITH NON-AFFECTIVE PSYCHOTIC DISORDERS, UNAFFECTED SIBLINGS AND HEALTHY CONTROLS

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Background: In patients with psychotic disorders, insecure attachment styles and impaired social functioning are highly prevalent. Insight in the association between attachment style and social functioning is clinically relevant as it can enhance our understanding and clinical approach to social dysfunction in psychotic disorders. Therefore, our aim was to explore the multi-cross-sectional association between attachment style and social functioning across time. Furthermore, we aimed to explore the impact of attachment style on change in social functioning over time.
Methods: This study was performed in a subsample of 119 patients with non-affective psychotic disorders, 128 unaffected siblings and 66 healthy controls within the Genetic Risk and Outcome of Psychosis (GROUP) Study. Data on attachment style (using the Psychosis Attachment Measure) and three social functioning domains, namely withdrawal, interpersonal behaviour and pro-social activities as assessed with the Social Functioning Scale (SFS) were collected on two moments in time. Generalized linear mixed models and linear regression models were used. Bonferroni correction for multiple testing was applied.

Results: In the patient group, a significant negative association was found between avoidant attachment and the social functioning domain pro-social functioning. In the sibling and control group, we found significant negative associations between avoidant attachment and the social functioning domains withdrawal and interpersonal behaviour. We also found a significant negative association between anxious attachment and the social functioning domain withdrawal in siblings. No significant associations were found between attachment style and change in social functioning across groups in the longitudinal analyses.
Discussion: Findings indicate that levels of insecure attachment are elevated in patients with psychotic disorders and have a negative association with social functioning in both patients, siblings and controls. These findings warrant specific attention for attachment style in the treatment of patients with psychotic disorders.

S12. MODELING REACTION TIME DISTRIBUTIONS INCREASES THE STATISTICAL POWER OF COGNITION TESTING

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Background: Drug development clinical trials often include testing sessions designed to measure participants' cognitive performance on domains such as processing speed, attention, visual learning and working memory. Reaction time (RT) data, typically reported as mean log-RT, and accuracy are used to quantify performance on standard cognitive batteries. We examined whether current approaches using mean log-RT to reduce an individual subject's performance data Results: in information loss relative to other approaches that more fully model individual subject's RT distributions, and thereby reduce the power to test specific hypotheses of cognition.
Methods: Reaction times were extracted from subject-level performance data during computerized cognitive tests (Cogstate tests of Detection, Identification, One Card Learning; note that the One Back task was not included in the current investigation because no healthy control data were available for this task). Baseline Cogstate data from 7 drug development clinical trials (schizophrenia, bipolar disorder, N=1,890 subjects) were compared to normative data obtained from healthy subjects (N=7,108). Parameters describing subject-level RT distributions were obtained by Bayesian estimation of population models using either ex-Gaussian or Wiener diffusion model residual likelihoods (note: the shifted Wald diffusion model was utilized for Cogstate detection since this task has a single component [reaction time] and the diffusion model is unnecessarily complicated). We evaluated two Methods: of analyzing Cogstate data for correctly categorizing subjects with a diagnosis of schizophrenia or bipolar depression versus healthy subjects: mean log-RT versus the parameters of RT distribution models (ex-Gaussian, Wiener Diffusion Model). Receiver operating characteristic (ROC) curves were used to evaluate the performance characteristics (sensitivity, specificity) of each analytic method for detecting a difference in Cogstate function between the clinical group and the healthy control group. Area Under the ROC Curve (AUCROC) was reported to summarize overall accuracy of each analytic approach.
Results: Each subject participating in a cognitive test session performed approximately 170-180 responses across the 3 Cogstate tests summarized here. Subject-level RT distributions were well-

described by ex-Gaussian and Wiener diffusion models, resulting in parameter estimates for each subject. On the Cogstate Identification task, both the Weiner Diffusion (AUC=0.815) and ex-Gaussian (AUC=0.825) models were better than mean log-RT (AUC=0.72) at correctly classifying clinical patients (vs. healthy controls). Similarly, on the One Card Learning task, both the Weiner Diffusion (0.745) and ex-Gaussian (0.719) models were better than mean log-RT (0.645) at correctly classifying clinical patients; and on the Cogstate Detection task, the shifted Wald diffusion model (0.740) was better than mean log-RT (0.607) at correctly classifying clinical patients.
Discussion: Analyzing subject-level responses during cognitive testing recovers information lost by mean log-RT, the latter being a widely used method for analyzing cognitive performance data. The ability to correctly classify subjects with schizophrenia or bipolar disorder (versus healthy controls) was improved by 10-13 percentage points using ex-Gaussian or Wiener diffusion models of baseline Cogstate data. Thus, improved analysis Methods: that more fully model individual subject's RT distributions may increase the statistical power to test specific hypotheses of cognition in clinical trials.

S13. PATHWAYS FROM COGNITIVE AND PHYSICAL EFFORT EXPENDITURE TO FUNCTIONING IN EARLY PSYCHOSIS: THE INDIRECT INFLUENCES OF MOTIVATION AND EXPRESSIVE NEGATIVE SYMPTOMS

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Background: Functional impairments are present in first-episode psychosis, and can persist with illness chronicity. Cognition and motivation are established predictors of functioning in psychotic disorders, limiting skill development and lowering willingness to engage in effortful tasks. The present work aims to elucidate the indirect roles of negative symptom dimensions on the relationship between cognitive versus physical effort expenditure and functional outcomes in early psychosis.
Methods: Thirty-six patients were recruited from the Early Psychosis Intervention Program in Ontario, Canada. Clinical symptoms were assessed using The Brief Negative Symptom Scale and represented by two factors: motivation and pleasure, which includes anhedonia, avolition, and asociality; and emotional expressivity, which includes blunted affect and alogia. Functioning in domains of work, independent living, family, and social networks was assessed using the Role Functioning Scale. Two adaptations of the effort expenditure for rewards task (EEfRT) assessed individuals' motivation to expend physical and cognitive effort. The EEfRT tasks present participants with options to complete a low effort task for a low reward ("easy choices") or a high effort task for a high reward ("hard choices").
Results: Lower proportions of cognitive hard choices were significantly associated with more severe motivation/pleasure symptoms and poorer life functioning. Lower proportions of physical hard choices were significantly associated with more severe expressive symptoms, but not motivation/pleasure symptoms. More severe expressive symptoms were associated with poorer life functioning. Life functioning shared negative associations with both motivation/pleasure and expressive symptoms. An indirect effect model explored whether motivation/pleasure symptoms explained the relationship between proportion of cognitive hard choices and concurrent life

functioning. This model was significant, $F(2,29) = 13.09$, $p = .0001$, accounting for 47% of the variance in functioning. Cognitive hard choices did not predict life functioning independent of motivation/pleasure symptoms, $\beta = .10$, $t(30) = 0.65$, $p = .52$. The effect of motivation/pleasure symptoms on functioning was significant, $\beta = .25$, Bootstrap SE = 0.11, BCa CI [0.052, 0.474]. A second indirect effect model assessed the role of expressive symptoms in the relationship between proportion of physical hard choices and concurrent life functioning. The model was significant, $R2 = .15$, $F(1,28) = 4.86$, $p = .04$. Physical hard choices did not predict functioning independent of expressive symptoms, $\beta = -.26$, $t(29) = -1.45$, $p = .16$. The effect of expressive symptoms on functioning was significant, $\beta = .21$, Bootstrap SE = 0.12, BCa CI [0.023, 0.478], indicating that expressive symptoms had an indirect effect on the relationship between physical hard choices and functioning.

Discussion: This study is the first to investigate the indirect effects of motivation on the relationships between effort expenditure and functioning in psychosis. In sum, the lower the proportion of cognitive hard choices made by patients, the higher the severity of motivation/pleasure symptoms, which in turn was associated with poorer life functioning. Regarding physical effort, patients who made fewer choices to expend physical effort, and had a higher severity of expressive symptoms, had poorer life functioning. Ultimately, our work developing a model of functioning that considers cognition and motivation to expend effort is necessary to inform the development of interventions to prevent the burden of functional impairment in psychosis.

S14. THE EFFECT OF CANNABIS DISCONTINUATION ON COGNITION IN FIRST EPISODE PSYCHOSIS: A ONE-YEAR LONGITUDINAL STUDY

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Background: There is a high prevalence of cannabis use in First Episode Psychosis subjects (FEP) with rates ranging from 30 to 50%. The relationship between cannabis use and neurocognitive functioning in FEP has yielded conflicting findings. Moreover, there is a scarcity of short and long-term studies aiming to investigate the effect of cannabis discontinuation on cognitive functioning in subjects at early stages of psychotic disorder.

Methods: We aim to determine whether one –year neurocognitive outcomes differ between first Episode Psychosis subjects (FEP) who continued (CU) or discontinued (CU) using cannabis defined as “at least once a week

This is a naturalistic observational12 months follow-up study aiming to investigate the effect of cannabis discontinuation on cognitive functioning in subjects in their first episode of psychosis including 156 FEP admitted to an outpatient early intervention service (EIP) of University Hospital Institut Pere Mata at Reus, Tarragona. Subjects underwent to complete clinical assessment and were asked for their frequency of cannabis use during the 3 months previous psychosis onset and at one year of follow up. To assess cognitive functioning the MATRICS Consensus Cognitive Battery (MCCB) was performed at baseline (T0) and at one year of follow-up (T1).

Sociodemographic , clinical and cognitive differences at T0 between users and non-users were compared. At T1 participants were grouped depending on their pattern of cannabis use at T1: "non-users (CNU), continuers or discontinuers". A repeated analysis of covariance (ANCOVAr) was performed for each clinical and cognitive domain as the within-subject factor (T0 and T1). Main effects of time and time by group interaction were analyzed. Results: were adjusted for gender differences

Results: Nearly 40% of FEPs were regular CU at T0. CU were more frequently men and performed significantly better in executive function domain than CNU. No differences were found in the severity of clinical variables.
At T1 nearly 47 % of CU discontinued cannabis. When the three groups: (non-users (CNU), continuers and discontinuers) were compared, there was a significant improvement in all cognitive domains over the time (main effect of time). A time by group interaction was observed in attention-vigilance domain ($F=3.08$, $p= 0.05$) and in the global index score ($F=3.40$, $p=0.03$). To determine the nature of these interactions, the sample was stratified by groups and controlled for gender differences. Both CNU and discontinuers significantly improved in attention- vigilance domain and in the global index score, while continuers did not.

Discussion: Our esults indicate that discontinuing cannabis improves some cognitive domains FEP one year after the psychosis onset. Cannabis reduction and cessation must be a crucial intervention to improve cognitive outcomes in psychosis.

S15. DIFFERENT ASPECTS OF RESILIENCE MODERATE THE EFFECT OF RISK ON SYMPTOMATOLOGY AND OF SYMPTOMATOLOGY ON PSYCHOSOCIAL FUNCTIONING WITHIN THE PSYCHOSIS CONTINUUM

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Background: Resilience is a key moderator of individual outcomes in severe mental illness such as psychosis. It has been suggested that resilience may alleviate the negative influence of adverse factors such as childhood trauma and thus help to protect against the development of psychopathology or worsening of symptoms.
Moreover, resilience may help to promote recovery and high psychosocial functioning levels independent of symptomatology. However, as most studies pursue a rather reductionist approach

focusing only on single aspects, the role of resilience in the complex interplay of the concepts of risk, symptomatology and psychosocial functioning within the heterogenous psychosis continuum is not well-understood.

Therefore, the aim of this study is to investigate the psychological concepts of resilience, risk, symptomatology, and functioning from an integrated view. A profound understanding of their cohesion, divergence and underlying mechanisms might inform prevention and intervention targeting these components.

Methods: PRONIA ('Personalized Prognostic Tools for Early Psychosis Management') is naturalistic longitudinal multicenter study funded by the European Union (grant agreement n° 602152). 10 university centers in five European countries participated in the evaluation of three clinical groups (individuals clinically at high risk of developing psychosis [CHR], patients with recent onset psychosis [ROP] and patients with recent onset depression [ROD]) as well as healthy controls.
In the current study, we analysed data of N = 1002 ROP, CHR and ROD patients and a wide spectrum of symptoms representing psychosis psychopathology. Overall severity of symptoms was assessed using a measure derived from the 'Global Assessment of Functioning' Scale (GAF-S). Functioning was measured using the 'Global Functioning: Social and Role' Scales (GF S/R) and the psychological risk factor of childhood trauma by the 'Childhood Trauma Questionnaire' (CTQ). Finally, we applied the 'Resilience Scale for Adults' (RSA) to measure personal and inter-personal resilience factors.

First, we conducted an explorative network analysis determining associations between two factors accounting for the effect of all other included components. Second, we analysed residuals of regression analysis predicting GF based on GAF as well as residuals of regression analysis predicting GAF based on CTQ. We tested correlation of the two sets of residuals to each other as well as to different RSA subscales.

Results: Network analysis revealed that the effect of childhood trauma on psychosocial functioning is mediated by resilience and symptomatology whereas childhood trauma affects symptomatology directly. No direct association was found between resilience and symptomatology. Resulting residuals from regression analyses between concepts were not correlated to each other. Accordingly, the two types of residuals were associated with different aspects of resilience.
Discussion: Our study sheds light on the role of resilience in the complex interplay of risk, symptomatology and psychosocial functioning. Results: indicate that different aspects of resilience seem to moderate the effect of risk on symptomatology and the effect of symptomatology on psychosocial functioning. These essential insights might help to maximize the potential of resilience for prevention and intervention of psychotic disorders. So far, the potential of resilience is not yet fully exploited as mental health care has been pursuing a rather symptom-oriented than resource-oriented focus.

S16. TRAIT ANHEDONIA IN SCHIZOPHRENIA: A SYSTEMATIC REVIEW AND COMPARATIVE META-ANALYSIS

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Background: Anhedonia, the reduced capacity to experience pleasure, has long been considered a prominent feature of schizophrenia spectrum disorders. Many domain-specific conceptualizations of anhedonia and pleasure capacity have been developed, and there currently exist a variety of self-report assessment tools that purport to assess these various domains. The current systematic review and meta-analysis (PROSPERO: CRD42020156169) aimed to quantify overall and domain-specific self-reported anhedonia in people with schizophrenia compared to non-psychiatric controls.
Methods: We performed a literature search of PsycINFO, MEDLINE and Embase databases for dissertations and peer-reviewed articles published in English prior to June 2021. Studies employing a psychometrically validated self-report measure of anhedonia, pleasure experience, or affect in people with schizophrenia, schizoaffective, or schizophreniform disorders; studies utilizing at least one clearly defined healthy or community control group for comparison; and studies providing sufficient data to calculate effect sizes were included in this review. Random and mixed effects meta-analyses, meta-regressions, and subgroup comparisons were run across domains of anhedonia to explore weighted mean effect sizes and their associated moderators.
Results: In total, 146 studies met inclusion criteria, yielding 390 Hedges' g effect sizes from the included comparisons. People with schizophrenia reported moderate-to-large elevations in overall and domain-specific anhedonia. A sensitivity analysis accounting for high risk of bias studies did not significantly impact results. Lastly, patient sex, education, negative symptom severity, antipsychotic class, and trait negative affect differentially moderated effect sizes across domains of anhedonia.
Discussion: Self-reported anhedonia is ubiquitously reported across trait measures in people with schizophrenia. Given the heterogeneity inherent in schizophrenia spectrum disorders, the consistent finding of self-reported anhedonia across the reviewed measures, and the differential impact of moderator variables across domains, there appear to be several pathways to elevated trait anhedonia scores in people with schizophrenia.

S17. TRUST AND PSYCHOSIS- A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Impaired trust in other humans is commonly seen in psychosis. Both paranoia and impairments in social cognitive function are proposed as the underlying pathogenic mechanism. Importantly, trust deficits lead to poor societal functioning. However, measurement of trust is difficult in experimental settings as the interactive nature of human interaction is critical for the measurement of trust. The use of neuro-economic games has allowed investigators to assess complex social interactions through experimental designs. The Trust game has been used widely to analyze individuals' ability to trust and their trustworthiness. However, the Results: of

individual studies are varied and inconclusive. Hence, we systematically reviewed the existing literature and conducted this meta-analysis to compile the existing literature in psychosis. We aimed to examine (a) whether patients with psychosis have trust deficits compared to healthy controls (b) to analyze the factors affecting trust deficits (c) whether relatives of patients with psychosis and those at high risk for psychosis also have impairments in trust.

Methods: We searched Cochrane Library, PubMed, and google scholar databases for English language studies that have examined trust in psychotic patients using the trust game, published up to November 2021. The primary outcome measures were the baseline money invested in a trust game by patients and controls. The meta-analysis was performed if at least 3 data sets of control and patient groups were available for that measure/design. We did the meta-analyses with a random-effects model to calculate standardized mean differences with 95% CIs. The Results: are described narratively wherever meta-analysis was not possible. Assessment of heterogeneity was done using I2 scores. Sensitivity analysis was done using leave-one-out analysis and publication bias was evaluated using Egger's test.

Results: The searches across the databases including cross-references yielded 465 publications of which 11 studies were included in the final analysis. The data from the 11 studies yielded 6 data sets to assess baseline trust in psychotic patients and 3 sets each to assess baseline trust in relatives of patients with psychosis and trust in co-operative and unfair contexts. Egger's test showed no significant publication bias for all comparisons. Baseline trust was significantly higher in controls (n=272) compared to patients with psychosis (n=183) (SMD- 0.39, 95% CI (0.14-0.64), P-0.002, I2 -35%). Sensitivity analysis by leave-one-out analysis revealed that none of the studies significantly influenced the summary effect size. On leaving out a study that had an exclusive adolescent sample, the psychosis group continued to have lower trust (SMD- 0.42, 95% CI (0.10-0.74), P-0.01, I2- 47%). Two studies had exclusive schizophrenia samples, but they did not show a significant difference in baseline trust. Two studies found that CHR individuals had significantly lower baseline trust compared to controls but were not significantly different compared to patients with psychosis. No significant difference in baseline trust was found between the healthy relatives of patients with psychosis and controls (SMD- 0.08, 95% CI (-0.20 to 0.36), P-0.58,I2=0). Patients with psychosis(n=53) showed lower trust compared to controls (n=70) in a 'co-operative' context (SMD- 0.56, 95% CI (0.01 to 1.12), P-0.05,I2=54%).But there was no significant difference between the trust shown by patients with psychosis or controls in an ' uncooperative' context (SMD- -0.10, 95% CI (-0.46 to 0.26), P-0.59,I2=0).

Discussion: The current meta-analysis suggests significant trust deficits in patients with psychosis, while also revealing impairments in the ability to learn to trust in relation to contexts.A major limitation of the current meta-analysis is the limited number of studies. As the number of studies was less than 10, we could not do a meta-regression to examine the relationship between symptom scores and trust behaviour. Considering the importance of trust behavior in day-to-day activities, impaired trust can considerably affect the social functioning and reintegration of patients with psychosis. Future studies with a bigger sample size are required to understand the nature of trust deficits and factors affecting this impairment.

S18. PREDICTORS OF EFFECTIVE GOAL MANAGEMENT TRAINING IN SCHIZOPHRENIA SPECTRUM DISORDERS AND PSYCHOSIS RISK SYNDROMES

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Background: Executive function (EF) is the most consistently impaired cognitive domain in schizophrenia and impairments are present prior to development of psychotic symptoms. Hence, impairment in EF is an important treatment target among persons with schizophrenia spectrum disorders and psychosis risk syndromes. EF encompasses higher-order mental processes involving top-down control of cognition, emotion and behavior necessary for goal-directed behavior, and is associated with important life outcomes such as health, education, and work.
Preliminary Results: from a randomized, controlled trial of the strategy training Goal Management Training (GMT) administered in an early-intervention for psychosis setting, showed improved self-reported EF in everyday situations following intervention. For more than half the participants that received GMT the improvement was a clinically reliable change. Since this was the first trial of GMT as a stand-alone intervention for executive dysfunction in this patient population, it is important to investigate who benefited the most from the intervention. An added challenge for clinicians and patients in choosing cognitive remediation is that there is often considerable discrepancy between subjective and objective measures of EF in clinical and healthy samples. Even though several studies have shown that the discrepancy between subjective and objective cognition is larger among persons with schizophrenia than in healthy controls, less is known about possible consequences of the discrepancy for cognitive remediation.

The present study investigated if the effect of GMT on subjective EF in individuals with either schizophrenia spectrum disorders or psychosis risk syndromes was dependent on subjective and objective EF at baseline. Furthermore, the study investigated if discrepancy between subjective and objective measures predicted effect of GMT.

Methods: Baseline scores from eighty-one participants (GMT n = 39 versus Waiting list control group n = 42) on the self-reported questionnaire Behavior Rating Inventory of Executive Function – Adult version (BRIEF-A) and neuropsychological tests of inhibition, shifting and working memory, as well as discrepancy scores between subjective and objective measures, were entered as predictors in a linear mixed model analysis for repeated measures. The outcome variable was change in subjective EF immediately after GMT and six months after intervention.
Results: The effect of GMT remained significant regardless of the discrepancy between subjective and objective measures. Greater subjective complaints at baseline predicted greater improvement after GMT, but the effect of GMT remained significant regardless of subjective and objective EF at baseline.
Discussion: Neither subjective nor objective EF at baseline were obstacles to successful strategy training using GMT. Previous research has noted concern over the discrepancy in objective and subjective measures of cognition and possible negative implications for cognitive remediation. However, the Results: of the present study indicate that clinicians may recommend GMT to persons with schizophrenia spectrum disorders or psychosis risk syndromes regardless of contradicting patterns of scores on subjective self-reports and neuropsychological tests of EF.

S19. DOES INDIVIDUALS WITH SCHIZOPHRENIA PRESENT A BIAS FOR NEGATIVE CONTEXTUAL INFORMATION WHEN ATTRIBUTING MENTAL STATES?

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Background: Impaired context processing is an important feature of schizophrenia (SZ) (Cohen and Servan-Schreiber, 1992; Green et al., 2005). It has been suggested to underlie impairments in theory of mind ability (ToM), i.e., the ability to attribute mental states such as intention, thought, belief to others (Hardy-Bayle et al., 2003; Champagne-Lavau et al., 2012). Different types of contextual information (e.g., contextual incongruity, stereotypes on a speaker) are not integrated in the same way by SZ individuals when they attribute mental states to a speaker (Champagne-Lavau et al., 2012; Champagne-Lavau and Charest, 2015). In addition, SZ individuals have been shown to present an attentional bias for negative information (Strauss et al., 2008; Demily et al., 2010). Thus, the aim of this study was to determine how the processing of contextual information influences ToM abilities in schizophrenia using a task of humor processing. More specifically, the objective was to investigate whether SZ individuals present an attentional bias for information with negative characteristics and for irrelevant information, leading them to misinterpret humor.
Methods: Ten individuals with a DSM-V diagnosis of schizophrenia and 30 healthy control (HC) participants matched for age and educational level were tested on their ToM ability using a task of humor processing with a verbal (story) and a visual (drawing) conditions. All participants were native French-speakers with no previous neurological history. Participants were asked to choose among four possibilities the appropriate punchline to make the stories or drawings funny. To test the existence of a possible bias for negative cues and for irrelevant information in schizophrenia, the response choice included a correct punchline, an incongruous punchline, a neutral punchline and an emotionally negative punchline. Participants were also submitted to a classical ToM task (CIT: Characters Intention Task, Sarfati et al., 1997), a neuropsychological evaluation (e.g., memory, flexibility, attention) and an emotional Stroop test (Demily et al., 2010) to look for emotional bias.
Results: Non-parametric analyses were performed on the percentage of responses. Mains Results: showed that SZ participants choose less often the correct punchline than HC participants in the verbal condition ($U = 81$; $p < .031$) and in the visual condition ($U = 69$; $p < .01$). Analyses of the errors revealed that SZ participants choose more often the emotionally negative punchline than HC participants ($U = 216$; $p < .039$) in the verbal condition while they choose more often the neutral punchline in the visual condition ($U = 218.5$; $p < .031$). Spearman correlations were found between performances on the humor task and the classical ToM task (verbal: $p < .039$; visual: $p < .044$) and flexibility test (verbal: $p < .019$; visual: $p < .001$) in both conditions. Interestingly, emotional choices (in both verbal and visual condition) were associated to a negative bias measured by the emotional Stroop (verbal: $p < .030$; visual: $p < .039$) and an attentional deficit (verbal: $p < .037$; visual: $p < .037$) in the SZ group.
Discussion: These Results: confirmed the SZ participants' impairments in ToM measured by humor processing and classical tasks (Corcoran et al., 1997; Marjoram et al., 2006). In the present study, such pattern of performance seemed to be linked to an attentional bias for information with negative characteristics leading SZ participants to misattribute mental states in the verbal

condition. Such result is also in line with the literature showing an attentional bias for negative cues in schizophrenia (Mitchell and Rossell, 2014). The sample should be increased to confirm these findings.

S20. THE ASSOCIATION BETWEEN FACIAL EMOTION RECOGNITION AND NEGATIVE SYMPTOM DOMAINS IN INDIVIDUALS WITH SCHIZOPHRENIA SPECTRUM DISORDERS

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Background: Research suggests that emotion recognition can be significantly impaired in individuals with a schizophrenia spectrum disorder (SSD). Hereby the presence of negative symptoms is theorized to play a crucial role. Facial emotion recognition deficits are assumed to be predictors of transition from clinical high risk to a schizophrenia spectrum disorder. So far, little attention has been given to the association of the subdomains of negative symptoms with the recognition of the particular basic emotions. The present study aimed to explore the relationship between the severity of each negative symptom domain and the ability to recognize the basic emotions.
Methods: A cohort of 66 individuals with a diagnosis of SSD was recruited at the Charité – Universitätsmedizin Berlin. Correlational and regression analyzes were conducted between the recognition of the basic emotions anger, disgust, fear, happiness, sadness and surprise using the tablet-based Emotion Recognition Task of the Cambridge Neuropsychological Test Automated Battery (CANTAB) and the different subdomains of negative symptoms via the rater-based Positive and Negative Syndrome Scale (PANSS). Analyzes were controlled for the covariates age, education and gender.
Results: Results: revealed that higher scores in blunted affect (N1) show a significant negative correlation with the performance in emotion recognition and in particular in recognizing happiness, disgust and fear. Difficulties in abstract thinking (N5) showed a negative correlation with the recognition of fear. Additionally, it was found that stereotyped thinking (N7) and difficulties in abstract thinking (N5) are significantly positive correlated with a higher response latency for participants in emotion recognition. After controlling for the covariates only the significant negative correlation of blunted affect (N1) with the recognition of happiness and the positive correlation of stereotyped thinking (N7) with response latency were left. The covariates age and education explained the majority of the effects.
Discussion: Individuals with SSD and high scores in the negative symptom domains blunted affect (N1) and stereotyped thinking (N7) showed impairments in recognizing basic emotions and in particular happiness. Conclusively impairments recognized in the subdomains of negative symptoms should be considered in individualized treatment approaches. Moreover, emotion recognition should be considered for early detection in the clinically high-risk population for psychosis. It would be also helpful for further studies to compare different measuring instruments used for emotion recognition and the symptom subdomains. For future research a longitudinal

design with network analysis would be useful to make causality statements regarding the associations investigated in our study.

S21. THE VIA FAMILY STUDY – AN INTEGRATED, SPECIALIZED AND FAMILY-BASED INTERVENTION FOR CHILDREN BORN TO PARENTS WITH SEVERE MENTAL ILLNESS

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Background: Children born to parents with severe mental illness have a well-documented increased risk of developing a mental illness themselves. They have a higher frequency of neurocognitive and motor impairments as well asemotional and behavioral problems already during childhood and are at same time a higher risk of growing up under adverse circumstances. An early, preventive strategy focusing on the entire family (a holistic approach) and the child's specific needs is often suggested but still lacking. Although many interventions have been tested and seem promising, evidence still needs to be developed. We hypothesized that by providing a flexible and tailormade and multidisciplinary intervention to each family based on their motivation and needs, the level of daily functioning of the child as well as the family would increase.

Methods:

A randomized controlled study, The VIA Family Study was carried out in a selected area of Copenhagen, Denmark. Families with at least one child between age 6 and age 12 were included in the study and randomized to either VIA Family Team Intervention or treatment as usual (TAU). At least one of the parents have been diagnosed with a severe mental illness (schizophrenia spectrum disorder, bipolar disorder or recurrent major depression) within the child's lifetime. Although outcome measures focused on the children between 6 and 12 years old, all family members were offered to participate in the intervention.

The families, who received the VIA Family team intervention were assigned to a multidisciplinary team consisting of a child- and adolescent psychiatrist, a psychologist, a nurse from adult psychiatry, a social worker and a family counsellor both from the social sector. The team offered the families a manual-based psycho educational course, parental training (Triple P) and chlidren's and parents' groups (that took place simultaneously) and all families had a case manager who they could turn to in all kinds of matters. The intervention lasted 18 months. Primary outcome measure was level of daily functioning of the child, while parental functioning and family function were secondary outcome measures along with quality of the home environment, parental stress and satisfaction with treatment. Data were supplemented with qualitative data concerning acceptability of the VIA Family treatment and the participant's perceptions of the idea of offering prevention in families with parental mental illness.

Results: A total of 92 families (including 114 children between 6 and 12 years of age) were randomized after baseline assessment and were all followed up and reassessed by blinded assessors after 18 months of intervention. The families in the intervention group received a variety of treatment elements, and of 47 families 42 families fulfilled criteria for receiving the intended multidisciplinary team intervention. Analysis are ongoing and will be presented, preliminary Results: showed no differences in child's daily functioning or parental functioning. However, we found a trend towards reduced levels of parental stress in the intervention group and a significant improvement of the level of support and stimulation in the home environment in the intervention group.
Discussion: Results and perspectives for future interventions will be discussed. Overall, the flexible and tailormade intervention model seemed to be highly acceptable and relevant for most families and Results: about the home environment are promising.

S22. DOPAMINE NEURON-SPECIFIC MANIPULATION OF GLUN2A RESULTS: IN DISTORTED SALIENCE ATTRIBUTION AND PSYCHOSTIMULANT SENSITIVITY IN ADOLESCENT RATS

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Background: NMDA receptor dysfunction has long been implicated in the etiology of schizophrenia and several other neurodevelopmental disorders. Recent whole exome/genome sequencing studies have further associated variants in the gene encoding the GluN2A subunit of the NMDA receptor (GRIN2A) with schizophrenia diagnosis. Critically, levels of this subunit are developmentally regulated and undergo changes in adolescence through early adulthood, when symptoms of schizophrenia typically manifest. We have found the key brain regions where GluN2A expression changes during adolescence are the dopamine neuron-containing ventral tegmental area (VTA) and substantia nigra (SN). Given that midbrain dopamine neurons have been historically implicated in the pathophysiology of schizophrenia, we sought to determine the effect of a dopamine cell-specific disruption of GluN2A during adolescence on behaviors and related functions relevant to symptoms of schizophrenia.
Methods: Cre-dependent CRISPR/SaCas9 viruses for Grin2a (cKO) or Rosa26 (control) were injected in the VTA of Th:Cre male and female rats after weaning. Adolescent animals were tested on a battery of behavioral tasks and for sensitivity to psychostimulants. Postmortem tissue was analyzed by immunohistochemistry or western blotting.
Results: Intra-VTA viral infusion led to a significant reduction of GluN2A in the VTA with IHC showing dopamine neuron-specific virus expression. The cKO animals were seemingly normal and did not show differences, as compared to controls, in spontaneous motor behavior in the open field or simple action-outcome associative learning. Differences were observed, however, in more complex paradigms such as the progressive ratio schedule of reinforcement and an appetitive-aversive cue reversal task with cKO animals showing disruptions that were indicative of distorted salience attribution. Additionally, we observed sex-specific effects of propsychotic drugs with the NMDAR antagonist MK801 producing an exaggerated response selectively in GluN2A cKO females.

Discussion: While further characterization is necessary, our Results: suggest that selective manipulation of the GluN2A subunit in adolescent dopamine neurons may provide a useful model for some aspects of genetic vulnerability to schizophrenia.

S23. THE IMPACT ON THE NEWBORN NEURODEVELOPMENT OF PRENATAL EXPOSURE TO SARS-COV-2 AND MATERNAL EMOTIONAL STRESS DURING THE COVID-19 PANDEMIC: PRESENTING THE SIGNATURE PROJECT

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Background: The COVID-19 pandemic, paradoxically, represents a valuable opportunity to carry out birth cohort studies of SARS-CoV-2 infected pregnancies that would allow us to advance the knowledge about the relationship between inflammation, brain development and the increased risk of suffering from neuropsychiatric disorders. In addition, the current availability of sophisticated biological techniques and evaluation procedures represents an unique opportunity for this purpose. Here, we present an ongoing birth cohort study of COVID-19–infected and uninfected pregnant women. Our main objective is to explore whether the presence of maternal SARS-CoV-2 infection and emotional distress during the pandemic would generate anomalous immune-inflammatory response in the offspring, which might jeopardize normal brain development and increase the likelihood of neurodevelopmental delays.

Methods: A prospective cohort study of SARS-CoV-2 infected and uninfected pregnant women and their infants is being conducted at Hospital Universitario Virgen del Rocío and the Instituto de Biomedicina de Sevilla (IBiS). The core variable of the study is the clinical and immunological characterisation of the newborns of COVID-19–infected (stratified by gestational trimester of infection) and unaffected mothers, with immunological, anthropometric, and neurodevelopmental evaluations at birth and at 12 months of age. To that end, longitudinal clinical and biological data of pregnant women and their newborns is being collected thoroughly, including structured obstetric records and ultrasonography images, complications during pregnancy, delivery and the neonatal period, blood biomarkers, hair samples, embryonic cells from umbilical cord and placenta, and standardized neurodevelopmental assessments of the child during the first year of life. In addition, the role of maternal stress during the COVID-19 pandemic in the development of offspring brain and behavior is being examined through interviews, scales and questionnaires. Statistical analysis will be conducted in accordance with the predefined statistical analysis plan. The study is approved by the local ethic committee and is funded by the Andalusia Regional

Government (Andalusian Program for Research, Development, and Innovation 2021) and the European Regional Development Fund (FEDER).
Results: The study is currently open to enrollment with the first case entered in August 2021. To date (7 December 2021) we have recruited 36 COVID-19–infected and 15 unaffected pregnant women. It is expected to enroll a total of 90 mothers in each cohort, equally distributed among first, second, and third trimester pregnancies.
Discussion: The present study is designed to test the following research hypotheses: (1) the group of newborns of mothers infected by SARS-CoV-2 will present biological markers suggestive of having an abnormal inflammatory state; (2) such inflammatory alterations in newborns would be related to clinical variables such as the time (gestational age) of maternal infection and its severity, as well as the degree of prenatal maternal stress during the COVID-19 pandemic; and (3) these alterations in fetal and perinatal inflammatory states would be associated with abnormal neurodevelopmental outcomes in the newborns, which may increase the later neuropsychiatric disorder risk, particularly that of autism spectrum disorders and schizophrenia. Since large sample sizes are usually needed to validate hypotheses and other groups are now conducting similar initiatives to us, we would like to make a call for collaborative research in order to homogenize data collection, procedures and outcomes.

S24. RECRUITMENT CHALLENGES: EXPERIENCES FROM THE CLINICAL TRIAL CHALLENGE

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Background: Recruitment and retention of patients in clinical, psychiatric research are often challenging. Although psychiatric patients seem to hold a rather positive view on research, researchers are often reliant on clinicians for referrals. Several studies have suggested that staff is the gatekeepers of recruitment and that various barriers can keep them from referring patients. Recruitment can make or break a study: Delays are costly, and the overall goals may become impossible to reach. Taking these points into account, we implemented several initiatives to improve the recruitment process during the initiation of the CHALLENGE trial. CHALLENGE is a randomized, multicenter, controlled trial investigating the effect of virtual reality assisted psychotherapy on treatment resistant voice hearing in patients diagnosed with schizophrenia spectrum disorders. Due to the novelty and confronting nature of the intervention, we expected that motivating recruitment strategies aimed at referrers would be vital for the study to recruit 266 participants.
Methods: Several initiatives were taken to enhance recruitment. Prior to recruitment, a survey was conducted among referrers screening for knowledge about, expectations to and attitudes toward the trial (baseline). Afterwards, information meetings were held for referrers and they were given the possibility of trying out the equipment and intervention. One month after initiation of the trial, the survey was repeated as to detect possible changes in attitudes (follow-up). Furthermore, in the

first year of recruitment additional initiatives were implemented to accommodate feedback given by clinicians and increase recruitment. Initiatives included enhancing personal contact between researchers and referrers; establishing an informative website and an easy electronical referral link; use of recruitment leaflets and posters aimed at patients and caregivers in the clinic; appointing "research ambassadors" at the recruitment site; treating referrers with cakes and candies; and increasing press coverage.
Results: In the survey, 85 participated at baseline and 79 at follow-up (26.3% of these were not part of the baseline survey). Staff attitudes were neutral to positive in the survey at baseline, and at follow-up 32% had an increase in positive expectations and no one reported a change towards negative expectations. At follow-up, 62% reported that they would introduce the trial to all patients meeting inclusion criteria, and 25% would only introduce the trial to patients they expected would benefit from the treatment. Insufficient knowledge of the trial was noted for 8% who were unsure if they would refer patients.
Discussion: After one year of recruitment, fewer patients than expected were recruited. Based on our survey and experiences, this was mostly due to clinicians' 1) forgetting to introduce the trial, 2) uncertainty and/or insufficient information, 3) wanting to protect the patients. Furthermore, easy procedures for referral were paramount and being introduced to the study by a research assistant improved the chances of successful recruitment. It is expected that the new initiatives described in the method section will be effective in overcoming these barriers and thus improving recruitment. Recruitment is a difficult process with several barriers. Based on our experiences from CHALLENGE, our recommendation is to use several diverse strategies and to establish and maintain a continuous collaboration with referrers. Specifically, installing a sense of co-ownership of the trail and making the research project an integrated part of the clinician's work environment seems vital.

S25. DIFFERENTIAL EFFECTS OF ARIPIPRAZOLE AND AMISULPRIDE ON NEGATIVE AND COGNITIVE SYMPTOMS IN PATIENTS WITH FIRST EPISODE PSYCHOSIS

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Background: The neurobiological underpinnings of negative symptoms and cognitive impairments have been associated with disturbances in cerebral networks and are suggested to be related to a hypodopaminergic function in prefrontal cortex. Aripiprazole is a partial dopamine D2 receptor agonist and is therefore suggested to improve negative symptoms and cognitive functions in schizophrenia. Amisulpride is a second-generation antipsychotic, but because of affinity to presynaptic D1 receptors in striatum, an effect on negative symptoms when given in doses below 300 mg has been suggested. Both compounds are recommended as first line treatment in patients with first episode psychoses. In the present study comprising two consecutive cohorts of initially antipsychotic-naïve patients with first episode psychoses, we compare the effect of six weeks monotherapy with aripiprazole and amisulpride, respectively, on negative symptoms and cognitive functions.
Methods: Antipsychotic-naïve patients with first episode psychosis were examined before and after six weeks of antipsychotic monotherapy with either aripiprazole or amisulpride. Psychopathology was measured using the Positive and Negative Syndrome Scale (PANSS) and the negative symptom dimension described by Wallwork recommended for first episode patients was used as primary outcome. Cognitive functions were measured using the Brief Assessment of Cognition in Schizophrenia (BACS) and the Cambridge Neuropsychological Test Automated Battery (CANTAB) and defined as secondary outcomes. To account for retest effect, the cognitive outcomes were z-normalized using means and standard deviations from matched healthy controls tested at the same timepoints. Analyses of variance (Repeated measures ANOVA) were performed to detect effect of time and possible cohort*time interactions.
Results: Longitudinal six week data were obtained from 47 patients (20 females, age 24.5 ± 6 years) treated with amisulpride (mean dose 276 ± 173 mg), and 48 patients (24 females, age 22.9 ± 4) treated with aripiprazole (mean dose 10 ± 4.7 mg). In both cohorts, patients improved significantly in PANSS total, positive, and general score (all p-values <.001). For the Wallwork negative symptom dimension, there was a cohort*time interaction ($F_{1,93}=4.29$, $p=.041$) and a significant effect of time ($F_{1,93}=6.033$, $p=.016$), which was driven by an improvement in patients treated with aripiprazole ($t_{47}=4.1$, $p<.001$), and not observed in patients treated with amisulpride ($p>.5$). For the eight selected cognitive functions, no cohort*time interaction was found, thus we found no superior improvement in any of the cognitive measures in patients treated with aripiprazole when accounting for retest effect.
Discussion: In the present analyses on patients with first episode psychoses who had not previously been treated with antipsychotic medication, we found a small but significant decrease in negative symptoms in patients treated with aripiprazole but not in patients treated with amisulpride. This support the notion that third generation antipsychotic compounds due to their partiel dopamine receptor agonism may be supperior for the treatment of negative symptoms. We found no indication of a superior effect on cognitive functions, thus Results: from previous studies pointing to an effect of aripiprazole on cognitive functions may have been biased by retest effects.

S26. A PHASE 3 PLACEBO-CONTROLLED STUDY EVALUATING THE SAFETY AND EFFICACY OF ADJUNCTIVE KARXT IN PATIENTS WITH INADEQUATELY CONTROLLED SCHIZOPHRENIA SYMPTOMS: CLINICAL RATIONALE AND DESIGN (ARISE STUDY)

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Background: Schizophrenia is a complex, chronic disorder that likely has many causes, but current pharmacologic therapies all continue to share direct affinity for the dopamine D2 receptor. A significant unmet medical need remains, given the well-known efficacy and tolerability limitations of current therapies, and has served as the impetus for searching for effective pharmacologic treatments that are devoid of any direct effects on dopamine receptors. One such approach is through central muscarinic receptors that are involved in acetylcholine-mediated regulation of key neural circuits implicated in schizophrenia.
KarXT is an investigational antipsychotic that is an M1/M4–preferring muscarinic receptor agonist. KarXT recently entered phase 3 development as monotherapy for treatment of schizophrenia after showing efficacy and tolerability in a phase 2 study. In addition to monotherapy KarXT studies, here we describe an adjunctive study where the goal is to assess adding KarXT to a current antipsychotic regimen when there continues to be inadequate response. KarXT has a different mechanism of action than all currently approved antipsychotics, and adjunctive KarXT may be one approach to improve clinical response over that achieved with currently available antipsychotics. Preclinical behavior models predicting antipsychotic activity show that xanomeline can augment antipsychotic activity of current D2-receptor antipsychotics. At present, there are no treatments approved in the United States for adjunctive treatment of schizophrenia.

Methods: ARISE is a 6-week, phase 3, randomized, double-blind, placebo-controlled, multicenter outpatient study in up to 400 adult patients with a primary diagnosis of schizophrenia who have demonstrated an inadequate response to a therapeutic regimen of selected first-line (eg, non-clozapine) atypical antipsychotic treatments. Eligible patients must have received and taken therapeutic doses for ≥8 weeks of one of the first-line atypical antipsychotics aripiprazole, lurasidone, paliperidone, quetiapine, risperidone, or ziprasidone and, despite this, continued to experience clinically relevant positive symptoms. The study includes a 5-week screening period, 6-week double-blind treatment period, and safety follow-up visit at the end of week 7. Based on individual tolerability and clinical response, KarXT will be flexibly dosed (mg xanomeline/mg trospium) between 75 mg/20 mg twice daily and 125 mg/30 mg twice daily vs matched placebo twice daily. The primary endpoint is the change from baseline in Positive and Negative Syndrome Scale total score at week 6 vs placebo. They key secondary endpoint is change from baseline in Personal and Social Performance Scale at week 6. Standard safety and tolerability assessments will be collected.

Results: This is a double-blind study for which Results: are not yet available. During the conference, we will present the rationale and study design. Recruitment has been initiated, and an update will be provided.

Discussion: To date, there have been no successful, fully powered, registrational, adjunctive treatment studies of patients with schizophrenia who have inadequate control of their symptoms with antipsychotic treatment. KarXT has a different mechanism of action (ie, muscarinic agonism) from any currently approved treatments and has demonstrated efficacy in a phase 2, inpatient, monotherapy efficacy study, suggesting that adjunctive KarXT has a reasonable probability of success as a treatment. The presentation will describe some of the clinical trial design features that could enhance the probability of success in the ARISE study.

S27. ATHENS MULTIFAMILY THERAPY AFTER A FIRST PSYCHOTIC EPISODE: ONLINE THERAPY DURING THE COVID-19 PANDEMIC

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Background: The Athens Multifamily Therapy Project (A- MFTP) aims to provide systemic multifamily group therapy to youths who experienced a first psychotic episode (FEP) and their families.
Methods: Since 2017, we run five groups of five-four families, with a duration of ten months and frequency every two weeks. Participants were recruited from the longitudinal study, Athens FEP Project, which aimed to investigate the involvement of genetic and environmental determinants on psychosis risk. During the Covid-19 pandemic, the provision of therapy to the current groups continued through online sessions. The psychopathology of each patient was measured with large battery of scales and family members filled Score 15 and RFQ 54.
Results: Participants were asked to answer qualitative questions on the perceived effectiveness of the therapy on their life as well as on the presenting problem(s) at three time points: middle, end of therapy and 6-month follow-up. All members highlighted the significance of the reciprocity in the group communication. They mentioned that "sharing" and "exchanging" experiences helped them listen to others and felt heard by them. They moved from feeling fear and embarrassment when discussing the diagnosis and the aftermath, to feeling safety and comfort talking about their difficulties.
Discussion: Qualitative analysis showed no difference in participants' perception of multifamily therapy as helpful between live therapy and online therapy. Results: suggest that MFT can be a viable way to provide early intervention in FEP even in at online modality

S28. IMPAIRED AND INTACT ASPECTS OF ATTENTIONAL COMPETITION AND PRIORITIZATION DURING VISUAL WORKING MEMORY ENCODING IN SCHIZOPHRENIA

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Background: People with schizophrenia (PSZ) are impaired in the attentional prioritization of non-salient but relevant stimuli over salient but irrelevant distractors during visual working memory (VWM) encoding. Conversely, the guidance of top-down attention by external predictive cues is intact. Yet, it is unknown whether this preserved ability can help PSZ overcome impaired attentional prioritization in the presence of salient distractors.
Methods: We employed a visuospatial change-detection task in 69 PSZ and 74 matched healthy controls (HCS). During the task, four Gabor patches with differing orientations were displayed

during the encoding phase. During encoding, two of the four patches flickered at a frequency of 7.5 Hz. Participants were instructed to focus either on the flickering (salient), or non-flickering (non-salient) patches at the beginning of each block. During retrieval, one patch was shown and participants had to decide if the orientation of the patch in that position was identical to or differed from the patch shown in the same location during encoding. During retrieval, we probed the information stored in working memory in two different ways. In 80% of trials, the patch was displayed at a location participants were instructed to focus on (target trials). In 20% of trials, the patch was displayed at a location participants were not instructed to focus on (catch trials). Before each trial either a predictive cue or a non-predictive cue was presented by briefly turning the fixation cross white. For the predictive cue, the white arms of the fixation cross indicated only the future location of the task relevant patches. For the non-predictive cue, the entire fixation cross turned white providing no location information. This resulted in a 3 x 2 design with the factors salience, cue type, and target type with four conditions; flickering predictive cue, flickering non-predictive cue, non-flickering predictive cue, non-flickering non-predictive cue. Cowan's K was calculated to measure the amount of information stored in working memory. We correlated each individual's effectiveness of attentional prioritization (Cowan's K for target trials minus Cowan's K for catch trials) across all four conditions with an independent estimate of their VWM capacity.
Results: We observed significant effects of group ($F(1,141) = 26.69$, $p < 0.001$), salience ($F(1,141) = 6.81$, $p = 0.010$), trial type ($F(1,141) = 306.68$, $p < 0.001$), trial type * group ($F(1,141) = 7.23$, $p = 0.008$), salience * trial type ($F(1,141) = 4.42$, $p = 0.037$), and cue type * trial type ($F(1,141) = 30.05$, $p < 0.001$). Across all conditions, PSZ stored significantly less information in VWM than HCS in target trials (all $p < 0.001$). There were no significant differences between groups in catch trials. Within target trials, PSZ stored significantly more salient than non-salient information with a non-predictive cue ($t(68) = -6.57$, $p < 0.001$, $d = 0.3$). With a predictive cue, PSZ stored significantly more salient information that with a non-predictive cue ($t(68) = 2.42$, $p = 0.018$, $d = 0.3$). In addition, PSZ stored significantly more non-salient information with the additional help of a predictive cue ($t(68) = 6.68$, $p < 0.001$, $d = 0.3$). Interestingly, HCS also stored significantly more salient that non-salient information with a non-predictive cue ($t(73) = 3.06$, $p = 0.018$, $d = 0.3$). For HCS, WM capacity did not correlate with the effectiveness of attentional prioritization across all conditions (Mean = 3.31, SD = 0.58, rs = 0.16, $p = 0.167$). For PSZ, we observed a significant correlation between WM capacity and the effectiveness of attentional prioritization across all conditions (Mean = 2.91, SD = 0.74, rs = 0.25, $p = 0.038$). However, there was no significant difference between groups across all conditions according to Fisher's r to z transformation ($z = -0.55$, $p = 0.291$).
Discussion: Our findings of impaired working memory capacity in schizophrenia support previous literature. Importantly, our Results: extend previous studies indicating that the top-down utilization of cues is intact in schizophrenia, while bottom-up attentional prioritization appears to be only modestly disrupted. Further, the absence of a difference in performance of catch trials indicates that the up-weighting of prioritization is impaired in schizophrenia, fitting to Results: of gamma oscillation studies. We hope the additional knowledge gained from this study will help improve the understanding of impaired cognitive processes in schizophrenia and further the beneficial potential of cognitive remedies.

S29. HIGH-INTENSITY INTERVAL TRAINING MAY REDUCE DEPRESSIVE SYMPTOMS IN INDIVIDUALS WITH SCHIZOPHRENIA; AN OBSERVER-BLINDED RANDOMIZED CONTROLLED TRIAL

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Background: High-intensity interval training (HIIT) shows several health benefits, thereof anti-depressive effects in individuals with major depressive disorder (MDD). Studies on the efficiency of HIIT in reducing symptoms in schizophrenia are sparse, but promising. This is, to our knowledge, the first observer-blinded parallel group randomized controlled trial to investigate the efficiency of HIIT in reducing psychotic and non-psychotic symptoms in individuals with schizophrenia.

Methods: Eligible for the study were individuals diagnosed with schizophrenia. Participants were recruited from two Norwegian outpatient clinics and randomly allocated to HIIT (n=43) or a comparison group performing computerized sport simulation described as low-intensity activities and aimed to control for time spent and social interaction (active video gaming, AVG, n=39). Both consisted of supervised sessions twice a week for three months, in addition to treatment as usual. Symptoms were blindly assessed at baseline (n=82), post-intervention (n=71) and at four months follow-up (n=57) using the Positive and Negative Syndrome Scale (PANSS, ratio version). Treatment effects on symptoms (overall symptoms and symptom domains differentiated by Wallwork five factor model) were estimated using mixed effects models (intention-to-treat protocol, n=82). Based on existing research across clinical populations, we hypothesized to find a larger reduction in overall symptoms following HIIT, but more specifically that HIIT would reduce depressive symptoms more than AVG.

Results: Preliminary Results: indicate a significant small reduction in overall symptoms at post-intervention and follow-up, corresponding to 9-12% decrease (total PANSS), but contrary to our hypothesis there was no significant difference between HIIT and AVG. In line with our hypothesis mean depressive symptom load (Wallwork depressed factor), estimated to 3.97 points (SE 0.28) [95% CI 3.41, 4.52] at baseline, was reduced significantly more in the HIIT group as compared to the AVG group at post-intervention (-1.03 points (SE 0.35), [CI 95% -1.71, -0.35], p=0.003). This persisted at follow-up. The between group effect corresponded to a small to moderate effect-size (Cohen`s d= -.37 [95% CI -0.62, -0.13]). Positive, negative, disorganized and excited symptoms mainly remained stable from baseline to post-intervention.

Discussion: The main finding was that HIIT reduced depressive symptoms more than AVG. We also found a small reduction in overall symptoms in the total sample. This may have clinical implications, as HIIT may serve as an add-on treatment alleviating depressive symptoms in individuals with schizophrenia. The mechanisms mediating the anti-depressive effects of HIIT in schizophrenia should be investigated in research to come.

ClinicalTrials 02205684.

S30. CULTIVATING RETENTION IN SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER STUDIES: PATIENT PREFERENCES FOR CLINICAL TRIAL METHODOLOGIES AND COVID19 MITIGATIONS

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Background: Clinical trials focusing on psychosis (i.e., schizophrenia and schizoaffective disorders) are beset by poor retention, averaging 50% (Levine et al., 2015). Ramifications of participant dropouts include expanded trials recruitment and duration causing greater expense, less statistical study power and less validity of the results, and potential early study termination (Gul and Ali, 2010). Study design and research site staff perspectives have been examined to explain low subject accrual; however, a review of the literature yielded no research surveying patients with a psychotic disorder regarding their methodological and site process preferences, especially when patients are familiar with studies from their previous participation. Exploring these factors is essential toward enhancing research participants' study retention (Page and Persch, 2013). In addition, since study procedures are frequently being implemented as a result of COVID19, it is crucial to survey patients on such contextual matters.

Methods: Patients diagnosed with a psychotic disorder seeking to screen for a clinical trial completed the Research Participant Preference Survey (RPPS), a 10-point Likert 45-item paper questionnaire categorized by various study methodological, site operational, and assessment procedures that motivate participating and remaining enrolled in a trial. Study procedural preferences were also queried respective of the current COVID19 pandemic. The RPPS took approximately 5 minutes to complete before patients screened for any clinical trial and was administered at five different US research sites (three in the West coast and two in the East) from May 2020 through November 2020. Survey data was analyzed using descriptive statistics, Pearson correlations, analysis of variance and Friedman test with post hoc Wilcoxon Signed Rank tests.

Results: A total of 195 subjects completed the RPPS, most diagnosed with schizophrenia (n=185; 95%) and having previous antipsychotic clinical trial participation (Mean [M}=4) to provide input on study processes and site operations. Preferences that strongly motivated enrolling and continuing study participation included free transportation (M=8.14), study compensation (M=8.54), access to mental health care (M=8.17), and site staff explaining the study rather than just receiving study information from the Consent Form (M=8.27). Wilcoxon pairwise comparisons indicated that study initiation and retention were motivated by shorter visits rather than longer ($p<.001$), more frequent outpatient visits ($p<.001$), and on-site assessments versus remote visits during COVID19 ($p<.001$). A Pearson analysis revealed stronger preferences for outpatient versus inpatient studies for subjects with less trial experience ($r=-.21$, $p=.005$). Participants had no significant differential preferences for self-report or clinician-administered assessments using paper or tablet. An analysis of variance indicated that racial minorities over their Caucasian counterparts significantly deemed site staff courtesy and respect as more valuable to their enrolling and continual study participation ($p=.008$).

Discussion: Data from the current study indicate preferences that motivate subjects to enroll and remain in clinical trial participation. These findings are informative to trial developers, such as knowing retention may be significantly hindered if a trial includes infrequent study visits (e.g., once a month). While sponsors and CROs may develop COVID19 remote study procedural contingency plans, subjects preferred assessments be conducted on site rather than at their homes. Potential explanation for our findings as well as study limitation will be discussed in the poster.

S31. META-ANALYSIS ON THE EFFECT OF PSYCHOTHERAPY IN AN INPATIENT SETTING: EXAMINING THE MODERATING ROLE OF DIAGNOSIS AND THERAPEUTIC APPROACH

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Background: The current meta-analysis investigates the efficacy of psychotherapy during psychiatric hospitalization and examines the moderating role of diagnosis and therapeutic approach.
Methods: We conducted systematic searches in literature databases, including PubMed, PsycInfo, and Google Scholar. In total, 37 samples were included for the meta-analysis with a total of 4,443 patients. Primary outcome was the standardized mean differences in clinical status measured by symptomatic and functional measures.
Results: The meta-analysis of 22 samples without a control group resulted in a very large effect size for the overall effect of treatment during psychiatric hospitalization that included psychotherapy (k=22, Cohen's d = 0.70, 95% Cl 0.36 to1.04). The meta-analysis of 15 samples with a control group resulted in a medium effect size for the contribution of psychotherapy to the improvement of patients' clinical status measured by symptomatic and functional measures (k =15, Cohen's d =0.43 95% CI 0.06 to 0.81). No significant effects were uncovered for psychotherapy orientation. Diagnosis was found to moderate the contribution of psychotherapy in an inpatient setting to the improvement of patients' clinical condition.
Discussion: Psychotherapy during psychiatric hospitalization is an effective treatment. Across the various samples, psychotherapy has moderate effect on the reduction of psychiatric symptoms beyond the overall effect of ward-treatment.

S32. COMBINING PHARMACOTHERAPY OF BI 425809 WITH COMPUTERIZED COGNITIVE TRAINING IN PATIENTS WITH SCHIZOPHRENIA: BASELINE DATA AND PATIENT DEMOGRAPHICS FROM AN ONGOING PHASE II TRIAL

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Background: Despite the significant patient burden it causes, there are no approved pharmacotherapies to treat cognitive impairment associated with schizophrenia (CIAS). BI 425809 is a novel glycine transporter-1 inhibitor that may improve glutamate transmission and neuroplasticity, currently under development for treatment of CIAS. A previous study demonstrated pro-cognitive effects of BI 425809 in patients with schizophrenia; however, concurrent cognitive stimulation could in theory enhance any pro-cognitive pharmacological effects on neuroplasticity. We present demographics and baseline data for a global multicenter trial exploring the efficacy of BI 425809 together with at-home computerized cognitive training (CCT) in patients with schizophrenia. Data are preliminary and subject to change.

Methods: This is an ongoing Phase II, double-blind, placebo-controlled, parallel-group, proof-of-concept trial in patients with schizophrenia on stable antipsychotic therapy across ~50 centers in 6 countries. Patients aged 18–50 years, compliant with CCT during the run-in period (completing ≥2 hours/week for 2 weeks), were randomized (1:1) to receive once-daily BI 425809 10 mg or placebo together with CCT for 12 weeks. Thereafter, minimum compliance for at-home CCT is 1 hour per week, with a target of ~30 hours across 3–5 sessions totaling 2.5 hours per week. Patients have been stratified to balance potential effects of age (18–40 and 41–50 years). The primary endpoint is change from baseline in neurocognitive composite T-score of the MATRICS Consensus Cognitive Battery (MCCB) after 12 weeks of treatment. Secondary endpoints include change from baseline in the Schizophrenia Cognition Rating Scale (SCoRS) total score, MCCB overall composite T-score, Positive and Negative Syndrome Scale (PANSS) total score, and (serious) adverse events. Novel exploratory endpoints include the Virtual Reality Functional Capacity Assessment Tool to assess daily functioning and the Balloon Effort Task to assess motivation in cognitive performance.
Results: Of the planned sample of 200 randomized patients, the overall treated population currently includes 173; 68% (n=118) are male, and the mean (standard deviation [SD]) age and time since first diagnosis are 38.3 (7.9) years and 13.5 (8.5) years. Overall, 47% (n=82) are White and 44% (n=76) are Black or African American; 81% (n=140) are from North America, 14% (n=25) from Europe, and 5% (n=8) from Australia/New Zealand. Mean (SD) baseline MCCB neurocognitive composite and overall T-scores (n=168) are 33.5 (11.7) and 32.2 (12.4). Mean (SD) baseline SCoRS total score (n=158) is 35.4 (8.6). Mean (SD) PANSS total and negative symptom scale scores (n=173) at baseline are 65.4 (14.4) and 17.6 (5.3). The median (Q1, Q3) CCT compliance over the on-treatment period for patients who have completed the study or discontinued early is 2.16 (1.33, 2.53) hours per week.
Discussion: This trial is, to our knowledge, the first to combine a novel pharmacotherapy for CIAS with at-home CCT and will indicate whether BI 425809 treatment together with concurrent cognitive stimulation provides an enhanced cognitive benefit. We also aim to demonstrate whether any observed improvements in neurocognition can translate into improved measures of daily functioning in patients with schizophrenia. Preliminary baseline characteristics are as expected for a population of clinically stable patients with schizophrenia, with baseline MCCB scores consistent with severe cognitive impairment. Preliminary CCT compliance exceeds the minimum and is close to the target, indicating the potential for at-home CCT to be implemented effectively in a multicenter clinical trial.

S33. A MULTI-CENTRE, DOUBLE-BLIND, RANDOMIZED PLACEBO CONTROLLED FEASIBILITY TRIAL OF ADD-ON SODIUM BENZOATE AND/OR N-ACETYLCYSTEINE IN PATIENTS WITH EARLY PSYCHOSIS

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Background: Oxidative stress pathways may play a role in schizophrenia through direct neuropathic actions, microglial activation and inflammation, and by interfering with NMDA receptor neurotransmission. N-acetylcysteine (NAC) has previously been shown to improve

negative symptoms of schizophrenia however, Results: from trials of other compounds targeting NMDAR neurotransmission have been mixed. This may reflect poor target engagement but might also suggest that risk mechanisms act in parallel.
Methods: A multicentre, twelve-week, 2x2 factorial design, randomized double-blind placebo-controlled feasibility trial of sodium benzoate (NaB) and/or NAC added to standard treatment in 68 patients with early psychosis. Primary feasibility outcomes included recruitment, retention, and completion of assessments as well as acceptability of the study interventions. Measures of psychosis symptoms, functioning and cognition were also completed.
Results: We successfully recruited our desired sample (n=68) and retained 78% (n=53) at 12-weeks, supporting the feasibility of recruitment and retention. There were no difficulties in completing clinical outcome schedules. Medications were well tolerated with no dropouts due to side effects. This study was not powered to detect clinical effect and as expected no main effects were found on clinical outcomes.
Discussion: We demonstrated the feasibility of conducting a clinical trial of NaB and NAC. NaB could synergize with NAC through several actions implicated in schizophrenia. NaB inhibits D-amino acid oxidase, which prolongs the action of D-serine at a positive allosteric site of the NMDAR, distinct from the NAC targeted redox site. NaB may exert anti-inflammatory effects by attenuating the expression of inducible NO synthase and cytokines in microglia, astrocytes, and macrophages.

S34. DISCOVR: RESULTS: OF A MULTICENTER RCT ON A SOCIAL COGNITIVE VIRTUAL REALITY TRAINING TO ENHANCE SOCIAL COGNITION IN PSYCHOSIS

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Background: Functional deficits, that is, problems in fulfilling appropriate social roles in daily life, are very common in people with a psychotic disorder. In recent years, Virtual Reality (VR) has emerged as a potential tool to improve SCT. Our research group has developed an immersive VR-SCT ('Dynamic Interactive Social Cognition Training in Virtual Reality': 'DiSCoVR') for people with a psychotic disorder.
Methods: This intervention was compared the an active VR-control condition in a multicenter RCT. Both interventions contained sixteen individual 45-60-minute on-site sessions, administered twice a week. Main study outcomes are social cognition and social functioning in daily life assessed with experience sampling.
Results: From baseline to post-treatment (n=72), none of the time*group interactions were significant, indicating an absence of treatment effects. A significant effect of time was observed for the SERS total score (b=9.84, 95% CI=3.81-15.87, p=.002), indicating overall improvement in self-esteem.
Discussion: We did not find any significant treatment effects. An effect of time on self-esteem was found at post-treatment, but not follow-up, suggesting a temporary improvement in self-esteem in both groups. One way to interpret these Results: is that, contrary to other SCT interventions, DiSCoVR does not improve social cognition or social functioning. This could be due to characteristics of the treatment protocol. Another possibility is that, contrary to the premise

of VR-SCT, our VR environments inadequately simulated reality. Adapting an established protocol to VR, could further elucidate the merit of VR as a training method.

S35. INTEGRATIVE COGNITIVE REMEDIATION IN SCHIZOPHRENIA: ANALYSIS OF BRAIN STRUCTURE AND FUNCTION

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Background: It has been shown that cognitive remediation, in addition to improving cognition in schizophrenia, can induce both structural and functional brain changes. However, Results: across studies are heterogeneous and little is known about the effect of integrative cognitive remediation combining different types of trainings on brain structure and function in this disease. The aim of this study was to analyze the functional and structural brain changes produced by an integrative cognitive remediation program which combined cognitive remediation, social cognitive training, and functional and social skill training in patients with schizophrenia.
Methods: Fifty-nine patients with schizophrenia from the Mental Health Network from Álava (Spain) were randomly assigned to either an experimental group who performed integrative cognitive remediation with the REHACOP program (n = 35) or to an active control group who performed occupational activities (n = 24). Both the cognitive remediation and occupational activities were carried out during 20 weeks, in sessions of 60 minutes, 3 days a week. T1-weighted, diffusion-weighted and functional magnetic resonance images were acquired during a resting-state and during a memory paradigm, both at baseline and follow-up. Voxel-based morphometry (VBM), tract-based spatial statistics, resting-state functional connectivity analyses with a region-of-interest approach, and brain activation during the memory paradigm with a model-based approach were used. Baseline differences in sociodemographic and clinical data were analyzed. Regarding neuroimaging data, baseline differences were analyzed with a two-sample t-test analysis. Longitudinal brain changes were analyzed with a 2x2 repeated-measure analysis of variance for group x time interaction. Finally, paired t-test analysis were used to explore intragroup changes. Total intracranial volume was included as a covariate in VBM and cortical thickness analyses, and antipsychotic medication in functional analyses. In addition, the negative symptoms variable was also included as a covariate in all longitudinal analyses, as baseline differences were found between the REHACOP group and the active control group. All neuroimaging analyses were performed at $p < .05$ corrected for multiple comparisons. Cortical thickness analyses were also performed with a threshold of $p < .01$.
Results: Two-sample t-test showed no baseline brain differences between groups. With regard to longitudinal analyses, no significant functional and structural brain changes related to the integrative cognitive remediation program were found in the repeated-measure analyses. Regarding intragroup analyses, the REHACOP group showed greater gray matter volume and cortical thickness in the right temporal lobe at post-treatment.
Discussion: Contrary to what was expected, there were not significant structural and functional brain differences between the REHACOP and the active control group. However, exploratory

intragroup paired t-tests showed that the REHACOP group had greater gray matter volume and cortical thickness at post-treatment in right temporal regions. These exploratory Results: are in line with some previous studies who reported a preservation or increase in the gray matter volume mainly in the right and left temporal lobe after cognitive remediation in schizophrenia.

S36. DO PATIENTS OF SUBGROUPS OF SCHIZOPHRENIA RESPOND DIFFERENTLY TO ANTIPSYCHOTIC DRUGS?

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Background: Relatively few antipsychotic drug trials in specific subgroups of patients with schizophrenia have been conducted. We examined whether the treatment effects in such subgroups differ from those of general patients with schizophrenia. If not, clinicians should rather base their decisions on trials and meta-analyses in chronic patients for whom more robust, more complete and more precise evidence is available.
Methods: We searched for randomised, double-blind antipsychotic drug trials in "general" patients with schizophrenia or the following subgroups: children and adolescents, first-episode, predominant/prominent negative symptoms, concomitant substance use, treatment resistant or elderly. Meta-analyses of the outcomes overall symptoms of schizophrenia, negative symptoms, positive symptoms, weight gain, prolactin increase, QTc prolongation, sedation were conducted for each subgroup and compared with those of the general population by subgroup analysis.
Results: We included 413 RCTs. Very few statistically significant subgroup differences were identified. Issues of multiple testing limit the interpretation of these statistically significant findings even further.
Discussion: There is little evidence that the relative treatment effects in specific subgroups of schizophrenia differ from those of general patients. Clinicians may therefore also consider the evidence in the well examined population of "general" patients in treatment decisions for specific subgroups.

S37. OPUS EARLY INTERVENTION SERVICES - DO THEY STILL WORK AFTER IMPLEMENTATION?

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Background: The Danish OPUS trial showed significant efficacy of early intervention service (EIS) for first-episode schizophrenia spectrum disorders compared to treatment as usual, leading to its implementation. We aimed to investigate whether the effectiveness of OPUS in real-world clinical practice is comparable to the efficacy seen in the trial.

Methods: We compared people receiving OPUS as part of the original randomized trial (OPUS-RCT) to those receiving standard treatment in the RCT (control-RCT) and those receiving OPUS after it was implemented in Denmark (OPUS-real-world). We investigated whether the three groups differed on register-based outcomes, e.g. use of secondary healthcare, functional outcomes, and death. Analyses were adjusted for relevant confounders.
Results: Compared with OPUS-RCT, OPUS-real-world (n=3,328) had a tendency towards lower mortality (HR=0.60, 95% CI 0.33-1.09) fewer and shorter psychiatric admissions, and possibly redeemed fewer prescriptions of antipsychotics and other psycholeptics after four or five years. While at first less likely to be working or studying, OPUS-real-world eventually had higher odds of working than OPUS-RCT (OR=1.49, 95% CI 1.07-2.09 after five years). The odds of being in a couple relationship were also higher in OPUS-real-world than in OPUS-RCT. Other outcomes showed less clear associations with treatment group. Generally, the control-RCT group fared worse than both of the OPUS-groups.
Discussion: The main limitation of this study was that the groups were not contemporaneous. Not only did OPUS maintain its efficacy after it was implemented as a standard treatment, it even paralleled or surpassed many of the effects observed when OPUS was conducted as a RCT. These Results: provide further evidence for implementation and funding of EIS worldwide.

S38. EFFICACY AND SAFETY OF A LONG-ACTING SUBCUTANEOUS ANTIPSYCHOTIC (LASCA) AGENT (TV-46000) IN PATIENTS WITH SCHIZOPHRENIA: A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, RELAPSE PREVENTION STUDY (RISE STUDY)

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Background: Long-acting injectable antipsychotic agents reduce rates of relapse, discontinuation, and mortality compared with oral formulations, in patients with schizophrenia. TV-46000 is a long-acting subcutaneous antipsychotic (LASCA) agent that combines risperidone and an innovative copolymer-based drug delivery technology in a suspension suitable for subcutaneous use that is being evaluated for administration once monthly (q1m) or once every 2 months (q2m).
Methods: The Risperidone Subcutaneous Extended-release study (RISE; NCT03503318) was designed to compare TV-46000 q1m and TV-46000 q2m with placebo (1:1:1; stage 2) in patients with schizophrenia who underwent stabilization on oral risperidone (stage 1). Primary endpoint was time to impending relapse. Secondary endpoints included proportions of patients with impending relapse at week 24 and proportions of patients who maintained stability at endpoint.
Results: 1267 patients were screened; 863 were enrolled, and 544 were randomized. Time to impending relapse significantly favored TV-46000 (hazard ratio [95% CI]; overall: 0.283 [0.184, 0.435], P<.0001; q1m: 0.200 [0.109, 0.367], P<.0001; q2m: 0.375 [0.227, 0.618], P<.0001) versus

placebo; TV-46000 prolonged time to relapse by 3.5, 5.0, and 2.7 times, respectively, versus placebo. Proportions of patients with impending relapse at week 24 were significantly lower for TV 46000 (overall: 9%; q1m: 7%; q2m: 11%) versus placebo (28%; P<.0001, P<.0001, P=.0001, respectively); proportions maintaining stability were significantly higher (83%, 87%, 80% vs 61%; P<.0001, P<.0001, P=.0001, respectively). TV 46000 was well tolerated without new safety signals versus accumulated safety data of oral risperidone and other long acting risperidone formulations.
Discussion: Treatment with TV-46000 (overall, q1m, or q2m) significantly prolonged time to impending relapse by 3.5, 5.0, and 2.7 times, respectively, versus placebo in patients with schizophrenia.

S39. SCHIZOPHRENIA AND CORTICAL ASSOCIATION FIBRES: A CONNECTOMIC STUDY

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Background: A variety of changes in neural architecture and function accompanies schizophrenia. The nature of these changes 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. They typically characterize the brain as a "small-world" graph whose nodes are split into semi-independent modules connected by hub nodes. In schizophrenia, these hub nodes are disrupted, resulting in increased segregation and reduced global efficiency. One model proposes that the hub nodes are highly susceptible to damage due to their central location in the network. As the disease progresses, the brain likely reroutes itself to bypass these conventional hubs. This model predicts a shift in connectivity strength toward peripheral regions of the cortex.
Methods: N=120 patients and N=60 healthy controls were recruited from an established cohort enrolled in the Prevention and Early Intervention Program for Psychoses (PEPP) in London, Ontario, as part of the previously funded TOPSY project. The sample size is adequate to detect the range of effect sizes reported in meta-analytical literature of graph theory measures in schizophrenia (>80% power, 5% type 1 error rate, independent t test of summary values). DWI tractograms were created using an MRTrix pipeline, parcellated with a data-driven fibre clustering approach, and translated to a non-directional association matrix weighted using a qT1-derived myelination coefficient. Using these matrices, the peripherilization of connectivity will be assessed using graph theory metrics. These data will be used to build a model of clinical outcomes using longitudinal data collected from our participants.
Results: Our preliminary data already support the involvement of the peripheral white matter, showing decreased fractional anisotropy in several superficial white matter tracts. Analysis of connectivity graphs in schizophrenia patients will contextualize these Results: with global connectivity changes. We expect to see a shift in connectivity from central hubs to the periphery, resulting in a flattened distribution of nodal connectivity strength, increased clustering of peripheral nodes, and redistribution of hub nodes away from the frontal-parietal lobes. These

findings will be assessed using both streamline-count and myelin-based measures of connectivity strength. We expect these metrics to predict the clinical outcomes of schizophrenia patients.
Discussion: Meaningful assessment of schizophrenia treatment requires reliable markers to track disease progression. Although dysconnectivity plays a major role in the pathophysiology of schizophrenia, its precise nature has not yet been fully characterized. This gap in knowledge makes the evaluation of novel therapies, such as anti-demyelinating agents, very challenging. Our work addresses this problem by describing a more complete account of cortical dysconnectivity and its relationship to clinical outcomes.

S40. USE OF CONNECTIVES IN PATIENTS WITH SCHIZOPHRENIA-SPECTRUM DISORDERS

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Background: Disorganized speech is a core diagnostic symptom of schizophrenia-spectrum disorders (SSD). Computational linguistic research has investigated cosine similarity as an objective measure of speech disorganization. So far, research has focused on similarity of subsequent words throughout spontaneous speech samples. Yet, given the central role of connectives (e.g., “because”) in signaling relations between words, disorganization might be best detectable in cosine similarity of narrower loci around connectives. To investigate if this is the case, we first need to know whether connectives and subtypes thereof are used by SSD patients and controls in similar ways. In this study, we investigate: a) the frequency of different connectives subtypes in speech of SSD patients and controls; b) their speech disorganization as signaled by connectives-related similarity; and c) the performance of different classifiers using connectives measures to distinguish between these groups.
Methods: Fifty patients with SSD and fifty control participants took part in this study. Spontaneous speech was elicited through a semi-structured interview. Counts of five different connectives subtypes (comparison, contingency, expansion, temporal, and multiclass) were extracted for each participant. Using a word2vec model, cosine similarities were calculated between connectives and the summed embeddings of the 3 words preceding and following them. As comparisons, for an equal number of fragments lacking connectives, the same calculation was done, as well as a sequential word-by-word calculation, as in previous studies. Mean, median, minimum, maximum, variance and range of similarity were calculated for all fragments and for all the different connectives subtypes. Differences between groups in proportion of connectives subtypes were assessed carrying out a generalized linear mixed-effects logistic regression model. Group differences for the connectives-related similarity measures were assessed through non-parametric multivariate analysis of variance and post-hoc Wilcoxon rank sum tests with Holm correction. Random forest algorithms using all measures were carried out to evaluate whether participants from each group could be distinguished with an accuracy above chance level.

Results: The logistic regression analyses showed an interaction between group and connective subtype. Specifically, patients used less contingency ($p<.01$) and multiclass connectives ($p<.001$) than controls, but did not differ in the other connectives subtypes. Importantly, similarity measures of speech surrounding connectives showed significant differences between groups ($p<.001$). Post-hoc analyses showed that, compared to controls, SSD patients had higher minimum similarity of temporal connectives (adj-$p<.001$), narrower range (adj-$p<.01$) and lower maximum (adj-$p<.01$) similarity of expansive connectives. Based exclusively on connectives measures, the best classifier reached 82.9% accuracy (79.1% sensitivity, 86.6% specificity). After adding the similarities of the fragments lacking connectives, the final classifier reached 88.1% accuracy (87.9% sensitivity, 88.4% specificity).
Discussion: Patients with SSD used less connectives of the contingency and multiclass subtypes compared to controls. One temporal and two expansive connectives-related similarity measures also differed between groups. A classification task based solely on connectives measures led to an accuracy > 80% in distinguishing SSD patients from controls. Our Results: suggest that focusing on connectives in spontaneous speech could strengthen computational models to detect SSD, with potential to ease diagnosis.

S41. EXPLAINABLE PSYCHOSIS PROGNOSIS PREDICTOR ON INCOMPLETE DATA

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Background: Machine learning (ML) provides a set of tools for processing and modeling raw data and knowledge extraction. Applications of ML models have shown some promise in clinical data analysis and more specifically psychosis prognosis prediction (PPP). However, the actual application of ML models in clinical practices is hindered by several factors including i) lack of generalization performance, ii) incomplete and heterogeneous data sources, and iii) lack of model explainability. Therefore, it is of high importance to develop new ML Methods: that can i) deal with multi-modal datasets with many missing records without compromising the model generalization performance; ii) provide a certain level of interpretability of model decisions at the individual patient level.
Methods: We present a novel approach for PPP on multi-modal clinical data. The proposed approach has three main components: i) a novel neural network (NN) layer for automatically dealing with missing values/modalities without the need for data imputation, ii) an NN architecture for multi-modal data fusion, iii) a counterfactual causal interpretation module. For i), we present a new NN layer that can automatically handle the missing values by neutralizing their effect on the final predictions. For ii), we present a simple NN architecture that provides the possibility for early and late feature fusion. And finally, for iii), we show how these components can be used in a counterfactual model interpretation paradigm to explain the prediction of the model at the single patient level.
We tested the proposed method on the OPTiMiSE dataset, an antipsychotic three-phase switching study: 495 patients with the first-episode schizophrenia-spectrum disorder. We used the data from the first phase of the study in which the patients were treated with amisulpride for four weeks. In

a PPP application, we aimed to predict the probability of patients' symptomatic remission based on PANSS scores. We used 12 different data modalities in our experiments ranging from clinical and behavioral assessments to biological measurements. In total, 13% of values in the dataset are missing. These missing values include complete or partial missed modalities.

Results: In a repeated 10-fold cross-validation scheme, the proposed method provides a reasonable classification performance (area under the ROC curve of 0.67+/-0.02, area under the precision-recall curve of 0.78+/-0.01, the sensitivity of 0.79+/-0.01, and specificity of 0.43+/-0.03) on data with missing values and modalities. Furthermore, our Results: show that the proposed model becomes indecisive when the model faces many unknowns, i.e., like a human agent, the model can say “I do not know” when receiving inadequate inputs. Moreover, our counterfactual analysis shows that the pattern of distinctive modalities is subject-specific and different from one subject to another.

Discussion: Here, we presented a new model for PPP on incomplete clinical data. The proposed model is convenient, intuitive, and reliable. It is convenient because it is straightforward in implementation and application. It is intuitive because it reacts to unknowns like a human agent; the more the unknowns, the less the actions. This property is crucial in delicate applications of ML in the medical domain in which the decisions made by machines can significantly affect the quality of life of patients. Furthermore, it provides an embedded mechanism to explain the decisions of complex NN models. This extra level of model explainability at the individual patient level is valuable in the clinical settings as it answers the ``Why?'' question often asked by the clinicians about decisions of black-box models, and hopefully, paves the way towards the new field of precision psychiatry.

S42. MODELS OF DYNAMIC BELIEF UPDATING IN PSYCHOSIS – A REVIEW ACROSS DIFFERENT COMPUTATIONAL APPROACHES

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Background: To understand the dysfunctional mechanisms underlying maladaptive reasoning of psychosis, computational learning models of decision making have widely been applied over the past decade. Thereby, a particular focus has been on the degree to which beliefs are updated based on new evidence, expressed by the learning rate in computational models. Higher order beliefs about the stability of the environment can determine the attribution of meaningfulness to events that deviate from existing beliefs by interpreting these either as noise or as true systematic changes (volatility). Both, the inappropriate downplaying of important changes as noise (belief update too low) as well as the overly flexible adaptation to random events (belief update too high) were theoretically and empirically linked to symptoms of psychosis. Whereas models with fixed learning rates fail to adjust learning in reaction to dynamic changes, more and more complex learning models have been adopted in samples with clinical and subclinical psychosis lately. However, it remains difficult to draw comparisons across findings of learning alterations in psychosis modelled by different approaches e.g., the Hierarchical Gaussian Filter and change point detection. Therefore, this review aims to summarize and compare computational definitions and

findings of dynamic belief updating in clinical and subclinical psychosis research across these different mathematical approaches.
Methods: We performed a literature search for publications citing a relevant paper from both modelling approaches (Hierarchical Gaussian Filter; Mathys et al., Front Hum Neurosc, 2011; and Change Point Detection Theory; Nassar et al., J Neurosc, 2010) and reporting Results: in participants from the psychosis spectrum. For a more comprehensive review, we extended our scope to other selected modelling approaches, such as, among others, extensions of Pearce-Hall learning and Hidden Markov Models. Regarding task designs, we restricted our review to learning tasks with dynamic environments and/or noisy inputs and excluded paradigms explicitly manipulating perceptual uncertainty.
Results: There was strong heterogeneity in tasks and samples; ranging from subclinical delusion to chronic schizophrenia as well as from binary reversal learning to more complex task designs with numeric predictions of changing means and variances of underlying distributions. Overall, psychosis was associated with lower behavioral performance that was linked to a failure to differentiate between uninformative noise and true environmental change. This was indicated by increased updating of beliefs and overestimation of volatility.
Discussion: Despite large heterogeneity in the methodological approaches, findings suggest that psychotic participants tended to overestimate the changes in the environment related to a state of high uncertainty about the task-adaptive responses. Thus, dynamic belief updating may be an important phenotype of psychotic experiences, which should be further investigated using a computational psychiatry with well-designed tasks meeting high standards of computational modelling in participants across the psychosis spectrum. Taken together, our review shows that computational psychiatry offers powerful tools to advance our mechanistic insights into the cognitive anatomy of psychotic experiences.

S43. REFINING THE COMPUTATIONAL STRUCTURE OF PERSECUTORY IDEATION

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Background: Persecutory ideation is common in illness and health, influenced by biological and social factors. Research has typically focused on general cognitive changes associated with pre-existing persecutory ideation although has not been able to explain the intentional content inherent in the experience; paranoia fluctuates over time, across different social contexts. This prevents the translation of basic science into treatment options as experimental treatment models will have few specific markers of change. Focusing on building refined formal theories that predict the dynamic attribution of harmful intent during social exchanges will improve the generalisability and specificity of experimental manipulations to treat and understand persecutory ideation.
Methods: We developed, validated, and tested a suite of computational models (formal theories) that describe and explain nuanced social changes during interpersonal exchanges. We assessed how specific social parameters may be influenced by social contexts and pre-existing persecutory ideation.

Results: Our social computational models demonstrate high replicability of observed data across two large samples (n = 1127; n = 693) through detailed simulation of social exchanges. We find that paranoia reduces the flexibility of harmful intent attributions (but not self-interest attributions), even when partner's change their behaviour, and beliefs around the prosociality (but not self-interest) of partner behaviours. We demonstrate that both effects replicate across two independent samples and that harmful intent attributional dynamics relate specifically to choice-stochasticity in non-social tasks, bridging general computational models of learning and specific cognitive models of paranoia.
Discussion: We demonstrate refined computational models that can describe the structure and form of paranoid inferences and behaviours, both of which show discriminate validity within models, and demonstrate discriminate relationships with general principles of learning. These formal theories are useful to specify where experimental treatments and manipulations may be influencing different dynamics within live paranoia.

S44. VOLATILITY ESTIMATES IN PEOPLE WITH SUBCLINICAL AND CLINICAL DELUSIONS

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Background: Research is inconclusive about the question whether aberrant behavioral and neural signatures of belief updating in individuals with schizophrenia are a general cognitive feature of the disorder or primarily related to delusional ideation. Yet, altered belief updating is at the core of learning theories trying to explain delusions (Ashinoff et al., 2021) and aberrant prediction error (PE) signaling is a candidate mechanism (Corlett et al., 2016). Aberrant PE signaling was indeed associated with deviating ventral striatal neural signatures in patients with schizophrenia (PSZ) (Radua et al., 2015). Alongside, PSZ (Deserno et al. 2020) and people at risk for psychosis (Cole et al. 2020) seem to overestimate environmental volatility which has been associated with altered prefrontal neural activity. We aim at dissociating how the presence of a disorder versus delusional ideation impact learning under uncertainty leveraging computational modelling and neuroimaging.
Methods: Adopting the computational modelling approach from Cole et al. (2020), we reanalyzed partially published data (Boehme et al., 2015; Deserno et al. 2020) from 86 individuals with clinical and nonclinical delusions after preregistering the analyses (https://aspredicted.org/8j4u7.pdf). During fMRI, participants performed a reversal learning paradigm with stable and volatile task phases. Bayesian Model Selection preferred a 3-level Hierarchical Gaussian Filter that formalizes learning as a multi-level process. Subsequent analyses were conducted in a subsample of 66 subjects (28.6 ± 7.41, 25 females) with participants being fit better than chance by the model. Computational parameters were compared between groups using 2x2 ANOVAs factorized by “delusion” and “disorder”. Behavioral trajectories and neural correlates of estimated volatility ($\mu 3$), belief uncertainty ($\sigma 2$), predicted environmental uncertainty ($\gamma 2$), precision weighted outcome-related PE ($\varepsilon 2$) and volatility-related PE ($\varepsilon 3$) were compared across groups and task phases.

Results: Healthy controls (HC) made more correct choices than PSZ ($F(1,62) = 7.72$, $p = .007$) and switched less between options ($F(1,62) = 5.61$, $p = .021$). The volatility-equilibrium parameter was higher in in PSZ compared to HC ($F(1,62) = 7.63$, $p = .008$). All trajectories of $\mu 3$, $\sigma 2$, $\gamma 2$, $\varepsilon 2$, $\varepsilon 3$ showed an increase across task phases. Generally, PSZ showed higher $\mu 3$ ($F(1, 62) = 8.54$, $p = .005$) and higher $\gamma 2$ ($F(1,61) = 5.47$, $p = .023$). The increase of $\varepsilon 2$ across task phases was larger in participants with delusions ($F(1.59, 98.67) = 3.39$, $p = .048$). The increase of y2 was larger in PSZ ($F(1.33, 82.3) = 4.74$, $p = .023$). We observed brain activation related to $\mu 3$, $\varepsilon 2$ and $\varepsilon 3$. HC showed stronger activation related to $\mu 3$ in the angular gyrus, medial frontal gyrus and anterior insula compared to PSZ. Participants with delusions showed stronger $\varepsilon 2$-related activation in the caudate, posterior insula, anterior cingulate and putamen whereas PSZ showed stronger activation in the midbrain. Lastly, individuals with delusions showed stronger activation related to $\varepsilon 3$ in the accumbens and anterior cingulate.
Discussion: Our Results: suggest that the occurrence of delusions versus the diagnosis of schizophrenia is related to different behavioral and neural signatures of belief updating. Patients with manifest schizophrenia showed overestimation of environmental volatility, associated with altered prefrontal neural coding of beliefs about environmental volatility. In contrast, delusions were associated with altered PE-signaling and increased activation in caudate and anterior insula in response to lower- and higher-level PEs. Future research should elucidate how medication, cognitive function as well as status and duration of illness moderate these relationships.

S45. SCHIZOTYPY CLUSTERS: THE IMPACT OF USING DIFFERENT QUESTIONNAIRES

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Background: Current models propose a three-factor structure of schizotypy, akin to that of schizophrenia symptoms (positive, negative, disorganized). While most studies focus on the individual factors, few have investigated schizotypy clusters, i.e. latent groups of the general population with specific schizotypy profiles. This is highly relevant: E.g. positive schizotypy is associated with poor functional outcome and increased psychosis risk only when paired with negative and disorganized schizotypy. Most studies identify four schizotypy clusters, one of which scores low on all factors and one that scores high on all factors, while the Results: regarding the other clusters are mixed. One possible explanation for this inconsistency is the use of different schizotypy questionnaires, which differ in their theoretical Background: and factor structure.
In the current study with a large healthy sample, we conduct cluster analyses based on two questionnaires with different theoretical Background:s and compare the resulting clusters: The Multidimensional Schizotypy Scale (MSS) is based on the current three-factor model of schizotypy and exhibits strong psychometrical properties. The Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE) covers a fourth factor, “impulsive nonconformity”, and emphasizes a non-pathological view of schizotypy. We hypothesize that the four-cluster solution for both cluster analyses will result in an “all-low” and an “all-high” cluster, and two clusters who predominantly score on one factor. We expect the clusters to correspond moderately between

questionnaires. For a descriptive exploration of schizotypy profiles in a small sample of early psychosis patients, we hypothesize that patients' profiles resemble those of the healthy clusters, whereby the "all-low" profile may be relatively underrepresented.

Methods: 653 healthy individuals completed the MSS and O-LIFE online. Recruitment of patients with early (≤5 years) non-organic psychosis (ICD-10 F20 – F29, F30.2) at the University Hospital of Psychiatry Zurich is ongoing.
Confirmatory factor analyses (CFA) were conducted for the items of the MSS and the items of the O-LIFE, to determine whether the data from our healthy sample fit the respective theoretical factor structure. We then conducted an exploratory graph analysis (EGA) with MSS and O-LIFE items combined, to explore whether the items of corresponding subscales of the MSS and O-LIFE load on the same factors. As preregistered on AsPredicted.com, we will conduct two model-based cluster analyses based on the z-standardized sum scores of the subscales (i.e. theoretical factors) of the MSS and of the O-LIFE. We will compare the clusters using the Rand Index. Individual patients' profiles will be compared descriptively with cluster profiles.

Results: The Results: from the CFA suggest that the theoretical factors are a good fit for our data (MSS: Comparative Fit Index/CFI = 0.913, Tucker-Lewis Index/TLI = 0.910, root mean squared error of approximation/RMSEA = 0.018; O-LIFE: CFI = 0.875, TLI = 0.872, RMSEA = 0.019). Preliminary Results: from the EGA suggest that most MSS and O-LIFE items of corresponding subscales load on the same factor, suggesting that the MSS and O-LIFE clusters in subsequent analyses may correspond more than expected.
Discussion: This is the first study to compare clusters based on two different schizotypy questionnaires. This could further our understanding of schizotypy clusters and of how the use of different questionnaires – which are often used interchangeably – may impact Results:. Exploring how patients' profiles resemble those of healthy clusters could help generating hypotheses regarding schizotypy profiles in patients.

S46. POLYGENIC AND POLYENVIRONMENT INTERPLAY ACROSS PSYCHOTIC DIAGNOSTIC CATEGORIES – THE EUGEI STUDY

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Background: Multiple environmental risk factors (ERF) play an important role in the development of both affective (AP) and non-affective psychosis (NAP). But how these work in

combination with the pre-existing established genetic vulnerability is yet to be clarified. Thus, the current work aims to study differences in gene and environment interplay in NAP and AP by: (i) exploring environment moderator effect accounting for polygenic vulnerability to different psychiatric disorders (SCZ, BD, depression); and (ii) attending to the cumulative environmental exposure by combining different factors into a polyenvironmental measure.
Methods: Based on the EUGEI study (EUropean Network of national schizophrenia networks studying Gene-Environment Interactions); we analysed 573 cases aged 18 to 64 years diagnosed with NAP, Bipolar Disorder or Psychotic Depression; and 1005 controls with European ancestry in 17 sites across 6 mostly European countries. Firstly, multinomial and simple logistic regression models were used to test whether the association of standardised genetic load (PRS-SZ, PRS-BD and PRS-D) with NAP and AP differs significantly when stratifying by exposure of several individual ERF. Secondly, independent logistic models including a polyenvironmental measure with each PRS alongside their interaction terms were run to test a potential polygenic and polyenvironment interaction with AP and NAP compared with controls.
Results: In NAP, associations for PRS-SZ were generally stronger in those non exposed to ERF, including cannabis (OR 3.4, 95%CI 2.17-5.33 vs OR 2.32, 95%CI 1.63-3.33); migration (OR 2.69, 95%CI 2.00-3.60 vs OR 2.36, 95%CI 1.05-5.33) and childhood adversity (OR 4, 95%CI 2.55-6.28 vs OR 1.85, 95%CI 1.27-2.68). On the other hand, in both NAP and AP, associations with PRS for the two affective disorders (PRS-BD and PRD-D) appear higher in the presence of environment exposure. More specifically associations with PRS-BD were stronger in NAP exposed to migration (from OR 1.31, 95%CI 1.03-1.66 to OR 2.61, 95%CI 1.41-4.83), cannabis (from n.s. to OR 1.51, 95%CI 1.12-2.60) and childhood adversity (from n.s. to OR 1.61, 95%CI 1.18-2.20); and associations with PRS-D were generally stronger in AP exposed to cannabis (from n.s to OR 1.49, 95%CI 1.14-1.95) and stressful life events (from n.s. to OR 1.67, 95%CI 1.13-2.46). No evidence of interaction was found between any of the PRS with the combined measure of polyenvironmental exposure for NAP or AP.
Discussion: No evidence was found of a synergistic effect of polygenetic loading and multiple environmental exposure on the onset of AP or NAP. However, AP seems to be the product of cumulative environmental insults in those with a higher genetic liability for affective disorder; while NAP seems to be due to two distinct pathways: a higher genetic load for schizophrenia acting additively but independently with environmental exposureñ and a higher genetic vulnerability for affective disorder potentially acting by increasing the sensitivity to exposure to environmental insults, in line with the affective pathway to psychosis.

S47. COROLLARY DISCHARGE AND ITS RELATIONSHIP WITH ANOMALOUS SELF-EXPERIENCES IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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Background: Sensations consequent to ourselves' actions are distinguishable from those of external origin, playing a key role in developing an intact sense of self. An altered sense of self is believed to be a causal factor of some of the symptomatology observed in psychosis. Corollary

discharge is the mechanism that allows us to distinguish between self-generated and externally generated perceptions.

During vocalization, N1 event-related potential (ERP) has been studied with electroencephalogram (EEG) as an index of corollary discharge-mediated auditory cortical suppression. To have more cognitive resources available for processing externally generated stimuli, during the speech, healthy subjects show suppression in N1. There is an inhibition of self-generated spoken sounds during vocalization compared to passive listening of stimuli. This speaking-induced suppression of the auditory cortex does not appear to happen in some psychopathological conditions such as schizophrenia. A deficiency of corollary discharge mechanism might be an explanation for the positive symptoms in psychosis, due to the difficulty to distinguish their thoughts and memories from external voices.

Methods: ERPs were recorded from 14 first-episode schizophrenic patients (FE), 20 patients with chronic illness (CH), 11 patients with bipolar disorder (BD), and 35 healthy controls (HC). The N1 ERP component was elicited during production (Talk), playback of vocalization (Listen-self), and an external voice recording (Listen-other). Talk condition assesses the agency effect; Listen-self condition assesses the ownership effect, and Listen-other condition assesses whether the identification of self-generated speech is due to motor processes or sensory processes involved in the recognition of physical characteristics.
Correlations were performed between the amplitude of the N1 component during the three conditions (Talk, Listen-self and Listen-other) and scores obtained from The Positive and Negative Syndrome Scale (PANSS) and The Inventory of Psychotic-Like Anomalous Self-Experiences (IPASE).

Results: Both FE and CH groups showed reduced Talk N1 suppression relative to HC. This lack of Talk N1 suppression was higher in FE group compared to CH. BD group did not show Talk N1 differences relative to HC. Listen-self and Listen-other N1 amplitudes were similar in all groups (patients and controls).
PANSS scores correlations showed that Talk N1 amplitude might be associated with higher positive and negative symptoms in FE and CH patients. IPASE scores (Self-Awareness and Somatization) showed positive associations with N1 amplitude in FE.

Discussion: The reduced Talk N1 suppression corroborates that putative efference copy/corollary discharge-mediated auditory cortical suppression during vocalization is deficient in FE and CH schizophrenia patients. This lack of suppression decreases from FE patients to CH, likely reflecting the effects of the antipsychotic or the brain maturation. The absence of differences related to the Talk N1 suppression from BD patients might indicate that the difficulty to distinguish thoughts and memories from external voices is not present in this group of patients. However, an increase in the patient sample is necessary to confirm these results.

S48. NO DIFFERENCES IN POSITIVE-NEGATIVE SYMPTOMS AND AUTISTIC TRAITS AMONG DIFFERENT SUBSETS OF ACUTE PSYCHOTIC DISORDERS

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Background: Psychoses are a cluster of conditions sharing altered relationship with reality such as the presence of hallucinations, delusions, and disorganized thinking. Schizophrenia, schizoaffective, and affective disorders (eg. mania and depression) often represent chronic and severe diagnoses associated with primary psychoses. Autism Spectrum Disorder (ASD) is a diagnostic cluster with different core symptoms but that frequently presents with psychosis.
Understanding whether these conditions may present with specific symptoms may improve diagnostic and therapeutic efficiency, especially in clinical settings such as Acute Inpatient Units.

Based on these premises, this study aims to assess whether three groups of inpatients with either schizophrenia (SZ), schizoaffective (SA), or affective (AF) acute psychosis can be differentiated using clinical instruments probing positive/negative/general symptoms and autistic traits.

Methods: We performed a monocentric observational study enrolling 51 subjects hospitalized at the Acute Psychiatric Inpatient Unit of Pavia, Italy between 2019 and 2021. Patients had to meet the following inclusion criteria: age between 18 and 65; ICD-10 diagnosis of either schizophrenic psychosis, schizoaffective disorder or mood disorder with psychotic symptoms; fluency in Italian. Exclusion criteria were: intellectual disability; neurological conditions that may cause psychotic symptoms.
Basic clinical and demographic data were collected from clinical records or interviews. Each enrolled patient signed an informed consent. Instruments used were: I)Positive And Negative Symptoms Scale (PANSS): a clinical, 30 items interview allowing to assess positive symptoms, negative symptoms, and general psychopathology domains in psychotic disorders. PANSS Autism Severity Scale (PAUSS) has been proposed as a subscale that uses 8 PANSS items to measure autistic features in patients with schizophrenia. II) Ritvo Autism Asperger Rating Scale, 14-items version (RAADS-14): a self-administered questionnaire assessing autistic traits, with a focus on sensory-motor symptoms.

PANSS was collected within 72 hours from admission and at discharge, while RAADS-14 was collected at discharge when the patient was in better clinical conditions for the self-administration of the instrument. ANOVA was used to test differences between the PANSS (total, positive symptoms, negative symptoms, general psychopathology, PAUSS) subscores and RAADS (total, mentalizing deficits, social anxiety, sensory reactivity) subscores.

Results: Patients had SZ (n=23), SA (n=15) or AF (n=14). Mean age was 39.35±10.16 for SZ, 39.40±8,78 for SA and 43.86±8.0 for AF. Interestingly, no significant difference was observed in all PANSS and RAADS-14 subscores ($p > 0.05$ in all measures).
Discussion: To the best of our knowledge, this is the first study exploring potential differences in terms of both clinical presentation of psychotic symptoms and autistic traits among three different diagnostic groups with acute psychosis. We found no significant differences. Limitations were limited sample size and the diachronic evaluation of symptoms, with no clinician-rated evaluations specific for manic/depressive symptoms or autism. Taken together, these considerations suggest the need of larger studies, with a prospective design, in order to disentangle the complex relationship between psychotic symptoms and autistic traits.

S49. EVERYDAY LIFE IN SCHIZOPHRENIA

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Background: Stability, predictability, and daily routines are important structuring and health-promoting elements in most peoples' lives. In schizophrenia, these structuring elements are often affected, and much therapeutic work, including psychosocial rehabilitation and recovery-oriented interventions, aims at strengthening these elements and improving the patients' ability to act autonomously in his or her own everyday life. If, however, such structuring elements of everyday life are markedly affected or changed from the norm, norm-driven therapeutic work may become less applicable. In this study, we wish to explore the everyday life of patients with schizophrenia, who have severe social dysfunction.

Methods: This study is an ongoing qualitative study, conducted at a mental health outpatient facility in Copenhagen. We will include 20 patients with schizophrenia, who are either homeless or unable to meet basic societal demands such as showing up for appointments at the outpatient clinic. The study explores the past days in the patient´s life, self-reported activities, social interactions, habits, duties, adaptation to changes in their life, and hopes for the future. All interviews are audio or video recorded and subsequently transcribed. The data analysis includes both bottom-up and top-down analyses. The bottom-up analysis will be coded according to the principles of content analysis.

Results: Our preliminary analysis indicates the following patterns of themes concerning the patients' everyday life:

- Generally, homeless patients appear more socially active in their everyday life than patients living in their own home (this difference is not explained by the homeless patients' inability to socially withdraw).
- Going to public places without interacting socially, e.g. going for a walk in the park, is described as an important source of social input, especially by those living in their own home.
- Public transportation represents a major obstacle, interfering with the patients' ability to socialize. Public transportation is described as the biggest problem of going somewhere.
- Both groups exhibit a disturbed perception of time, affecting their ability to socialize.

Discussion: This study contributes important knowledge about structuring elements in the everyday life of patients with schizophrenia, who have severe social dysfunction. This has potential for adding nuance to psychosocial rehabilitating and recovery-oriented interventions for patients with schizophrenia.

S50. LANGUAGE FUNCTIONING IN SCHIZOPHRENIA IS RELATED TO FORMAL THOUGHT DISORDER

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Background: Defined as disturbances in thought processing, formal thought disorder (FTD) is one of the core and extensively investigated syndromes in schizophrenia (SZ). Language and communication disorders are a part of FTD. Although some studies show a link between thought and language or communication disorders, it is still unclear how language functioning and thought processing are related to each other. Thought and Language Disorder Scale (TALD) is a comprehensive and valid scale covering not only positive/negative but also objective/subjective symptoms. Accordingly, the current study explores the link between FTD, assessed by TALD, and language functioning in patients with SZ.
Methods: The patients who met DSM-5 criteria for SZ, aged 25 and 49, were recruited from the Department of Psychiatry, Ankara Etimesgut Şehit Sait Ertürk State Hospital. Turkish version of TALD (TALD-TR) was used to detect FTD symptoms. Clinical Global Impression-Severity Scale (CGI) was administered to assess illness severity. Language functioning was investigated by using phonemic (letters: /k/, /a/, /s/) and semantic (category: animals) verbal fluency, Scale for Scoring the Inclusion and Quality of the Parts of a Story, syntactic complexity and Boston Naming Test (BNT). Syntactic complexity and Scale for Scoring the Inclusion and Quality of the Parts of a Story were calculated from the story told by the patients depending on 8 Thematic Apperception Test (TAT) cards.
Results: The sample included 24 patients (mean age 37.5 ± 7.84) with 12.5% (N=4) female participants. Exclusion criteria for the study included mental retardation. The mean duration of education was 9.96 ± 2.98 years, and the mean duration of illness was 16.5 ± 7.97. Partial correlation analysis, controlling for age and education, showed that subjective negative FTD was associated with language impairments. It also correlated negatively with the scores of BNT, syntactic complexity, and phonemic and semantic verbal fluency. BNT and syntactic complexity also had significant negative correlations with objective negative FTD. Furthermore, total score of FTD was significantly correlated negatively with the scores of syntactic complexity and phonemic fluency. However, no relation was detected between Scale for Scoring the Inclusion and Quality of the Parts of a Story and FTD scores.
Discussion: These preliminary Results: indicate that an impairment in thought processing can be linked with an impairment in language and communication systems in SZ. In line with the literature, negative FTD and total score related to syntactic complexity and verbal fluency. Besides, there was a significant negative correlation between BNT and both objective and subjective negative FTD. To our knowledge, the relationship between these variables is a novel finding in FTD research. Language and communication are important aspects of psychological and social wellbeing in daily life. Because of this close relationship between language and FTD, speech and language therapy should be considered one of SZ's primary treatment goals. For future studies, comparison with healthy individuals and adding neuroimaging techniques in designs would further help interpret the results.

S51. AUTISTIC SYMPTOMATOLOGY IN ULTRA HIGH-RISK PATIENTS: PRELIMINARY FINDINGS

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Background: Several studies have evaluated the level of autistic symptomatology in schizophrenia patients and its correlation with social cognition or theory of mind. The rate of autism spectrum disorder (ASD) symptoms in schizophrenia patients can be over 50%. However, to our knowledge, there are no studies on autistic symptoms in Ultra High Risk (UHR) patients. This study aims to compare the degree of autistic symptoms in a sample of UHR patients with a clinical group of patients diagnosed with Schizophrenia and a group of mood disorders.

Methods: Fifty-four subjects were recruited from the Psychiatric Unit of the University Hospital Campus Bio-Medico in Rome. Specifically, 18 patients with a diagnosis of Schizophrenia (SCZ), 18 patients with Ultra-High Risk for psychosis (UHR), and 18 patients with mood disorders (Mood) were recruited. The diagnoses of Schizophrenia and mood disorders were made according to DSM-5 criteria. The condition of UHR was assessed using the Structured Interview for Psychosis-Risk Syndromes (SIPS). Current substance use and the presence of relevant neurological comorbidities were considered exclusion criteria.

Results: Using the PANSS Autism Severity Score (PAUSS) scale, we found that the degree of autistic symptomatology in UHR patients is significantly lower compared to schizophrenia patients, but greater than a group of mood disorders patients. Moreover, we found a significant correlation between autistic symptomatology and the severity of formal thought disorders.

Discussion: To our knowledge, this is the first study that investigates the presence of autistic symptoms in UHR patients measured with PAUSS. Our Results: suggest the hypothesis that a certain level of autistic symptomatology is already present in the prodromal phases of psychosis. Moreover, current preliminary findings appear to confirm Bleuler's hypothesis about autism and association disorders as core features of psychosis.

S52. A META-ANALYSIS ON PROVERB COMPREHENSION IN SCHIZOPHRENIA CONSIDERING 60 YEARS OF RESEARCH

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Background: Deficits in the comprehension of proverbs have long been considered as a hallmark symptom of schizophrenia. Traditionally, the problems of schizophrenia patients with proverb interpretation, as an example of figurative language processing deficit, has been linked to an inability to abstract from the literal words. Accordingly, the comprehension of proverbs in schizophrenia patients has often been measured with two concepts: the degree of abstraction as the “figurative meaning” and concreteness as the “literal meaning” in a patient’s verbal response of an answer in a multiple-choice test (Gorham, 1956). At the same time, the question of the effect size and specificity of the deficit is just as old as its early assessments (e.g., Andreasen, 1977). Although several narrative reviews are available, no meta-analysis has compared effects to clinical controls. Thus, the aim of the meta-analyses was to compare the degree of abstract and concrete

responses to proverbs in schizophrenia patients to healthy controls (1) and clinical controls (2), as well as to examine the impact of answer type for abstract and concrete responses (3) in terms of multiple-choice vs. verbal responses.
Methods: We performed a systematic literature search on experimental proverb comprehension studies in schizophrenia. Pubmed, Google Scholar and PsychInfo databases were considered. For the selection of studies, we applied the following criteria: 1) empirical study, 2) quantitative measurement of abstract and concrete answers in a proverb test in schizophrenia patients (SCZ) and 3) a clinical (CC) or healthy control (HC) group. Excluded were case studies, other figurative expressions (e.g., idioms) and other performance measurements of proverb comprehensions (e.g., response time, bizarre thinking).
Results: 29 studies provided enough data to be included in the meta-analysis. For the comparison of SCZ to HC subgroup analyses were performed on response format (multiple-choice vs. verbal response) in concrete and abstract measurements each. For clinical controls, studies were divided in depressed vs. non-depressed subgroups. Studies have been published between 1956 and 2020, with Gorham proverb test (Gorham, 1956) being the most established one and depressive patients being the most common clinical control group. Studies were predominantly older than 30 years. Compared to HC, Results: showed abstract responses were significantly less frequent in SCZ (24 studies, d: -1.08, 95% CIs: -1.47, -0.70, p <.001), while concrete responses were significantly higher (12 studies, d: 0.80, 95% CIs: 0.29, 1.30, p <.001). There were no significant subgroup differences in response format (both p >.05). Compared to CC, SCZ showed lower abstract responses (14 studies, d: -0.42, 95% CIs: -0.78, -0.05, p =.02), while there was no significant difference in concrete responses (8 studies, d: 0.44, 95% CIs: -0.26, -1.14, p = .22). Subgroup comparisons on depressive vs. non-depressive clinical controls were not significant (both p >.05).
Discussion: In general, we found that abstraction to be clearly lower in schizophrenia patients' responses to proverbs compared to healthy and clinical control. However, giving a concrete or 'literal' response to a proverb seemed to be rather transdiagnostic in nature, with higher concreteness compared to healthy, but not clinical controls. Contrary to effects described in right hemisphere lesioned patients, in schizophrenia the effects were comparable in verbal response and multiple-choice format. Given the decade-long role of verbal proverb explanation in everyday psychopathology assessment, the diagnostic specificity of proverb comprehension is astonishingly low. Further research comparing schizophrenia with other diagnosis is needed.

S53. OCCURRENCE OF PSYCHOSIS AND BIPOLAR DISORDER IN ADULTS WITH AUTISM: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Evidence suggests that individuals with autism spectrum disorder present with increased rates of co-occurring psychosis and/or bipolar disorder. Considering the peak age of onset for psychosis and bipolar disorder occurs in adulthood, we investigated the co-occurrence of these disorders in adults with autism.
Methods: We conducted a systematic review and meta-analysis (PROSPERO CRD42018104600) to (1) examine the prevalence of psychosis and bipolar disorder in adults with autism, and (2)

review potential risk factors associated with their co-occurrence. Studies reporting on prevalence rates or risk factors associated with the co-occurrence of psychosis and/or bipolar disorder in adults with autism were included (search range 1980 - September 2021). Random-effects models were used to estimate the pooled prevalence of these co-occurring disorders.
Results: Fifty-three studies were included. The pooled prevalence for the co-occurrence of psychosis in adults with autism was 9.4% (N = 63,657, 95%CI = 7.52--11.72). The pooled prevalence for the co-occurrence of bipolar disorders in adults with autism was 7.5% (N = 31,739, 95%CI = 5.79--9.53).
Discussion: Psychosis and bipolar disorder occur at a substantially higher prevalence in adults with autism compared to general population estimates. While there is an overall dearth of research examining risk factors for these disorders in autism, adult males with autism are at increased likelihood of co-occurring psychosis, and females at higher likelihood of co-occurring bipolar disorder. Older age is associated with increase prevalence of psychosis in autism. These Results: highlight the need for ongoing assessment and monitoring of these disorders in adults with autism.

S54. JUMPING TO CONCLUSIONS AS POTENTIAL OUTCOME PREDICTOR AT 5-YEAR-FOLLOW-UP FOLLOWING A FIRST EPISODE OF PSYCHOSIS (FEP)

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Background: Several studies have found higher prevalence of the jumping to conclusions (JTC) bias among individuals with psychosis, even at FEP, compared to controls. Only a few studies have investigated their outcome prediction, finding that patients who display the JTC bias at FEP have worse clinical outcome (Rodriguez et al., 2019). Therefore, this study aimed to test social, functional, and clinical outcome prediction of the baseline JTC in a sample of FEP after 5-year-follow-up.
Methods: 134 patients with First Episode Psychosis (FEP) and 91 controls from the GAP study and the London subsample of the EUGEI study were followed up after 5 years. Sociodemographic, clinical and neuropsychological assessments were performed at baseline and 5-year-follow-up. JTC bias was measured through the 60:40 beads task. Social outcome was measured considering information about level of education, accommodation, relationship, and employment status. Clinical outcome was evaluated on the basis of information about number of hospital admissions and proportion of time spent in hospital. Functional outcome was assessed through the Global Assessment of Functioning (GAF) measuring both overall symptoms severity and disability associated with the illness at follow-up (American Psychiatric Association (APA), 1994; Endicott

et al., 1976). In STATA 15, ordinal, linear, and multinomial logistic regressions were estimated to test the association of JTC with clinical outcome (n. of admission and proportion of time spent in hospital from baseline to follow up), with functional outcome (GAF symptoms and disability scores) and social outcome (changes in marital, employment, and living status between baseline and follow-up).

Results: Ordinal and linear regressions investigating prediction for clinical and functional outcome showed that number of beads drawn at baseline was not associated with higher hospitalisation (OR=1.1, 95% CI 0 .9 - 1.1) nor proportion of time spent in hospital (B=-0.1, 95% CI -0.3 to 0.2) nor GAF scores (symptoms: B=-0.6, 95% CI -1.5 to 0.2; disability: B=-0.8, 95% CI -1.8 to 0.1). When analysing social outcome using multinomial logistic regression models with no covariates, DTD at baseline modestly predicted steady patterns in living (RRR=0.9, 95% CI 0.8 – 0.9, p=0.007), marital (RRR=1.1, 95% CI 1.1 – 1.2, p<0.001), and employment status (RRR=1.1, 95% CI 1.1 – 1.2, p=0.001). When adjusting for covariates, p values were no longer significant although the effects (RRR) did not change.

Discussion: This study considered other than clinical outcome in terms of number of admissions, time spent in hospital, symptoms severity, and level of disability, also social outcome in terms of changes in living arrangement, marital status and employment as real-world indicators of social functioning (Tulloch et al., 2006). Although jumping to conclusions as a cognitive bias has been suggested to be relevant to social processing in terms of compromising the accurate processing of social information (Grossman and Bowie, 2020), our findings raised only weak associations of jumping to conclusions with achievements of important indicators of social function such as living independently, relational and employment status. Future research using a prospective design is warranted to detect different trajectories and investigate the role of this deficit in psychosis while also accounting for genetic load.

S55. A CONFIRMATORY FACTOR ANALYSIS OF COMPETING PANSS NEGATIVE SYMPTOM MODELS

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Background: Factor analytic studies of Positive and Negative Syndrome Scale (PANSS) consistently report two-domain model of negative symptoms: Expressive Deficit (ED) and Social-Amotivation (SA), however no studies hitherto have addressed which PANNS model best represents negative symptom construct. We examined PANSS negative symptom competing models to determine which of these best fits the data. We then tested the effect of medication and illness severity on the stability of the most robust model and investigated its external validity.
Methods: Of 446 FEP medication naïve/minimally treated patients 368 (83%) completed a 4-week trial with Amisulpiride and were re-assessed with PANSS. Confirmatory Factor Analysis (CFA) was performed to test existing PANSS models. Hierarchical multiple regression analysis was conducted to assess the degree of change between identified symptom dimensions and investigate associations with clinical and demographic parameters
Results: The 9-item PANSS model provided the best fit for the actual data: CFI = 0.98, GFI = 0.97, TLI = 0.97 and RMSEA = 0.06 (CI 90%: 0.04–0.08), BIC =191.9, AIC = 101.7. Each baseline symptom dimension strongly predicted its own dimension, at follow up, SA: SA ($\beta = .59$, $p < .001$), DE ($\beta = .03$, $p = 0.5$) post-treatment; ED: ED ($\beta = .56$, $p < .001$), SA($\beta = .13$, $p = 0.01$). SA dimension was associated with more severe depression and poorer functioning, whereas ED with younger age.
Discussion: The 9-item PANSS model incorporating SA and ED dimensions is the winning model and the findings provide evidence for its external validity.

S56. PREVALENCE, PHENOMENOLOGY, AND CORRELATES OF HALLUCINATIONS AND DELUSIONS IN YOUNG ADULTS FROM A RAPIDLY DEVELOPING MIDDLE EAST COUNTRY

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Background: We were interested in the determinants of the trajectory from psychotic experiences (PEs) to clinical psychosis. In particular, what profile of positive symptoms is associated with risk of clinical psychosis [hallucinations only, delusions only or mixed], in a population in Qatar (a rapidly developing global economy). Specifically, we asked: what symptoms of the mixed profile (positive and negative symptom profile, severity, low mood) and socio-cultural factors are shared between clinical-risk and non-clinical-risk samples?
Methods: We used the locally validated Questionnaire for Psychotic Experiences (QPE) programmed in Qualitrics to determine: lifetime and current (past week) prevalence of phenomenology along with Cognitive (Qualitative) Interviews. We stratified a systematic probability sample of eligible students > 18-years old in full-time study between September 2020 and 2021. Initial email invites were followed by three email and phone reminders. We defined four groups based on presence or absence of PEs: no hallucinations or delusions, hallucinations only, delusions only or mixed profile, comparing the groups using Chi-square test of associations (statistical significance based on p-value ≤ 0.05).
Results: We included 3189 people (629 male, 2560 female) 84.4% aged 18-29, 73% never married, 68.2% Qatari, 91.3% financially secure. Past week prevalence of any PEs was 18.9% (CI 17.5-20.3), 4.2% auditory hallucinations (CI 3.5-4.9), 2.5% visual hallucinations (CI 2.0-3.1),

15.3% delusions (CI 14.0-16.6), and 2.3% (CI 1.8-2.8) had mixed profile of hallucinations and delusions. Of 118 who experienced auditory or visual hallucinations in the past week, 35% experienced them at least once a day.

As compared with the other groups, those with a mixed profile experienced: hallucinations that were more distressing (p=0.0043), of longer duration (p= 0.002), of more negative content (p=0.001), comprised more commands (p≤0.0001), had more interaction with them (p=0.003), and were associated with more functional impairment (p=0.012). Mixed profile symptoms were more common in never married (p≤0.0001). Suicidal ideation was relatively common being more severe when hallucinations were associated with delusions (63.8%) compared with no hallucinations or hallucinations alone (p≤0.0001), as were depressive symptoms (76.8%, p≤0.0001).

Discussion: Psychotic symptoms are significant in Qatar particularly when hallucinations are mixed with delusions. Hence public health measures need to take these symptoms into account in screening for those at risk of clinical psychosis, particularly when associated with depressive or suicidal thoughts, and in unmarried, less advantaged groups.

S57. THE RELATION BETWEEN CHILDHOOD TRAUMA, NEGATIVE SYMPTOMS AND COGNITION IN PSYCHOSIS: THE ROLE OF GENDER, METABOLIC AND IMMUNE PARAMETERS

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Background: Childhood trauma (CT) is associated with increased negative symptoms and poorer cognition in schizophrenia spectrum disorders (SSD). As inflammatory and metabolic abnormalities have been previously linked to these factors, we aimed to investigate whether inflammatory and metabolic parameters may moderate the relationship between CT and negative symptoms and cognition. As previous studies found gender differences in the presence and role of CT in psychosis, we also performed gender specific analyses.
Methods: 187 first episode psychosis patients and 115 recent-onset psychotic disorder patients were included (men: n = 218; women: n = 84). Spearman correlation analyses were performed to assess correlations between Childhood Trauma Questionnaire (CTQ) total scores, negative symptom scores of the Positive And Negative Symptoms Scale (n = 302), Brief Assessment of Cognition in Schizophrenia (BACS) total scores (n = 281), C-reactive protein (CRP) (n = 302) and the number of metabolic abnormalities (n = 133) (blood pressure, glucose, triglycerides, HDL, waist circumference, BMI). Moderated hierarchical multiple regression analysis with interaction effects for possible moderators (i.e. metabolic factors*CT and CRP*CT), correcting for covariates (i.e. age, gender, chlorpromazine equivalent dose and smoking (cigarettes/day)). Subsequently, all analyses were performed for men and women separately.
Results: [preliminary] CTQ scores were associated with negative symptoms ($\beta = 0.215$; $p < 0.001$), both in women ($\beta = 0.235$; $p = 0.032$) and in men ($\beta = 0.222$; $p = 0.001$). CTQ scores were not associated with BACS scores ($\beta = -0.005$, $p = 0.939$), and neither for women and men when

analyzed separately ($p > 0.05$). No associations between BACS scores, negative symptoms or CTQ scores and CRP or metabolic factors were found ($p > 0.05$). Moderated hierarchical multiple regression did not reveal moderation effects of CRP or metabolic abnormalities on the relation between childhood trauma and cognition ($p > 0.05$). Gender specific analyses also did not reveal statistical significant results, when correcting for multiple testing.
Discussion: As far as we know, this is the first study investigating the moderating effect of immune and metabolic factors on the relation between CT and negative symptoms and cognition, in a relatively large SSD sample. Our Results: support the findings of previous studies that childhood trauma is associated with more negative symptoms in SSD but we did not find decreased cognition in patients with higher levels of CT. The hypothesis that the effect of childhood trauma on negative symptoms and cognition is moderated by immune and metabolic abnormalities is not supported by our data.

S58. MEDIATION AND MODERATION IN AN ADAPTIVE RANDOMISED TRIAL OF COGNITIVE REMEDIATION DELIVERY IN PEOPLE WITH A DIAGNOSIS OF SCHIZOPHRENIA

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Background: Cognitive remediation (CR) treatments benefit functioning, but we do not yet know the mechanism behind these improvements. A recent trial demonstrated that group or one-to-one therapy produced the most functional benefit, that both were cost effective and that more CR hours Results: in more functional benefit. It is often assumed that CR works by improving cognition which mediates the functioning benefits, but this has not been explored in large enough samples, nor have the models considered potential moderators at the same time.
Methods: This is a secondary analysis of post-treatment data (n=377) from a randomised controlled trial which tested three different Methods: of providing CR. We investigated, (i) whether a simple causal path between CR hours and/or delivery method could explain the variation in functional benefit, and (ii) built a mediational model using this pathway to overall functioning (Goal Attainment Score; GAS), with a composite cognitive score as a potential mediator measured at post-therapy. We further examined whether baseline total symptoms moderated the path between CR hours and cognition, and whether baseline negative symptoms moderated the path from cognition to functional outcome. We also tested whether the effects of these potential moderators occurred either via the mediator or along the direct pathway between CR hours and functioning.
Results: CR produced a significant GAS benefit for each hour of therapy ($p=0.003$), irrespective of the implementation arm (3df Wald chi-square = 4.47, $p=.215$). The mediated path from CR hours to cognition and cognition to functional outcome (GAS) was, however, small and non-significant (Coeff= .014, 95% CI =-0.010, 0.037, $p=.256$). Total symptoms did not moderate either

the path to cognition nor the direct path between treatment and outcome (p= 0.211 and p=0.896 respectively). However, negative symptoms significantly moderated the effect of cognition on outcome (p= 0.015) with high negative symptoms reducing the functional gains of improved cognition.
Discussion: Although larger changes in overall cognition were associated with larger changes in the GAS score outcome, overall cognition improvements did not mediate the relationship between hours of therapy and functioning. Previous models did not take into account negative symptoms which were shown to interfere with the translation of cognitive improvements into functional gains.

S59. SEX DIFFERENCES IN THE ASSOCIATION OF PERIPHERAL INFLAMMATION, PANSS SCORES AND SEX IN SCHIZOPHRENIA

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Background: There is a growing literature regarding a relationship between neuroinflammation and schizophrenia, however, little is currently known about a potential sex-specific relationship between psychopathology when starting antipsychotic monotherapy and its change over one month and peripheral inflammation.
Methods: The sample consisted of 116 (52.6% male) patients with schizophrenia who were started on monotherapy with a second-generation antipsychotic. Sociodemographic and clinical data were collected at baseline. Psychopathology was rated at baseline and after 2 and 4 weeks of treatment using the Positive and Negative Syndrome Scale (PANSS). Blood samples (full blood count, CRP) were taken at the same points in time. Besides CRP, the integrative immune inflammation markers neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR) and systemic immune-inflammation index (SII = NLR × platelets) were considered.
Results: Data of 116 cases were available for baseline analysis and of 57 cases at weeks 2 and 4. PANSS (sub)scores decreased significantly from baseline to consecutive follow-ups, and the two sexes did not differ in this regard. Similarly, no significant sex differences were found in CRP levels, NLR, MLR, and SSI. The Results: of Spearman rank correlation revealed no statistically significant association between PANSS (sub)scores, neuroinflammation markers, and sex at any time of investigation.
Discussion: In the light of these findings, the two sexes do not differ in regards of changes in psychopathology and inflammatory biomarkers.

S60. EFFECT OF PERSISTENT CANNABIS USE AND MANIA IN RECOVERY FROM FIRST EPISODE PSYCHOSIS

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Background: Cannabis use often precedes the onset of First Episode Psychosis (FEP) and poorer outcomes after FEP. Symptoms of mania may delay time to remission; however, the association between mania and persistent cannabis use in the recovery of FEP is underexplored. This study aimed to explore the effect of mania and persistent cannabis use in the recovery of FEP.
Methods: Secondary analysis of longitudinal data from the National EDEN study of participants with FEP aged 14–35 years. The independent variable for Mania symptoms (from Youngs Mania Rating Scale) and Persistent Cannabis use (from Kavanagh Drug Check scale revised version) were used in the analysis. Outcome variables of recovery were time in complete remission (from Relapse and Recovery assessments), Positive and Negative Symptoms scale total scores (PANSS-Total) and Global Assessment of Functioning total Scores (GAF-Total). The data were divided into 4 groups for comparison; Persistent Cannabis use with significant mania symptoms at any time point (PCMS group); Persistent cannabis use without significant mania symptoms (PC only group); Significant Mania symptoms without persistent cannabis use (MS only group) and No persistent cannabis use or mania symptoms (NPCMS group).
Analysis: 649 participants data was analysed. A logistic regression/General linear mixed modelling was performed for analysing the outcome measures between-group differences (PCMS: 55; MS only: 206; PC only: 39; NPCMS: 349). Further, a mediation analysis was performed with mania symptoms (independent variable), persistent cannabis use (mediator) and maximum time spent in remission (outcome variable).

Results: Odds of complete remission in FEP patients in the PCMS group were 65% less, and the MS only group was 62% less than the NPCMS group ($P < 0.001$). No significant between-group difference was noted in the recovery of PANSS total and GAF total scores. In mediation analysis, odds of a maximum time spent in remission was directly decreased by 2% with every point increase in mania symptoms score and 2% by every point negative recovery of mania symptoms score. Higher mania symptoms increase the odds of persistent cannabis use by 12%, and persistent cannabis use decreases the odds of maximum time in remission by 11 %. The indirect effect of mania symptoms on recovery through persistent cannabis use was minimal.
Discussion: Mania symptoms and persistent cannabis use both negatively affect the recovery of FEP. Persistent cannabis use has a synergistic effect with mania symptoms on remission. This knowledge could allow increased h focus on the importance of exploring mania symptoms in persistent cannabis users to improve the recovery of FEP.

S61. DISCOVERING THE MOLECULAR MECHANISMS UNDERLYING CANNABIS-INDUCED INCREASED RISK FOR SCHIZOPHRENIA: DIFFERENTIAL AKT FUNTIONAL STATUS AND 5-HT2AR EXPRESSION IN PLATELETS OF SCHIZOPHRENIA SUBJECTS WITH OR WITHOUT CANNABIS ABUSE

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Background: Cannabis use has a higher prevalence in individuals with schizophrenia (SZ) compared to the general population, being the most widely used illegal substance among these subjects. Additionally, cannabis use may represent a risk factor in individuals with an underlying genetic predisposition to SZ. In either case, cannabis use disorder (CUD) is highly prevalent (~26%) among SZ patients and it is associated with a lower age of onset. It has been suggested that SZ patients with comorbid CUD could represent a clinically distinct subgroup with different antipsychotic efficacy profile. However, exclusion criteria in some studies make this subpopulation understudied. Thus, studies regarding differential features among these patient subgroups are extremely scarce.

Serotonin 2A receptors (5-HT2AR) are involved in psychotic symptoms and, like Akt kinase, they are known to be modulated by THC. Moreover, their presence in blood platelets make them interesting proteins for the study in patients by a minimally invasive technique as blood extraction.

This project aims to study the molecular mechanisms underlying the relationship between cannabis abuse and schizophrenia. We evaluated 5-HT2AR protein expression, and Akt functional status (total Akt/ phospho (Ser473Akt)) in platelet homogenates of patients with SZ, CUD or both diagnoses (DUAL), compared with sex and age-matched control subjects (C).

Methods: Platelets were purified by total blood centrifugation in a density barrier solution. Platelet-containing phase was recovered, washed, homogenized and their containing proteins solubilized for western blot. Data were analyzed with GraphPad PrismTM version 9.0 (GraphPad Software, San Diego, CA, USA). Comparisons between groups were made using a two-way ANOVA followed by Tukey's post-hoc test.

Results: A significant increase in 5-HT2AR immunodensity was observed in platelet homogenates of CUD (+35%, n=14, $p<0.01$) and SZ patients (+60%, n=14, $p<0.001$), but not in DUAL subjects (n=8) comparing with C (n=36). SZ patients also showed a decrease in total Akt immunoreactivity (-60%, n=12, $p<0.05$) and an increase in phospho(Ser473)-Akt immunoreactivity (+45%, n=12, $p<0.05$), comparing with C subjects (n=33); resulting in a two-fold increase in phospho(Ser473)Akt/Akt ratio ($p<0.05$). Neither CUD nor DUAL patients showed significant changes in Akt status.

Discussion: These findings suggest that SZ, CUD and DUAL patients show different 5-HT2AR and Akt protein expression patterns, and are in line with studies suggesting clinical differences among groups. These Results: demonstrate that alterations in the 5-HT2AR and/or the Akt pathway could be good candidates for key biomarkers for future selective prevention in individuals with an increased susceptibility to develop schizophrenia following cannabis use.

S62. IMPLICATIONS OF LOCKDOWN DURING THE COVID-19 PANDEMIC ON RELAPSES OF PATIENTS IN FOLLOW-UP IN A FIRST EPISODE PSYCHOSIS PROGRAM

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Background: According to recently published studies people with a prior mental health diagnosis experienced greater psychological distress during the COVID-19 pandemic. Our study proposes to analyse possible clinical variables associated with the clinical worsening of patients with a first episode of psychosis (FEP) during lockdown due to the COVID-19 state of emergency.
Methods: We studied 141 patients with active follow-up in a FEP Program during the lockdown due to the state of emergency in Spain (between 15/3/2020 and 15/5/2020) of COVID-19 (15 At Risk Mental States (ARMS), 126 FEP). The users included in the FEP program are 16 to 35-year-old people who have presented a first affective or non-affective psychotic episode and people with an ARMS. The follow-up is from 3 to 5 years. The clinical worsening of the patients (defined as anxiety, stress or worsening of psychotic symptoms that requires optimisation of treatment or hospital admission) was recorded. Logistic regression was used to explore the association between predictor variables and risk of clinical worsening in the FEP subsample (N=126). A $p<0.05$ value was considered significant.
Results: The analysed group includes 141 patients, 89.36% of those inside the first episode of psychosis group and the rest in the ARMS group. 36.2% of the group are women.
12% suffered from either anxiety or stress and an 8.5% displayed a worsening in the psychotic symptoms and hence required pharmacological adjustments.

22% of patients worsened during the lockdown period, with no significant differences between the ARMS group (29.4%) and FEP group (21.0%). Six patients (4.3%) required hospital admission during follow-up. During the two months of follow-up, 519 visits were undertaken (67.6% phone call, 22.7% face-to-face, 9.6% home). In logistic regression, neither age, gender, nor duration of follow-up in the Program were associated with the risk of clinical worsening. Patients with schizophrenia or schizophreniform disorder were at a lower risk for hospital admission (OR= 0.24, p= 0.028) compared to other psychoses.

Discussion: Although the lockdown due to COVID-19 constitutes a stressor for a significant proportion of patients with a FEP, patients with schizophrenia show a lower risk of worsening than other psychoses, when measured in the number of hospital admissions required. Patients with a schizophrenia or schizophrenia-like diagnosis display higher scores in negative symptoms scales. This group of patients show an increased tendency of isolation and social withdrawal. This leads us to hypothesize that the forced lockdown (less of a stressor in such patients) could reduce the severity of the disorder when measured in the number of hospital admissions in said period.

S63. IMPROVING PREDICTION OF PSYCHOSIS IN YOUTH AT CLINICAL HIGH-RISK: PRE-BASELINE SYMPTOM WORSENING AND CORTICAL THINNING AS MODERATORS OF THE NAPLS2 RISK CALCULATOR

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Background: In the clinical high-risk for psychosis (CHR-P) paradigm, risk calculators estimating individuals' likelihood of converting to psychosis have the potential to assist with prognosis and intervention selection. Validation of these models in external samples and ultimate clinical implementation have been hindered by diverse sample that result in differing risk level distributions. These differences may be attributed, in part, to progression and duration of prodromal symptoms prior to ascertainment. To examine this, we tested whether duration of symptom worsening prior to ascertainment was a moderator of performance of the NAPLS2 risk calculator. As illness progression has also been detectable in measures of cortical thickness, we also examined whether this moderated effect mapped onto rates of cortical thinning detectable within the first three months of follow-up.

Methods: Participants from both the NAPLS2 and NAPLS3 sample were included in this study. A random 50-50 train-test sample split was performed on the combined sample prior to model validation. Participants were grouped as either "long symptom duration" or "short symptom duration" based on the median number of days since positive symptom increase prior to baseline. The NAPLS2 risk calculator model was applied in each of these groups and validated in the corresponding group in the validation sample. Subsequently, in a subset of NAPLS3 participants for whom follow-up scans were available, percent change in cortical thickness was combined with the risk score for each individual to predict psychosis transition and to determine the additive predictive power above and beyond clinical measures within each symptom duration group.

Results: A total of 1300 participants comprised the combined NAPLS2/NAPLS3 sample. The median duration since positive symptom worsening was 120 days. Performance metrics predicting conversion to psychosis in the validation sample are reported. In the full sample (11.3% conversion rate), the risk calculator achieved an AUC of 68% (Sensitivity/Specificity/Balanced accuracy [Se/Sp/BAC] = 0.66/0.65/0.65). In the long duration group (n = 621, 9.3% conversion rate), an AUC of 69% was achieved (Se/Sp/BAC = 0.63/0.66/0.64). In the short duration group (n = 618, 13.1% conversion rate), an AUC of 68% was achieved (Se/Sp/BAC = 0.63/0.66/0.65). In the NAPLS3 imaging subsample (n = 274), percent change in cortical thickness improved predictive power for the full sample (AUC = 77%, Se/Sp/BAC = 0.69/0.75/0.72), slightly improved predictive power for the long duration group (AUC = 72%, Se/Sp/BAC = 0.67/0.69/0.68) and significantly improved predictive power in the short duration group (AUC = 80%, Se/Sp/BAC = 0.71/0.75/0.73). In addition, the shorter duration group was younger in age and had a higher level of baseline prodromal symptoms than the longer duration group.

Discussion: This is the first study to demonstrate a moderation effect of the NAPLS2 risk calculator that could help determine the applicable risk distribution for newly ascertained patients in clinical practice. Patients with a shorter duration between prodromal symptom increase and ascertainment may best align with risk distributions conferring higher risk of conversion (mean = 0.13) and patients with a longer duration between prodromal symptom increase and ascertainment,

who may best align with risk distributions conferring a lower risk of conversion (mean = 0.08). Further, the finding that decrease in cortical thickness differentially improves prediction in the short duration but not the long duration group suggests that underlying neurological differences in this group may contribute to more rapid clinical worsening and worse outcomes. These finding should be validated in external CHR samples but has the potential to help move these risk calculator models closer to clinical implementation.

S64. EXAMINING NEGATIVE SYMPTOM DIMENSIONS AND COGNITIVE CONTROL AS PREDICTORS AND MODERATORS OF PHYSICAL AND COGNITIVE EFFORT EXPENDITURE FOR REWARDS IN EARLY PSYCHOSIS

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Background: Schizophrenia patients demonstrate less physical and cognitive effort compared to healthy controls. Allocation of both types of effort are associated with functioning. The contributors to reduced effort modulation are poorly understood in the early stages of psychotic illness. Negative symptom severity inconsistently predicts effort impairments in schizophrenia. Cognitive control, the mental representation of reinforcement properties and costs of goal-directed behavior, is related to negative symptoms and impaired functioning, but remains untested as an antecedent or moderator of reduced effort modulation. The current study sought to test the following hypotheses in early psychosis: (1) negative symptoms will inversely predict effort, (2) cognitive control will positively predict effort, (3) for patients with high levels of negative symptoms, cognitive control will not have an effect on effort but for patients with lower levels of negative symptoms, greater cognitive control will predict higher likelihood of effort allocation.
Methods: Early psychosis patients (n = 34) participated in assessments of expressive negative symptoms, motivation/pleasure negative symptoms (Brief Negative Symptom Scale), and cognitive control (AX-CPT). Effort assessments involved Treadway's physical effort expenditure for rewards task and our novel and structurally parallel task on cognitive effort. On these tasks, participants chose to complete a low effort/low pay-off or high effort/high pay-off activity.
Results: Generalized Estimated Equation Model 1 indicated that expressive (Wald $\chi2 = 2.54$) and motivation/pleasure (Wald $\chi2 = 2.26$) symptoms did not have significant main effects on hard trial choices across both effort tasks, p's > .05. Model 2 indicated that cognitive control did not independently predict effort expenditure (Wald $\chi2 = 0.22$, $p = .64$). In Model 3, a significant interaction between expressive symptoms, cognitive control, and effort emerged; At relatively low expressive symptoms (1st quartile), greater cognitive control predicted higher likelihood of physical effort expenditure ($b = 0.56$, $p = .001$), but cognitive control did not have significant effects at moderate to severe levels of expressive symptoms (2nd to 4th quartile) and for all levels of motivation/pleasure symptoms, p's > .05. Cognitive control did not significantly moderate the effect of negative symptom dimensions on cognitive effort expenditure, p's > .05.
Discussion: In early psychosis, cognitive control may aid decisions to expend high physical effort for rewards when expressive symptoms are relatively low, but the benefits of cognitive control diminish for patients with motivation/pleasure symptoms, patients with moderate to severe expressive symptoms, and when tasks demanded cognitive effort. Findings raise two possible interpretations that can be explored in future research: (1) cognitive control may not moderate

negative symptoms and cognitive effort expenditure until this ability further decompensates in chronic psychotic illness (2) the inconsistent relationship between negative symptoms and effort expenditure in schizophrenia could be due to individual differences in cognitive control and negative symptom profile.

S65. EXAMINING THE RELATIONSHIP BETWEEN POSITIVE AND NEGATIVE DIMENSIONS OF SCHIZOTYPY, LONELINESS, DEPRESSION, AND PERCEIVED SOCIAL SUPPORT

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Background: Although schizotypy is associated with prodromal forms of schizophrenia, the link between schizotypy and loneliness is limited. Past research has demonstrated an association between positive schizotypy and negative schizotypy with mood disorders and social withdrawal. We sought to extend this research and elucidate the relationship between loneliness, dimensional factors of schizotypy, and associated symptom profiles. We aimed to examine: 1) whether positive and negative schizotypy predicted loneliness; 2) whether negative schizotypy moderated the relationship between positive schizotypy and loneliness; 3) whether negative schizotypy moderated the relationship between positive schizotypy and depressive symptoms; and 4) whether negative schizotypy moderated the relationship between positive schizotypy and perceived social support.

Methods: A sample of 795 participants were recruited to complete the study through Amazon Mechanical Turk, as part of a larger study on mental health and quality of life during the COVID-19 pandemic. To examine aim 1), simple linear regression analyses were conducted. To evaluate aims 2), 3), and 4) moderation analyses were conducted using PROCESS version 4.0 through the Statistical Package for the Social Sciences Version 28.

Results: Simple linear regression analyses demonstrated that both positive ($\beta = .232$, $p < .001$) and negative ($\beta = .242$, $p < .001$) schizotypy were associated with loneliness. Negative schizotypy significantly moderated the relationship between positive schizotypy and loneliness, $b = -1.029$, $t = -3.13$, $p = .002$. Simple slopes analyses revealed that when negative schizotypy levels are low ($b = -.603$, $t = 5.84$, $p < .001$) the relationship between positive schizotypy and loneliness was stronger, than when negative schizotypy levels were high ($b = 2.073$, $t = 5.32$, $p = < .001$). There was no significant interaction between negative schizotypy or positive schizotypy to predict depression ($b = -.152$, $t = -1.05$, $p = .29$) or perceived social support ($b = .228$, $t = 1.74$, $p = .08$). The main effects of both positive schizotypy ($b = 1.620$, $t = 5.32$, $p = < .001$) and negative schizotypy ($b = .861$, $t = 5.20$, $p = < .001$) were significantly associated with depression. Additionally, while positive schizotypy ($b = -.216$, $t = -.78$, $p = .43$) did not significantly predict perceived levels of social support, the main effect of negative schizotypy ($b = -1.976$, $t = -13.18$, $p = < .001$) was significant.

Discussion: Preliminary evidence suggests that both positive and negative dimensions of schizotypy predict loneliness. However, while both positive and negative schizotypy significantly predicted depressive symptoms, only negative schizotypy predicted levels of perceived social support. Our research also supports the importance of targeting features of negative schizotypy (e.g. anhedonia, avolition, social withdrawal), to help mitigate perceived loneliness in individuals who are at risk of developing psychosis.

S66. A FAMILY STUDY ON FIRST EPISODE OF PSYCHOSIS PATIENTS: EXPLORING NEUROPSYCHOLOGICAL PERFORMANCE AS AN ENDOPHENOTYPE

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Background: Family studies provide the opportunity to investigate endophenotypes as a powerful neurobiological platform to better understand the underlying neurobiological mechanisms of schizophrenia spectrum disorders. Shared features between the patients and their first-degree relatives may shed some light on the path to identify potential causes of psychosis, and to implement preventive and therapeutic interventions.
This study aimed to explore and compare neuropsychological measures in a cohort of first episodes of psychosis (FEP) patients, their first-degree relatives and healthy controls (HC), participants on the project called PAFIP-FAMILIES.

Methods: Statistical analyses were performed using one-way ANOVA, followed by multiple comparisons test when appropriate. Age, sex and years of education were considered as covariates.
Results: From the 387 eligible FEP patients, at least one relative of 133 participated in PAFIP-FAMILES. Information from those 133 FEP, a total of 244 first-degree relatives (146 parents and 98 siblings) and 202 HC constituted this study (see Figure 1). In general, relatives showed an intermediate neuropsychological performance between the HC and the FEP patients (see Figure 2). Specifically, siblings performed similar to HC on the domains verbal memory, visual memory, working memory, motor dexterity and theory of mind, since their values practically overlap. The parents presented significant deficits, similar to the FEP patients, in executive functions; and a trend towards significance on attention.
Discussion: These findings suggest that executive and attention dysfunction might have a greater family aggregation and could be a relevant cognitive endophenotype for psychotic disorders. The study shows the potential of exploring intrafamily neuropsychological performance supporting neurobiological and genetic research in schizophrenia spectrum disorders.

S67. EXPLORING SPEECH AS A BIOMARKER FOR SCHIZOPHRENIA SPECTRUM DISORDER AND BIPOLAR DISORDER

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Background: Accurate diagnosis of psychiatric disorders relies mostly on subjective measures such as self-reported symptoms as well as observation and interpretation by healthcare professionals. Reliable biomarkers would be of great value to increase specificity and sensitivity of the diagnostic process, but such biomarkers are lacking in this field. Such a biomarker may be found in speech, as speech is a complex process involving many brain regions and often altered in psychiatric disorders such as schizophrenia spectrum disorders, and recent technological advances allow for the automated analysis of speech parameters that are not immediately audible by the human ear. The current study explores possible acoustic speech parameters as a biomarker for schizophrenia spectrum disorder (SSD) and bipolar disorder (BD).
Methods: Speech recordings 66 participants in total were analyzed, of which 23 patients with BD, 10 patients with SSD, 23 healthy controls matched to BD patients and 10 healthy controls matched to SSD patients. BPRS-E symptom dimensions were used to investigate the correlation between speech parameters and specific groups of psychiatric symptoms. Patients' speech parameters were compared to those of healthy controls.
Results: Depressive BPRS-E symptom dimension scores correlated negatively with speech rate($rs[31] = -.40$, $p = .02$) and positively with loudness variation ($rs[31] = .36$, $p = .04$). Negative psychotic symptom scores ($rs[31] = -.49$, $p = .004$) and total BPRS-E symptom scores ($rs[31] = -.39$, $p = .02$) both correlated negatively with mean voiced segment length.
Both patient groups had a lower speech rate (BD: $U = 23.00$, $p < .001$, SSD: $U = 16.00$, $p = .02$) and articulation rate (BD: $U = 15.00$, $p < .001$, SSD: $U = 8.00$, $p = .007$), a shorter mean voiced segment length (BD: $U = 28.00$, $p < .001$, SSD: $U = 10.00$, $p = .008$), a longer mean unvoiced segment length (BD: $U = 31.00$, $p < .001$, SSD: $U = 18.00$, $p = .02$) and more variation in pitch (BD: $t[44] = -2.86$, $p = .01$, SSD: $U = 18.00$, $p = .02$), but less variation in loudness than healthy controls (BD: $U = 98.00$, $p < .001$, SSD: $U = 15.00$, $p = .02$). Moreover, speech of SSD patients was found to contain more jitter ($t[18] = -2.52$, $p = .04$) and shimmer ($U = 19.00$, $p = .03$) (measures of decreased voice quality) than speech of healthy controls.

Discussion: We found speech rate and mean voiced segment length to be promising biomarkers for BD and SSD respectively. Furthermore, mean voiced segment length may be an objective measure of general psychiatric symptom severity in these patients and could therefore be useful in clinical practice. Automated speech analysis is a promising method towards the development of objective biomarkers for BD and SSD.

S68. CHANGES IN DYNAMIC RESTING STATE CONNECTIVITY IN YOUNG PATIENTS WITH FIRST EPISODE PSYCHOSIS

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Background: The evidence so far suggests that psychotic disorders are characterized by alterations in brain functional networks. While most studies have focused on the spatial

configuration of these connections, it has been demonstrated that during rest, the brain transitions in a non-random way across stable periods (or "meta-states"), in organized temporal patterns. So far, this has only been studied in adult patients with chronic schizophrenia, while this has not been examined in affective disorders. Adolescence is a crucial period in terms of the development of brain networks and assessing individuals at illness onset has the potential to help understand processes associated with the aetiopathogenesis of the disease. Here we aim to measure temporal dynamics of brain connectivity (dFC) in individuals with recent, adolescent-onset psychosis (FEP).
Methods: Ninety-five FEP patients aged 10 to 22 years, with an illness duration of less than 1 year, were compared with 57 age and gender-matched healthy volunteers (HV) using clinical and cognitive measures. FEP patients were sub-divided into affective (bipolar disorder or depressive disorder with psychotic symptoms) or non-affective (schizophrenia spectrum disorders) psychoses. Participants underwent rs-fMRI acquisition with closed eyes in a 3Tesla scanner (Magnetom Prismafit, Siemens). Images were motion-corrected (Parkes et al., 2018) and the BOLD signal was extracted from 638 similarly sized regions. A connectivity matrix was computed per time point using the multiplication of temporal derivatives (Shine et al., 2015). For each subject, temporal connectivity matrices were clustered according to their similarity using K-means, yielding 15-30 clusters or meta-states. For each meta-state, a directional graph was constructed, from which graph-measures summarizing transition dynamics were computed (Ramirez-Mahaluf et al., 2020). The first set of general linear models (GLM) tested the effect of group (schizophrenia spectrum disorders and affective psychoses vs HV), adjusting for covariates (age, sex, and framewise displacement), for each graph-analytic measure. The second set of GLM was used to assess the association of clinical variables (age, sex, symptom severity, general cognitive performance, and anti-psychotic dose) with each of these parameters within the whole FEP sample. P-values were FDR corrected for multiple comparisons.
Results: FEP patients with schizophrenia spectrum disorders exhibited higher modularity (Q) (pQ=0.04), and less global efficiency (GE) (pGE=0.02), and cost efficiency (CE) (pCE=0.02) than HV, while patients with affective psychoses showed no differences relative to HV. Within the FEP group as a whole, we found that the higher general cognitive performance, the better the GE and CE (pGE=0.04, pCE =0.04), and the lower Q, cost, leap size, and immobility (pQ=0.04, pCO=0.02, pJSS=0.04, pDiS=0.03, respectively).
Discussion: Our Results: suggest that FEP patients with schizophrenia spectrum disorders tend to transition between meta-states in a less random manner than HV, with some transitions being less frequent regardless of the similarity between meta-states. Within the FEP group as a whole, cognitive function was linked to almost all dFC measures: poorer cognitive capacity was correlated with less integration and coherence between the different meta-states. This extends previous findings of an association between temporal dynamics and cognitive skills in healthy individuals. Our Results: suggest that dFC may provide a useful insight into brain-based biomarkers which specifically characterize patients with early-onset, non-affective psychosis.

S69. LACTATE DEHYDROGENASE CONCENTRATION IN CEREBROSPINAL FLUID AND EARLY TREATMENT RESPONSE IN FIRST-EPISODE PSYCHOSIS

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Background: A poor response to antipsychotic therapy in the first two weeks of schizophrenia treatment may justify a prompt switch to alternative medication in some cases. We aimed to explore whether cerebrospinal fluid (CSF) biomarkers might predict early response to antipsychotic treatment in first-episode psychosis (FEP).
Methods: Ninety-eight FEP inpatients were studied. A lumbar puncture was performed at index admission to study CSF parameters (glucose, total proteins, lactate dehydrogenase [LDH]). The Positive and Negative Syndrome Scale (PANSS) was used to assess psychopathological symptoms at baseline and two weeks later. We used Wallwork PANSS factors to categorize symptoms in positive and negative subscores. Lack of early response was defined as a reduction lower than 20% in PANSS positive subscore at two weeks with optimal antipsychotic treatment doses. First antipsychotic was changed in these non-responders patients. Logistic regression was also used to explore the association between CSF biomarkers and lack of response while adjusting for age, gender, cannabis use, duration of untreated psychosis (DUP) and PANSS negative symptoms.
Results: 18 out of 98 (18.4%) of FEP patients did not respond to first antipsychotic treatment at week 2. Higher LDH CSF concentrations were associated with a lack of antipsychotic treatment response at two weeks (OR= 1.059, CI95%: 1.015 to 1.105, p= 0.008). Glucose or total proteins in CSF were not associated with antipsychotic treatment response. The area under the curve of the COR curve for LDH CSF concentrations was 0.69.
Discussion: Our study suggests that LDH CSF concentrations are associated with the early treatment response to the first antipsychotic treatment in FEP.

S70. LONGITUDINAL CHANGE TRAJECTORIES OF PERSONALITY TRAITS CAN PREDICT SEVERITY OF PSYCHOTIC LIKE EXPERIENCES IN A NATURALISTIC SAMPLE: RESULTS: FROM THE IMAGEN CONSORTIUM

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Background: Psychotic-like experiences (PLEs) occur in about 15% of the healthy population, as transient experiences without any functional impairment or required treatment. Although the distinction between psychotic symptoms and PLEs is not fully understood, their occurrence is related to a four-fold increased risk of a psychosis diagnosis. Cross-sectional studies provided evidence about the multifaced dimensions of psychosis risk, but how risk for the disease unravels across the lifespan remains unclear. Indeed, grasping the patterns of transformations that precede PLEs onset might clarify which kind of early changes contribute most to psychosis susceptibility. Thus, this study aimed to identify, using an individual longitudinal tracking perspective, how cognitive, environmental and personality trajectories of change might predict final PLEs severity.
Methods: A total of 784 subjects recruited by the Imagen consortium were selected and randomly split into two independent groups: the discovery (DS) and the validation (VS) samples included 526 (females=291) and 258 (females=132) participants, respectively; the age range in both samples was 13-15 years at baseline (BL) and 21-24 years at follow-up 3 (FU3). For each individual, Latent Growth Curve Models were implemented to compute two longitudinal scores of individual change over time across each of 40 variables, collected across three-time points (BL,

FU2, FU3): the pool of selected features included working memory, decision-making, and go-no go performances scores (CANTAB); use and abuse scores for 7 substances (European School Survey Project on Alcohol and Drugs scales); personality traits, temperament and character scores (NEO Five-Factor Inventory, Temperament, and Character Inventory, Substance Use Risk Profile Scale). Individual intercept and slope values entered three independent classifiers (cognition, environment, personality), aimed at predicting high vs. low PLEs (assessed through the Community Assessment of Psychic Experiences 42) at FU3 via Support Vector Machine, within a double-cycle, nested cross-validation (CV) framework. The algorithm was trained in the DS and replicated into the VS. To assess if our model was related to other relevant clinical outcomes, we computed an ANOVA to test the association between the classification categories predicted by the algorithm and Strength and Difficulties Questionnaire (SDQ) FU3 scores.
Results: The model based on personality trajectories of change predicted PLEs severity with a balanced accuracy (BAC) of 69.6% in the DS and 61.5% in the VS. The environmental model (DS: BAC=52.5%; VS: BAC=50%) and the cognitive model (DS: BAC=49.6%; VS: BAC=50%) instead performed at chance-level. Within the personality-based model, increased levels of neuroticism and hopelessness over time contributed most reliably to classification accuracy (CV Ratio>0.5). In both samples, subjects correctly classified as having high PLEs based on the personality model also showed significantly higher SDQ scores, in the hyperactivity and emotional disruption risk domains ($p<.001$).
Discussion: The developmental trajectories of specific personality traits predict part of the severity level of PLEs, suggesting a possible role of the evolution of personality traits during adolescence in influencing psychosis risk. The association of the algorithm accuracy with the risk of developing both emotional and hyperactivity disorders suggests the clinical relevance of these two psychopathological dimensions for early identification and intervention: in fact, this result highlights how specific changes during personality development might be also associated with other measures of psychiatric vulnerability, related with PLEs severity.

S71. VR-SOAP- VIRTUAL REALITY TREATMENT FOR IMPROVING SOCIAL ACTIVITIES AND PARTICIPATION OF YOUNG PEOPLE WITH PSYCHOSIS: A PILOT STUDY

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Background: Young people with a psychotic disorder have the same social goals in life as their healthy peers, but stay behind in realizing those goals. They want to have pleasurable social (leisure) activities, friends, a partner and a satisfying job. However, their social networks are smaller, they participate less often in social leisure activities and are less successful in work and education [1]. As a result, they report a lower quality of life and insecurity about the future. To this end we developed and piloted a new Virtual Reality treatment for improving Social Activities and Participation (VR-SOAP).
The main determinants of social interaction difficulties have been identified and are shown in box 1

Box 1. Determinants of social interaction difficulties in participants with psychotic disorders.

1. Neurocognitive deficits and negative symptoms

Attentional control, information processing, initiating, planning, motivation, reward processing

2. Social cognition problems Emotion perception, attribution, theory of mind, empathy

3. Residual psychotic and affective symptoms

Paranoid ideations, social anxiety

4. Adverse social experiences over the life course

Childhood trauma, exclusion, stigma mental illness

5. Poor communication skills

Responding and sending, affiliative, instrumental role and interactional skills

However, these difficulties differ in prevalence and severity between individuals. Additionally, each of these difficulties are multifaceted, overlapping and interrelated.

Therefore VR-SOAP is designed as a modular treatment to address the contributing causes that are specific to the individual, i.e., the participant and therapist will opt for those modules that most closely relate to the causes of impaired social functioning.

Practicing with a broad range of social situations is at the heart of the treatment. VR role playing games in which these skills are practiced and consolidated are therefore recurrent in all sessions.

Methods: A dual centre pilot study was conducted to investigate the acceptability and feasibility of VR-SOAP. In total 5 participants aged between 18 and 35 with a DSM-5 diagnosis in the psychosis spectrum and social functioning difficulties were included. Before and after the treatment the PANSS, BNSS, and different questionnaires were administered along with ecological momentary assessments (EMA) in which the patient filled in a diary 5 times a day for 14 weeks. Extensive interviews targeting different domains of the theoretical framework of acceptability (TFA)[2] were conducted both with participants and therapists separately.

Results: Both participants and therapists reported the therapy to be acceptable. All participants managed to complete all 14 sessions. No dropouts were encountered. Generally, participants were enthusiastic about the treatment and mentioned being more confident in their social interactions. Skills that participants believed to have obtained were “starting and continuing a conversation” and “to look for positive things”. Participants mentioned to be satisfied with the treatment regarding their set goals. Two of the participants mentioned that they still need more time to improve their social skills though they did mention an improvement in this domain. According to both participants and therapists the treatment targets in VR-SOAP are highly relevant for young adults with psychosis. None of the participants mentioned VR-SOAP to have significant opportunity costs. A potential pitfall of the therapy that was mentioned during the interview by therapists was time pressure. Of the participants only one-person experienced time pressure.

Discussion: In this pilot study VR-SOAP was found acceptable on multiple domains of the TFA framework. From the interviews with both participants and therapist it can be concluded that all participants improved at least on one domain though there were significant individual differences. However, to actually quantify these Results: and generalize these findings to the patient population a large-scale follow-up study is necessary.

Therefore, a multicentre RCT has started in November 2021. A total of 116 people (18-35 years) with a DSM-5 diagnosis in the psychosis spectrum will be included. Participants will be allocated

to either VR-SOAP (experimental group) or VRelax (active control group). With this trial the effect of VR-SOAP on social contacts, leisure activities and participation in society will be investigated whilst non-specific effects (e.g., time with therapist and in VR) are being controlled for.

S72. TRAJECTORIES OF TOBACCO USE IN INDIVIDUALS AT CLINICAL HIGH RISK FOR PSYCHOSIS

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Background: Prevalence of tobacco use is much higher in patients with psychosis (61.6%%), and individuals at clinical high risk for psychosis (CHR-P) (16.6-46%) compared to the general population (20.7%). Tobacco smoking has been associated with higher severity of (subclinical) positive symptoms in these groups, although less consistently in CHR-P and the general population. It is possible that not all tobacco users, but specifically continuous heavy users or those who increase their tobacco use are at higher risk of poor outcome. In the current study, we aimed to identify two-year trajectories of tobacco smoking behaviour in a CHR-P sample. Subsequently, we examined baseline predictors of most likely trajectory class membership and associated clinical outcome over time.

Methods: 324 UHR subjects from the multicenter European Gene-Environment Interactions (EU-GEI) study were included in current analyses. Latent class mixed model analysis (LCMM) was used to identify and visualize clusters of participants with similar trajectories of tobacco smoking assessed at baseline, 6, 12 and 24 months follow-up. To examine associations between baseline characteristics and trajectory class membership chi-square test and analyses of variance (ANOVA) were conducted. Mixed effects models were applied to investigate associations between trajectory class and longitudinal outcome in attenuated psychotic symptoms (APS) and emotional disturbance as assessed with the Comprehensive Assessment of At-Risk Mental States (CAARMS), while accounting for covariates. Finally, cox proportional hazard analyses investigated associations with transition risk.

Results: Participants were classified into one of four latent smoking trajectory classes, namely (i) persistent high smoking (n=110), (ii) decrease in smoking behaviour (n=29), (iii) persistent low smoking (n=165) and (iv) increase in smoking behaviour (n=20). Individuals in the persistently high and increasing class were older compared to those in the persistently low smoking class. Individuals in the low smoking class reported less current cannabis use at baseline compared to all other trajectory classes. Regarding longitudinal outcome over time, pair-wise comparisons revealed significant interaction effects with higher increase in APS in the high trajectory class compared to the low (ES=9.770, SE=4.873, p=.046) and decreasing trajectory class (ES=18.182, SE=7.612, p=.018) at two-year follow-up. Furthermore, higher decrease in emotional symptoms at two-year follow-up was found in the decreasing trajectory class compared to the high (ES=-10.396, SE=3.414, p=.003), increasing (ES=-11.347, SE=4.551, p=.014) and low trajectory class (ES=-11.378, SE=3.290, p=.001).

Discussion: Increase in APS in the high smoking class compared to the decreasing and low trajectory class might indicate persistent tobacco smoking as a potential risk factor for an unfavourable clinical course. However, no associations were found with an increased risk for transition. Possible covariation between decrease in smoking behaviour and emotional symptoms warrants further investigations, e.g. with more detailed every-day life assessment in order to understand causal interrelations.

S73. ASSOCIATIONS BETWEEN MARKERS OF ACUTE AND CHRONIC INFLAMMATION AND MENTAL DISORDERS IN EARLY ADULTHOOD: A NESTED CASE-CONTROL STUDY

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Background: Studies of blood-based inflammatory markers have suggested that low-grade inflammation occurs in association with several mental disorders, including psychotic disorders. However, markers of chronic inflammation (such as soluble urokinase plasminogen activator receptor [suPAR]) and inflammation regulation (such as alpha-2-macroglobulin) are less well studied. Furthermore, the relationship between inflammatory markers and co-morbidity is not well understood, and young adults are under-represented in studies to-date.
Aims: We aimed to: 1) compare levels of select plasma inflammatory markers between young people aged 24 years with and without mental disorders (psychotic disorder, moderate/severe depressive disorder and generalised anxiety disorder [GAD]); and 2) evaluate associations between inflammatory markers and psychiatric co-morbidity (number of mental disorders).

Methods: Sample: The study sample comprised 781 participants of the Avon Longitudinal Study of Parents and Children who completed assessments for mental disorders and provided plasma samples at age 24 years. This included 377 case participants who met criteria for psychotic disorder (n=35), moderate/severe depressive disorder (n=202) or GAD (n=268) and 404 control participants who did not meet such criteria.
Outcomes: Psychotic disorder was assessed using the Psychosis-Like Symptoms Interview. In line with previous studies, this outcome was defined as having at least one definite psychotic experience not attributable to sleep or fever which recurred at least once per month over the previous six months, and was associated with severe distress, marked impairment of the participant's social or occupational functioning, or led them to seek help from a professional source. Moderate/severe depressve disorder and GAD were assessed using the Computerised Interview Schedule Revised and defined according to International Classification of Diseases v10 criteria.

Markers: Plasma concentrations of eight acute inflammatory markers (interferon-gamma, interleukin [IL]-6, IL-8, IL-10, tumour necrosis factor-α, C-reactive protein, soluble intercellular adhesion molecule 1 and soluble vascular cell adhesion molecule 1) were measured using

multiplex enzyme-linked immunoassay. Levels of these markers were standardised and summed to derive an acute inflammation composite score (AICS). Concentrations of suPAR and alpha-2-macroglobulin were measured using enzyme-linked immunoassays and standardised before analysis.

Analysis: Logistic regression was used to compare inflammatory marker levels in cases and controls for each outcome. Poisson regression was used to evaluate associations between inflammatory markers and psychiatric co-morbidity (number of mental disorders). Models were adjusted for sex, body mass index, cigarette smoking, regular cannabis use and employment status. Missing data for exposures and covariates were imputed using multiple imputation and estimates were combined across ten imputed datasets.

Results: Compared to controls, there was evidence that the case group had slightly higher mean BMI (25.3 vs 24.1 kg/m2, p<0.001) as well as higher proportions for female sex (75.1% vs 52.7%, p<0.001), daily tobacco smoking (21.0% vs 6.4%, p<0.001), regular cannabis use (11.1% vs 3.2%, p<0.001) and unemployment (14.5% vs 7.2%, p=0.001).
There was evidence of associations between psychotic disorder and AICS (adjusted odds ratio [aOR] 1.11, 95% confidence interval [CI] 1.02 – 1.21) and suPAR (aOR 1.73, 95% CI 1.17 – 2.57), with weak evidence for an association with A2M (aOR 1.50, 95% CI 1.00 – 2.83).

There was evidence for an association between depressive disorder and suPAR (aOR 1.30, 95% CI 1.05 – 1.62) but not for AICS or A2M.

For GAD, there was little evidence of associations with AICS, suPAR or A2M.

There was weak evidence for an association between suPAR and number of mental disorders (Poisson coefficient 0.10, 95% CI 0.01 – 0.19) but not for AICS or A2M.

Discussion: Compared to controls without mental disorders, 24-year-olds with psychotic disorder had higher inflammatory burden as indexed by raised markers of acute inflammation (AICS) and chronic inflammation (suPAR), with comparatively weaker evidence for depressive disorder followed by GAD. suPAR may have a role as a transdiagnostic marker of psychopathology, but this requires confirmation in further studies of young adult samples. Limitations of this study include its cross-sectional nature (which limits causal inferences) and low sample size (particularly for psychotic disorder).
Conclusions: These Results: suggest that there is dysregulation of markers of both acute and chronic inflammation in young people with psychotic disorder. The findings have implications for the understanding of the role of inflammation in mental disorders, and particularly psychotic disorder, in early adulthood.

S74. USE OF A BAYESIAN NETWORK MODEL TO PREDICT PSYCHIATRIC ILLNESS IN INDIVIDUALS WITH 'AT RISK MENTAL STATES' FROM A GENERAL POPULATION COHORT

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Background: The 'at risk mental state' (ARMS) paradigm has been introduced in psychiatry to study prodromal phases of schizophrenia. With time it was seen that the ARMS state can also precede mental disorders other than schizophrenia, such as depression and anxiety. However, several problems hamper the paradigm's use in preventative medicine, such as varying transition rates across studies, the use of non-naturalistic samples, and the multifactorial nature of psychiatric disorders. To strengthen ARMS predictive power, there is a need for a holistic model incorporating—in an unbiased fashion—the small-effect factors that cause mental disorders.
Methods: Bayesian networks, a probabilistic graphical model, was used in a populational cohort of 83 ARMS individuals to predict conversion to psychiatric illness. Nine predictors—including state, trait, biological and environmental factors—were inputted.
Results: Dopamine receptor 2 polymorphism, high private religiosity, and childhood trauma remained in the final model, which reached an 85.51% (SD= 0.1190) accuracy level in predicting conversion.
Discussion: This is the first time a robust model was produced with Bayesian networks to predict psychiatric illness among at risk individuals from the general population. This could be an important tool to strengthen predictive measures in psychiatry which should be replicated in larger samples to provide the model further learning.

S75. THE OPUS YOUNG TRIAL - EFFICACY OF EARLY INTERVENTION VERSUS TREATMENT AS USUAL FOR CHILDREN AND ADOLESCENTS WITH A FIRST EPISODE PSYCHOSIS. PROTOCOL OF A RANDOMISED CLINICAL TRIAL

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Background: In Denmark, the incidence of schizophrenia and other psychotic disorders in childhood and adolescence is increasing, and the early onset of psychotic disorders is associated, with high risk of low quality of life, low rates of recovery, substance misuse, higher rates of suicide, violence, and legal problems, low educational and vocational attainment, and a significantly reduced life expectancy of 15-20 years.
To address the evident need to improve the treatment of psychosis in children and adolescents, we developed a new psychosocial intervention and treatment manual (OPUS YOUNG) based on the OPUS manual targeting young adults.

The overarching purpose of the OPUS YOUNG trial is to improve the treatment and outcome of first-episode psychosis in children and adolescents. No trials have investigated Early Intervention Services in samples of patients below age 18 years with a randomized controlled design. We will compare the efficacy and cost-effectiveness of OPUS YOUNG to treatment as usual (TAU) in adolescents with first-episode psychosis aged 12-17 years.

Methods: Between June 2021 and June 2023, we will include 284 participants and randomize them 1:1 to a two-year intervention of OPUS YOUNG versus TAU. We will conduct a blinded assessment of treatment effects after 12 months, after 24 months (treatment endpoint), and at 30 months to evaluate the sustainability of the intervention effects.
The OPUS YOUNG treatment manual builds on the Danish evidence-based intervention for young adults, OPUS, adapted to meet the specific needs of adolescents. The OPUS YOUNG intervention consist of 1) intensified support for caretakers and relatives including siblings; 2) social cognition and interaction training; 3) individual cognitive behavioral case management; 3) school or educational support; 4) prevention and treatment of substance misuse; and 5) algorithm for personalized psychopharmacologic treatment.

Our primary outcome at treatment endpoint will be a blinded investigator assessment of social functioning. Secondary key outcomes measures are positive and negative symptoms, client satisfaction, and health-related quality of life. Further outcomes are general psychopathology, neurocognitive functioning, social cognitive functioning, self-efficacy, experience of service, treatment alliance, the use of pharmacotherapy, school adherence, family burden, substance misuse, adverse treatment effects, and health economic measures.

Results: The Results: will be ready for presentation in 2025
Discussion: The overwhelming individual and socio-economic burdens of psychotic disorders combined with the severe prognosis and increasing incidence of early-onset schizophrenia spectrum disorders, emphasize the urgent need for high-quality clinical trials to direct and enforce best clinical practice. The experimental intervention in this trial integrates the most promising psychosocial and pharmacological treatments and promotes resilience in an age-appropriate program for early-onset psychosis.

S76. GAMING DISORDER AMONG PSYCHOTIC PATIENTS: A SCOPING REVIEW

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Background: Gaming disorder has only been recognized as a behavioral addiction in the latest version of the International Classification of Diseases by the World Health Organization in 2019. This draws attention to the growing interest in understanding the impact of video games on mental

health. Whereas links between substance addictions and psychotic disorders have been well studied, research on behavioral addictions (e.g. gaming disorder) among people with psychotic disorders is scarce, even if the adverse impact of these conditions are widely recognized by clinicians. This scoping review aimed to summarize the current state of knowledge on this comorbidity and to identify knowledge gaps.
Methods: We used Levac's six-stage methodology for scoping review. Two hundred and twelve articles from seven databases were identified. These articles were screened by a pair of independent reviewers. Eight articles were included following the consensus of the two reviewers.
Results: Available literature only consisted of 6 case reports of 9 patients and two empirical studies. No available data allowed us to determine the prevalence or incidence of gaming disorder among patients with psychotic disorders. In the included cases, there were two presumed psychosis-triggering mechanisms and it seemed that excessive video game play or abrupt gaming disruption may trigger psychosis in some individuals. In one empirical study, it was found that schizophrenic patients experiencing self-stigma used video games as a coping strategy to help them connect with others through the anonymity that the Internet provides. Lastly, no GD measurement scale has been validated for the psychotic population.
Discussion: The Results: highlight a significant lack of knowledge on psychotic disorders comorbid with gaming disorder. Only a few reported cases and two studies exposed the direct association between those two conditions. Knowledge of video games is essential to psychiatrists because asking about this habit often leads to a significant amount of information in the patient's assessment. It would also be beneficial to investigate the patients' motivations for gaming and the causal link between different psychotic symptoms and the development of a GD. Only a few reported cases and a single study exposed the direct association between those conditions. Future studies should focus on 1) the prevalence, incidence, and risk factors of psychotic disorders in patients with GD; 2) The incidence of GD in patients with psychotic disorders; 3) creating new tools aimed to screen for GD in psychotic patients. These findings will help to deploy adequate resources to manage these patients.

S77. CHILDHOOD TRAUMA IN CHILDREN AT FAMILIAL HIGH RISK OF SCHIZOPHRENIA OR BIPOLAR DISORDER: A LONGITUDINAL STUDY THE DANISH HIGH RISK AND RESILIENCE STUDY – VIA 7 AND VIA 11

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Background: Schizophrenia and bipolar disorder are severe mental illnesses, and children born to familial high risk of these two disorders, will have a higher risk for developing severe mental illness themselves. Furthermore, it is known that exposure to childhood trauma increases the risk for later development of severe mental illness. However, to our knowledge, no other studies have examined childhood trauma among children at familial high risk of schizophrenia (FHR-SZ). And studies examining childhood trauma among children at familial high risk of bipolar disorder (FHR-BP) are rare.
This study is a part of the longitudinal, prospective cohort study The Danish High Risk and Resilience Study – VIA7 and VIA11. The aim of this study is to examine the prevalence of childhood trauma in a cohort of children at FHR-SZ or FHR-BP compared to population-based controls (PBCs).

Methods: At baseline assessment (age 7 years) 512 children at FHR-SZ (N=199), FHR-BP (N=118) and PBCs (N=195) were examined. At the first four-year follow-up (age 11 years) 451 children at FHR-SZ (N=172), FHR-BP (N=104) and PBCs (N=175) participated (retention rate 87.3%). Childhood trauma was measured with the semi-structured clinical interview; Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version – PTSD-section (K-SADS-PL PTSD-section).
Results: Children at FHR-BP had a two-fold increased risk of exposure to any lifetime (age 0-11 year) childhood trauma compared with PBCs. Both children born to FHR-SZ and FHR-BP had a nearly two-fold increased risk for being exposed to any childhood trauma during early childhood (0-7 years) and a 1.5 increased risk during middle childhood (7-11 years). Children at FHR-SZ and FHR-BP had more than 3 times higher risk for being exposed to interpersonal trauma during their lifetime (0-11 years) compared to PBCs. Moreover, the risk for exposure to interpersonal trauma was highest during early childhood (age 0-7 years) as children at FHR-SZ had almost 7

times higher risk for interpersonal trauma and children at FHR-BP had almost 5 times higher risk for interpersonal trauma from age 0-7 years compared with PBCs. During middle childhood (7-11 years) both high risk groups had more than double risk for interpersonal trauma compared with PBCs. Lastly, both children at FHR-SZ and FHR-BP had a higher prevalence of exposure to multiple types of trauma compared with PBCs during their lifetime. Similar findings regarding exposure to multiple types of trauma were found in early and middle childhood.
Discussion: In our study, children at FHR-SZ and FHR-BP are at increased risk for being exposed to childhood trauma compared with PBCs. Thus, these children are not only genetically at risk for development of severe mental illness, but also at environmental risk. This study underscores the need for early detection and prevention of childhood trauma in children at familial high risk of schizophrenia or bipolar disorder.

S78. PRE-ONSET SELF-HARM IS ASSOCIATED WITH DISTINCT CLINICAL TRAJECTORIES DURING A FIRST EPISODE OF PSYCHOSIS

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Background: Self-harm and suicide attempts are relatively common before the onset of psychosis and are potential markers of affective dysregulation. During the first episode of psychosis (FEP), individuals with pre-onset antecedents of self-harm or suicide attempts may thus follow distinct clinical trajectories. The current presentation examines the associations between pre-onset self-harm or suicide attempts and clinical outcomes during the first two years of treatment for FEP, and contrasts these precursors to subthreshold psychotic symptoms, another pre-onset predictor of outcomes.
Methods: We systematically recruited individuals with incident FEP in a catchment-based FEP service in Montreal, Canada. We retrospectively assessed pre-onset self-harm, suicide attempts and subthreshold psychotic symptoms using semi-structured interviews with participants and relatives, complemented by a review of medical records. Pre-onset self-harm was defined as deliberate, non-suicidal self-injury (e.g., head banging, cutting) that preceded FEP onset. In a subset of participants with available data, we also measured pre-onset suicide attempts. Pre-onset subthreshold psychotic symptoms included attenuated or brief psychotic symptoms consistent with the At-Risk Mental State. Outcomes included repeated measures of positive, negative, depressive, and anxiety symptoms as well as functioning over the first two years of treatment for FEP. We used chi-squared and Kruskal-Wallis tests, and linear mixed models with quadratic effects of time.
Results: Of 321 participants (30.2% women; median age at FEP onset: 22 years), 38 (11.8%) had pre-onset self-harm and 240 (74.8%) had pre-onset subthreshold psychotic symptoms. Individuals with pre-onset self-harm had a longer duration of untreated psychosis and were more likely to have comorbid substance use disorder compared to individuals without pre-onset self-harm. Pre-onset self-harm was not associated with diagnoses of affective versus non-affective psychosis at baseline. On average over the two years of follow-up, pre-onset self-harm was associated with higher levels of positive symptoms (standardized mean difference [SMD]=0.37; 95% confidence interval [CI]: 0.11, 0.62), depressive symptoms (SMD=0.78; 95% CI: 0.51, 1.05), and anxiety symptoms (SMD=0.48; 95% CI: 0.20, 0.77), and lower levels of functioning (SMD=-0.38, 95% CI: -0.72, -0.05). Except for functioning, these associations were robust to adjustment for

comorbid substance use disorder or affective psychosis at baseline. For depression and anxiety, differences associated with self-harm decreased over time and were no longer significant by two years. Of a subsample of 94 participants, 15 (16%) had pre-onset suicide attempts, and this antecedent was associated with higher levels of depression and anxiety that improved during follow-up. In contrast to pre-onset self-harm or suicide attempts, pre-onset subthreshold psychotic symptoms had no association with any clinical outcome over follow-up.
Discussion: Pre-onset self-harm stands out as a risk factor for poorer longitudinal outcomes following FEP onset. Specifically, we found elevated levels of positive symptoms, depression and anxiety associated with pre-onset self-harm. The improvement of depression and anxiety over follow-up may reflect the effects of comprehensive FEP treatment on affective distress, as indexed by self-harm or suicide attempts. Although individuals with these pre-onset antecedents are not representative of the total FEP population, their distinct trajectories highlight clinical needs that may require and benefit from early intervention approaches.

S79. ANTIPSYCHOTIC TAPERING SPEED AS PREDICTOR FOR PSYCHOTIC RELAPSE AFTER FIRST-EPISODE PSYCHOSIS: PRELIMINARY FINDINGS

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Background: The prevention of relapse is a crucial treatment target in first episode psychosis (FEP) patients, as up to 85% of FEP patients experience a psychotic relapse within 5 years of remission from the first episode. Current guidelines recommend continuation of antipsychotic (AP) treatment during the first year after remission, because AP use aids in preventing relapse. However, patients and clinicians may have several reasons to reduce or discontinue AP medication early. When tapering AP medication, a gradual reduction is preferred over rapid discontinuation. Although gradual dose reduction may intuitively reduce relapse risk, this notion is not supported by a large body of evidence. Therefore, this study investigates the association between AP tapering speed and psychotic relapse in the first year after recovery from FEP in 78 patients. As self-report on medication use is not always accurate, we here present unique dispensation data from pharmacies to calculate tapering speed.
Methods: This study is part of the ongoing HAMLETT trial (Begemann et al., 2020), which is a randomised controlled discontinuation trial. Half of the participants is randomised to the continue group (where 25% reduction is allowed), the other half to the discontinue group. Participants were recruited from mental health care centres throughout the Netherlands and included in the trial when in remission (for 3 to 6 months) from FEP. For this study, participants with a follow-up of at least one year were included. The definition of relapse was based on hospitalisation due to worsening of psychotic symptoms, the clinical judgement of the treating psychiatrists and a score of ≥ 4 on any item from the positive subscale of the positive and negative syndrome scale (PANSS). Use of antipsychotic medication was based on data from the Dutch Foundation for Pharmaceutical Statistics (SFK). SFK collects dispensation data from community pharmacies in the Netherlands. Information from this dataset included dispensation dates of AP medication and daily dose (standardized in Defined Daily Doses; DDD), among others. Data was available from more than 90% of participating pharmacies. Tapering speed (in DDD/day) was calculated as the difference

of AP dose at remission and at the end of AP discontinuation, divided by the number of days in between (n=78). Data was analysed using binary logistic regression models. Covariates were measured at baseline and included age, sex, years of education (YOE), and duration of FEP (in months).
Results: Within the first year follow-up, 47% (n=37) of FEP patients experienced a relapse. Covariates did not significantly predict the occurrence of relapse ($\chi2(4)=1.02$, $p=0.91$). In a model adjusted for covariates ($\chi2(5) = 2.09$, $p=0.84$), tapering speed was not significantly related to relapse (relapse: -0.04±0.17, non-relapse: -0.01±0.03 DDD/day, OR=0.04, p=0.47). Similarly, in a model without covariates, tapering speed was not significantly associated with relapse (OR=0.03, p=0.41). Assumption testing for multi-collinearity between tapering speed and the covariates did not indicate any violations ($r<0.7$). In specific, these analyses did not show a significant relation between tapering speed and the covariates age, sex, YOE and duration of FEP (r=-0.18, 0.04, 0.14,-.10, $p>0.05$, respectively).
Discussion: The Results: of this study are preliminary and should be interpreted carefully. These initial analyses suggest that AP tapering speed may not be related to relapse. Yet, we are aware of the limited sample size. New pharmacy data has been requested at the time of writing. We aim to extent the study sample to up to 200 participants with a follow-up time of at least a year in the coming months.

S80. THE RELATIONSHIP BETWEEN PSYCHOTIC AND PTSD SYMPTOMS IN ADULT SURVIVORS OF DEVELOPMENTAL PSYCHOLOGICAL TRAUMA AT RISK OF PSYCHOSIS: FINDINGS FROM THE MULTICENTRE IMPACT STUDY

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Background: Developmental psychological trauma induces vulnerability to psychosis and PTSD. It has been proposed that processes involved in PTSD may underpin psychotic symptoms in trauma survivors. Plausible mechanisms include that psychotic symptoms may reflect intrusive memories of trauma. We hypothesised that PTSD symptom severity and meeting the diagnostic threshold would predict the frequency of positive psychotic symptoms. We also explored whether intrusive experiences correlated with psychotic symptoms in individuals at risk of psychosis.
Methods: We recruited individuals who were then split into four groups using the Childhood Trauma questionnaire and Community Assessment of Psychic Experience (CAPE) in the UK and South Korea. These included 623 healthy survivors of developmental trauma (HDT+), 482 healthy controls (HDT-), 838 survivors of developmental trauma with subclinical psychotic symptoms (SDT+) and 167 controls with subclinical symptoms (SDT-). Conducted online, we measured PTSD symptoms using the International Trauma Questionnaire (ITQ). Within a subsample of the UK SDT+ group, we used a trauma-intrusion interview and the Comprehensive Assessment of At-Risk Mental States (CAARMS) to provide subjective measures (0 to 100) of trauma memories and psychotic symptoms.
Results: 32.2% of adult survivors of developmental trauma with an at-risk mental state for psychosis (SDT+) met self-report thresholds for PTSD (7.9%) and CPTSD (24.3%). Within the whole sample, the severity of PTSD symptoms (B=0.47, SE=0.02, $p<.01$), meeting PTSD (B=3.65,

SE=0.74, p<.01) and CPTSD thresholds (B=6.70, SE=0.43, p<.01), predicted the frequency of positive psychotic symptoms. Specifically, the ITQ PTSD subscale on memory intrusions significantly correlated with CAPE positive psychotic symptoms (r=0.39, p<.01). Within the UK SDT+ subsample (n=28), intrusive memories and images were experienced on average 3.7 times a week. There were significant positive correlations between the frequency of intrusions and distress caused by perceptual abnormalities as well as unusual thoughts (r=.492, p=.023, r=.485, p=.030). Additionally, the higher the CAARMS rating and the distress caused by perceptual abnormalities, the more participants experienced intrusions as being in the 'here and now' (r=.546, p=.005, r=.473, p<.035) and possessing a higher degree of emotion (r=.571, p=.002). Lastly, the higher the CAARMS rating of unusual thoughts, the more frequently intrusions were experienced (r=.433 p=.024) and the more emotion-laden they were (r=.629, p=.012).
Discussion: Using cross-cultural data, this is the first study that suggests meeting PTSD or CPTSD clinical thresholds predicts subclinical psychotic symptoms in adults who have experienced developmental trauma. Within trauma survivors at risk of psychosis, trauma-related intrusions were highly vivid and emotional, suggesting that PTSD characteristics are prevalent in those at risk of psychosis. These findings suggest that people with at-risk mental states should be screened for PTSD. Further work is needed to investigate whether treating PTSD attenuates the risk of psychosis.

S81. NMDA RECEPTOR PATHWAY POLYGENIC SCORE IS ASSOCIATED WITH BRAIN GLUTAMATE IN SCHIZOPHRENIA

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Background: Dysfunction of glutamate neurotransmission has been implicated in the pathophysiology of schizophrenia and may be particularly relevant in severe, treatment-resistant symptoms. The underlying mechanism is thought to involve hypofunction of the NMDA receptor. We investigated whether pathway polygenic scores, composed of genetic variants within NMDA receptor encoding genes, are associated with cortical brain glutamate levels in schizophrenia.
Methods: Anterior cingulate cortex (ACC) glutamate was measured in 70 participants across 4 research sites using Proton Magnetic Resonance Spectroscopy (1H-MRS). NMDA gene sets were sourced from the Molecular Signatories Database and corresponding NMDA receptor pathway polygenic scores were constructed using PRSet. The NMDA receptor pathway polygenic scores were weighted by SNP associations with treatment-resistant schizophrenia, and relationships with ACC glutamate were tested. As a second exploratory analysis we then examined the relationship between ACC glutamate and NMDA receptor pathway polygenic scores containing SNPs weighted by associations with treatment responsive schizophrenia.
Results: A higher NMDA receptor complex pathway polygenic score was significantly associated with lower ACC glutamate (β = -0.25, 95% CI = -0.49, -0.02, competitive p = 0.03). When SNPs included in the NMDA receptor complex pathway polygenic score were weighted by associations with treatment responsive schizophrenia, there was no association with ACC glutamate (β = 0.05, 95% CI = -0.18, 0.27, competitive p = 0.79).

Discussion: These Results: provide initial evidence of an association between common genetic variation implicated in NMDA receptor function and ACC glutamate levels in schizophrenia. This association was specific to when the NMDA receptor complex pathway polygenic score was weighted by SNP associations with treatment-resistant, but not treatment responsive forms of schizophrenia.

S82. ASSESSING THE IMPACT OF NRN1 ON CLINICAL HALLMARKS OF SCHIZOPHRENIA BY COMBINING MOLECULAR AND NEUROIMAGING ANALYSES

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Background: Schizophrenia (SZ) has been associated with neuroanatomical and synaptic plasticity changes. Among the molecular actors with key roles in these processes, the Neuritin1 gene (NRN1) has emerged as an interesting candidate gene since it is associated with the risk for SZ and cognitive performance, it is one of the most differentially methylated genes in SZ prefrontal cortex and its expression seems to be sensitive to neurotherapeutic agents. We designed a multifaceted study (genetic, epigenetic, and expression approaches) to study the impact of the NRN1 gene on different clinical, cognitive and brain imaging features.

Methods: Eleven polymorphisms at NRN1 were genotyped (AB Taqman assays) in all the samples. First, genetic association analyses were conducted in two independent samples with patients divided in early-onset (EO, onset <= 18 years) or adult-onset (AO): a family-based sample (80 EO trios and 71 AO trios) and a case-control sample (87 EO / 138 AO / 120 HC). Second, the impact of NRN1 on clinical and cognition was evaluated using the Positive and Negative Syndrome Scale (PANSS), the Global Assessment of Functioning scale (GAF), intelligence

quotient (WAIS), and the Wechsler Memory Scale (WMS) (164 SZ / 109 HC). Third, the role of NRN1 in brain structure (106 SZ / 90 HC, FreeSurfer ROIs) and function (39 EO / 39 AO / 39 HC, n-back task) was assessed using images acquired from a single MRI scanning session (1.5T). Lastly, the correlates between NRN1 expression (EpiTYPER™) and methylation (qRT-PCR) were evaluated in post-mortem hippocampus and prefrontal cortex (10 SZ multi-treated / 10 SZ treated with clozapine / 10 SZ non-treated / 30 HC).

Results: First, we identified NRN1 genetic variants associated with EO SZ both in the family and case-control samples. Second, NRN1 was associated with patients' WMS and GAF scores. Third, NRN1 genetic variants showed differential effects on temporal and occipital lobes cortical thickness, conditional to the diagnosis status. Moreover, the same variants related to earlier onset were associated with prefrontal cortex activity changes in early-onset cases compared to HC.

Lastly, we observed NRN1 expression differences between patients treated with clozapine and those not medicated. Although no methylation differences were found between patients and HC we observed differential methylation-expression correlates. Also, methylation levels of the distal part of the CpG island expanding NRN1 gene body were correlated with differences in surface area of temporal and prefrontal regions between patients and HC.

Discussion: Our findings support the previously described association of NRN1 genetic variability with SZ, while adding information about its impact on age at onset, symptoms severity and brain structure and function. In addition, the relationship between expression levels and treatment status expose NRN1 as a relevant actor in the molecular pathways related to antipsychotic effects. Also, the observed expression differences appear to be mediated by differences in methylation levels of key CpG along the gene. Interestingly, NRN1 epigenetic variability also modulates brain structure. Therefore, our study evidences that both NRN1 genetic and epigenetic variability contribute to the complex manifestation of SZ, encouraging us to further explore the role of genetic-epigenetic interactions in modulating the phenotype.

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S83. GENETIC AND NEURODEVELOPMENTAL MARKERS IN SCHIZOPHRENIA-SPECTRUM DISORDERS: ANALYSIS OF THE COMBINED ROLE OF THE CANNABINOID RECEPTOR 1 GENE (CNR1) AND DERMATOGLYPHICS

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Background: The aetiology of schizophrenia-spectrum disorders (SSD) is associated with differences in neurodevelopmental trajectories, influenced by genetic and environmental factors.The subtle developmental abnormalities associated with SSD can be assessed by markers such as the dermatoglyphic pattern deviances (Radua 2018). This association is based on the shared embryonic ectodermal origin of the epidermis and the central nervous system and, on the common signaling pathways guiding the development of ectodermal derivates. The endocannabinoid system is highlighted as a putative key factor of this association due to its implication in cell-fate processes during neurodevelopment (proliferation, differentiation and, migration), its role in epidermal differentiation (Galve-Roperh 2013), its developmental sensitivity to disrupting environmental factors (Schmidt-Kastner 2006) and, its association with SSD risk. Therefore, we aimed to test if the Cannabinoid receptor 1 (CNR1) gene in interaction with dermatoglyphic measures impacts SSD liability.
Methods: The sample consisted of 112 healthy controls (HC) and 97 patients with SSD. We genotyped two CNR1 SNPs (rs2023239-A/G and rs806379-A/T). In bilateral finger and handprints, we assessed the following dermatoglyphic markers: the total palmar a-b ridge count (TABRC), its fluctuant asymmetry (FA), and the pattern intensity index (PII). First, we conducted a case-control genetic association analysis. Second, we evaluated the effect of the two SNPs on the dermatoglyphic measures within diagnostic groups. Finally, we explored the interplay between CNR1 variability and the dermatoglyphic measures on the risk for SSD. Analyses were conducted in PLINK through regression models controlled for sex. The reported p-values are those obtained after 10,000 permutations.
Results: Genetic association Results: showed that both CNR1 SNPs were associated with the risk for SSD: the G-allele carriers of the rs2023239 were overrepresented among HC (W=-4.00, OR[95%CI]=0.29[0.15-0.53], $p<0.001$), while the T-allele carriers of the rs806379 were overrepresented among patients (W=3.77, OR[95%CI]=3.25[1.76-6.00], $p<0.001$). Both variants modulated dermatoglyphic measures in HC: the G-allele carriers of the rs2023239 presented higher PII scores ($\beta=0.35$, $p=0.02$) and the T-allele carriers of the rs806379 had lower TABRC ($\beta=-4.37$, $p=0.04$). There was a rs2023239 x PII interaction on SSD risk (W=9.82, $p=0.04$), suggesting an inverse risk modulation depending on the PII and the rs2023239 genotype. The G-allele carriers (rs2023239) with higher PII presented a lower predicted probability towards SSD risk, while AA homozygous who also had high PII depicted the opposite relationship with the risk.
Discussion: Our Results: add evidence to previous studies on the association of CNR1 with the risk for SSD (Gouvea 2017). Also, they represent novel data on the role of the endocannabinoid system in the development and variability of dermatoglyphic patterns, in line with the known role of the Cannabinoid receptor 1 in epidermal differentiation and skin development (Maccarrone 2003). Finally, the identified interaction opens new avenues of investigation and suggests that the combined use of genetics and dermatoglyphics may help in the assessment of neurodevelopmental alterations predisposing to SSD, encouraging future studies leading to the development of better diagnostic tools.
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S84. LIFETIME CANNABIS USE AND CHILDHOOD TRAUMA ASSOCIATED WITH CNR1 GENETIC VARIANTS INCREASE THE RISK OF PSYCHOSIS IN A BRAZILIAN POPULATION

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Background: Cannabis use and childhood trauma are associated with psychosis (Setién-Suero et al., Eur J Psychotraumatol, 2020, 11(1):1748342). Moreover, gene-environment (GxE) interactions increase psychosis risk (Gayer-Anderson et al., Soc Psychiatry Psychiatr Epidemiol, 2020, 55(5):645-657). However, identifying the genetic variants involved and how they interact with environmental risk factors underlying psychosis remains challenging. Aim: To investigate whether there are GxE interactions in the relationships of childhood trauma, lifetime cannabis use, and single nucleotide variants (SNVs) of N-methyl-d-aspartate receptor (NMDAR: GRIN1, GRIN2A and GRIN2B), dopamine D2 receptor (D2R: DRD2) and cannabinoid receptor type 1 (CB1R: CNR1) with psychosis.

Methods: In a population-based case-control study nested in an incident study (STREAM, Brazil) (Del-Ben et al., Br J of Psychiatry, 2019, 215(6):726-729), part of the EU-GEI consortium (Gayer-Anderson et al., Soc Psychiatry Psychiatr Epidemiol, 2020, 55(5):645-657), 143 first-episode psychosis patients (FEPp) and 286 community-based controls of both sexes aged between 16 and 64 years were included over a period of 3 years. Twenty-four SNVs of NMDAR (GRIN1: rs4880213, rs11146020; GRIN2A: rs1420040, rs11866328; GRIN2B: rs890, rs2098469, rs7298664), D2R (rs1799978, rs7131056, rs6275, rs2242591), and CB1R genes (CNR1: rs806380, rs806379, rs1049353, rs6454674, rs1535255, rs2023239, rs12720071, rs6928499, rs806374, rs7766029, rs806378, rs10485170, rs9450898), were genotyped from peripheral blood DNA using a custom Illumina HumanCoreExome-24 BeadChip. Environmental adversities were evaluated using the Cannabis Experience Questionnaire (Di Forti et al., The Lancet Psychiatry, 2009, 6(5):427–436) and the Childhood Trauma Questionnaire (Grassi-Oliveira et al., Rev Saude Publica, 2006, 40(2):249-55). Associations between 24 SNVs and environmental risk factors were performed using the nonparametric multifactor dimensionality reduction software (version 3.0.2), considering 10 data divisions as the same best model for cross-validation, and $p \leq 0.05$ as significant.

Results: Single locus analysis showed no association of the 24 SNVs with psychosis; however, gene-gene and gene-environmental analysis were significant for the polymorphic loci rs12720071 and rs7766029 in CNR1. The best association model was the two-factor representing by the combination of CNR1 rs12720071 with lifetime cannabis use [testing accuracy of 66.4%, cross-validation consistency (CVC) of 10/10, $p<0.001$], while the combination of CNR1 rs12720071 with childhood trauma showed a testing accuracy of 62.1%, CVC of 6/10 and $p<0.05$, both suggesting a change in risk of psychosis. Moreover, the interaction of CNR1 rs7766029 with both

lifetime cannabis use and childhood trauma presented a testing accuracy of 69.3%, CVC of 8/10 and $p<0.05$ for association with psychosis. No significant associations between the environmental factors and other SNVs were found.
Discussion: We found a significant interaction between CNR1 genotypes and two important environmental risk factors in their association with first-episode psychosis. Variant homozygous genotypes in CNR1 were associated with a lower risk of psychosis when cannabis use or childhood trauma were absent, while the same allele increased the risk of psychosis when the environmental factors were present. The model that included both environmental factors showed that cannabis use abolished the protective association of rs7766029-T-allele with psychosis in the absence of childhood trauma. Our Results: suggest a gene-environmental interaction involving the CNR1 gene and trauma and cannabis in psychosis. Our Results: suggest a gene-environmental interaction involving the CNR1 gene and trauma and cannabis in psychosis. We also speculate that cannabis use and CNR1 genotypes may induce neuromodulatory dysfunctions in dopaminergic and glutamatergic pathways, especially in the presence of another environmental risk factor contributing to the pathophysiology of psychosis.

S85. DISENTANGLING THE SHARED GENETIC DETERMINANTS OF RISK-TAKING AND SCHIZOPHRENIA

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Background: Increased risk-taking is a core symptom of mania but is less strongly associated with schizophreniform psychosis. Nonetheless, both disorders are linked to higher rates of risky behaviours such as smoking, alcohol use and aggression. A recent large-scale genome-wide association study (GWAS) for risk-taking found significant positive genetic correlations with both schizophrenia and bipolar disorder, indicating shared genetic determinants. However, genetic correlations do not capture all possible genetic overlap and do not identify specific shared genetic variants. We aimed to investigate the shared genetic architecture of risk-taking, schizophrenia and bipolar disorder beyond genetic correlation.
Methods: We acquired summary statistics from GWAS for risk-taking (n = 466,751), schizophrenia (n = 82,315) and bipolar disorder (n = 413,466). Risk-taking was measured by a single questionnaire item. We applied the bivariate causal mixture model (MiXeR) to risk-taking and, in turn, schizophrenia and bipolar disorder. Although most genetic variants associated with schizophrenia, bipolar disorder and risk-taking remain to be discovered, MiXeR infers the total number of shared and unique "causal" variants for a given pair of traits from the distribution of z-scores from each GWAS without identifying specific shared genetic variants. We used the conjunctional false discovery (conjFDR) method to identify specific genetic loci shared between each pair of traits using a threshold for statistical significance of conjFDR<0.05. The identified genomic loci were functionally characterised by the Functional Mapping and Annotation (FUMA) online tool . Putative causal genes were mapped to shared genetic variants using three strategies: positional mapping, eQTL mapping and chromatin interaction mapping. Differential expression of

mapped genes was tested across all human tissues using the Genotype-Tissue Expression (GTEx) database.
Results: MiXeR estimated that 9.6K out of 10.2K variants associated with schizophrenia were shared with risk-taking, compared to 6.6K out of 8.6K variants associated with bipolar disorder. This was despite moderate positive genetic correlations (risk-taking/SCZ: rg=0.22, p=7.41e-16; risk-taking/BIP: rg=0.33, p=2.35e-31). Using conjFDR, we identified 100 genetic loci shared between schizophrenia and risk-taking and 106 shared between bipolar disorder and risk-taking. 76% and 88% of these shared the same direction of effect on each disorder and risk-taking, respectively. Twenty-nine of these loci were novel findings in schizophrenia, 52 were novel findings for bipolar disorder, and 37 were shared across both mental disorders. Genetic loci shared between schizophrenia and risk-taking were mapped to 131 putative causal genes, including the GABA receptor subunit GABRA2 and a neurodevelopmental tyrosine kinase EPHA5. In contrast, shared loci between bipolar disorder and risk-taking were linked to 142 putative causal genes, including well-known bipolar risk gene CACNA1C and synaptic cell adhesion molecule CADM2. Mapped genes were differentially expressed in highly overlapping brain regions across both schizophrenia and bipolar disorder, with a prominence of cortical and sub-cortical structures including the caudate, putamen and nucleus accumbens.
Discussion: Despite differences in the clinical presentation of risk-taking within each psychotic disorder, we revealed similar shared genetic architectures. Both disorders shared large proportions of causal variants, with moderate positive genetic correlations. This pattern is indicative of shared genetic variants with a mix of the same and opposite effect directions on each trait. This, in turn, may be indicative of non-specific genetic overlap present across multiple complex behavioural traits, as well as overlapping molecular mechanisms. Nonetheless, the slightly stronger genetic correlation between bipolar disorder and risk-taking, alongside the higher proportion of conjFDR-discovered loci with the same effect direction, suggests closer genetic alignment, a potential explanation for the different clinical presentations. Using conjFDR, we also highlighted several candidate genes which may provide opportunities for further investigation. Tissue enrichment analysis implicated several sub-cortical structures, many of which have been implicated in the frontal-striatal reward circuit, which, in turn, has been implicated in risk-taking.
This study was limited by the lack of trans-ancestral samples and the brief and simplistic measure of risk-taking. Future studies using more deeply phenotyped and ancestrally diverse samples are required to shed further light on the genetic basis of risk-taking in psychotic disorders.

S86. EXPLORING EPIGENETIC MEDIATING MECHANISMS LINKING CHILDHOOD ADVERSITY AND PSYCHOSIS IN PATIENTS WITH FIRST EPISODE OF PSYCHOSIS – DATA FROM THE EUGEI STUDY

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Background: Epigenetics is emerging as an important mechanism modulating the interactions between genetic and environmental risk factors in the aetiology of psychiatric disorders, including psychosis. DNA-methylation (DNAm) has shown to be sensitive to the impact of environmental exposure such as childhood adversity (CA) in different mental disorders, however whether DNAm mediate the CA-psychosis association is yet to be explored in an Epigenome-wide Association Studies (EWAS) context. We aim to explore, in a large sample of First-Episode of psychosis (FEP), whether changes in DNAm methylation mediate the link between CA, measured as a composite measure, as abuse and neglect, and psychosis.
Methods: EWAS profiling using the Illumina Infinium Methylation EPIC array in human peripheral blood tissue from 366 FEP and 517 healthy population controls as part of the EUGEI (European network of national schizophrenia networks studying Gene-Environment Interactions) study was used. The moderate to severe cutoff score from the Childhood Trauma Questionnaire (CTQ) Manual was applied to create the Polyvictimisation score. Polyvictimisation score ranged from 0-5 for the composite measure, 0-3 for abuse and 0-2 for neglect. First, linear regression models examining the associations between CTQ scores and psychosis was tested; second, we regressed each DNAm CpG across the entire DNA on polyvictimization scores and alternatively regressed case control status on each of the probes, adjusting by age, sex, country, batch effects, cell type, smoking core, 10 principal components and antipsychotic medication history. Lastly, Divide-Aggregate Composite-null Test (DACT) for the composite null hypothesis of no mediation effect was conducted. We adopted Efron's empirical null framework for assessing statistical significance. Enrichment analyses were conducted with missMethyl package with the KEGG data set, to explore potential biological pathways involved in the mediation between adversity and psychosis.
Results: CA in various forms was associated with psychosis (composite: OR = 3.09; p = <0.00; abuse: OR = 2.95; p<0.001; neglect: OR = 3.25; p=<0.001). None of the probes appeared to significantly mediate the adversity-psychosis association according to Bonferroni correction (p<8.13379772e-8), however 28, 34 and 29 differentially methylated probes (DMPs) located in 21, 27 ,20 genes passed a more relaxed discovery threshold (p<5x10-5) for composite, abuse and neglect respectively. These included genes previously associated to SCZ in EWAS studies such as PANK1, SPEG, PKNOX2, HDAC5, TSNARE1, TTC7B, NEK6, ZHX2, TMEM114, SORT1, PPP2R2D, VARS and NMB. Downstream gene ontology analyses showed enrichment for pathways such as the dopaminergic (FGF20), glutamatergic (ZHX2), and histaminergic functions (HRH2); and a great variation in the biological pathways according to abuse and neglect was observed.
Discussion: DNAm changes in genes previously associated with schizophrenia in EWAS studies may mediate the CA-psychosis association. We confirm a possible mediating role of glutamatergic and dopaminergic pathways in this association, while the role of the histaminergic function requires future replication. The low overlap between mediating genes and pathways according to abuse and neglect suggest differential biological trajectories between CA and psychosis depending on the type of adversity.

S87. STIGMA AND SCHIZOPHRENIA: AN ERP STUDY

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Background: Reducing stigmatizing beliefs about mental illness could have a large impact on the lives of people with schizophrenia. However, most evaluations of the efficacy of anti-stigma interventions are based on self-report. This study takes the first step toward developing an objective, event-related potential (ERP) measure of implicit bias toward people with schizophrenia.

Methods: We investigated whether event-related potentials (ERPs) elicited by faces could be modulated by a spurious mental health diagnosis.We recorded EEGs from 27 undergraduates while they viewed happy and angry faces; they were told half of the people in the photos were mentally healthy while the other half had a diagnosis of schizophrenia, which was indicated by the color of the frame around each face. Afterward, participants rated how dangerous each face looked to them. We measured the amplitudes of the early, face-specific, N170 and a later P3 component.

Results: Participants rated faces with the schizophrenia designation as more dangerous than those designated as mentally healthy. There were significant interactions between facial expression and mental health label for both amplitudes of both the early N170 and later P3 ERP components. Angry expressions elicited larger N170s than happy ones, but only for faces with the schizophrenia label. In contrast, happy faces with the schizophrenia label elicited larger P3s than those with the mentally healthy designation.

Discussion: The mental health designation of the faces that participants viewed affected how they processed them. Our N170 Results: suggest that angry faces with the schizophrenia designation appeared to be particularly salient and automatically grabbed our participants' attention, at least initially. Therefore, might have found these faces the most threatening and so were particularly attentive to them. In contrast, the P3 finding suggests that later attentional processes were recruited more when someone with a diagnosis of schizophrenia looked happy, perhaps indicating that participants found this combination surprising. The study shows that ERPs can provide an objective measure of implicit bias toward people with schizophrenia. In future, this method could be used to assess anti-stigma interventions.

S88. ADHERENCE TO ANTIPSYCHOTIC MEDICATIONS AND RISK OF CARDIOVASCULAR HOSPITALIZATION AMONG SCHIZOPHRENIA-SPECTRUM PATIENTS: A 10-YEAR HISTORICAL PROSPECTIVE STUDY

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Background: People with schizophrenia spectrum disorder have a higher risk for early mortality due to cardiovascular diseases. Treatment with antipsychotic compounds (APC) is aimed at reducing the psychotic symptoms burden. Adherence to APC, early in the disease course, may presumably indirectly affect physical health outcomes. the objective of this study was to investigate the association between early short-term adherence to APC and cardiovascular disease (CVD) hospitalization among patients with schizophrenia-spectrum disorders in along-term follow-up.

Methods: The cohort included CVD-free participants aged between 30 and 65 years with a first diagnosis of schizophrenia or schizoaffective disorder at 1.1.2008 and subsequently. Data were retrieved from Clalit Health Services (CHS) electronic database. Adherence to APC [ATC3 group N05A (except lithium)] was defined by the ratio between purchased and prescribed prescriptions during an initial exposure period of six months following diagnosis. CVD hospitalizations and all-cause deaths were identified through 31.12.2017. Cox models were constructed to assess the hazard ratio (HR) for CVD hospitalization associated with APC adherence, adjusted to CVD risk factors.
Results: A total of 32,451 participants (mean age, 45.7 years; 41.2% women) were analysed, with 32.7% showing good adherence (>80%) and 25.1% non-adherent (0%). During a median follow-up of 4.52 years, 1,088 participants (3.4%) were hospitalized for CVD. Adjusted for age, sex, year of diagnosis and CVD risk factors, adherence was inversely associated with CVD in a dose-response pattern, with HRs of HR 0.73 [95% CI:0.63-0.86] for the >80% group, 50%-80% had HR 0.78 [95% CI:0.65-0.93], 20%-50% had HR 0.86 [95% CI:0.70-1.04] and <20% group had HR 0.97 [95% CI:0.71-1.32], compared with no adherence (Ptrend<0.001). The association was stable even following adjustment to adherence to cardio-metabolic drugs or use of clozapine or long-acting injections. The cost associated with CVD hospitalization was reduced in the good adherence group compared to non-adherence.
Discussion: Patients with schizophrenia-spectrum disorders who take their medications more regularly, specifically early in the course of illness, during the first six months following diagnosis, have a reduced risk of CVD hospitalization during follow-up. This association is also reflected in reduced health costs related to hospitalizations associated with better adherence. Our findings highlight the need for early detection of CVD risk factors and intervention aimed at improving APC adherence, especially among non-adherent patients, in close proximity with diagnosis. Improving mental health status with better symptom control through medications is associated with better physical health, specifically CVD, outcomes.

S89. PSYCHOSIS, INVERSE CARE LAW AND SUBJECTIVE DISTRESS IN TIMES OF COVID-19: A SURVEY STUDY

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Background: The COVID-19 pandemic was declared a public health emergency which has led to economic, psychological, and social instability. The pandemic has entailed dramatic consequences particularly in vulnerable populations, among which psychiatric patients are included. The objective of this study was to evaluate perceived levels of psychological distress in people consulting a Mental Health Center (MHC) in Madrid, as well as to analyze potential modulating factors.
Methods: Patients attending Usera's MHC service were individually surveyed on COVID-19 related issues. Moreover, sociodemographic and clinical data were collected from their clinical record, upon patient consent.

Results: A sample of 251 patients (60.2% women, mean age 48.13±0.95 years) was surveyed during Spain's COVID-19 third wave. In terms of functionality, 57.4% of participants were classified as having Common Mental Disorder (CMD), 27.9% as Severe Mental Disorder (SMD) and 14.7% presented Severe Mental Disorder included in a Continuity Care Service program (SMDCCS). Regarding diagnosis, patients were divided into three categories: depressive disorders (52.2%), psychotic disorders (25.1%) and anxiety (22.7%).
In total, 15.5% of the sample reported being infected with SARS-CoV2 virus; 33.9% reported severe illness or death of a close relative by COVID-19; 78.7% of participants concerned on someone close to them dying or getting severely ill by COVID-19. Regarding the COVID-19 pandemic, 46.6% believed to have worsened from their previous mental health pathology, 60.2% claimed to feel anguish, 47.6% reported feeling depressed, and 25.2% referred poor sleep quality. Finally, 33.6% stated their economic situation to have worsened, and 64.1% concerned on the potential near-future downturn.

Younger age was related to more socio-economic instability. Perceived socio-economic instability, anxiety and depressive diagnoses, and a higher rate of medical visits were significantly associated with higher levels of psychological distress. On the other hand, patients with a psychotic diagnosis referred lower levels of perceived psychological distress and socioeconomic instability. Regarding the diagnosis axis (anxious<depressive<psychotic), the lower the diagnostic category, the higher the risk of perceived psychological distress (B = - 0.65, IC95 (-0.94, -0.35), p<.01).

Discussion: The COVID-19 pandemic has become a main contributor of mental health deterioration, as shown by our Results: on perceived psychological distress among MHC patients. Patients with a psychotic diagnosis referred less psychological distress than those with apparently less severe diagnoses (i.e., anxiety and depressive diagnoses), regardless of functionality.
These results could be explained by the Inverse Care Law in Mental Health, stating that patients with non-psychotic disorders are more resource-demanding, and therefore receiving more medical attention. An optimization of patient follow-up resources across the multiple pandemic waves could be preserved through a proactive approach of care provision, based on Continuity of Care Services and affirmative action towards the assistance of less demanding patients.

S90. MENTAL HEALTH IN INDIVIDUALS WITH SEVERE MENTAL DISORDERS DURING THE COVID-19 PANDEMIC: A LONGITUDINAL INVESTIGATION

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Background: Research on the long-term mental health impact of the COVID-19 pandemic across mental disorders is limited, and information on the impact of public health policy measures with varying strictness is missing. This study therefore aimed at investigating psychological distress among residents of Tyrol (Austria) and South Tyrol (Italy) at the early stages of the pandemic (T1)

and five months thereafter (T2) and examined how sociodemographic, protective, and risk factors relate to change over time.
Methods: 115 people with severe mental illness (SMI; schizophrenia spectrum disorder, bipolar disorder, major depressive disorder with psychotic features) or major depressive disorder without psychotic features (MDD) and 481 community controls without mental disorders participated in an online survey. Next to the collection of sociodemographic and COVID-19 related variables, the Brief Symptom Checklist, the Resilience Scale, the Multidimensional Scale of Perceived Social Support, the Three-Item Loneliness Scale, and the Multidimensional State Boredom Scale-Short Form were used to assess psychological distress, resilience, perceived social support, loneliness, and boredom.
Results: Levels of psychological symptoms and the prevalence of psychological distress were significantly higher in individuals with MDD (T1: 47.8%, T2: 44.9%) compared to patients suffering from SMI (T1: 23.9%, T2: 23.9%) and control subjects (T1: 13.9%, T2: 13.1%). Psychological distress was predicted by a lower degree of both resilience and perceived social support as well as loneliness and boredom. Notably, the prevalence of clinically relevant psychological symptoms remained unchanged among each group over time.
Discussion: These findings suggest a negative long-lasting impact of the pandemic on mental health of people both with and without mental disorders. Accordingly, there is the urgent need for governments to have policies in place to alleviate the potential threat of COVID-19 on the mental health of the population, and targeted interventions focusing on the specific needs of various groups (including those with no mental health disorders) are essential.

S91. DIFFERENTIATING KINDS OF SYSTEMIC STRESSORS WITH RELATION TO PSYCHOTIC-LIKE EXPERIENCES IN LATE CHILDHOOD AND EARLY ADOLESCENCE: THE STIMULATION, DISCREPANCY, AND DEPRIVATION MODEL OF PSYCHOSIS

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Background: Conceptualizations that distinguish structural, systems-level occurring environmental exposures (e.g. neighborhood crime, cultural factors, neighborhood income inequality) are lacking; the stimulation (lack of safety and high attentional demands), discrepancy (social exclusion and lack of belonging), and deprivation (SDD; lack of environmental enrichment) theory of psychosis and stressors occurring at the systems level has not been directly tested.
Methods: Exploratory factor analysis was conducted on 3,207 youths to test whether subjective measures would separate into distinct factors. Confirmatory factor analysis was conducted in 3,208 youth testing the fit found using exploratory factor analysis. Associations with psychotic-like experiences (PLEs) were explored, and the strength of associations were compared across domains for both objective (Census-derived neighborhood metrics) and subjective (self-report) measures.
Results: Although model fit was suboptimal, five factors were defined, and four were consistent with the SDD theory and related to PLEs. Objective and subjective or self-report exposures for deprivation showed significantly stronger PLE associations compared with discrepancy and objective stimulation factors. Objective and subjective or self-report measures converged overall,

although self-report stimulation exhibited a significantly stronger association with PLEs compared with objective stimulation.
Discussion: Considering distinct systems-level exposures could help clarify putative mechanisms and psychosis vulnerability. The preliminary approach potentially informs health policy efforts aimed at psychopathology prevention and intervention.

S92. IMPROVING OUTCOMES IN FIRST EPISODE PSYCHOSIS SERVICES: RESULTS: ON PSYCHIATRIC HOSPITALIZATIONS

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Background: Psychiatric hospitalizations of individuals with a first episode psychosis (FEP) are important indicators of FEP service (FES) quality and economic value. Psychiatric hospitalizations can be unpleasant for patients and their families, disrupt community functioning, and endanger the treatment alliance with FES. Hospitalization is also a reliably measurable proxy for relapse or illness severity, and is the largest driver of direct healthcare cost in the US. The clinic for Specialized Treatment Early in Psychosis (STEP) previously demonstrated reductions in both the frequency and the duration of psychiatric hospitalization in a randomized comparison with usual care. We evaluated STEP's more recent impact on the risk and duration of hospitalization with a larger and more naturalistic sample, and more careful measurement of the Duration of Untreated Psychosis (DUP).
Methods: STEP accepts individuals aged 16-35 with recent onset (DUP<3 years) non-affective psychosis, and residing in a 10-town catchment (population 400,000) within New Haven County, Connecticut. All admissions to STEP between February 2014 - September 2019 were included (N= 189). Medical records of the sole regional acute healthcare provider (Yale New Haven Health-YNHH) were queried from Feb 1, 2013 through June 30, 2020 for number and duration of admissions to psychiatric inpatient and emergency units (ED). The extended observational period spans 1733.3 person-months (median follow up=5.7, IQR 1.8-15.1 months) before, and 7966.5 person-months (median=41.3, IQR 26.4 – 57.1 months) after admission to STEP. Poisson regression models, adjusted for over dispersion, were used to estimate incidence rate ratios (IRRs), with associated 95% CI, for hospitalization rates across all explanatory variables. Negative binomial regression analysis was used to compare length of stay (LOS) before vs after STEP enrollment. We assessed the moderating effect of DUP on hospitalization risk and duration.
Results: Among 186 who utilized YNHH, 159 (85.5%) had at least one inpatient psychiatric admission before enrollment to STEP vs 146 (78.4%) after. Admission to STEP was associated with a 90% reduction of cumulative hospital length of stay (LOS) (inpatient, and ED) (RR=0.10; 95%CI, 0.07-0.14; P<0.0001) and inpatient LOS (RR=0.10; 95% CI, 0.07-0.14; P <0.0001).
Overall hospitalization per month decreased after admission to STEP from a mean of 0.65 days (SD 1.46) to 0.05 days (SD 0.06) per month. Overall hospital utilization was reduced by 77%

(RR=0.23; CI 0.14-0.20, p < 0.0001), as were admissions to inpatient (Reduction of RR=82%), and emergency units (RRR=65%).

The effect of STEP care on hospitalization was moderated by DUP. The risk of psychiatric hospitalization increased for 30 day prolongations in delay from: psychosis onset to first antipsychotic (IRR=1.09, CI 1.05-1.13, p<.0001); first antipsychotic to admission to STEP (IRR=1.04; 95% CI 1.02-1.06; P < .0001); psychosis onset to admission to STEP (IRR=1.08; 95% CI 1.06-1.10; P < .0001).

Discussion: Engagement in STEP reduced the frequency and duration of psychiatric hospitalization. Delayed access to antipsychotics or FEP services significantly reduced FES effectiveness, and present modifiable targets to improve hospitalization outcomes. Despite overall benefit, many patients were hospitalized after admission to STEP with significant heterogeneity (22.6% had no hospitalizations after admission).
Results of additional mediator and moderator analysis will also be presented and discussed.

S93. PREVALENCE OF PSYCHOLOGICAL REACTIONS AND SUICIDAL IDEATION THROUGHOUT ONE YEAR OF THE CORONAVIRUS DISEASE 2019 (COVID-19) PANDEMIC IN PATIENTS WITH SEVERE MENTAL DISORDER

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Background: COVID-19 pandemic has had an important impact on mental health of global population, particularly of people with mental disorders (García-Alvarez et al., 2020). Also, previous research report higher anxiety responses in people with severe mental disorder (SMD) (as patients with psychotic or bipolar disorder) versus healthy controls during the first weeks after the state of emergency and lockdown due to pandemic in Spain (González-Blanco et al., 2020).
This study aims to describe the effects of the COVID-19 pandemic and social restrictions on mental health in patients with SMD during three distinct periods (acute, short-term, and long-term).

Methods: This one-year study is a secondary analysis of a larger study that collected data at three different periods: April 16 to April 23, 2020 (first survey - S1 -), October 14 to November 8, 2020 (second survey - S2 -), and March 16 to March 31, 2021 (third survey - S3 -).

From the whole sample, we have only included patients that reported a diagnosis of SMD (bipolar disorder, schizophrenia or psychotic disorders).

Participants completed the Spanish Depression, Anxiety, and Stress Scale (DASS-21) and the Paykel Suicide Scale (PSS). Active suicidal ideation (ASI) during the last month was defined as a positive answer to PSS items 3 and/or 4 (thought of taking their life or seriously considering taking their life). The prevalence with 95% confidence interval (CI) of different psychological reactions and ASI were calculated.

Results: We recruited 18,180 subjects using a virtual respondent-driven snowball sampling method (S1 April 2020, n = 6108; S2 October-November 2020, n = 6418; S3 March 2021, n = 5654). From the whole sample, 183 participants reported a diagnosis of SMD (S1, n = 61; S2, n = 91; S3, n = 31). Most of them were females (S1 - 63.9 %, S2 - 87.9 %, S3 - 77.4 %), and with a mean age (standard deviation) of: S1 – 45 (14.74), S2 – 35.74 (11.63), and S3 – 41.03 (14.75), respectively.
The prevalences of psychological response throughout the study period followed different patterns in the case of depression and suicidal ideation on the one hand, and anxiety and stress on the other. In the case of the depressive response, it followed an inverted-V pattern with the following prevalences: S1 = 57.36 %, S2 = 79.12 % and S3 = 41.9%. In the case of anxiety and stress responses, an increase in their prevalences was observed, which was subsequently maintained: S1 = 27.87 % and 24.59 %, S2 = 51.65 % and 51.65 %; S3 = 48.39 % and 51.61 %, respectively.

Furthermore, the prevalences of ASI followed a similar pattern to the depressive response, as expected: S1 = 8.20 %, S2 = 28.57 % and S3 = 16.13 %.

Discussion: More than a half of patients with SMD reported at least one maladaptative psychological reaction throughout the three periods (acute, short-term, and long-term), being the short-term period (November 2020) the moment of maximum impact. Depressive response was particularly prevalent (almost 80%) at S2. Regarding suicidal ideation, more than ¼ of patients reported ASI at S2. These percentages were higher than those reported in the general population (Ruiz et al., 2021; Saiz et al., 2021)
In conclusion, patients with SMD showed a relevant psychological impact of COVID-19 pandemic and social restrictions, and they were especially vulnerable to suicide risk, in the short-term period.

S94. FIRST OUTPATIENT CONTACT FOR SCHIZOPHRENIA SPECTRUM DISORDERS DURING LOCKDOWN IN ITALY: EMERGING EVIDENCE FROM A CATCHMENT AREA OF APPROXIMATELY 10 MILLION PEOPLE

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Background: Lombardy, the most densely populated Italian region, presented the highest case fatality rate worldwide during the earlier stages of the COVID-19 pandemic. A strict lockdown was enforced by institutions between March and May 2020, during which all non–urgent

outpatient services were discontinued. However, full functionality was maintained for Departments of Mental Health and Addiction (DMHAs). In this context, we previously reported a case series of First-Episode Psychosis (FEP) patients hospitalized in the second month of lockdown. Our preliminary observation suggested that intense psychosocial stress associated with a novel, potentially fatal disease and lockdown restrictions might have triggered FEP (D'Agostino et al., 2021). In a follow–up study, hospitalized patients with FEP were found to be significantly older, and to have significantly less co–morbid substance abuse in 2020 than patients with FEP in the previous year (Esposito et al., 2021). However, a broader epidemiological observation is necessary to identify signals of increased access to care for novel Schizophrenia spectrum diagnoses in the general population. The Italian mental health system provides a community–based model of care that is organized according to local health districts which serve a well-defined geographic area. Each district is served by a DMHA, which supplies a range of in- and outpatient services. Here we employed a registry–based approach to assess the impact of the pandemic on first outpatient contacts for psychosis within Community Mental Health Centres (CMHCs). The number of first psychiatric visits for Schizophrenia spectrum and other psychotic disorders carried out in all regional CMHCs during the first six months of 2019 and 2020 were compared.

Methods: We retrieved sociodemographic and clinical data from the regional register for mental health services. Descriptive statistics were employed to report information on service use. First psychiatric visits across all CMHCs were extracted by assigned ICD–10 main diagnosis for each month during the two observation periods (January – June 2019 and January – June 2020). Odds ratio calculations were performed to determine whether exposure to restrictive measures could be associated with increased odds of a first psychiatric visit for a Schizophrenia spectrum diagnosis.

Results: A total of 111,780 people had at least one contact with a CMHC in 2020, compared to 124,052 in 2019. In the first semester of 2020, the number of outpatient service contacts was consistently lower than the previous year (-10.59%). The largest drop was recorded in March and May (-21.89% and -16.86% respectively) in the provinces that were most affected by the early impact of the viral outbreak.

In the first six months of 2019, 13,462 first psychiatric visits were performed in the 58 CMHCs of Lombardy, 608 of which for patients diagnosed with Schizophrenia spectrum and other psychotic disorders. In the same months of 2020, 9,850 first psychiatric visits were performed (-26.83%), 518 of which for Schizophrenia spectrum and other psychotic disorders (5.18 vs 5.26%, p=n.s.). When only the three months of strict lockdown (March, April and May) were considered, 3,637 first psychiatric visits were recorded in 2020 (-47.27% compared to the previous year), 227 of which for Schizophrenia spectrum and other psychotic disorders (6.24% vs 5.07% in 2019, OR 1.23, 95% CI 1.04–1.46, p=0.0182). In April, the odds of a Schizophrenia spectrum/other psychotic disorder diagnosis during a first psychiatric visit was significantly higher than observed in the first semester (OR=1.69, 95% CI 1.32–2.18, p<0.0001) and in the same month of the previous year (OR=2.13, 95% CI 1.55–2.93, p<0.0001).

Discussion: Our study is the first to describe the impact of the pandemic on first outpatient contacts for psychosis in a large public mental health system, with a catchment area of approximately 10 million people. Despite a substantial reduction of firs psychiatric visits, a relative increase of Schizophrenia spectrum diagnoses was recorded. Compared to all other diagnoses at first contact, this was especially clear in the second month of lockdown. Although several alternative explanations may be advanced, including the possibility that other clinical conditions encompassing minor urgency delayed access to services during lockdown, these findings appear

to confirm that novel cases of Schizophrenia spectrum diagnoses rose during the early stages of the pandemic in Italy.

S95. EFFICACY AND ADHERENCE OF THE SPANISH VERSION OF COGITO APP IN SCHIZOPHRENIA SPECTRUM DISORDERS: A TWO-STAGE PROJECT

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Background: Depressive symptoms in schizophrenia spectrum disorders (SSD) are associated with poor quality of life, worse outcomes, worse prognosis and increased suicide attempts. The COGITO-Spanish version app is a free mobile application with second and third generation cognitive-behavioral therapy exercises, oriented to work on effective and functional coping of depressive symptoms and quality of life. However, at the moment it has not been tested neither in psychosis nor in Spanish-speaking people.
The main objective of this project is to evaluate the feasibility and efficacy of the COGITO app on depressive symptoms and quality of life (primary outcomes), as well as its impact on self-esteem, self-stigma, insight and cognitive biases (secondary outcomes) in Spanish-speaking people with SSD.

Methods: The project is divided into two stages:
1) A pilot study to obtain information on the feasibility of the research process, in order to calculate the sample size and plan the statistical analysis in the main trial. This study will be carried out with people with SSD from Spain.

2) To conduct the main trial in Spanish-speaking population with SSD from Spain and Latin American countries.

In both stages, we will perform a randomized controlled trial with a two-group design (experimental/control) and with pre and post assessments. The study will be disseminated in social networks and Qualtrics® will be used to digitize the entire research process. The whole process follows CONSORT guidelines. The first follows pilot and feasibility studies, and the second part follows CONSORT e-health for randomized controlled trials. To protect the transparency of the entire research, we will publish both protocols on www.clinicaltrials.gov and in international journals. The pilot study is in the process of approval by the ethics committee of both participating centers: PSSJD and UKE.

Statistical analyses of this pilot study will be calculated using the t-student test to assess differences between groups, and with logistic regression analysis for repeated measures. Sociodemographic scores will be considered as covariates. In accordance with the CONSORT guideline for pilot and feasibility trials, the present study will be crucial in determining the sample size calculation for the main trial. We also expect to obtain information on the feasibility and viability of the trial. As for the main project, we plan to perform MANCOVA analysis with an exploratory moderation analysis with confounding factors.

Results: We expect to find that frequent users of the mobile application reduce depressive symptoms, and/or increase quality of life. We also expect to analyze the variables involved in users who did not use the app, in order to know in depth their characteristics. We also expect the intervention to cause a decrease in self-stigma and an increase in self-esteem. In addition, given that cognitive biases are addressed in multiple modules of the app, we also expect patients to have an increased awareness of their cognitions, as well as a decrease in cognitive biases. In terms of insight, we expect to find two profiles of patients, those who by improving their cognitive awareness, may improve or worsen their depressive symptoms

Discussion: So far, there is little information on the profiles of app users with SSD. Moreover, despite the advances made in recent years, the supply of mobile-based interventions for DSS in general and in the Spanish-speaking population in particular, is scarce. Through this study we aim to find a low-threshold treatment option for those who cannot access health services, as well as a support tool between sessions for users who are in therapy. On the other hand, we will collect information on the profile of adherent and non-adherent patients that will be useful for researchers and clinicians working with people with DSS in both Europe and Latin America.

S96. HEMIZYGOUS KO OF MID1 RECAPITULATES THE BEHAVIOURAL PHENOTYPE INDUCED BY PRENATAL IMMUNEACTIVATION

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Background: Environmental insults during sensitive prenatal or postnatal developmental periods are critical in shaping adult physiology and central nervous system (CNS) functions. Indeed, early-life programming effects may play an essential role in the pathogenesis of neuropsychiatric diseases including schizophrenia, autism, and bipolar disorder. Previously, we demonstrated that maternal immune activation causes long-term and genome-wide changes in the offspring's prefrontal DNA methylome, and Mid1 stood out as the gene showing the most extensive changes in adult methylation. In turn, these changes led to a marked decrease in Mid1 mRNA expression. Interestingly, this gene has been associated with cellular and developmental functions related to brain development and maturation. Against this ackground, the main aim of the present study was to investigate whether a transgenic mouse model of Mid-1 (Mid1 KO) could recapitulate the behavioral changes induced by prenatal immune activation, and thus support the idea that altered methylation of the Mid1 gene might be a molecular mechanism mediating the negative effects of prenatal maternal immune activation.

Methods: Behavioural testing in adult Mid-1 KO males started on postnatal day (PND) 100. The tests included paradigms assessing spatial recognition memory (Y-maze), social interaction (SI), and prepulse inhibition (PPI) of the acoustic startle reflex. Perfusion with PBS or PFA 4% was performed prior to brain collection for molecular analysis and immunostaining. Total RNA was isolated using the Qiagen AllPrep RNA Mini kit and quantified by the TaqMan qRT-PCR reaction using the iScript one-step real-time PCR kit. IHC analysis on the Corpus Callosum region of the brain was performed to assess changes in white matter composition.

Results: Behavioural tests and molecular analyses performed in male Mid-1 KO mice recapitulated our previous findings in male offspring of immunologically challenged mothers. In

detail, Mid-1 KO mice show reduced sociability in the social interaction test, and deficits in sensorimotor gating as assessed using PPI of the acoustic startle reflex. Performance in the Y-maze spatial recognition memory test also showed a decrease in time spent in the novel arm. In addition, IHC analyses performed on the Corpus Callosum region show a different composition in the white matter of Mid-1 KO mice compared to Wt.
Furthermore, qRT-PCR analyses of mRNA from different brain regions of mice treated with prenatal viral-like immune activation Poly I:C, confirm our Results:, showing a strong decrease in Mid1 gene expression.

Discussion: Maternal immune activation causes long-term and genome-wide changes in the offspring's prefrontal DNA methylome. Depletion of the Mid1 gene in male animals recapitulates the behavioural profile induced by prenatal immune activation, suggesting that the epigenetic dampening of Mid1 expression in PolyI:C mice could be a molecular mechanism mediating the adverse effects of exposure to prenatal infection.

S97. COMPLEMENT RESPONSES AND SYNAPTIC CHANGES AFTER TRANSIENT MICROGLIA DEFICIENCY IN THE ADOLESCENT PREFRONTAL CORTEX

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Background: Microglia are the resident immune cells of the brain parenchyma and account for 5-12% and 0.5-15% of the total cell population in the adult mouse and human brain, respectively. Besides their classical immunological functions, microglia contribute to the remodeling of synaptic connections through phagocytic mechanisms. Commonly referred to as "synaptic pruning", this process involves microglia-mediated engulfment of pre- and postsynaptic material that is tagged with components of the complement system. While genetic evidence links altered expression of complement components with increased risk of schizophrenia, possible downstream effects of altered microglial activity on the complement system remain largely unknown. Therefore, the present study examined the complement responses in a mouse model of selective and transient depletion of microglia in the adolescent prefrontal cortex (PFC). In addition, we investigated the effects of transient prefrontal microglia depletion on synaptic densities and functions in the adult PFC.
Methods: Brain region-specific and transient depletion of prefrontal microglia during adolescence was induced by a single, bilateral stereotaxic injection of clodronate disodium salt (CDS) into the medial portion of the PFC in 6-week-old C57BL/6 mice. Control mice received a bilateral stereotaxic injection of phosphate-buffered saline (PBS). The magnitude and specificity of microglia depletion were ascertained by post-mortem immunohistochemistry at 1, 5, 10, and 40 days post-injection (dpi), whereas mRNA levels of the complement components C1qa, C1qb, C3, and C4b were quantified at these dpi intervals using quantitative real-time PCR (qRT-PCR). Engulfment of synaptic particles by microglia was examined by means of quantifying the number of Bassoon+ presynaptic puncta residing within surface-rendered microglia at 10, 20 and 40 dpi. The densities of excitatory and inhibitory synapses were assessed using co-localization studies of VGLUT1+/PSD-95+ and VGAT+/Gephyrin+ double-immunofluorescence, respectively, whereas

dendritic complexity and spine densities were investigated using Sholl analysis and quantification of filopodia, long-thin, mushroom and stubby spines on biocytin-filled pyramidal dendritic sections that were surface-rendering with Imaris. Finally, whole-cell voltage clamp recordings of layer 2/3 pyramidal cells of the PFC were conducted to assess the functional properties of synapses in adult mice.
Results: A single intra-PFC injection of CDS led to a robust (~ 80% depletion) but temporary (~ 1 week) microglia deficiency in the adolescent PFC without affecting other cell types, such as astrocytes and neurons. The expression of C3 and C4b was markedly (2-3 fold) upregulated in mice that were subjected to transient microglia depletion, starting from 5 dpi and persisting into the 40 dpi interval. On the other hand, the expression of C1q genes (C1qa and C1qb) was transiently reduced (i.e. at 1 and 5 dpi), which paralleled the transiency of the CDS-induced microglia depletion. The number of Bassoon+ synaptic puncta was initially decreased in prefrontal microglia of CDS-injected mice at 10 dpi, but was then increased at 20 dpi and, to a lesser extent, at 40 dpi. Furthermore, CDS-induced microglia deficiency in the adolescent PFC led to reduced densities in excitatory (Vglut+/PSD-95+) and inhibitory (Vgat+/gephyrin+) synapses in the adult PFC, decreased dendritic complexity of adult prefrontal neurons and resulted in electrophysiological changes that are indicative of an excitatory-inhibitory imbalance in adult prefrontal circuits.
Discussion: Using a selective and transient loss-of-function approach, our study identified dynamic changes in complement expression and microglial uptake of synaptic particles following transient microglia deficiency in the adolescent PFC. Our data further show that prefrontal microglia deficiency in adolescence has lasting effects on synaptic structures and functions in adulthood. Besides offering other unique opportunities for preclinical schizophrenia research, our model system enables researchers to study the neurobiological consequences of non-genetic upregulation of C3 and C4b arising from transient microglia deficiency during specific stages of brain maturation.

S98. ADOLESCENT STRESS INDUCES CHANGES RESEMBLING SCHIZOPHRENIA: POSSIBLE INVOLVEMENT OF REDOX DYSREGULATION AND MATRIX METALLOPROTEINASE 9

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Background: Stress exposure during adolescence is a major risk factor for the development of psychiatry disorders, including schizophrenia (SCZ). Redox dysregulation, which may be a consequence of stress exposure, is thought to have a pivotal role in SCZ and is a consistent finding in people with SCZ and individuals at-risk for psychosis. Redox dysregulation is characterized by an imbalance between cellular antioxidant capacity and an increase in reactive oxygen species, such as hydrogen peroxide (H2O2) and superoxide (O2-) and is linked to abnormalities in mitochondria function. Among several effects, H2O2 and O2- activate matrix metalloprotease 9 (MMP-9). MMP-9 regulates several neuroplastic processes during developmental stages. Alterations in MMP-9 expression/activity are also found in SCZ patients, but it is unclear whether MMP-9 dysregulation leads to SCZ symptoms. We propose that adolescent stress induces

mitochondrial dysfunction, redox dysregulation, and higher MMP-9 activity in the ventral hippocampus (vHip), leading to behavioral and circuitry deficits resembling SCZ. Abnormalities in the vHip are proposed to underlie the hyperdopaminergic state in SCZ and have been associated with different symptoms.
Methods: Adolescent male Sprague-Dawley rats were exposed to daily footshock sessions for 10 days (postnatal day, PND 31 – 40) and 3 sessions of restraint stress for 1h (PND 31, 32, and 40). Behavioral tests (light-dark box, social interaction, and object recognition test) were performed in naïve and stressed rats in late adolescence (PND 47-50). The activity of pyramidal glutamatergic neurons in the vHip and spontaneous activity of dopamine neurons in the ventral tegmental area (VTA) in adulthood (PND 75) were evaluated through in vivo electrophysiology. To characterize the impact of adolescent stress in the redox system of vHip (PND 41 and 51), we evaluate mitochondrial function by high-resolution respirometry, levels of O2- were measured by DHE staining and MitoSox Assay, and H2O2 consumption and peroxidase activity were assessed by AmplexRed Assay. Gel zymography was performed in the PND 41, 51, and 75 to evaluate MMP-9 gelatinolytic activity.
Results: Adolescent stress caused anxiety-like behavior and cognitive impairment and decreased social interaction. Stressed animals also showed increases in the firing rate of pyramidal neurons in vHip and the number of spontaneously active VTA DA neurons, consistent with evidence indicating that vHip hyperactivity drives a hyperdopaminergic state. In addition, adolescent stress induced mitochondrial dysfunction in the vHip of stressed rats since oxidative phosphorylation capacity was decreased. Increased H2O2 production and endogenous peroxidase activity were found in the vHip of stressed rats in PND 41, which were normalized in PND 51. O2- levels measured in the vHip were increased in PND 41 and 51. Also, MMP-9 gelatinolytic activity in the vHIP of adolescent stressed rats was increased in PND 41 and 51.
Discussion: Our findings indicate that early adolescent stress induced changes in the redox system and increased MMP-9 activity in the vHIP. These changes remained until late adolescence and were associated with behavioral and circuitry deficits related to SCZ. These findings can provide a better understanding of the mechanisms in which adolescent stress can act as a risk factor for SCZ and possible interventions to prevent transition to psychosis in at-risk individuals. Financial support: FAPESP, CAPES, and CNPq.

S99. GASTROINTESTINAL DYSFUNCTION IN BIPOLAR AND SCHIZOPHRENIA SPECTRUM DISORDERS: PSYCHOTROPIC MEDICATION, FRIEND FOR THE BRAIN AND ENEMY FOR THE GUT?

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Background: Recent studies have pointed to the gut-brain axis as a possible new treatment venue in psychiatric disorders. Disruptions in the gut-microbiome, observed in multiple studies, may play a role in psychiatric disorders. Moreover, studies indicate that disruptions in the microbiome and intestinal immune activity lead to the development and worsening of gastrointestinal (GI) symptoms and inflammation. However, research into the specific GI symptoms and the effect of psychotropic medication on these symptoms is scarce. In this study we aim to compare GI

complaints in bipolar disorder (BD) and schizophrenia spectrum disorder (SSD) patients to a healthy control group. In addition, we aim to investigate if there is an association between psychotropic medication and GI symptoms in patients.
Methods: A study will be conducted on patients with either SSD or BD (n=150). These two patient groups will be assessed for GI symptoms using the Gastrointestinal Symptom Rating Scale (GSRS), consisting of fifteen questions divided into five clusters: reflux, abdominal pain, indigestion, diarrhea, and constipation. The GSRS score of both patient groups will be compared to a control group of healthy individuals (HC, n=150), who are matched for age and sex. Moreover, the effect of antipsychotics, antidepressants and mood stabilizers on GI symptoms will be studied.
Results: Preliminary Results: in a smaller group (n=66) already show significantly higher GSRS scores in the patient group compared to the HC in all five clusters ($p<0.01$). When the patient group was separated by diagnosis, the BD group had significantly more abdominal pain, indigestion, diarrhea and constipation complaints compared to the HC ($p<0.01$). The SSD group had significantly more reflux and diarrhea complaints compared to the HC ($p<0.01$). By the time of the conference we expect the groups to be complete (n=150) and to also show our data on the association between psychotropic medication and GI symptoms.
Discussion: This is one of the first studies using the GSRS as a parameter for GI complaints with regard to BD and SSD. Preliminary Results: show increased gastrointestinal symptoms in BD and SSD patients compared to a healthy control group. The GI tract could be an easily accessible route for possible future treatment interventions, such as diets, food supplements, pre-, pro- or antibiotics, for GI complaints and psychiatric disorders.

S100. CRE-ACTIVATION IN ERBB4-POSITIVE NEURONS OF FLOXED GRIN1/NMDA RECEPTOR MICE IS NOT ASSOCIATED WITH MAJOR BEHAVIOURAL IMPAIRMENT

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Background: Despite intense research, the molecular and cellular mechanisms of psychotic disorders, like schizophrenia and anti-NMDA receptor (NMDAR) encephalitis that emerge often during post-adolescence, are only partly understood. Previous genetic models of NMDAR hypofunction restricted to parvalbumin-positive interneurons indicate the necessity of an early postnatal impairment to trigger schizophrenia-like abnormalities, whereas the cellular substrates of NMDAR-mediated psychosis at adolescent/adult stages are unknown. Neuregulin 1 (NRG1) and its receptor ErbB4 represent schizophrenia-associated susceptibility factors that closely interact with NMDAR, the latter expressed in a much larger neuronal population than parvalbumin-positive interneurons. To determine the neuronal populations implicated in “late” NMDAR-driven psychosis, we analyzed the effect of the inducible ablation of NMDARs in ErbB4-expressing cells in mice during late adolescence.
Methods: We employed the Cre/loxP recombination system and tamoxifen-controlled gene manipulation for time- and cell type specific depletion of NMDARs during late adolescence at the age of 7 - 8 weeks in ErbB4-expressing neurons. For the demonstration of the cell type specific

gene inactivation we employed the Cre-inducible tdTomato indicator mouse. After recovery the 10 – 14 days old mice were transferred to the behavioural facility and subjected to the behavioral test battery for the next 2-3 weeks. We assessed nesting behaviour, locomotion and exploration, anxiety, prepulse inhibition, cognition and stress coping.
Results: The tamoxifen-inducible NMDAR deletion during this late developmental stage did not induce behavioral alterations resembling depression, schizophrenia or anxiety. Our data indicate that post-adolescent NMDAR deletion, even in a wider cell population than parvalbumin-positive interneurons, is also not sufficient to generate behavioral abnormalities resembling psychiatric disorders.
Discussion: To our knowledge, our study provides the first characterization of a genetic model of inducible genetic ablation of NMDAR during late adolescence in neurons expressing ErbB4. Our data indicate that post-adolescent deletion of NMDAR even extended to a much larger neuronal population than parvalbumin-positive interneurons is insufficient to trigger behavioral changes associated with psychosis, suggesting the need of either an early developmental glutamatergic impairment or of other, possibly environmental triggers to lead to the clinical manifestation.

S101. GLUCOSE DYSREGULATION IN ANTIPSYCHOTIC-NAïVE FIRST EPISODE PSYCHOSIS PATIENTS: IN SILICO EXPLORATION OF GENE EXPRESSION SIGNATURES

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Background: Glucose dysregulation may represent a premorbid or intrinsic feature of psychosis spectrum disorders (PSDs). Specifically, individuals who are in the earliest stages of the illness (first episode psychosis or FEP) and have minimal antipsychotic (AP) exposure demonstrate prediabetic traits that are not fully explained by factors such as illness duration and antipsychotic use. As well, genetic studies support a causal biological link between glucose dysregulation and schizophrenia. We aimed to examine whether PSDs and glucose dysregulation disorders share an overlap at the gene expression level by comparing transcriptomic signatures of AP-naïve FEP patients with prediabetic patients, as well as identify potential mechanisms and drug treatments for intrinsic glucose dysregulation in PSDs.
Methods: Based on pre-specified inclusion criteria, we systematically compiled: 1) peripheral transcriptomic studies of AP-naïve FEP patients from Ovid PsychINFO, EMBASE, and MEDLINE databases, and 2) peripheral transcriptomic datasets of prediabetes patients from Gene Expression Omnibus (GEO) database. Differential expression (DE) datasets were extracted from the AP-naïve FEP studies and pre-processed. Raw gene expression data from GEO were pre-processed and subject to DE analysis. Then, adaptively weighted Fisher's method (AW-Fisher) was used to meta-analyze AP-naïve FEP DE datasets together and prediabetes DE datasets together. The resulting DE datasets of AP-naïve FEP and prediabetes were meta-analyzed together again through AW-Fisher to identify common differentially expressed genes (DEGs) with $p<0.05$. The common DEGs were subject to pathway analysis via Metascape. Finally, the common DEGs

were analyzed using Integrated Library of Integrated Network-Based Cellular Signatures (iLINCS) to identify FDA-approved drugs with signatures that are discordant (i.e. reverse of) the common DEGs and may represent potential drug treatments.
Results: We included 5 AP-naïve FEP studies and 2 prediabetes datasets. AP-naïve FEP and prediabetes shared 338 common transcriptomic signatures. The top pathways were mainly involved in endoplasmic reticulum stress (protein n-linked glycosylation, ubiquitin-mediated proteolysis, protein folding, and ubiquitin-dependent endoplasmic reticulum associated protein degradation (ERAD)), mitochondrial dysfunction (negative regulation of ATP and cellular carbohydrate metabolic process), and lipid metabolism (lipid biosynthetic process and regulation of lipid biosynthetic process). Several drugs were identified to have signatures that are the reverse of the common DEGs between AP-naïve FEP and prediabetes, most notably the anti-diabetic agent metformin and lipid lowering agent simvastatin.
Discussion: Our findings suggest that PSDs and glucose dysregulation disorders share common gene expression changes. These changes may mediate intrinsic glucose dysregulation and psychopathology through endoplasmic reticulum stress, mitochondrial dysfunction, and dysregulated lipid metabolism. Further, metformin and simvastatin represent potential treatment options for intrinsic metabolic dysfunction and could hold important implications for improving cardiometabolic outcomes in PSDs.

S102. EXPLORING THE VASCULATURE IN THE MIDBRAIN OF SCHIZOPHRENIA CASES BY SINGLE NUCLEUS RNA SEQUENCING

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Background: Schizophrenia (SZ) is a heterogeneous psychiatric disorder with a complex genetic background. The midbrain region has been associated with SZ due to the presence of dopaminergic neurons, that are implicated in the pathophysiology of SZ. Besides the dopaminergic system, the midbrain contains a diverse array of cells that may also contribute to SZ pathology through other mechanisms. Blood vessels of the brain are composed of endothelial cells, pericytes and astrocytes and recent evidence suggests that perturbations in the brain vasculature and the blood brain barrier (BBB) might be involved in SZ pathology (Kelay et al. 2018). In addition, a high inflammatory profile has been described in a subgroup of patients with SZ and this subgroup is associated with increased BBB permeability and decreased cognitive performance (Cai et al. 2020, Purves-Tyson et al. 2020).
Methods: We obtained fresh frozen midbrain sections from 14 controls and 15 SZ cases from the Stanley Brain Collection. The cases had been previously grouped into high and low inflammation cases based on expression of inflammatory cytokines. Our selection included 4 SZ high-inflammatory cases and 10 SZ cases with normal inflammation profile. We isolated the nuclei with fluorescence activated nucleus sorting (FANS) and enriched for relatively low abundant brain cell types, such as vasculature-related cells, by negative selection for neuronal nuclei (NEUN positive) and oligodendrocyte nuclei (OLIG2 positive) (Gerrits et al. 2021). We generated single nucleus RNA-sequenced data using a 10X Genomics platform. Unbiased clustering analysis and

expression of marker genes was used to identify vasculature-related cell types. Subclustering analysis, gene set enrichment and comparisons with previously published datasets were carried out to identify subpopulations among the main vasculature-related brain cell types. With generalized linear modeling, we compared the proportion of the different cell and cell subtypes between SZ, SZ-high-inflammation and control samples.

Results: We identified and characterized midbrain fibroblasts, pericytes, smooth muscle, mesenchymal, ependymal, endothelial cells and astrocytes. Endothelial cell clusters could be separated into capillaries, arteries, and 2 subtype of veins. Astrocytes represented the more abundant vasculature-related cell type and could be segregated into 6 different subpopulations, including 2 immune related, 2 fibrous and 2 protoplasmic subtypes. Proportions of all the mentioned subtypes were similar in SZ as compared to controls. However, the proportion of a protoplasmic astrocyte subtype was higher among SZ-high inflammation cases compared to control cases. Genes differentially expressed by this protoplasmic subtype were related to synapse function.

Discussion: Here we report a fine-grained cellular and molecular characterization of the human midbrain vasculature and vasculature-related cells. We did not detect alterations in the cellular composition of the vasculature in SZ midbrain samples. Interestingly, a subtype of protoplasmic astrocytes was enriched in the SZ-high inflammation group, with differentially expressed genes related to synaptic function rather than to inflammation. This data suggests that inflammation might be interacting with astrocytic activities in at least a subgroup of SZ patients, contributing to SZ pathology.

S103. SERUM ALBUMIN CONFORMATIONAL DISTURBANCES IN PATIENTS WITH FIRST EPISODE OF SCHIZOPHRENIA CAN BE REVEALED BY NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

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Background: Introduction. High-tech approaches can give wide perspectives for the development of new diagnostic and prognostic Methods: and new Methods: for evaluation of efficacy of therapy of mental disorders.

Objectives. High resolution nuclear magnetic resonance 1H (HRNMR 1H) spectroscopy in strong magnetic field gives possibility to reveled qualitative and quantitative changes of different metabolites in biological fluids in pathological conditions.

Aim. To investigate HRNMR 1H spectra of blood serum and its albumin fraction in first episode schizophrenia (FES) patients.

Methods: There were investigated 19 patients with FES and 6 healthy controls. None of the patients received antipsychotic therapy before the admission.

HRNMR 1H spectra of blood serum and serum albumin were measured on Avance-600 (Bruckr, USA). Serum concentration calculated by serum albumin concentration was 50 mg/ml, albumin fraction concentration in water solutions was 25 mg/ml.

Results: There was detected amplification of intensity CH2 –proton lipid signals in blood serum. It points out on increase of long chain lipids concentration in serum of FES patients. At the same time there was observed in albumin water solution spectra amplification of intensity of methyl protons signals of non esterifyed fatty acids of albumin molecule of FES patients using HRNMR 1H spectroscopy. That indicates on the increase of quantity of fatty acid molecules, i.e. on the changes in albumin ligand loading, or on the amplification of fatty acids methyl group mobility, i.e. on changes of albumin molecule conformation.

Discussion: Conclusion. High-resolution 1H NMR spectra of the serum from FES patients indicate on the changed proportion between various lipid fractions bound to albumin in comparison with controls.

High-resolution 1H NMR spectra of albumin isolated from the serum of FES patients confirmed the hypothesis about different ligand load of the albumin in healthy subjects and FES patients.

These results point out on the albumin conformational disturbances in FES patients.

S104. INTESTINAL INFLAMMATION AND PERMEABILITY IN BIPOLAR AND SCHIZOPHRENIA SPECTRUM DISORDERS

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Background: The gut-brain axis has received increasing attention over the past years, in view of its potential involvement in the pathophysiology of severe mental disorders such as bipolar disorder (BD) and schizophrenia spectrum disorders (SSD).The extent to which different abnormalities of the gastrointestinal tract contribute to this link are still subject to further research. In this study we aim to investigate whether markers of intestinal inflammation and permeability differ in patients with BD and SSD compared to healthy controls and whether these markers are associated with disease severity.

Methods: For this study, SSD or BD (n=145) and healthy controls (n=145) were/will be included. Serum lipopolysaccharide binding protein (LBP), soluble CD14 (sCD14) and zonulin were/will be measured with commercially available ELISA kits. Similarly, α1-antitrypsin, calprotectin and zonulin will be measured in feces of patients and controls. Psychiatric symptom severity was/will be evaluated, using the brief psychiatric rating scale(BPRS).

Results: (This study is ongoing and expected to be completed by March 2022. Thus the Results: presented here are preliminary, but expected to be presented in their totality in April 2022.) Multiple linear regression showed that diagnosis, age and sex had a collective significant effect on sCD14 levels ($F(3,112)=11.382$, $p<0.000$, $R2=0.213$), while diagnosis of BD or SSD was the only significant predictor in the model ($t=-4718$,$p<000$). The above mentioned predictors had no significant effect over LBP levels.

Discussion: Conclusions will be discussed when dataset and statistical analysis is completed.

S105. LOW-GRADE INFLAMMATION, FAMILIAL LIABILITY AND THE PSYCHOSIS CONTINUUM MODEL

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Background: There is significant heterogeneity in investigations of psychosis symptom domains and inflammation as related to different illness stages, antipsychotic exposure, and confounding adjustment. Moreover, previous studies were limited to one or two immune markers, typically IL-6 or CRP. The psychosis continuum model is an attractive strategy to study biological mechanisms of psychosis while overcoming illness-related confounding by disease duration, prolonged exposure to antipsychotics, metabolic changes, and poor lifestyle factors. According to this model, attenuated psychotic symptoms (psychotic experiences; PEs) exist in the general population and share many aetiological and pathophysiological Background:s with psychosis. The investigation of biological correlates of PEs can help to understand the pathophysiology of psychosis and identify promising targets for early intervention. We investigated associations between transdiagnostic PEs and plasma levels of pro- and anti-inflammatory mediators in a sample of community controls and first-degree relatives (unaffected siblings) of patients with recent psychosis. We also tested if associations differed between non-inflamed and inflamed subgroups (i.e., CRP>3mg/L but <10mg/L).

Methods: Data were retrieved from a population-based, case-sibling-control study conducted in Ribeirão Preto-SP, Brazil (STREAM), which integrates the EU-GEI consortium. Samples included 66 unaffected siblings of patients and 235 community controls. Dimensions of PEs (positive, negative, depressive) in siblings and controls were assessed using the Community Assessment of Psychic Experiences. Cytokines (IL-1β, IL-4, IL-6, IL-10, TNF-α, IFN-γ, TGF-β) and hsCRP were measured in plasma (multiplex). General linear models were adjusted for sex, age, body mass index, tobacco smoking and corrected for multiple testing (Benjamini-Hochberg, 5%). Statistical significance was set at $\alpha \leq 0.05$.

Results: In siblings, positive PEs were positively associated with IFN-γ (b=0.51; p=0.02) but negatively related to IL-6 and TGF-β (b=-0.38, p=0.004; b=-0.34, p=0.004). Negative PEs were positively and negatively related to IFN-γ (b=0.54; p=0.05) and IL-4 (b=-0.23, p=0.05), respectively. In the control group, IFN-γ was positively associated with negative symptoms (b=0.13, p=0.02), but statistical significance was lost after multiple correction. We also observed that associations between PEs and inflammatory mediators in siblings were specific to the inflamed subgroup (29%). In this subgroup, both IFN-γ and IL-10 were positively 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), and TNF-α was negatively correlated with the positive dimension (b=-1.03, p=0.02). No significant associations were found in non-inflamed siblings or subgroups of controls.

Discussion: Significant associations were only found in siblings and were specific to the inflamed subgroup, suggesting that familial liability to psychosis is likely to play a role. The Th1-related cytokine IFN-γ, previously known as a trait marker for psychosis, was positively associated with transdiagnostic PEs along the continuum. On the other hand, state markers (IL-6, TGF-β) and the anti-inflammatory cytokine IL-4 were negatively related to PEs. The Results: support the trait concept of IFN-γ for psychopathology and indicate that state markers may fluctuate along the continuum. A potential disarrangement in adaptive Th1-IFN-γ/Th2-IL-4 may be important for negative PEs.

S106. TUMOR NECROSIS FACTOR IS ASSOCIATED WITH ALTERED ACTIVATION IN VENTRAL STRIATUM AND ANTERIOR INSULA IN RESPONSE TO REWARD AND EFFORT

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Background: Increasing data implicates inflammation as a driver of negative symptoms in patients with schizophrenia. Relative to the mechanism by which inflammation effects negative symptoms, inflammation has been shown to decrease ventral striatum activation in response to reward in healthy controls and depressed patients. Negative symptoms, specifically motivational deficits, have been associated with decreased activation of the ventral striatum in response to reward anticipation. Thus, we hypothesized that inflammation would be associated with motivational deficits as well as altered signaling in reward-relevant regions.
Methods: 37 patients with schizophrenia, on medications, were recruited from Grady Hospital in Atlanta, Georgia. Patients were excluded if they had evidence of 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), which has subscores for a motivated behavior factor as well as an expressivity factor. Relationships between inflammatory markers and negative symptoms were assessed with spearman correlations. A subset of subjects (n=22) performed the Monetary Incentive Delay Task (MID) and the Effort Based Decision Making Task (EBDM) in a 3T fMRI scanner. A standardized preprocessing pipeline was used. For MID task imaging data, a predefined nucleus accumbens 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: Increases in CRP, a non-specific marker of inflammation, were significantly correlated with decreases in the BNSS motivated behavior factor ($r=-0.340$, $p=0.042$) and specifically the avolition subscale ($r=-0.438$, $p=0.029$). No association was found for the BNSS expressivity factor ($p>0.8$). Regarding more specific inflammatory mediators, tumor necrosis factor (TNF) at higher concentrations were associated with lower activation in the nucleus accumbens in response to reward anticipation in the MID task (Win>Neutral contrast; = beta= 0.462, p = 0.039) [both the left (peak left [-14, 22, -8], T = 3.48, p (uncorrected) = 0.001) and right (peak right [4, 22, -6], T = 2.73, p (uncorrected) = 0.003)]. Higher concentrations of TNF were also associated with

increased activation in the right anterior insula (beta = 0.690, p <0.001) in response to increasing effort on the EBDM task (peak [38, 20, 6], T = 4.35, p (uncorrected) < 0.001).
Discussion: These data support a relationship between inflammation and negative symptoms, and specifically motivational deficits. TNF may lead to negative symptoms through reduced ventral striatum activation in response to reward and increased anterior insula activation in response to increasing effort. The ventral striatum is involved in the regulation of reward and previous data has demonstrated that inflammation may target brain reward circuitry, including the striatum. The anterior insula is involved in interoceptive processing and punishment prediction errors. Previous data has shown that the anterior insula may be sensitive to inflammation in response to punishment prediction errors. These findings support the hypothesis that inflammation may target the ventral striatum and anterior insula to lead to reward and effort processing deficits that may underlie negative symptom severity.

S107. MANUAL QUALITY CONTROL WITH FREESURFER 7: KEY PROBLEM AREAS AND IMPORTANCE OF CORRECTIONS

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Background: Freesurfer (FS) is a software suite that provides a full processing stream for structural MRI images, including automatic functionality for anatomical volumetric segmentation of grey matter (GM) and white matter (WM). This automatization can result in significant time savings, especially with larger datasets.
Striving for accurate structural volume estimates is key, as volumes of specific brain regions may be affected in various psychotic disorders including schizophrenia (Brugger and Howes, 2017). Automatic segmentation by FS has been shown to occasionally misidentify the edges and volume of GM and WM. This can be counteracted with manual quality control (QC).

Earlier work with an earlier version, FS 5, has shown benefits of manual QC may be limited (Beelen et al., 2020). This work addresses the importance of QC of GM/WM segmentation errors with FS 7.

Methods: The structural brain data of 44 first-episode psychosis patients, ages 18-40, was automatically processed by FS 7. The images then underwent QC by a single researcher who corrected errors in skull stripping and GM/WM segmentation. Error locations and volume differences were recorded.
The whole dataset that will be used for the study (n=101, 34 females) was gathered between December 2010 and July 2016 as part of the Helsinki Early Psychosis Study in Finland. Image acquisition was done by a 3T Siemens MAGNETOM Skyra whole-body scanner.

Results: Preliminary Results: from the processed subjects (n=44) show that the volumetric changes due to QC are very small both with regard to whole brain GM (0.09%) and WM volume (0.04%). The most significant volume changes are in the optic chiasm (5.11%).

The errors were distributed unevenly in the brain, with 3 key regions seeing the majority of the 97 identified errors. 24 errors (24,7%) were in the lateral orbitofrontal cortex, at the optic chiasm. 20 errors (20,6%) were in the vicinity of the cerebellar tentorium. Finally, 19 errors (19,6%) were located at the paracentral lobule, near the longitudinal fissure. The other 34 errors were primarily distributed across the cortical meninges. 47 errors were in the left hemisphere, and 50 in the right hemisphere.

No images had obvious and significant processing errors such as large areas of the brain excluded from the brain mask.

Discussion: Preliminary Results: suggest that QC of structural images Results: only in minor differences in GM/WM volume, except for optic chiasm volume. Most errors are located at the cerebellar tentorium, the optic chiasm, and the paracentral lobule. Thus, unless the research project requires significant precision of the most affected areas, manual quality control may not be necessary.
These results are in line with previous studies that investigated the effects of QC with earlier versions of FS and found benefits of manual QC may be limited.

Full results with all subjects (n=101, 34 females) and a comparison between patients and healthy controls is presented in the meeting.

S108. THE INTERACTION BETWEEN EARLY LIFE COMPLICATIONS AND PRS FOR SCHIZOPHRENIA IS ASSOCIATED WITH BRAIN ACTIVITY DURING EMOTION PROCESSING IN HEALTHY SUBJECTS

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Background: Consistent findings suggest that genetic and non-genetic factors concur in explaining risk for schizophrenia (SCZ). Particularly, genome-wide association studies (GWAS) indicate that several genetic variants are associated with diagnosis of this brain disorder. Also, early life complications (ELCs) represent a risk factor for SCZ, which has been shown to influences the effect of cumulative genomic risk (Ursini et al, 2018). However, there are no studies investigating relevance of the interaction between SCZ-related genetic variants and ELCs on biological phenotypes crucially associated with the disease. Anomalies in emotion processing are key for SCZ, and several studies suggest abnormal functional response in the emotion-related brain network in patients, as well as in their healthy relatives. On this basis, the aim of the current study is to investigate the interaction between polygenic risk of SCZ and ELCs on brain activity during processing of stimuli eliciting activity of the emotion brain network.
Methods: 169 healthy subjects were included in the study. Putative ELCs for all participants were evaluated with the McNeil–Sjöström scale (McNeil et al, 1994), and allowed to identify individuals with (N=111) or without (N=58) serious ELCs in their anamnesis using a previously

published method (Ursini et al, 2018). Furthermore, subjects have been genotyped and a polygenic risk score (PRS; p<5e-08) for each individual was calculated using the sum of an individual's statistically independent risk alleles, weighted by their effect size (odds ratio) derived from the GWAS findings (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Each subject performed two runs of an event-related fMRI task (Blasi et al. 2009), During both runs, angry, fearful, happy and neutral facial expressions from a validated set of facial pictures were presented to the subjects. During one run (implicit processing), subjects identified the gender of each face. In the other run (explicit processing), participants had to decide if they would like to "approach" or "avoid" the face. SPM12 was used for imaging analysis. For both runs, vectors were created for angry, fearful, happy, and neutral faces. Residual movement was modeled as a regressor of no interest. Predetermined condition effects at each voxel were created using a t statistic, producing a statistical image for BOLD responses to brain processing of stimuli representatives of each condition, versus fixation crosshairs during both runs. ANOVA was then used at the group level to investigate the main effect of ELCs, of facial expression, of the task, of PRS and their interactions. Significance level was set a p<0.05, whole-brain family-wise error corrected. Post-hoc Pearson's test was performed on signal change extracted from significant clusters of interest.
Results: There was a significant interaction between PRS and ELCs in the left Inferior Frontal Gyrus (IFG) (x, y, z: -52, 16, 16; k: 94; Z: 4.22; pFWE: 0.02). Specifically, there was a positive correlation between PRS and IFG activity in subjects with an anamnesis of serious ELCs, while the correlation was negative in subjects without an anamnesis of ELCs, regardless of the type of emotion and the type of task.
Discussion: These Results: suggest that ELCs may modulate the relationship between genetic risk of SCZ and brain activity during emotion processing and add evidence to the crucial relevance of the interaction between genetic and non-genetic factors for biological phenotypes implicated in this brain disorder. ELCs may converge with genomic risk factors in affecting the anomalies of emotional processing, which are key for SCZ.

S109. REDUCED MAGNETIC MISMATCH NEGATIVITY AS A TRANSDIAGNOSTIC FACTOR OF PSYCHOSIS

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Background: Mismatch negativity (MMN) is a pre-attentive event-related potential that measures the brain cortical response to occasional odd stimuli, indexing brain adaptability to environmental changes. Abnormal auditory processing of deviant stimuli, as reflected by MMN, is often reported in schizophrenia. At present, it is still under debate whether this dysfunctional response is specific to the full-blown schizophrenia diagnosis or rather a transdiagnostic marker of psychosis in general. The present study tested the transdiagnostic nature of reduced MMN in patients with

schizophrenia (SCZ), with bipolar disorder (BD), with a first episode of psychosis (FEP), and in people at clinical high risk for psychosis (CHR).
Methods: Source-based MEG activity evoked during a passive auditory oddball task was recorded from 129 patients grouped according to diagnostic subgroup (48 P-SCZ, 27 P-BD, 20 P-FEP, and 34 P-CHR) and 129 healthy controls also divided into four subgroups, age- and gender-matched with the diagnostic subgroups (48 NC-SCZ, 27 NC-BD, 20 NC-FEP, and 34 NC-CHR). The magnetic MMN (mMMN) was analyzed as Event-Related Field (ERF) peak amplitude, Theta power and Theta Inter-Trial Phase Coherence (ITPC) to test whether reduced mMMN is a transdiagnostic factor of psychosis, without a significant interaction with the diagnostic profile. Additional pre-planned analyses investigated each diagnostic subgroup to establish the significance of the mMMN amplitude reduction for each diagnosis.
Results: The clinical group as a whole showed reduced mMMN ERF peak amplitude ($F(1,242) = 19.91$, $p < .001$), Theta power ($F(1,242) = 12.11$, $p < .001$), and Theta ITPC ($F(1,242) = 17.26$, $p < .001$). There was no statistically significant interaction between diagnostic subgroup and mMMN reductions ($Fs < 1$). Focusing on the pre-planned subgroup contrasts, the mMMN ERF peak amplitude was smaller in patients than controls in SCZ, BD, and FEP ($ts < 2.41$, $ps > .021$) but not in CHR ($t(63) = 1.16$, $p = .253$). In the time-frequency domain, only SCZ showed significant Theta power ($t(93) = 3.43$, $p < .001$) and Theta ITPC reductions ($t(93) = 3.31$, $p = .001$). BD, FEP, and CHR did not show significant Theta power reductions ($ts < 1.87$, $ps > .050$), but these groups presented marginally significant ITPC decreases (BD: $t(50) = 1.72$, $p = .093$; FEP: $t(36) = 1.95$, $p = .060$; CHR: $t(63) = 1.89$, $p = .070$).
Discussion: The observation of significant mMMN alterations in people experiencing psychosis, also for diagnoses other than SCZ, suggests that this neurophysiological response may be a transdiagnostic marker of psychosis. Additionally, our findings show preliminary evidence of significantly lower Theta ITPC in individuals at risk for psychosis compared to matched controls. Lower ITPC in patients than controls suggests that a deficit in functional integration might be the source of mMMN reduction in mental conditions characterized by psychosis.

S110. NEUROANATOMICAL HETEROGENEITY IN INDIVIDUALS AT CLINICAL HIGH-RISK FOR PSYCHOSIS

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Background: Individuals at Clinical High Risk for Psychosis (CHR) present with either Attenuated Psychotic Symptoms (APS), Brief Limited Intermittent Psychotic Symptoms (BLIPS), and/or genetic vulnerability (GRD), and demonstrate a heightened risk for transition to a first episode of psychosis compared with the general population. However, the CHR state encompasses substantial variability; individuals at CHR demonstrate heterogeneity across clinical profiles and outcomes such as transition to psychosis, functional status and remission or persistence of symptoms. The extent of neuroanatomical heterogeneity in the CHR state is largely undetermined and may aid in the identification of clinically meaningful subgroups. Furthermore, the elucidation of such sources of variability are vital in order to further the cause of precision psychiatry and to inform the development of predictive and prognostic models. The CHR Working Group within the ENIGMA consortium offers a unique opportunity to investigate neuroanatomical heterogeneity in the CHR paradigm in a large-scale and harmonised dataset of structural magnetic resonance imaging.

Therefore, leveraging data from the ENIGMA CHR Working Group, we sought to quantify the heterogeneity and homogeneity of neuroanatomical profiles in individuals at CHR compared with healthy controls, and in relation to clinical features. We predicted that there would be significantly greater neuroanatomical heterogeneity evident in individuals at CHR compared with healthy controls. Here, I will present our findings on neuroanatomical heterogeneity in the CHR state, using both group-level and personalised indexes of variability.

Methods: We investigated neuroanatomical variability in the CHR state across twenty-nine international sites, leveraging clinical and neuroimaging baseline data from the ENIGMA CHR Working Group, with longitudinal follow-up for transition to psychosis. The sample included 1579 individuals at CHR and 1243 healthy controls. We applied two indexes of inter-individual variability; first, we applied the Variability Ratio to investigate between-group neuroanatomical heterogeneity in 68 regions of interest according to cortical surface area, 68 corresponding regions of cortical thickness, 16 subcortical volumetric regions and Intracranial Volume. The Variability Ratio uses a logarithmic formula to produce an index of variability between two populations. Second, we further characterised group-level heterogeneity using the Person-Based Similarity Index (PBSI). The PBSI score calculates a personalised index of neuroanatomical similarity, which is first determined for each individual within the CHR and healthy control groups referenced to members of the same group, and further for individuals at CHR referenced to a 'normative' neuroanatomical profile. This approach enabled us to identify CHR individuals who markedly deviated from the 'norm', and to assess whether this deviance was associated with clinical characteristics.

Results: We will first present group-level findings of neuroanatomical heterogeneity and homogeneity, indexed by the Variability Ratio according to: i) group status (CHR compared with healthy controls), and ii) clinical outcome (CHR individuals who subsequently transitioned to psychosis compared with those who did not). Second, we will present the personalised estimates of variability according to the PBSI, and their relation to clinical features, such as psychopathology.

Discussion: In order to reach the full potential of precision psychiatry, we must first better elucidate sources of heterogeneity within the CHR state. Our investigations into neuroanatomical heterogeneity and homogeneity hold importance for the further development and implementation of neuroimaging-based prognostic and predictive models within the CHR field. Further research is required to quantify heterogeneity across other crucial features within the CHR state, with a

particular focus on predictors which are commonly employed in precision models within the existing literature.

S111. THE COMPLEXITY AND CLINICAL IMPLICATIONS OF THEORY OF MIND DEFICITS IN FIRST-EPISODE SCHIZOPHRENIA

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Background: From January 2022, it is recommended that 90% of all Danish patients with first-episode schizophrenia (FES) between 14-35 years of age, should be evaluated on social cognition, including theory of mind (ToM).
Here, we highlight the importance of including the complexity of ToM deficits when evaluating ToM test Results: in a clinical setting. We argue that the evaluation should include potential interactions with psychotic symptoms, negative symptoms and complex aspects of cognition such as executive functions (EF).

Methods: In this study, 31 FES and 29 HC were ToM tested with the Animated Triangles Test (ATT) (implicit ToM) and Brüne´s Picture Sequencing Task (explicit ToM). Using fMRI, effective brain connectivity was measured by the social cognition paradigm from the Human Connectome Project (Barch et al 2013). EF was measured with BADS (Behavioural Assessment of Dysexecutive Syndrome). Negative and positive symptoms were measured with SANS and SAPS.
Results: Explicit ToM was independent of EF while a significant relationship was found between implicit ToM and complex aspects of EF (planning and problem solving). Using fMRI, we found an increase in feedforward connectivity from area V5 to posterior superior temporal sulcus (pSTS) in FES patients compared to controls. In addition, patients with a higher degree of positive symptoms had more disinhibition within pSTS. Furthermore, we found that symptom severity within Diminished Expression (DE), composed of the SANS subscales Affective flattening and Alogia, was the best predictor of ToM performance in ATT compared to both total SANS score, Avolition-Apathy (AA) composed of SANS subscales Avolition-Apathy and Anhedonia-Asociality.
Discussion: Our results show that both psychotic symptoms, aspects of negative symptoms and aspects of EF interact in particular with implicit ToM.

S112. REDUCED STRUCTURAL CONNECTIVITY RELATES TO PSYCHOMOTOR SLOWING IN SCHIZOPHRENIA

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Background: Psychomotor slowing is present in up to 50% of patients with schizophrenia and is associated with poor quality of life and lower functional outcome. Understanding the neural substrates underlying psychomotor slowing is crucial to develop novel therapeutic approaches that might be tailored for each patient's needs. In this study, we compared the motor network structural connectivity between slowed and not slowed patients with schizophrenia and healthy controls.
Methods: We included data from 57 slowed (age: 36.0 ± 12.0 years, 45.6% female) and 20 non-slowed patients with schizophrenia (age: 37.2 ± 12.4 years, 45% female), as well as 40 healthy controls (37.4 ± 12.9 years, 50% female). We defined slowing as scoring ≥ 15 points in the Salpêtrière Retardation Rating Scale. We assessed activity level with 24 hours actigraphy, catatonia symptoms with the Bush-Francis Catatonia Rating Scale (BFCRS), Parkinsonism with the Unified Parkinson Disease Rating Scale (UPDRS) part III, and psychotic symptoms with the Positive and Negative Syndrome Scale. We acquired multi-shelled diffusion-weighted images with 123 directions in a 3T scanner. We first corrected images for movement and eddy currents using FSL 6.04. Then, we performed a tractography analysis using the Quantitative Imaging Toolkit to model structural connectivity with a hybrid algorithm, which combines probabilistic and deterministic approaches for an optimal compartment selection. This approach can extract the major white matter pathways of the brain, known as fiber bundles. We extracted fractional anisotropy (FA) values from 15 bundles covering the motor network (corpus callosum (CC) – supplementary motor area (SMA) connections, CC – precentral gyrus connections, CC – premotor area (PMA) connections; bilateral corticospinal tracts, thalamocortical pathways to PMA, SMA, pre- and postcentral gyrus tracts, and U-fibers of the motor cortex). Then, we compared each fiber bundle's mean FA-values between the three groups using an ANCOVA with age and gender as covariates of no interest. Finally, in patients with PS, we explored the association between the used clinical variables and the mean FA values of each fiber bundle.
Results: The three groups did not differ in age ($F = .17$, $p = .85$) or gender ($X2 = .22$, $p = .90$). We found significant differences between groups in the fiber bundle exploring CC and SMA connections: slowed patients had lower FA than non-slowed patients ($p = .026$) and healthy controls ($p = .011$). Mean FA values in this tract correlated with parkinsonism in slowed patients ($r = -.28$, $p = .04$). Our exploratory correlation analyses revealed significant correlations of CC-PMA bundle with activity level, left motor U-fibers with catatonia and parkinsonism, and bilateral corticospinal tracts with psychotic symptoms.
Discussion: We found impaired structural connectivity in the corpus callosum and SMA connections in slowed patients with schizophrenia. The examination of two patient groups with and without slowing allows differentiation of neural changes that are specific for slowing from alterations attributable to schizophrenia in general. Therefore, we may assume that the impaired structural connectivity in the corpus callosum and SMA connections is associated with motor slowing. The correlation between parkinsonism and reduced connectivity further supports this interpretation. As the SMA is easily accessible for non-invasive brain stimulation techniques and our Results: suggest its involvement in motor slowing, the SMA may be a promising target for novel stimulation therapies.

S113. THE NEURAL PATTERN OF DISTINCT FORMAL THOUGHT DISORDER DIMENSIONS IN PSYCHOSIS

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Background: Formal thought disorder (FTD) includes impairments of language and subjective thought processes and occurs in various mental disorders. In schizophrenia, FTD is a core symptom and a predictor of poor global and functional outcomes. The most consistent FTD subdomains are positive and negative FTD, as well as objective and subjective FTD. Although many studies emphasize clinically relevant dimensions within this group of symptoms, there are only a few investigations of the neural underpinnings associated with these FTD dimensions. The aim of the current study is to explore the neural underpinnings associated with the four distinct FTD dimensions. We expect to see different brain regions involved with different FTD dimensions.

Methods: We included 83 in- and outpatients diagnosed with schizophrenia spectrum disorders in the current study. To assess FTD we used the thought and language disorder rating scale (TALD), which is a comprehensive 30-item rating scale covering a wide array of FTD symptoms including both objectively observable, as well as subjective symptoms in the positive and negative dimensions. Thus, the TALD in comprised of four subscales: Objective Positive (OP), Objective Negative (ON), Subjective Positive (SP) and Subjective Negative (SN). To assess the neural correlates of these four dimensions, we acquired three neuroimaging markers at 3T: cerebral blood flow (CBF), cortical thickness (CortTh) and grey matter volume (GMV). We acquired whole-brain CBF using arterial spin labelling, CortTh in a whole brain analysis and GMV by using voxel-based morphometry. For all the imaging analyses, we controlled for age, medication and total intracranial volume. For CBF and GMV we set a cluster – forming threshold of $p = .005$ and a p value qFDR corrected $< .05$ for the cluster-wise threshold. For the CortTh analysis we used Monte Carlo simulation to correct for multiple comparisons and a cluster-wise forming threshold of $p < .05$.

Results: We found that a higher TALD total score was associated with increased CBF in bilateral ventromedial (vmPFC) and ventrolateral prefrontal cortex (vlPCF) ($p < .001$). In addition, higher OP score was associated with increased CBF in right vmPFC, bilateral parietal/temporal cortices and bilateral cerebellum ($p < .005$), and higher GMV in the left cerebellum ($p < .05$). In contrast, higher ON score was associated with a decreased CBF in the supplementary motor area (SMA) ($p < .05$). Moreover, higher SP was associated with increased CortTh in left vlPFC and in right inferior frontal gyrus ($p < .005$) in Broca's area. Finally, higher SN was associated with increased CBF in the left dorsolateral prefrontal cortex (DLPFC), bilateral vmPFC and bilateral inferior temporal cortices ($p < .05$), as well as, with decreased CortTh in bilateral DLPFC ($p < .005$).

Discussion: This study aimed to explore the underlying neural correlates of the four subscales of the TALD, representing four distinct FTD dimensions in schizophrenia. Not only did we find different patterns of brain alterations in the different FTD dimensions, but we found distinct neural alterations depending on the Methods: used (CBF, CortTh and GMV). Strikingly, a distinct pattern emerged with reduced neural activity in the SMA in ON, but increased neural activity in OP in the vmPFC or with SN in the DLPFC. We conclude that the neural underpinnings differ between FTD

dimension, suggesting distinct subgroups with differential treatment targets for FTD in schizophrenia.

S114. RESTING STATE MAGNETOENCEPHALOGRAPHIC MICROSTATES ABNORMALITIES IN GLOBAL EXPLAINED VARIANCE ARE RELATED TO POSITIVE SYMPTOMS

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Background: Microstates (MS) are configurations of scalp activity topographies, reflecting epochs of relatively stable neuronal activity patterns over short time spans (lasting from 60 to 150 ms) in resting-state. Previous electroencephalography (EEG) studies found four canonical MS in the general population. Abnormalities in two MS have been highlighted in patients affected by schizophrenia or first episode psychosis; moreover, EEG microstates have been recently proposed as a candidate endophenotype of schizophrenia, but it is still not clear whether these abnormalities reflect a biomarker of illness from its onset or rather an epiphenomenon of symptoms severity or chronicity or treatment effects. To investigate this issue, we used MS identified with Magnetoencephalography (MEG) in controls, in subjects at Clinical High Risk (CHR) and in patients with First Episode of Psychosis (FEP) as well as with chronic Schizophrenia (SCZ).
Methods: We recruited a group of subjects including 37 CHR, 14 FEP, and 49 SCZ. We also recruited a group of 98 healthy subjects (HS) matched with the clinical population for demographic variables. Severity of psychotic symptoms was measured with the Positive and Negative Syndrome Scale (PANSS) in CHR, FEP and SCZ. All participants underwent a 5-minute eyes-closed resting-state MEG acquisition. We performed a k-means cluster analysis on the HS sample to identify prototypical mMS cluster maps. Best-fitting number of clusters was determined with meta-criterion validation. We then backfit the obtained mMS on HS, CHR, FEP and SCZ groups signal, computing for each subject the global explained variance (GEV) of each mMS – a measure reflecting the similarity between individual activity and mMS topographical maps . First, we studied mMS differences between groups with ANCOVA, covarying for age and gender ; then, we performed another ANCOVA to investigate the association between mMS GEV with positive symptoms , covarying for age and gender.
Results: The number of clusters in HS determined by meta-criterion validation was 6. mMS1 exhibits a left anterior polarity; mMS2 a right posterior polarity; mMS3 shows anterior and posterior polarities; mMS4 consists in a right anterior polarity, mMS5 and mMS6 have lateral polarities and, respectively, a right-medial anterior and a centro-posterior polarity. For mMS 1,2,3,4 and 6, we found statistically significant differences between groups (ps FDR <.01); in post-hoc analyses, a significant reduction was found in SCZ as compared with HS (ps FDR <.01) and CHR (ps FDR <.05); the difference between CHR and SCZ was not significant in mMS6. Across groups, we found a significant negative relationtiship between positive symptoms and mMS1, 2 and 3 GEV (p FDR<.015).
Discussion: In line with previous EEG studies, our Results: revealed abnormalities in mMS in patients affected by full-blown psychosis: mMS topographies found in HC were less correlated

with brain activity topographies found in SCZ (as shown by GEV reduction). No significant reduction was found in CHR as compared with HS, suggesting the absence of this neurophysiological alteration in people at risk, whereas FEP were intermediate between CHR and SCZ, potentially suggesting an electrophysiological pattern increasing over disease stages. Moreover, mMS1, mMS2 and mMS3 GEVs were related to severity of positive symptoms. Progressive GEV reduction in psychosis might reflect increasing abnormalities in brain circuitry and neurotransmission, associated with the severity of positive symptoms. Our Results: suggest that GEV might be useful as a biomarker of disease, supporting the application of mMS in clinical research to stage psychotic illness and develop personalized treatments. However further studies are needed for full validation.

S115. DIFFERENCES IN MORPHOMETRIC INDICES AND CORTICO-THALAMIC STRUCTURAL CO-VARIATION ACROSS SCHIZOPHRENIA PATIENTS, INDIVIDUALS AT FAMILIAL RISK FOR SCHIZOPHRENIA AND HEALTHY CONTROLS

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Background: Previous studies reported altered grey matter volumes in patients with schizophrenia (SCZ) and people at familial high risk for schizophrenia (FHR), i.e., their unaffected first-degree relatives. Moreover, several studies identified widespread brain morphological abnormalities and that differentiated SCZ from healthy controls (NC).
However, there is considerable heterogeneity in the effect sizes of brain differences and in the morphometric co-variation patterns abnormalities across these studies, with unresolved discrepancies between the structural alterations reported in SCZ and open questions regarding alterations in FHR.

Therefore, our aim was to investigate at a network-level the potential association between familial risk for schizophrenia and, respectively, (i) the volume of seven thalamic subdivisions, and (ii) alterations in the structural co-variation between these subdivisions and whole-brain cortical morphometric indexes through a meta-analytic approach.

Methods: Structural images were collected from two 3T MRI scanners, Signa and Philips, respectively, generating two cohorts. The Signa cohort included 338 NC (M(age) = 26.24, SEM = 0.34, 43% m), 28 FHR (M(age) = 36.53, SEM = 1.14, 40% m) and 51 SCZ (M(age) = 31.64, SEM = 0.92, 69% m). The Philips cohort included 117 NC M(age) = 24.29, SEM = 0.32, 61% m), 13 FHR (M(age) = 26.73, SEM = 1.09, 66% m) and 30 SCZ (M(age) = 26.62, SEM = 0.92, 21% m). In each cohort, the effect of seven thalamic subdivisions (anterior, intralaminar, medial, posterior, pulvinar, ventral-posterior, ventral) and group (NC, FHR, SCZ) on thalamic volumes, as well as their interaction, were assessed by repeated measures ANCOVA, after regressing out nuisance covariates (sex, age, quadratic age, ventricular and intracranial volume). Pairwise random-effects meta-analysis served to generate cumulative effect sizes (standardized mean differences (SMDs),

p<0.05). Subsequently, three bilateral matrices (mean co-variation between the two hemispheres) were computed for each cohort: thalamic volumes/cortical volumes, thalamic volumes/cortical thickness, thalamic volumes/cortical surface (p<0.05 False Discovery Rate (FDR) corrected) and then summarized in three meta-analytic matrices through random-effect meta-analysis. The effect of group on each meta-analytic matrix was assessed by Kruskal-Wallis ANOVA (pFDR<0.05).
Results: Significant differences were found between NC and SCZ (no significant differences with FHR), whereby SCZ showed lower estimates than NC in total thalamic volume (SMD=-0.39, 95% CI: [-1.94, 1.22]; p=0.004), right posterior subdivision volume (SMD=-0.01, 95% CI: [-0.02, -0.01]; p=0.008) and right posterior-ventral subdivision volume (SMD=-0.04, 95% CI: [-0.06, -0.03]; p=0.020). In addition, a group effect was found on structural co-variation between thalamic volumes and, respectively, cortical volumes ($\chi2$= 121.19, p<0.001), cortical thickness ($\chi2$=232.05, p<0.001), cortical surface ($\chi2$=194.89, p<0.001). Specifically, thalamic co-variation with cortical volumes showed that FHR were in an intermediate position between SCZ and NC, with significant differences from both (pFDR<0.001).
Discussion: Our results revealed the presence of morphometric abnormalities associated with diagnosis of schizophrenia, but not with familial risk for this disorder. On the other hand, structural co-variation between thalamic and cortical volumes placed FHR in an intermediate position between patients and controls. Our Results: suggest that that these differences may reveal familial effects more difficult to detect with standard voxel-based morphometry approaches, which do not account for the investigation of brain-network relationships.

S116. EFFECTS OF PSYCHOMETRIC SCHIZOTYPY ON CORTICO-HIPPOCAMPAL LEVELS OF GLUTAMATE AND RESTING-STATE ACTIVITY: A PILOT STUDY

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Background: Previous research indicates that cortico-hippocampal functional dysconnectivity and neurochemical alterations may contribute to the development of psychosis. McCutcheon et al., 2021 found a weaker correlation between frontal glutamate concentrations and functional connectivity of the salience network in patients with schizophrenia. Previously, healthy individuals with subclinical psychotic-like experiences (or schizotypy) have displayed higher hippocampal activity, cortico-hippocampal resting-state dysconnectivity, and altered interactions between cortical glutamate levels and resting-state and task-based fMRI activity. Whether this relationship is also detectable at the subclinical ends of the psychosis continuum is unknown. We sought to test the hypothesis that schizotypal traits would be related to the nature of the relationship between cortico-hippocampal connectivity and cortical glutamate levels.
Methods: This pilot study recruited 11 healthy volunteers. The schizotypal personality questionnaire (SPQ) was used to measure schizotypy levels. Glutamate levels in the anterior cingulate cortex (ACC) and left hippocampus, and resting-state brain activity/connectivity were measured using proton magnetic resonance spectroscopy and functional magnetic resonance imaging respectively, on a Discovery MR750 3T scanner at the Invicro-London imaging centre. Hierarchical linear modeling and partial correlation analysis were conducted to investigate the relationship between the SPQ cognitive-perceptual, interpersonal, disorganized subscale and total

scores, cortical and hippocampal glutamate levels (corrected for tissue voxel composition) and regions of interest-based resting-state brain activity indices including regional amplitude of low-frequency fluctuation (ALFF), regional homogeneity (ReHo) and functional connectivity between the ACC and hippocampus. Age, sex, and head motion parameter were set as confounding variables.

Results: The Results: showed that when SPQ total scores were set as dependent variable, the statistical Results: from model 1 (age, sex, and head motion) to model 2 (ALFF values of ACC) was: $\Delta F\ (1, 6) = 10.46$, $p = 0.02$, and correlation r value is -0.80; and to model 2 (ReHo values of hippocampus): $\Delta F\ (1, 6) = 11.68$, $p = 0.01$, correlation r value is -0.83. When SPQ cognitive-perceptual scores were set as dependent variable, from model 1 to model 2 (glutamate levels of hippocampus) was: $\Delta F\ (1, 6) = 4.26$, $p = 0.09$, correlation r value is 0.64. When SPQ interpersonal scores were set as dependent variable, from model 1 to model 2 (ALFF values of ACC) was: $\Delta F\ (1, 6) = 4.79$, $p = 0.07$, correlation r value is -0.67; and to model 2 (functional connectivity within ACC) was: $\Delta F\ (1, 6) = 6.38$, $p = 0.05$, correlation r value is 0.72. When functional connectivity within ACC was set as dependent variable, from the same model 1 to model 2 (glutamate levels of ACC) is: $\Delta F\ (1, 6) = 6.82$, $p = 0.04$, correlation r value is 0.73.

Discussion: Overall, these preliminary findings suggest that regional resting-state activity and cortico-hippocampal glutamate levels are related to the expression of psychotic-like experiences in healthy individuals. The correlations are similar to some previous findings of patients with schizophrenia and individuals with schizotypy. These findings may have implications for a possible developmental continuum from behaviour traits to clinical symptoms and characterising the mechanisms underlying cortico-hippocampal alterations across the extended psychosis phenotype. However, these are preliminary in a small sample and there are certain discrepancies between studies requiring validation with larger datasets.

S117. NEUROMELANIN MRI AS BIOMARKER FOR TREATMENT RESISTANCE IN FIRST EPISODE SCHIZOPHRENIA PATIENTS

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Background: Treatment resistance (TR) in schizophrenia is a major clinical problem with 20-35% of psychotic patients showing non-response to standard antipsychotic treatment. A biomarker that could predict TR is needed to reduce delays in effective treatment. A well-established finding in schizophrenia, using [18F]F-DOPA PET imaging, is increased striatal dopamine synthesis, but interestingly TR patients do not show this altered synthesis. [18F]F-DOPA however is too costly and invasive to use for TR screening. A novel neuromelanin-sensitive MRI sequence (NM-MRI), which indirectly measures striatal dopamine synthesis, has potential as biomarker for TR. NM-MRI signal is indeed increased in schizophrenia patients, but has not yet been evaluated in TR. The current study assessed NM-MRI as a biomarker for TR and investigated if TR patients show lower NM-MRI signal than responders.

Methods: 61 first episode schizophrenia patients underwent an MRI scan at baseline. Treatment response was determined during six months follow-up. A patient was classified as TR after showing no adequate response to a minimum of two sufficiently dosed conventional antipsychotics. MRI scans were conducted on an 3 Tesla Ingenia MRI scanner equipped with a 32-channel sense head coil. T1-weighted scans were acquired for processing of the NM-MRI image (TR/TE=4.1/9.0 msec; 189 slices; FOV=84×284×170 mm; voxel size= 0.9×0.9× 0.9 mm, FA = 8°). NM-MRI scan contained a T1-weighted gradient recalled echo sequence with resonance magnetization transfer preparation pulses (TE/TR=3.9/260 msec, FA=40°, 8 slices, slice thickness=2.5 mm, in-plane resolution=0.39×0.39 mm2, FOV=162×199 mm, NSA=2;) and was placed perpendicular to the fourth ventricle floor with coverage from the posterior commissure to halfway through the pons. NM-MRI signal in the Substantia Nigra (SN) was measured as contrast ratio (NMcr), with the Crus Cerebri (CC) as reference region. The toolbox described by Wengler (2020) was used for processing of the NM-MRI scan. First the T1-weigthed scans were used to normalize the NM-MRI scans to MNI standard space using ANTS 2.3.1.6 The normalized NM-MRI scans were then spatially smoothed using 3D Gaussian kernels with full-width-at-half-maximum of 1 mm. Template masks from a previous study were used to obtain the signal intensity (S) of the SN and CC. NMcr was calculated at each voxel in the NM-MRI images as NMcr= (Ssn – mode(Scc)/ mode(Sc)) * 100. A One-way ANCOVA was conducted to assess group differences between TR and responders on mean NMcr controlling for age. Age was added as covariate, since neuromelanin levels in the SN show an inverted U-shaped age effect.

Results: At six months of follow-up 15 patients were classified as TR and 46 patients as responders. The two groups did not significantly differ on gender, IQ, use of medication, and substance use. However, the mean age of TR patients was lower than responders, $t(59)= -2.876$ $p = 0.007$. The ANCOVA revealed a significant effect of group (TR versus responder) on mean NMcr after controlling for age, $F(1,58) = 5.064$, $p = 0.028$. Age was not a significant covariate ($F(1,58) = 0.457$, $p = 0.502$). In addition no correlation was found between age and NMcr ($r =0.177$, $p =0.172$).

Discussion: Significantly lower NMcr levels were found in TR patients compared to responders. These findings are in line with the [18F]F-DOPA PET studies showing lower dopamine synthesis in TR compared to responders. This study demonstrates the promise of NM-MRI as biomarker for TR although the application of NM-MRI as a predictor for TR remains uncertain given the overlap in NMcr levels between TR and responders. A possible explanation for this might be that binary categorizing patients as either TR or responders is not appropriate as the response to antipsychotics could be a spectrum, including a group of partial responders. This will be further assessed. In addition, we will map the regional voxelwise variation within the current template mask. The template mask is purposefully over inclusive to ensure that all SN voxels are included in the mask and conversely some voxels outside the SN might be incorrectly included. This could influence the mean signal intensity to various degree in different subjects. No correlation was found between age and NMcr. Even though neuromelanin is known to increase with age, this increase is most steeply until the age of 20. Since the mean age of our two patients groups (21.3 and 24.3 years) is slightly higher, the effect of age on our Results: might be limited.

This study demonstrated the potential of NM-MRI as a biomarker for TR in schizophrenia. Even though the Results: of this study show significant differences in NMcr between TR and responders, the predictive value of NM-MRI still requires further investigation.

S118. FIXEL-BASED ANALYSES OF WHITE MATTER IN ANTIPSYCHOTIC NAIVE PATIENTS WITH FIRST-EPISODE SCHIZOPHRENIA AND THE CLINICAL CORRELATES

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Background: Growing evidence support the dysconnectivity hypothesis of schizophrenia. However, suboptimal image processing, clinical diversity, antipsychotic exposure and substance use has hindered insights to the microstructural properties of patients' white matter alterations. Fixel-based analysis (FBA) is a novel method to extract fibre-specific measures of micro- and macrostructure such as fibre density and fibre-bundle cross-section, as obtained from diffusion magnetic resonance imaging (dMRI). We applied FBA to compare a large sample of antipsychotic-naïve patients with first-episode schizophrenia to a group of healthy controls, and to investigate clinical correlates.

Methods: Eighty-six patients and 112 matched healthy controls underwent dMRI. Group comparisons on fixel-based measures were examined with multivariate general linear modelling. Psychopathology was assessed with the Positive and Negative Syndrome Scale. Correlations were tested between fixel-based measures and predefined psychosis-specific versus anxio-depressive symptom dimensions. We hypothesized, that patients would present with reduced fixel-based FD, FC, and FDC when compared to healthy controls. Further, we expected psychosis-specific symptoms would associate with fixel-based measures differently than anxio-depressive symptoms.

Results: Patients had reduced fibre density in the body of corpus callosum and in the middle cerebellar peduncle ($p<0.05$). Significant correlations between fibre density, fibre-bundle cross-section and psychosis specific symptoms were located to corticospinal tract. Significant negative correlations between fibre density, fibre-bundle cross-section and the anxio-depressive symptoms

were located to genu and splenium of corpus callosum. Results: were replicated when excluding participants with recreational substance use.
Discussion: FBA revealed specific micro- and macrostructural properties of disturbed white matter in symptom-distinct tracts in antipsychotic-naïve schizophrenia patients. Alterations related to fibre density and cross-section is linked differently to psychosis-specific versus anxio-depressive symptoms. FBA appear to enable a more itemized approach to investigate the relationship between WM structure and specific clinical symptoms.

S119. EEG MICROSTATES ACROSS PSYCHOTIC DISEASE PROGRESSION

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Background: EEG microstates represent the spatiotemporal succession of quasi-stable polarities of scalp potentials. Disturbance in their sequence or frequency could constitute a possible endophenotype of schizophrenia (da Cruz et al. 2020). It is postulated that psychosis is characterised by an imbalance between an increased self-referential mode (microstate class C), and a decreased attentional mode (microstate class D), reflecting a disconnection between mental states and information received from the environment (Michel and Koenig, 2018). Here, we explored whether this microstate imbalance existed on a continuum from ultra-high-risk (UHR), to first-episode psychosis (FEP), and recent-onset schizophrenia (SCZ).
Methods: We retrospectively included 26 UHR, 49 FEP, and 38 SCZ, who consulted in an early intervention clinic at Sainte-Anne Hospital, Paris. All underwent a standard resting-state EEG with 20 surface electrodes, for most of them before medication was introduced. EEG preprocessing was done with MNE-python. Bandwith filter was set between 0.5 and 40 Hz, data was re-referenced to the average reference, and a visual correction for artefacts was done for each recording separately. Microstate analysis was done with the pycrostates package (V. Férat) : i) global field power peaks were extracted from a concatenation of the first 60s of each recording ; ii) a modified K-means with a four clusters solution was applied to the peaks sequence ; iii) backfitting of the resulting topographies was then applied to each of the entire recordings. A mixed ANOVA then included disease stage as a between-subjects factor and microstate class as a within-subjects factor and pairwise two-sided tests were done between classes C and D at each stage, for each of the microstates characteristics : global explained variance, occurrence, coverage, and mean duration.
Results: The four clusters solution found the A, B, C, D topographies class classically described in the literature. We observed a prevalence of class C compared to class D, which was accentuated and increasingly more significant at later stages of disease. For coverage: in UHR, T-stat = 1.13, p = 0.27; in FEP, T-stat = 1.98, p = 0.05; in SCZ, T-stat = 3.16, p = 0.003. For global explained variance: in UHR, T-stat = 1.02, p = 0.31; in FEP, T-stat = 0.21, p = 1.26; in SCZ, T-stat = 2.99, p = 0.005. For mean duration: in UHR, T-stat = 1.18, p = 0.25; in FEP, T-stat = 0.96, p = 0.34; in SCZ, T-stat = 2.55, p = 0.015. For occurrence: in UHR, T-stat = 0.76, p = 0.46; in FEP, T-stat = 3.23, p = 0.002; in SCZ, T-stat = 2.77, p = 0.009.
Discussion: Our Results: replicate the first literature reports on the imbalance between microstates C and D in early psychosis. It extends the observation of a predominance of class C above class D across the spectrum of disease, and shows that the level of the imbalance is accentuated at later

stages. This suggests the relevance of microstates as potential biomarkers of state in the progression of psychosis.

S120. NEURAL CORRELATES OF EMPATHIC ACCURACY IN AUTISM-SPECTRUM AND SCHIZOPHRENIA-SPECTRUM DISORDERS

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Background: Social cognitive deficits are central features of autism spectrum disorder (ASD) and schizophrenia spectrum disorders (SSDs), yet limited research has examined how the neural correlates of social cognition compare across ASD and SSDs. Here, we used the empathic accuracy (EA) fMRI task to examine neural correlates of accurately identifying another's emotional state. The EA task probes both lower-order emotion recognition and higher-order theory of mind social processes. Our primary objective was to assess and compare the neural correlates of EA in a large sample of ASD, SSDs and typically developing control (TDC) participants. Our secondary objective was to examine the neural correlates of EA for positive and negative EA task videos, separately.

Methods: A total of 174 participants (aged 16-34) with useable EA fMRI-task data were included for analysis (ASD: n=59, 21.2[3.97] years, 23-female; SSDs: n=56, 25.3[4.54] years, 19-females; TDC n=59, 25.8[3.93] years, 32-female). During fMRI scanning, participants watched 9 EA task videos of individuals detailing autobiographical events, and provided continuous ratings of how positive/negative they thought the individual felt (9-point scale). Data were acquired on 3T Prisma scanners across three sites: 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). EA task data were analyzed using a GLM, implemented in AFNI, with EA scores as parametric modulators (activation maps therefore reflect brain activity that varies with EA). Group-level analyses were conducted with FSL's PALM, using 1000 permutations (thresholded at $p<0.05$ FWE-corrected). We examined group-wise comparisons and main effects by group. This analytic approach was repeated for positive/negative EA task videos.

Results: EA performance differed across groups ($F(2,171)=7.31$, $p<0.01$); SSDs group performed lower than the ASD and TDC groups (all $p<0.01$). EA performance also differed across group for positive ($F(2,171)=4.29$, $p=0.02$) and negative ($F(2,171)=4.27$, $p=0.02$) videos; SSDs group had lower EA performance than the TDC group for positive ($p=0.01$) and negative ($p=0.02$) videos. EA performance did not differ between ASD and TDC groups (all $p>0.05$). Activity in brain regions that related to EA did not differ across groups for the full EA task, or positive/negative videos separately. Within ASD and SSDs groups, widespread activity in the right hemisphere, including within brain regions implicated in social cognition (e.g., superior temporal sulcus, temporal pole, inferior parietal lobule, temporo-parietal junction), were positively related to EA. No brain-behavior associations were found (at $p<0.05$ FWE-corrected) in the TDC group. While no neural correlates of EA were found during positive videos in the ASD and SSDs groups, activity

in visual regions were negatively related to EA during positive videos in the TDC group. Across all groups, activity in brain regions implicated in social cognition, including those listed above, were positively related to EA during negative videos.
Discussion: Our data suggest that accurately detecting negative affect recruits brain regions implicated in social cognition, largely from the right hemisphere, which appear to be driving our overall EA task effects. Though the SSDs group had poorer EA task performance than the ASD and TDC groups, our findings suggest that ASD and SSDs groups feature similar correlational patterns between neural activity and EA, with some interesting overlap between clinical groups and dissimilarity with the TDC group.

S121. STUDYING THE ABERRANT ACTIVITY OF PRIMARY MOTOR AND VISUAL CORTEX ON SCHIZOPHRENIA PATIENTS BY USING THE VISMOTOR TASK: AN FMRI STUDY

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Background: This study is part of the Clinical Deep Phenotyping (CDP) project of the Department of Psychiatry and Psychotherapy of LMU, which combines numerous measurement techniques to study the psychosis spectrum. This approach intends to identify clinically relevant endophenotypes of psychosis that can facilitate and make possible more promising therapies for cognitive deficits in this specific group.
Numerous studies have shown different activity patterns on simple visual and motoric processes between schizophrenia patients and healthy control. However, most of these studies are performed using the EEG methodology, leaving the neuroimaging literature regarding the simple visual and motoric functions of schizophrenia relatively scarce. The majority of the existing studies use complex tasks, making thus the interpretation and reliability of the Results: questionable. In this (undergoing) study, we tested for the first time the feasibility of a simple visual and motoric (VISMOTOR) task on schizophrenia patients.

Methods: Twenty (20) participants (10 schizophrenia) performed the VISMOTOR task while being scanned on a 3T Magnetom Prisma MR Scanner. We adapted the VISMOTOR task from the Human Connectome Project (HCP), with slight changes in the number of blocks. The task was composed of a 4 Hz rounded flickering checkerboard display, with red targets appearing on either the left or the right side of the checkerboard. Targets were presented for 500ms, with a fixed interstimulus interval (ITI) of 2500ms. The location of targets (left vs. right) between sets was randomized. Twelve (12) total blocks of visual checkerboard were presented during the scan, while each block contained nine (9) targets. A 1800ms green plus was shown between the blocks. We analyzed the data using a block design, where the presentation of the checkerboard is taken as the task block and the 1800ms green plus between blocks as the pseudo-resting state.
Behavioral Results: In general, schizophrenia patients showed an overall performance reduction during the VISMOTOR task, compared to the healthy control. Significant differences were found in the reaction time for the correct responses ($p<0.05$) and the number of missing responses ($p<0.05$). No other differences were found on other aspects of the task (left accuracy, right

accuracy, total accuracy, and involuntary movements; $p>0.05$), although the performance on all of these aspects was reduced for schizophrenia patients.

Imaging Results: Our Results: showed good readability of the task for both schizophrenia and healthy control. There were no significant differences between groups for the activity on the Primary Visual Cortex ($p>.05$). However, schizophrenia patients showed a higher cluster size activation pattern throughout all of the visual cortex, compared to the healthy control.

Differences were found regarding the activity pattern on the Primary Motor Cortex, with schizophrenia patients showing a higher activation than the healthy control ($p<.05$). Although expected from prior studies, we failed to see an activation on the frontoparietal network. Differences between groups were also found for the pseudo-resting state. Compared to healthy control which did not show any significant cluster activation, schizophrenia patients showed increased activity on the Primary Visual Cortex, left Broca's area, and Right Inferior Temporal Gyrus.

Discussion: Based on preliminary results, it can be suggested that schizophrenia patients show an aberrant activity for basic visual and motoric processes. Compared with the healthy control, this study found a hyperactivity pattern for basic visual and motoric areas in the schziophrenia group. Moreover, we found some significant activation for the schizophrenia group during the pseudo-resting state, which was absent for the healthy control. To the best of our knowledge, this study shows for the first time the feasibility of using the simple VISMOTOR task on patients with schizophrenia and the potential of this task on identifying promising schizophrenia endophenotypes markers on basic visual and motoric processes. Further research by combining other techniques (e.g., EEG, retinal neurophysiology, neuropsychological testing, etc.) can generate complementary evidence and lead to a better understanding of cognitive deficits in schizophrenia.

S122. STRUCTURAL BRAIN VOLUME CHANGES IN SALIENCE NETWORK REGIONS AND ASSOCIATIONS TO COGNITIVE FUNCTIONING IN SCHIZOPHRENIA PATIENTS - INTERMEDIATE RESULTS: OF THE CDP STUDY

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Background: Genetic and clinical analyses show similarities in a variety of diagnoses, suggesting that a common neurobiological substrate may exist across mental illness. Meta-analytic studies indicate that gray matter loss in all diagnoses occurs in three major brain areas: the dorsal anterior cingulate (dACC), the right insula (RIns), and the left insula (LIns). In our Clinical Deep Phenotyping (CDP) study, patients with schizophrenia-spectrum disorders underwent structural MRI analysis of T1- and T2 - weighted sequences. We focused on areas of the salience network as transdiagnostic markers. The volumetric gray matter regions were correlated with z-score transformed values of the Brief Assessment of Cognition in Schizophrenia (BACS) battery, which

covers several cognitive domains primarily affected in schizophrenia-spectrum disorders, such as working memory and executive functioning.
Methods: Study participants: Schizophrenia-spectrum disorders (SSD) and healthy controls (HC) with an age: ≥18 years and ≤ 65 years at inclusion. Fifty-five participants with a SSD and 61 HC were included in our preliminary analyses.
Structural T1-weighted datasets from the S1200 HCP cohort were used for further independent validation (age between 22 and 35 years). The CDP sample was examined with multimodal MRI (T1w, T2w, rsfMRI, MRS, DTI, subsample: visuo-motor fMRI task) on a 3T Siemens Prisma scanner. The HCP Aging Imaging Protocol and additionally a SVS Spectroscopy sequence were used. The SSD sample was divided into remitted and non-remitted (remission according to PANSS RSWG criteria) and treatment-resistant and non-treatment-resistant patients (clozapine lifetime treatment as proxy for treatment-resistance). Standardized z-scores were created from BACS scores based on the total sample including all study participants.

We evaluated gray matter (GM) and white matter (WM) volumes of different brain regions as follows: a 10-mm sphere from Goodkind et al. for the single regions (LIns, RIns, and dACC) and the contiguous cluster from all areas. In addition, we used the larger salience network template of Laird et al. based on 31,724 subjects, which measured, among other variables, correlations to cognitive domains. For the GM and WM comparisons between SSD and two healthy comparison groups, we defined a Bonferroni corrected threshold of $p<0.05$, the z-scores of the BACS subtests and the BACS composite score were correlated with GM volumes and a significance threshold of $p<0.05$ was defined.

Results: The Results: of MRI analysis showed significant differences in the Salience network GM volume by Goodkind (SNG) and the Salience Network by Laird (SNL) between HC and SSD. Significantly lower volumes of SNG ($p<0.001$) and SNL ($p<0.01$) were observed in SSD compared to HC. Moreover, SSD patients with clozapine lifetime treatment and SSD patients without clozapine lifetime treatment showed significantly lower volumes of SNG in GM compared to HC ($p<0.001$). SSD patients also showed significantly lower BACS composite Z-scores in comparison to HC ($p<0.001$). Reduction of RIns volumes was observed in SSD patients in remission compared to HC ($p<0.001$). The same Results: were observed in non-remitted SSD patients compared to HC in GM ($p<0.01$). For Pearson correlations between different GM volumes and cognitive z-scores, we found significant correlation coefficients between different groups, with the highest correlation coefficient between dACC and BACS-VM z-score in SSD in remission.
Discussion: In SSD a deviation in the GM volume of salience network areas with the most marked difference in the right insulae could be detected. Remission and non-remission status show profiles that need to be validated in larger samples. These structural MRI differences are directly associated with the Results: of the BACS test battery.

S123. FUNCTIONAL NEUROANATOMY OF PERSECUTION IN PSYCHOSIS RELATES TO THE DYSCONNECTIVITY OF CORTICAL EXECUTIVE AND EVALUATIVE NETWORKS

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Background: A growing literature challenges pharmacological theories that locate core positive symptom mechanisms in subcortical structures such as the ventral striatum. To examine the functional neuroanatomy of a single aspect of positive symptoms, persecutory ideation, we employed a social decision-making task called the Minnesota Trust Game (MTG). MTG parametrically varies risk to resolve different aspects of decision making, including risk aversion, rational mistrust, and lastly spite sensitivity which is the participant's concern that an anonymous partner may be willing to incur a loss to make the participant suffer a greater loss. This assay therefore contrasts closely controlled conditions to identify local activity and network connectivity patterns across the brain. Previously, spite sensitivity measured with this task was associated with persecutory ideation. Partially replicating previous work from our lab, the current findings implicate a key role for connectivity patterns between executive and evaluative networks in cortex in early psychosis patients.
Methods: 49 patients in the early course of psychosis completed the MTG during scanning using a within-group correlational design to control for other illness-related factors. During the task, participants chose between taking a small, safe amount of money ($10) or trusting a partner to choose between fair ($20 for both) and unfair monetary outcomes. In some instances, there was a benefit for the partner to choose the unfair option (Rational Mistrust condition, e.g. $25 for the partner and $0 for the participant), while in other instances it came at a relative cost to them to ensure the participant also lost money (Suspiciousness condition, e.g. $15 for the partner and $0 for the participant), which would reflect spite from the partner. Participants with difficulty trusting in the Suspiciousness condition are therefore considered spite sensitive.
Results: Behaviorally, patients were overall more trusting during Suspiciousness trials, relative to Rational Mistrust. However, as predicted, patients who reported more persecution trusted less in the Suspiciousness condition ($\boldsymbol{\beta}$ = -.287, p = .007). In terms of functional neuroanatomy, the Rational Mistrust condition was associated with decreased caudate nucleus activity, while the Suspiciousness condition was associated with increased medial prefrontal and lateral orbitofrontal cortex (OFC) activation. When examining canonical networks similar to those from our previous findings (Wisner et al. 2021, Task-related neural mechanisms of persecutory ideation in schizophrenia and community monozygotic twin-pairs. Human Brain Mapping), we non-significantly replicated a negative correlation between persecution and left fronto-parietal network (FPN)-OFC connectivity (rs(47) = -.19, p = .091), and further found significant correlations between persecution and left and right FPN-OFC/insula/dorsomedial PFC connectivity (rs(47) = -.38 and -.34, respectively, p's < .02), highlighting the potential relationship between cortical dysconnectivity and the manifestation of positive symptoms.
Discussion: While subcortical structures may still play a role as antecedents of spite sensitive decisions and persecutory ideation, these observations suggest the engaged neural mechanisms are largely cortical, and may involve a reduction in executive control governing the evaluative and affective aspects of those choices. These findings therefore dovetail a number of treatment-related approaches for regulating psychotic thoughts, such as CBT for psychosis.

S124. GREATER INDIVIDUAL VARIABILITY IN FUNCTIONAL BRAIN ACTIVITY DURING WORKING MEMORY PERFORMANCE IN SCHIZOPHRENIA SPECTRUM DISORDERS (SSD)

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Background: Heterogeneity has been a persistent challenge in understanding Schizophrenia Spectrum Disorders (SSD). Traditional studies make use of case-control comparisons or linear brain-behaviour statistical approaches, which tend to show variable Results: and may not reflect individuals. A growing body of evidence suggests heterogeneity in brain function is the norm rather than the exception in healthy populations; this is likely especially true in SSD. In order to better characterize brain heterogeneity underlying behaviour and psychiatric disorders, there is a need for a shift away from group aggregate averages and consider individual metrics that can best characterize variability. We examined individual variability in functional brain activity in SSD and typically developing controls (TDC) during a working memory (WM) task that is known to be impaired in SSD.

Methods: Neuroimaging and behavioural data were extracted from age and gender-matched groups of 34 TDC and 56 individuals with SSD (n=90) from two datasets originating from outpatient clinics at the Centre for Addiction and Mental Health (CAMH) in Toronto, Canada. Functional activity in response to an N-Back WM task (3-Back vs 1-Back) was examined between and within groups. Through the use of a recently developed novel metric, individual variability was quantified via the correlational distance of fMRI activity maps between participants; the mean correlational distance from one participant to all others was defined as a 'variability score'.

Results: Mean correlational distance of functional brain activity across SSD (0.63 ± 0.043) was significantly higher than TDC (0.60 ± 0.034) ($F(2,84)=7.62$, $p=0.00090$); TDC showed patterns of task-related activation more similar to the overall group whereas SSD had more idiosyncratic brain responses. At the group level, a case-control comparison suggested SSD had reduced activity in task-positive and task-negative networks. However, when individuals with SSD were separated by median individual variability (0.62) into equal subgroups of high and low variability, the low variability group showed no differences relative to TDC while the high variability group showed little activity at the group level. In SSD but not TDC, variability was also related to cognitive performance ($F(1,84)=5.25$, $p=0.024$); response accuracy during the N-Back task was not significantly different between the low variability group and TDC ($t=1.46$, $p=0.15$) whereas the high variability group performed significantly worse than TDC ($t=2.80$, $p=0.0065$).

Discussion: Our Results: demonstrate a subset of low variability individuals with SSD have similar functional brain activations and behavioural outcomes to controls, suggesting a normative range of cognitive abilities and function despite diagnosis. This is important as it implies diagnostic-based group differences between SSD and TDC are being driven by a subset of individuals with atypical activity patterns, whereas many show normal brain function. By validating the use of within-group heterogeneity as a measure of interest, we encourage future studies to move away from a group-average comparison approach. Enhancing the field's understanding of neurobiological diversity in individuals with SSD may have implications for individualized treatment and targeted intervention; setting the stage for more personalized approaches.

S125. HISTAMINE-3 RECEPTOR LEVELS IN PSYCHOTIC DISORDERS: A MULTI-MODAL PET-MR BRAIN IMAGING STUDY

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Background: Histamine-3 Receptors (H3R) expressed centrally are involved with the regulation of histamine release, as well as other neurotransmitters that are implicated in psychotic disorders. Pre-synaptically, H3R acts as a heteroreceptor which when activated by histamine, inhibits the release of glutamate, dopamine, and acetylcholine. Inhibition of H3R in preclinical studies have borne promising findings for the treatment of psychosis, particularly cognitive impairment. It has been proposed that the mechanism underlying symptomatic improvement, is an increase of glutamate transmission in the frontal cortex. Post-mortem data have found alteration of H3R expression in schizophrenia, but this has not yet been examined in vivo. To address this, we investigated H3R levels in patients with schizophrenia and examined the relationship with measures of glutamate.

Methods: A total of n=24 volunteers took part in the study (12 patients with schizophrenia and first episode psychosis, and 12 matched controls). They underwent a dynamic, continuous 90-minute PET acquisition using a selective H3R ligand [11C]MK-8278, to examine its volume of distribution (VT). All scans were performed at the same time of day to control for effects of diurnal variation of histamine release. The striatum and dorsolateral prefrontal cortex (DLPFC) were defined as regions of interest a priori, based on previous post-mortem findings. Subsequent magnetic resonance spectroscopy imaging (1H-MRS) was performed to measure glutamate levels in the anterior cingulate cortex (ACC) and striatum. These regions were selected due to evidence of H3R modulation of glutamate release in preclinical data.

Results: There was no significant effect of group in either the striatum ($t_{21}=1.177$, $p = 0.252$) or DLPFC ($t_{19}=0.794$, $p=0.437$) on VT. In patients, we found a significant inverse relationship between VT and ACC glutamate levels in both the striatum (rho=-0.745, p=0.008) and DLPFC (r=-0.812, p=0.004) which survived correction for multiple comparisons. In controls, there was no significant correlation between VT and ACC glutamate levels in either the striatum or DLPFC. We did not find any significant correlation between ROI VT and striatal glutamate in either patients or controls.

Discussion: Our findings do not support previous post-mortem data that patients with schizophrenia have increased H3R levels compared to healthy controls. In part, this could be attributed to a proportion of the patients enrolled in our study were unmedicated (n=7), whilst those examined in post-mortem data were all patients who received long term treatment with antipsychotics. This implies that the alteration of H3R levels identified in the post-mortem data

may have been driven by the effects of medication. We did not proceed with analysing the effect of medication status in our cohort as we were not adequately powered to do so. We also found a significant inverse relationship between H3R expression in patients and cortical glutamate levels, which corroborates preclinical evidence of H3R involvement in the release of glutamate. Preclinical studies have evidenced that H3R inverse agonists ameliorated behavioural deficits found in models of schizophrenia, potentiated the effects of antipsychotics, and increased the transmission of neurotransmitters such as dopamine, glutamate, and acetylcholine in cortical regions through the involvement of pre-synaptic H3R. The majority of H3R expressed in the striatum are post-synaptic on medium spiny neurons and influence signalling of the direct and indirect pathways. Our findings of a non-significant relationship between H3R and striatal glutamate levels may be due to the localisation of striatal H3R. These findings provide further evidence of the involvement of H3R in psychotic disorders.

S126. RESPONSES TO POSITIVE AFFECT AND UNIQUE CONNECTIVITY IN INDIVIDUALS AT CLINICAL HIGH-RISK FOR PSYCHOSIS

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Background: Individuals at clinical high-risk for psychosis (CHR) report experiencing dampened positive affect, and while this deficit appears to be an important clinical marker, our current understanding of underlying causes is limited. One promising avenue that has not yet been examined relates to dysfunctional regulatory strategies (i.e., abnormal use of dampening, self-focused, or emotion-focused strategies).
Methods: Participants (57 CHR and 56 healthy controls) completed the Response to Positive Affect Scale, clinical interviews, and resting-state scan examining nucleus accumbens (NAcc) connectivity.
Results: Individuals at CHR for psychosis showed greater dampening (but no differences in self/emotion-focus) in response to positive affect compared to healthy controls. In individuals at CHR, higher levels of dampening and lower levels of self-focus were associated with higher positive and lower negative symptoms. Dampening responses were related to decreased dorsal and rostral anterior cingulate cortex- NAcc connectivity in the CHR group but increased dorsal and rostral anterior cingulate cortex-NAcc connectivity in the healthy control group. Self-focused responses were related to increased dorsolateral prefrontal cortex-NAcc connectivity in the CHR group but decreased connectivity in the healthy control group.
Discussion: Dampening and self-focused responses were associated with distinct neural correlates compared to peers, suggesting unique mechanisms underlying these emotion regulation strategies. Responses to positive affect may be a useful target for cognitive treatment, but individuals at CHR show distinct neurocorrelates and may require a tailored approach.

S127. LONGITUDINAL CHANGES IN CORTICAL THICKNESS IN ADOLESCENTS AT CLINICAL HIGH-RISK THAT DEVELOP A PSYCHOTIC DISORDER

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Background: Cortical thickness abnormalities have been widely reported in individuals at clinical high risk for psychosis (CHR-P), yielding heterogeneous Results:. Longitudinal studies have shown greater cortical thinning in fronto-temporal regions in individuals at CHR-P that develop a psychotic disorder (CHR-P-P) versus those who do not (CHR-P-NP). However, these findings rely mainly on adult samples, and little is known about the impact of neurodevelopmental processes -such as synaptic pruning- taking place during adolescence, on the etiopathology of transition to psychosis.

Methods: Fifty adolescents aged 11 to 17 years meeting SIPS/SOPS criteria for CHR-P and 54 healthy controls (HC) were included in this prospective, longitudinal, case-control study. During the 18-month follow-up period 14 individuals at CHR-P developed a psychotic disorder (28.0% transition rate). All participants underwent a comprehensive socio-demographic and clinical evaluation at baseline and 18 months. Neurological disease, head trauma history with loss of consciousness and previous or current psychotic disorder were exclusion criteria for the whole sample. High resolution T1-weighted images were acquired on a 3 Tesla Siemens scanner at Hospital Clinic Barcelona and on a 1.5 Tesla General Electric scanner at Hospital Sant Joan de Déu at baseline and at 18 months follow-up, or at the time of transition to psychosis for individuals at CHR-P-P. Images were processed with the longitudinal pipeline implemented in FreeSurfer 6.0, cortical parcellation employed the Desikan-Killiany brain atlas. A longitudinal two stage model was performed in order to: (1) compute the regional symmetrized percentage of change (spc), which is the rate of change relative to the average thickness: spc = 100 * rate/avg, and (2) analyze between group differences using the general linear model within the mri_glmfit function in FreeSurfer 6.0, controlling for age, sex and scan. Correction for multiple comparisons was performed using Montecarlo clusterwise correction (threshold 0.05). An inter-site compatibility study showed high inter-site correlation coefficients (r>.6) for CTH measures, in a HC sample (N=9). The study was approved by the local Ethical Review Board.

Results: A total of 104 individuals with two available MRI time points were included in the analysis. There were no significant differences between CHR-P-P, CHR-P-NP and HC in gender

(% females: 78.6% vs 69.4% vs 51.9%; $\chi 2=4.8$, p=.090) and age (14.6 ± 1.6 vs 15.2 ± 2.0 vs 15.7 ± 1.6; F=2.2, p=.117). There were no significant differences in chlorpromazine equivalent doses for antipsychotics at baseline between CHR-P-P and CHR-P-NP (58.3 mg/day vs 40.0 mg/day; t=.7, p=.448).
No significant differences in spc in CTH were found between all the individuals at CHR-P and HC. When accounting for transition to psychosis, individuals at CHR-P-P showed a steeper rate of cortical thinning compared to HC in the right precuneus (cwp=0.0016) and supramarginal gyrus (cwp=0.0074); HC showed greater cortical thinning compared to CHR-P-P in the lateral occipital cortex bilaterally (right: cwp=0.0016; left: cwp=0.0016). CHR-P-P showed greater cortical thinning than CHR-P-NP in the right supramarginal gyrus (cwp=0.0002), isthmus of cingulate gyrus (cwp=0.0016) and pars opercularis of the inferior frontal gyrus (cwp=0.0333). CHR-P-P showed less cortical thinning than CHR-P-NP in the right (cwp=0.0274) and left lateral occipital cortex (cwp=0.0002), and right pericalcarine (cwp=0.0411). No significant differences in spc were found between CHR-P-NP and HC.

Discussion: In our study the CHR-P group as a whole did not show any differences in relation to HC in terms of CTH, which is in line with recent meta-analytic findings (Fortea et al., 2021). However, CHR-P-P showed greater cortical thinning over time in comparison to CHR-P-NP and HC, mainly located in parietal regions. This differs from the largest evidence base so far in this field, which has found predominantly fronto-temporal disruption in samples mostly representing adults at CHR-P-P. In contrast, our Results: mirror findings in young genetic risk and early onset psychosis samples, which have also observed early changes in parietal gray matter, which have been suggested to progress to fronto-temporal cortices at later ages. This study lends support to the fact that psychosis may impact brain structure during adolescence in a different way than when onset of the disease takes place during adulthood, in interaction with normative brain maturation.

S128. STEP BY STEP: A NOVEL APPROACH TO INVESTIGATING FEEDBACK LEARNING IN PSYCHOSIS

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Background: Successful social interactions require the capacity for inferring the intentions of others,and learning from social feedback. Patients with schizophrenia experience severe difficulties in these social cognitive functions,and show reduced trust in others. Trust is an essential part of human behaviour, and depends on the expectation of reciprocity of the interaction partner. Interpretation of the behaviour of the interaction partner requires mentalising, and learning from their behaviour involves reward learning. To investigate the responses to social feedback in depth in psychosis, we modelled trust behaviour in response to feedback on a trial by trial basis, in a trust game. The game was programmed in a cooperative manner, whereby reciprocating trust by investing larger sums was regarded as feedback responsive, and decreasing investments was unresponsive. We also investigated the neural correlates of mentalising and reward-learning, comparing patients with first-episode (FEP) and chronic psychosis with healthy controls.

Methods: Forty-one chronic patients, 99 FEP, and 38 healthy controls played the investor against a cooperative partner in a multi-round trust game during fMRI scanning. The partner returned the investment multiplied by factor 1, 1.5 or 2, at equal percentages. Chances of a return multiplied by factor 2 increased with every increase of investment. A proportional value relative to the investment of the previous round was calculated, by dividing the investment of the current round with the investment of the previous round. Whenever the investment was decreased, the value was negative. This resulted in a feedback responsiveness value per trial and a mean value over the game. Region of interest analyses were performed on mentalising and reward processing areas, during the investment and repayment phases of the game. Associations with symptoms were explored.
Results: Groups did not differ regarding baseline trust. Mean trust over trials was significantly lower in both patient groups compared to controls. Patients also showed reduced response to feedback during the game but did not significantly differ from each other. Feedback responsiveness was not associated with the factor of return. During investments, chronic patients activated the temporo-parietal junction more than FEP and controls. FEP and healthy controls activated the caudate and right putamen more than chronic patients. During repayments, both patient groups activated the right putamen more than healthy controls. No significant associations were found between symptoms and feedback learning, nor neural outcomes.
Discussion: Responding to feedback appears to be impaired in both patient groups, which is in contrast with the existing literature reporting intact learning in FEP. Consequently, investments during the game did not significantly differ between FEP and chronic patients. Neural activation was also similar between groups. However, patients showed reduced activation in the putamen, indicating reduced reward learning, as evident in the behavioural outcomes. Increased mentalising activation in chronic patients may suggest greater effort in assessing the intentions of the other player. However, they did not result in a similar response to feedback compared to controls, suggesting inefficient neural processing. Interestingly, at the behavioural level, FEP performance differed from controls, whereas at the neural level most differences were found between controls and chronic patients, suggesting compensatory mechanisms in FEP. The novel analysis gives a detailed insight in trial by trial feedback response and could usefully be applied to other larger datasets, to prove its validity.

S129. ERBB4 DELETION FROM FAST-SPIKING INTERNEURONS CAUSES SCHIZOPHRENIA-RELEVANT PHENOTYPES AS MEASURED WITH TRANSLATIONAL NEUROIMAGING

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Background: In vivo imaging findings of schizophrenia and at-risk patients, have demonstrated various macroscopic abnormalities in the hippocampus such as increased cerebral blood flow, increased glutamate concentrations, and small decreases in [11C]UCB-J binding, a putative marker of synaptic density. Post-mortem and animal studies suggest that hippocampal parvalbumin-expressing (PV+) interneuron dysfunction may be present in schizophrenia. However, the relationship between PV+ dysfunction and in vivo neuroimaging phenotypes remains to be

understood. In this study, we sought to address this issue by using multimodal neuroimaging in the well-validated ErbB4 animal model of specific PV+ disruption.
Methods: Adult ErbB4 conditional mutant mice (Lhx6-Cre;ErbB4F/F, n=12, 5 females, 94.7 ± 12.3 days) and wild type mice (WT, n=12, 9 females, 99.5 ± 8.6 days) were imaged using a 9.4T small animal MRI system (Bruker Biotech). We measured cerebral blood flow (CBF) in the dorsal and the ventral hippocampus using arterial spin labelling (ASL), and concentration of glutamate, glutamine, and GABA in the ventral hippocampus using proton magnetic resonance spectroscopy (1H-MRS), from each animal in a single scanning session. After scanning, brains were collected for post-mortem autoradiography analysis with [3H]UCB-J. Autoradiographs were sampled for the dorsal CA1, medial CA2 and ventral CA3 subfields. For CBF and [3H]UCB-J binding, group differences were investigated using two-way mixed ANOVAs with genotype as between-subject factor and region of interest as within-subject factor. Any significant interactions were followed up with multiple comparison testing. For 1H-MRS, we analysed group differences using independent-sample t-tests per metabolite. Significance was set at p=0.05 and Bonferroni-adjusted as appropriate.
Results: Following up on an interaction effect between region and genotype ($F(1,20)=11.91$, $p=0.0025$, $\eta 2=0.37$), resting CBF was increased in the ventral hippocampus of ErbB4 mice compared to WT littermates ($t(40)=2.541$, $p=0.030$, $d=0.950$). ErbB4 mouse mutants also showed elevated levels of glutamine in the ventral hippocampus ($t(20)=4.988$, $p<0.001$, $d=2.188$), while no effects were observed for glutamate or GABA. Finally, [3H]UCB-J specific binding was decreased across all hippocampal regions of interest in ErbB4 mouse mutants compared to WT littermates ($F(1,18)=4.663$, $p=0.045$, $\eta 2=0.21$).
Discussion: These findings demonstrate that mice with a specific PV+ interneuron disruption recapitulate some of the most robust neuroimaging abnormalities observed in schizophrenia and clinical-high risk patient samples. Increased ventral hippocampal blood flow, glutamatergic metabolites and decreased synaptic density converge with ASL, 1H-MRS and PET studies in humans. Interestingly we detected alterations in glutamine, a precursor of glutamate, while human studies have generally identified alterations in hippocampal glutamate. However, at the lower field strengths commonly used in humans, glutamine contaminates this signal and often Glx, a composite of glutamate and glutamine, is reported. Given that 1H-MRS measures the total concentration of metabolites and does not distinguish between their synaptic and intracellular pool, glutamine concentrations may present a better indicator of glutamatergic activity. Overall, these data provide new translational evidence for the involvement of PV+ interneuron disruption in the pathophysiology of schizophrenia and its neuroimaging markers, involving increased hippocampal activity and glutamatergic drive, and decreased synaptic density.

S130. STRUCTURAL BRAIN CHANGES RELATED TO PERSISTENT AVOLITION IN PATIENTS WITH SCHIZOPHRENIA

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Background: Previous studies on cortical brain changes related to persistent negative symptoms resulted in discrepant findings, and the heterogeneity in negative symptoms might be one of the contributing factors to this discrepancy. However, very few studies have investigated changes related to persistence of a single symptom. Avolition is defined as the reduction in the motivation for initiation and persistence in goal-directed activities, and is a core symptom of schizophrenia. In this study, we aimed to investigate cortical brain changes in schizophrenia patients with and without persistent avolition on selected regions of interest, which were previously associated with persistent negative symptoms in the literature.
Methods: Neuroimaging, clinical and demographic information for 59 patients with schizophrenia and 59 healthy controls were acquired from Northwestern University Schizophrenia Data and Software Tool (NUSDAST) through SchizConnect, a web-based portal that integrates various publicly available neuroimaging datasets (funded by NIMH grant 1R01-MH084803). Patients were divided into two groups depending on persistence of avolition/apathy scores over the Scale for the Assessment of Negative Symptoms measured at two time points two years apart. Eleven patients were involved in persistent avolition group and 48 patients were involved in non-persistent avolition group. Cortical thickness and gray matter volumes of bilateral anterior cingulate cortices, fusiform gyri, orbitofrontal cortices, parahippocampal gyri and superior temporal gyri were compared between the two patient groups as well as in healthy controls with the region of interest (ROI) approach. The significance threshold was set at $p < 0.05$ and Bonferroni correction was applied according to number of ROIs.
Results: Patients with persistent avolition had significant volume reductions in the left anterior cingulate cortex compared to healthy controls. Bilateral parahippocampal gyri were also thinner in patients with persistent avolition than both in non-persistent avolition patients and healthy controls. The volume of the left superior temporal gyrus was smaller in non-persistent avolition group when compared to healthy controls. There was no cortical thickness difference between the non-persistent avolition group and healthy controls.
Discussion: Overall, results of this study suggests that schizophrenia patients with persistent avolition have structural brain changes on frontal and temporal regions when compared to patients without persistent avolition and healthy controls.

S131. GLUTAMATERGIC METABOLITES IN THE PSYCHOSIS SPECTRUM: FROM HIGH RISK SAMPLES TO FIRST EPISODE PSYCHOSIS

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Background: The N-methyl-D-aspartate receptor hypofunction model of schizophrenia suggests that dysfunction of these receptors leads to an excess release of glutamate and could explain the brain structural abnormalities characterizing these patients. However, glutamatergic pathways underlying transition to psychosis are yet unclear
Methods: Youth with first episode psychosis (FEP), within the first 5 years of disease, and high risk for psychosis individuals (HR) –including psychosis risk syndrome meeting SIPS/SOPS criteria and offspring of parents with bipolar disorder or schizophrenia –were recruited and scanned with a 3T Siemens scanner. Magnetic resonance spectroscopy was performed using a 2x2x2 cm3 voxel (VOI) placed in the middle frontal region. Ratios of glutamate (Glu), and glutamate + glutamine (Glx) were quantified using LCModel.
Results: 18 FEP, 33 HR and 32 healthy controls (HC) were included in the analysis. There were no significant differences between groups in mean age (16.4±2.1 vs 15.7±2.7 vs 16.8±1.9; F=2.0, p=.139), but a trend in gender (%females: 33.3% vs 57.6% vs 68.8%; X2=5.9, p=.052). Multivariate models controlling for gender showed no significant differences in Glx, but a trend level difference in Glu between groups (F=2.9, p=.062). Mean values suggested increased Glu levels in HR samples (1.38±0.16) compared to FEP (1.27±0.20) and HC (1.31±0.15).
Discussion: Our findings support the fact that Glu and Glx in the prefrontal cortex may have an impact in the development of psychotic disorders since early stages including individuals at risk. These findings suggest a possible hyperglutamatergia in premorbid stages leading to psychotic illness that may normalize –or even decreased – afterwards, possibly related to treatment or compensatory mechanisms. Changes in glutamatergic metabolites may need to be examined in larger samples

S132. THE USE OF LONG-ACTING INJECTABLES IN PENNSYLVANIA FIRST-EPISODE PSYCHOSIS COORDINATED SPECIALTY CARE 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.
In early psychosis, short duration of untreated and/or persistent psychosis and retention in care are important contributors to better outcome and recovery. As of 2021, in Pennsylvania (PA) there were 14 First Episode Psychosis (FEP) CSC programs in operation across urban and rural settings,

including community and academic sites. We examined the naturalistic use of LAIs compared to oral antipsychotics (OAP) across PA CSC programs in association with participant demographics, clinical symptoms, functioning and retention.

Methods: Since 2017, PA FEP sites have collected demographic, clinical and functional data at admission and every 6 months to evaluate programmatic CSC efforts. All 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.

Results: As of November 2021, 510 FEP persons with reported medication data at admission had enrolled in CSC care across PA. At intake,13.7% were on LAIs, 72.4% on oral antipsychotics and 13.9% on no antipsychotics. Persons on LAI were significantly more likely to be a person of color, and older. They also had experienced later onset of illness, longer duration of illness, greater number of hospitalizations and lower role functioning at admission. Follow up assessments at 6- and 12-month intervals revealed similar reduction in clinical symptoms (BPRS) and traumatic stressors (PSS), and improvement in functioning in LAI versus oral medication groups. Ninety persons with medication data at admission underwent premature CSC disengagement. In this group, we found that on admission 17.8% were on LAIs, 71.1% on oral antipsychotics and 11.1% on no antipsychotics. At the assessment period prior to disengagement, 34.0% were on LAIs, 46.8% were on OAP, and 19.1% on no antipsychotics (n=47).

Discussion: Preliminary analyses in a naturalistic sample of FEP persons undergoing CSC care in Pennsylvania finds that a significant percentage were on LAIs at admission to CSC care and throughout 6- 12 months of treatment. Treatment with LAIs was associated with improvement in clinical symptoms, perceived stress and functioning similar to oral antipsychotics. Given the reasons for LAI treatment, we suggest that many FEP persons would have experienced worse outcome if not on LAIs.

S133. THE GPR52 AGONIST HTL0041178 ATTENUATES SUB-CHRONIC PCP-INDUCED REVERSAL LEARNING DEFICITS IN THE RAT

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Background: Sub-chronic phencyclidine (scPCP) produces robust deficits in tests of relevance to cognition in schizophrenia including reversal learning (RL) in rats in our laboratory (Cadinu et al., 2018 Neuropharmacol 142: 41-62) and elsewhere. GPR52 is a Gαs coupled orphan G-protein coupled receptor (GPCR), highly expressed on both dopamine D1 cortical pyramidal neurons and D2 striatal medium spiny neurons (Sawzdargo et al., 1999 Mol. Brain Res. 64(2):193-198). Altered frontocortical D1 receptor availability has been suggested to contribute to cognitive impairments associated with schizophrenia (CIAS; Abi-Dargham, 2003 World Psychiatry, 2(3):166-71). Recent findings revealed that depending on receptor localisation, a GPR52 agonist can act like a dopamine D1 receptor activator or inhibitor of dopamine D2 receptor function (Komatsu et al, 2014 PloS One, 9 (2): e90134), and may therefore improve both the cognitive and positive symptoms of schizophrenia (Nishiyama et al, 2017 J of Pharmacol and Exp Ther 363(2) 253-26). Aim: Here

we investigate the effect of a novel selective GPR52 receptor agonist, HTL0041178, and compared its effects to the D1 receptor agonist, SKF-38393 and the D2 receptor antagonist, fluphenazine in our scPCP model for CIAS.
Methods: Adult female Lister Hooded rats were trained to perform an operant reversal learning task as previously described (Neill et al, 2016 26(1): 3-14). Rats received scPCP (2 mg/kg) or vehicle (1 ml/kg) i.p. twice daily for 7 days, followed by 7-days washout. In experiment 1, scPCP-treated rats received HTL0041178 (1.0, 3.0, 5.0, 10.0, 15 and 30 mg/kg; p.o.) or vehicle and were tested 2 hrs later. In experiment 2, scPCP-treated rats received fluphenazine (0.1, 0.2, 0.4 mg/kg, i.p.) or vehicle and were tested 1 hr later. In experiment 3, scPCP-treated rats received SKF-38393 (0.75, 1.5, 3.0, 6.0 mg/kg, i.p.) or vehicle and were tested 1 hr later.
Results: In all experiments sub-chronic PCP significantly impaired reversal phase performance ($P<0.01$-0.001), as consistently demonstrated in our laboratory. In experiment 1, the scPCP-induced deficit was significantly reversed by HTL0041178 at 5.0-30 mg/kg ($P<0.01$-$P<0.001$). Interestingly, in experiment 2, fluphenazine failed to antagonise the scPCP-induced deficit ($P>0.05$). In experiment 3, SKF-38393 at 6.0 mg/kg significantly attenuated the scPCP-induced deficit ($P<0.05$). Data were analysed by ANOVA followed by post-hoc LSD test.
Discussion: These findings show that HTL0041178 reversed the scPCP-induced reversal-learning deficit in a manner comparable to the D1 receptor agonist SKF-38393 and suggest that the GPR52 receptor may be a potential new target for the treatment of CIAS.

S134. EARLY STAGE TREATMENT WITH POSITIVE ALLOSTERIC MODULATOR OF THE MGLU2 RECEPTOR JNJ-46356479 PARTIALLY IMPROVES COGNITIVE DEFICITS AND SCHIZOPHRENIA-LIKE BEHAVIORS IN A POSTNATAL KETAMINE MICE MODEL

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Background: Glutamatergic dysregulation is one of the main pathophysiological theories of schizophrenia (SZ). Given the lack of efficacy of antipsychotics on treating negative and cognitive symptoms, glutamate (GLU) inhibitors could be a good pharmacological strategy to improve these symptoms. Positive allosteric modulators (PAM) of the metabotropic GLU receptor 2 (mGluR2), such as JNJ-46356479 (JNJ), inhibit the presynaptic release of GLU. At animal level, we have previously reported that JNJ treatment in adult mice partially improves neuropathological deficits and SZ-like behaviour in a postnatal ketamine (KET) mouse model. Dealing with GLU storm during early stages of SZ may be particularly effective to prevent the disease appearance or slow the psychosis progression and the clinical deterioration of patients. We aimed to evaluate the efficacy of a prodromal JNJ treatment in reversing behavioural deficits induced in the postnatal KET mice model of SZ.
Methods: C57BL/6J pups were exposed to KET (30mg/kg) on postnatal days (PND) 7, 9, and 11 to transiently disrupt NMDAR function. Then, mice were daily treated subcutaneously with 10 mg/kg of JNJ-46356479 (JNJ) or clozapine (CLZ), as a clinical AP of reference, in the adolescent

period (PND 30-60). A wide range of behavioural tests were performed in adult animals, once they reached PND 80, to evaluate cognitive and negative behaviours related to SZ and to assess the locomotor activity and anxiety-related behaviour of these animals. All mice in each experimental group (vehicle, JNJ, CLZ, KET, KET+JNJ and KET+CLZ) underwent: (1) Y-maze; (2) Novel object recognition test (NOR); (3) Three-Chamber sociability and novelty test; (4) Five-trial social memory test; (5) Motor test battery; (6) Rotarod test, and (7) the Open Field Test (OFT).
Results: In the Y-maze, no differences were found in time spent in the familiar neither the novel arm between groups. All groups of treatment also showed similar spontaneous alternation. However, while controls, as well as mice treated with JNJ or CLZ, spent significantly more time exploring the novel object, mice exposed to KET did not show a preference for it, which was recovered in those animals exposed to KET and treated with JNJ, but not in those treated with KET+CLZ. In the three-chamber test, all animals demonstrated a significant preference for spending time sniffing a familiar littermate rather than a toy. However, when the choice was between the familiar littermate and an unfamiliar conspecific, the KET group did not demonstrate a preference for social novelty, which was recovered when animals exposed to KET were treated with JNJ. This recovery was not observed in animals treated with KET+CLZ. In the five trial, after four trials being exposed to the same mouse, the control group, as well as those animals treated with JNJ or CLZ, increased interaction time when a novel mouse was presented in the fifth trial. This expected dishabituation was not shown in the KET group. Interestingly, mice were exposed to KET and treated with JNJ or CLZ recovered an interest in the novel animal. Any relevant difference in motor function or coordination was detected. General activity and anxiety analyzed on the open field was similar in all groups.
Discussion: These data provide evidence that pharmacological treatment with a PAM of the mGluR2 such, as JNJ-46356479, in early stages could help improve cognitive and negative symptoms related to SZ, even in a better way than the CLZ treatment. This could have relevant clinical translational applications since the early administration of mGluR2 modulators that inhibit glutamate release at the beginning of critical phases of SZ could prevent or slow the deteriorating course of the disease.

S135. EFFECTS OF N-ACETYL-L-CYSTEINE TREATMENT DURING PREPUBERAL PHASE IN MAM RATS

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Background: Schizophrenia is disorder characterized by a range of associated symptoms. There is evidence of possible relations between this disease and oxidative stress and neuroinflammation. The MAM model consists in administration of a mitotoxin, methylazoxymethanol acetate, in female rats at the 17th gestation day, temporarily blocking neurogenesis, causing important behavioral deficits in the offspring, such as prepulse inhibition (PPI), social interaction (SI), hyperlocomotion induced by psychostimulant. N-acetyl-L-cysteine (NAC) acts as a precursor of glutathione (GSH), the main brain antioxidant, reduced in schizophrenic patients. NAC administration in MAM rats has been considered effective lowering behavioral deficits. Data on the effects of NAC treatment in the prodromal phase patients are still unknown. Therefore, the

present study intends to investigate the effects of chronic NAC treatment in MAM rats offspring, during the prepuberal phase.
Methods: All procedures were approved by CEUA-UFABC (6094240919). Pregnant rats were treated with MAM (25mg/kg; i.p.) or saline (vehicle) at GD17 (treat1) and their male offspring was treated with NAC (250mg/ kg; i.p.) or saline (vehicle) during 15 days starting at PD25 (treat2). Animals were divided in four groups: Sal-Sal, MAM-Sal, Sal-NAC and MAM-NAC (n=6-8/group). At PD40, animals were submitted to behavioral tests of hyperlocomotion induced by a low dose of psychostimulant (MK-801), prepulse inhibition (PPI), novel object recognition (NOR) and social interaction (SI). At PD90 behavior tests were repeated. Analysis of variance (ANOVA) were performed for the mean distance and proximity between subjects provided by EthoVision and for active behaviors (X-Plo-Rat) during the SI test. Repeated measures ANOVA were performed using intra-subject factors age (P40-P90), period (0-10, 10-20 and 20-30 min, for displacement and velocity in the arena), stimulus (pulse, PP69-P, PP73-P, PP81-P, in startle analysis), intensity (PPI69, PPI73, PPI81, in %PPI analysis), object (familiar and new) for NOR and factors between subjects treat1 (Salina or MAM) and treat2 (Saline or NAC).
Results: Significant effects were observed on treat1 and treat2, both increasing the average distance between animals; on treat1 reducing the duration of "auto-grooming", treat1 and treat2, both reducing "following", and treat1 increasing the frequency of "stand up" and "biting" during SI. In the NOR test, there were main effects of the object factor (rats spending more time with new object), age (PD90>PD40) and treat1 (Sal>MAM). In hyperlocomotion test, there were significant effects of age (PD40>PD90), period (0-10>10-20;20-30) and treat1 (MAM>Sal) in the distance covered and the period in the maximum speed. In the PPI, there were significant effects of stimuli (pulse>prepulses) and age (PD90>PD40).
Discussion: Results: show higher motor activity in PD40 (distance and speed in 0-10 min) and MAM hyperlocomotion compared to control. The PPI test indicated a reduction in startle for all prepulse intensities and decrease in %IPP in PD40 animals compared to PD90. In the NOR test, MAM rats explored new objects for a shorter time compared to the control, showing impairment in long-term memory. Finally, MAM animals presented deficits in SI, NOR and hypersensitivity by psychostimulant, however prepuberal treatment with NAC was not able to reverse these behavioral impairments, evaluated at both ages, PD40 and PD90.

S136. EFFECTS OF INHALED THC AND CBD ON SERUM ENDOCANNABINOIDS AND RELATED N-ACYL ETHANOLAMINES: RESULTS: FROM THE ECBD RANDOMISED CONTROLLED TRIAL OF VAPORISED CANNABIS IN HEALTHY VOLUNTEERS

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Background: Cannabis produces its psychoactive effects by acting on the endocannabinoid system (ECS). Constituents of the ECS include the endogenous ligands of the cannabinoid

receptors, anandamide (AEA) and 2-arachidonylglycerol (2-AG), and their precursor lipid arachidonic acid (AA). Delta-9-tetrahydrocannabinol (THC) is the main psychoactive component of cannabis and has been shown to produce acute psychotomimetic effects. Cannabidiol (CBD), the second most abundant cannabinoid produced by cannabis, is non-intoxicating and has been found to improve psychotic symptoms in multiple clinical trials. In addition, CBD has been shown to reduce psychotomimetic effects of THC.

The mechanism of CBD's neuroprotective actions has yet to be elucidated. Results: from in vitro and human studies suggest that CBD may indirectly modify the ECS by antagonising the degradation of the endocannabinoid AEA, leading to increased AEA levels in the body. We investigated the effects of inhaled cannabis vapour with varying ratios of CBD:THC on levels of serum AEA, 2-AG, AA and six biologically related N-acyl ethanolamines in healthy volunteers.

Methods: In a randomised, double-blind, cross-over design, 46 healthy participants attended four experimental visits with a minimum one-week washout period in-between. At each visit participants received a dose of vaporised cannabis product containing 10mg THC plus either 0, 10, 20 or 30mg CBD (equalling CBD:THC ratios of 0:1, 1:1, 2:1 and 3:1). Five blood samples were collected each visit: pre-cannabis inhalation (baseline), immediately post-inhalation (0min), and 5-, 15- and 90-min post-inhalation. Plasma levels of analytes were measured using high-performance LC/MS.

For each analyte, plasma concentrations across 5 timepoints were compared using repeated measures ANOVA, controlling for CBD:THC ratio. Mean change in levels of plasma analyte from baseline was calculated at each time point for each CBD:THC ratio, and the areas under the curves (AUCs) calculated and compared using one-way ANOVA controlled for baseline plasma levels. Linear mixed-effects models were fitted to analyse differences in peak levels of endocannabinoids compared to baseline.

Results: Plasma levels of AEA, docosatetraenylethanolamide (DEA), oleoylethanolamide (OEA) and N-arachidonoyl-L-serine (ARA-S) significantly increased post-inhalation, before falling to pre-inhalation levels by 90min. The effect was irrespective CBD:THC ratio. Pre-inhalation plasma levels of AEA and DEA significantly increased between the 1st and 4th visit. There was no effect of CBD dose on the plasma levels of any analyte in either AUC or peak timepoint analyses.

Discussion: The inhalation of THC, irrespective of accompanying CBD, led to an acute increase in plasma levels of the endocannabinoid AEA and the ethanolamines DEA, OEA and ARA-S. This is not dissimilar to the Results: of Thieme et al. 2014, who found that plasma AEA increased after an IV dose of THC, before falling to pre-dose levels. However, our Results: do not show an increase in plasma 2-AG as seen by Thieme, possibly due to differences in drug administration.

In contrary to our hypothesis, the ratio of CBD:THC did not affect the plasma concentration of AEA or any other endocannabinoid. It is possible that this is due to the acute and relatively small doses of CBD used in comparison to previous experiments. For example, in Leweke et al. 2012 a daily oral dose of 800mg CBD led to a significant increase in AEA and OEA after 14 days. The question remains as to whether chronic dosing is required for CBD to increase levels of AEA. While it's not possible to determine the exact cause, pre-inhalation levels of AEA did increase between the first and final experimental visit, suggesting a possible repeat-dose effect.

S137. MODULATION OF STRIATAL ADENOSINERGIC FUNCTION BY HTL0041178, A SELECTIVE GPR52 AGONIST

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Background: Caffeine, a non-selective adenosine receptor antagonist, is a psychostimulant which increases rodent locomotor activity principally via blockade of adenosine 2A receptors (A2AR). These receptors are densely expressed on the terminals of GABAergic striatopallidal neurons in the indirect pathway of the basal ganglia, in which dopamine D2 receptors (D2R) are co-expressed. Tonic activation of A2AR decreases the affinity of D2R to dopamine, while antagonism of A2AR facilitates dopaminergic signalling. A number of antipsychotic agents have been shown to block hyperlocomotion induced by caffeine and indeed the adenosine hypothesis of schizophrenia posits that hyperdopaminergia may be secondary to a loss of function of the adenosine system. GPR52, a constitutively active Gαs G protein-coupled orphan receptor, is predominantly expressed in the striatum on D2R striatopallidal neurons and a recent spatiomolecular mapping study showed a distinct overlap of GPR52 with A2AR in a subpopulation of striatal neurons. The aim of the present study was to explore whether HTL0041178, a selective GPR52 agonist, would modulate rat hyperlocomotor activity stimulated by caffeine or the selective A2AR antagonist istradefylline. An in vitro competition assay was also performed to determine whether a GPR52 agonist would alter the affinity of caffeine or istradefylline for A2AR.

Methods: Locomotor studies: after 1h habituation to the locomotor cages, male Sprague-Dawley rats (n=12 per group) were dosed with vehicle, risperidone (0.6 mg/kg, IP) or HTL0041178 (3, 10 and 30 mg/kg, PO). One hour later, they were dosed with vehicle/caffeine (15 mg/kg, SC) for the caffeine study, or vehicle/istradefylline (10 mg/kg, IP) for the istradefylline study, and locomotor activity was assessed for 2h. Data are back-transformed means, adjusted for differences between treatment groups in activity during the 30 minutes prior to treatment with test compound. They were analysed using a general linear model with treatment, cohort and cage rack as factors. HTL0041178 was compared to vehicle by Williams' test. Samples were taken at the end of the study to confirm plasma and brain concentrations of HTL0041178.

In vitro competition assay: striatal membrane suspensions were incubated with HTL0041178 (1 μM) for 10 minutes and then with [3H]ZM241385 and either assay buffer (total binding), SCH442416 (non-specific binding), caffeine (10 concentrations 100-1E6 nM) or istradefylline (10 concentrations 0.01-1,000 nM) for 30 minutes. Log-transformed data were analysed by two-way analysis of variance with treatment and assays as factors.

Results: Treatment with HTL0041178 resulted in a dose-dependent reduction of both the caffeine- and istradefylline-induced hyperlocomotor responses, reaching statistical significance ($p<0.05$) at all doses tested. Risperidone also significantly reduced ($p<0.05$) caffeine- and istradefylline-induced hyperlocomotion. The presence of HTL0041178 had no effect on the affinity of caffeine or istradefylline for A2AR as measured in the in vitro assay.

Discussion: The present study demonstrates that a highly selective GPR52 agonist can modulate the behavioural response to A2AR antagonists without directly affecting A2AR binding. Interestingly, Nishiyama et al (2017) demonstrated that the locomotor response to istradefylline was significantly augmented in GPR52 KO mice compared to WT mice. Due to its localisation on D2R neurons, GPR52 has been proposed as a target for the treatment of psychosis but its specific

co-expression with A2AR and a potential role in the interplay between the adenosinergic and dopaminergic systems warrants further investigation.

S138. DISCONTINUATION OF ANTIPSYCHOTIC MEDICIN - A NATURALISTIC COHORT STUDY

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Background: Deprescribing is defined as the reduction or discontinuation of a medication when its current and potential risks outweigh its current or potential benefits, keeping in consideration the patient's medical status, functioning, values and preferences. Reducing antipsychotic medication is a controversial matter, as lack of evidence for the long term benefits paws the way for strong personal beliefs about the ratio between harms and benefits. Deprescribing is not to be understood as an intervention that necessarily leads to reduction in medication, but as an approach where risks and benefits are continuously assessed in every patient, considerations are shared openly and reduction can be initiated at any time the expected benefits does not outweigh the expected harms.
We suggest that deprescribing antipsychotic medication should be based on the same thorough evidence as initiation of medication. The overarching aim of the Tailor 2 project is to generate knowledge that qualify and enrich the shared decision making process of tapering antipsychotic medication.

Methods: This is a naturalistic cohort following 200 patients diagnosed with schizophrenia spectrum disorders from the point in time they initiate discontinuation of antipsychotic medication. It is a non-interventional design with no additive controls apart from diagnostic validation at baseline and descriptions of a range of clinical parameters during the discontinuation. Recruitment will take place from early intervention teams in Denmark.
Inclusion criteria:

- Age 18+ years
- Diagnosed with schizophrenia spectrum disorder (ICD-10: F2)
- Regular treatment with antipsychotic medication
- Planning discontinuation/tapering of antipsychotic medication

How many succeeds in discontinuing antipsychotic medication and what are the consequences if it fails?

In this descriptive analysis, we will describe the course for a group of patients starting from the decision to reduce or discontinue antipsychotic medication. We will differentiate between good outcomes (no medication, no deterioration in recovery) and poor outcomes with irreversible consequences of a relapse

Most patients who have been prescribed antipsychotic medication due to psychosis, will run risk of deterioration when medication is discontinued. The decision is based on a personal weighting of pros and cons, which is why its important to describe the proportion who can completely cease

antipsychotic medication, without any deterioration on long-term. In earlier studies, psychotic symptoms are the endpoint. We suggest that using a patient-oriented outcome will improve the usability of data, as a subgroup might live fine with an increase in psychotic symptoms. Therefore, we will describe the proportion who discontinue medication with no change in sense of recovery, measured as personal recovery. It is our hope that this descriptive analysis, using patient centered outcomes, can feed into the clinical conversation about deprescribing, and counteract the tendency of the doctor to be biased by his or her latest cases.

Data for this descriptive analysis will be collected at baseline, 1 year, and two year with face-to face meetings, and monthly telephone calls between baseline and 1 year. Quarterly phone calls between 1 and 2 year. 5 and 10 years follow up using register-based data.

Results: This study is currently running and will have Results: by the end of 2024.
Discussion: We hope these four studies, based on an observational cohort of individuals initiating deprescribing of antipsychotics, can contribute to the evidence base of deprescribing. The data we can generate, can be used to balance risks and benefits using outcomes relevant for the patients and the balance can be personalized based on a risk profile. The conversations can hopefully be improved through a deeper understanding of the dynamic network between medication and recovery, and awareness about withdrawal symptoms may make it easier to prepare the deprescribing process.

S139. INTERACTION OF ANTIPSYCHOTIC AND MOTOR EFFECTS OF ANTIPSYCHOTIC DRUGS: AN INDIVIDUAL PARTICIPANT DATA META-ANALYSIS

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Background: Antipsychotic medications mitigate psychotic symptoms but may also have adverse motor effects, such as tardive dyskinesia, parkinsonism or akathisia. It is theorized that both effects are mediated by modulating the type 2/3 dopaminergic receptors in the striatum, a region involved in the processing of reward/salience, cognitive and motor information. Despite this common theoretical mechanism, it is not well known whether developing any of these motor side effects with antipsychotic treatment has any relationship to the degree of treatment responsiveness to antipsychotic medication in psychosis. Previous research may have been underpowered, involved selection bias, and may not have disentangled the placebo from true medication effects. Addressing this question may be important in elucidating the mechanism of action of antipsychotic medication.
Methods: We conducted an individual participant data meta-analysis of randomized placebo controlled trials of antipsychotic drugs for the treatment of acute psychosis in individuals with a primary psychotic disorder (i.e, schizophrenia or schizoaffective disorder), accessed through the Yale Open Data Access (YODA) project. Each trial was re-analyzed to obtain total psychopathology scores (i.e., Total Positive and Negative Syndrome Scale) over time in

individuals who had been randomized to either placebo or antipsychotic treatment. Individuals were classified as having or not experienced tardive dyskinesia, parkinsonism, or akathisia at baseline and throughout the trial, following standardized dichotomization of symptom scores in the Abnormal Involuntary Movements Scale for tardive dyskinesia, Simpson Angus Rating Scale for parkinsonism, and Barnes Akathisia Scale for akathisia. We conducted a linear regression, in which the time*group interaction was the control analysis for antipsychotic efficacy, and time*group*motor side effect (i.e., tardive dyskinesia, parkinsonism or akathisia) the test case for an effect of developing motor side effects on the ability to respond to antipsychotics. These interaction terms were meta-analyzed to generate pooled estimates using a random-effects model.
Results: Data from 5 randomized placebo controlled antipsychotic trials was reanalyzed (n=2269; 1697 randomized to antipsychotics vs 572 randomized to placebo). Liability to develop tardive dyskinesia, parkinsonism, and akathisia was 7.3% (n=124) vs 5.9% (n=34), 3.9% (n=67) vs 4.5% (n=26), and
7.2% (n=123) vs 7.2% (n=41) in the treatment vs placebo group respectively. In a random-effects meta-analysis, there was a significant time*treatment interaction on total psychopathology (b=0.08; 95% CI=0.05-0.1). When meta-analyzed, none of the 3-way interactions for tardive dyskinesia (b=0.0; 95% CI=-0.07-0.07), parkinsonism (b=-0.01; 95% CI=-0.31-0.1) and akathisia (b=-0.02; 95% CI=-0.08-0.05) were statistically significant.

Discussion: Using an approach that maximizes power and minimizes selection bias and placebo/nocebo effects, our data reflected antipsychotic efficacy which was unrelated from the motor effects of antipsychotic drugs. These data question that the mechanisms for both effects are shared.

S140. INDIVIDUAL-PATIENT-DATA (IPD) META-ANALYSIS OF THE EFFICACY OF CLOZAPINE VERSUS OTHER SECOND-GENERATION ANTIPSYCHOTIC DRUGS IN PATIENTS WITH TREATMENT-RESISTANT SCHIZOPHRENIA

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Background: Up to a third of patients with schizophrenia do not adequately benefit from treatment with antipsychotics and are considered treatment resistant. The antipsychotic clozapine is believed to be more efficacious than other antipsychotics and is used routinely in treatment-resistant schizophrenia despite major side effects. However, according to the current state of evidence, superiority of clozapine over other second-generation antipsychotics, which have better side effect profiles, has not been reliably demonstrated.
Methods: We are conducting a systematic review of clinical trials with Individual-Patient-Data (IPD) meta-analysis in which we include blinded (at least single-blind) randomized-controlled trials (RCTs) with participants with a treatment-resistant form of schizophrenia, schizophreniform disorder, or schizoaffective disorder (following the diagnostic criteria and the definitions of treatment resistance of the original studies). We apply no restrictions in terms of setting, age,

gender, or ethnicity. However, we exclude trials with a duration of less than 6 weeks, trials with high risk for bias arising from the randomization process, trials with an approach not focusing on treatment such as pure neuroimaging studies, and trials from mainland China due to methodological concerns. From cross-over trials we only use the first phase.
The primary outcome is overall symptoms of schizophrenia as measured by validated scales such as the Positive and Negative Syndrome Scale (PANSS) or the Brief Psychiatric Rating Scale (BPRS).

Eligible trials were identified searching Cochrane Schizophrenia Group's trial register.

We will synthesize Results: with a hierarchical random-effects meta-analysis and meta-regression model which allows to combine IPD and study-level data. In the meta-regression model, we will include participant, intervention and study characteristics, such as baseline severity, duration of illness, age, sex, previous antipsychotics, type and dose of antipsychotic, study duration, definition of treatment resistance, or sponsoring.

Results: We identified 18 eligible trials with 1613 participants comparing clozapine to olanzapine, risperidone, ziprasidone, zotepine, haloperidol (as active comparator) or SGAs as a group. For 12 studies (1089 participants) IPD-data is available, for 6 studies (524 participants) aggregate data is available. Currently, we extract the relevant data and harmonize the IPD-datasets for analysis. Preliminary Results: of the meta-analysis will then be presented on the poster.
Discussion: With IPD-meta-analysis, we investigate the efficacy of clozapine in comparison to other second-generation antipsychotics for treatment-resistant schizophrenia, and whether efficacy is associated with specific participant, intervention and study characteristics. A Discussion: of preliminary findings will be provided on the poster.

S141. INSULIN PATTERNS AND PREGNANCY DIFFICULTIES IN PATIENTS INITIATING CLOZAPINE

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Background: Schizophrenia is a complex disorder characterized by a gene x environment interaction. In between the environmental factors, prenatal risk events have been associated not only with the diagnosis of schizophrenia but also with the development of other disturbances in the cognitive or clinical realm as epiphenomena. In the general population prenatal factors modify through epigenetic mechanisms the mechanisms controlling insulin/glucose metabolism for a better survival. Recent research has highlighted the importance of prenatal environmental markers such as birth weight in the metabolic disturbances underlying early mortality and morbidity excess found in patients.
Methods: 30 patients diagnosed with resistant-psychosis (12 females) initiating clozapine were evaluated at baseline, 8 and 18 weeks. Anthropometric, pharmacological and clinical variables were included. Linear mixed model analyses were performed to assess the evolution of insulin levels over the 18 week considering the presence or absence of difficulties during pregnancy.
Results: Difficulties during pregnancy (p=0.033) are associated with insulin values independently of potential confounders such as time (p=0.207), age (p=0.035), clozapine levels (p=0.118) or body mass index evolution over time (p=0.451).
Discussion: Difficulties during pregnancy are associated with insulin values in patients initiating clozapine. Our Results: support the effect of prenatal factors in the later development of metabolic abnormalities in patients highlighting the need of describing and characterizing early life stressful events.

S142. IMPACT OF CLOZAPINE TREATMENT ON SARS-COV-2 INFECTION IN PATIENTS WITH SEVERE MENTAL DISORDER

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Background: Clozapine, an antipsychotic with an indication for treatment-resistant schizophrenia, is associated with an increased risk for infections, including pneumonia. Emerging evidence point that treatment with clozapine could affect both innate and adaptative immune system. We aimed to investigate if psychotic patients under clozapine treatment have increased risk of COVID-19 infection compared to psychotic patients under other antipsychotic treatments. We also explored if the clozapine group has more symptomatic COVID-19 compared to the non-clozapine group.
Methods: We recruted 552 patients with a psychotic spectrum disorder that were attending the mental health outpatient unit from Corporació Sanitària Parc Taulí (Sabadell, Spain), of whom 263 were under treatment with clozapine and the remaining 263 under treatment with antipsychotics other than clozapine. Both treatment groups were matched for age and sex. Patients undergoing immunomodulatory treatment of any kind or suffering from comorbid immunosupressive conditions were excluded from the analysis. We collected data from clinical records, including SARS-COV-2 infection, number of symptoms presented and severity of infection measured by 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 potencial confounders as body mass index, smoking status and prescribed antipsychotic doses.
Results: The prevalence of SARS-COV-2 infection was higher in the clozapine group compared to the group of other antipsychotics with a trend towards statistical significance (OR=2.2, 95% CI 0.83-5.9). Among patients who were infected with SARS-COV-2, patients with clozapine had more symptomatic disease than those treated with other antipsychotics (85% vs 33%, p=0.025). We did not found differences in relation to the severity variables of the infection.
Discussion: Our study suggests that patients with a psychotic disorder receiving clozapine treatment have a more symptomatic COVID-19 than patients with a psychotic disorder taking antipsychotics other than clozapine. The effect of clozapine in the immune system could be the mechanism that explains this associations. Larger samples are needed to explore whether patients with clozapine have a greater severity of SARS-COV-2 infection.

S143. GABA ALTERATION IN PATIENTS WITH TREATMENT-RESISTANT SCHIZOPHRENIA: A 1H-MRS STUDY

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Background: Gamma-Aminobutyric Acid (GABA) is the primary inhibitory neurotransmitter in the central nervous system. GABAergic dysfunction has been implicated in the pathophysiology of schizophrenia. Clozapine, the only approved drug for treatment-resistant schizophrenia (TRS), involves the GABAergic system as one of its targets. However, no studies have investigated the relationship between brain GABA levels, measured by proton magnetic resonance spectroscopy (1H-MRS), and clozapine response in patients with TRS.
Methods: This study enrolled patients with TRS who did not respond to clozapine (ultra-resistant schizophrenia: URS) and who responded to clozapine (non-URS), patients with schizophrenia who responded to first-line antipsychotics (first-line responders: FLR), and healthy controls (HCs). We measured GABA levels in the midcingulate cortex (MCC) using 3T 1H-MRS MEGA-PRESS and compared these levels between groups. The associations between GABA levels and symptom severity were also explored within the patient groups.
Results: A total of 98 participants (URS: n=22; non-URS: n=25; FLR: n=16; HCs: n=35) completed the study. We found overall group differences in GABA levels ($F(3,86)=3.25$, $p=0.04$). Specifically, patients with URS showed higher GABA levels compared to those with non-URS ($F(1,52)=8.40$, $p=0.03$, Cohen's $d=0.84$). GABA levels in the MCC showed no associations with any of the symptom severity scores within each group or the patient group as a whole.
Discussion: Our study is the first to report elevated GABA levels in the MCC in patients with schizophrenia who are resistant to clozapine treatment compared to those who are responsive. Longitudinal studies are required to evaluate if GABA levels are a suitable biomarker for predicting clozapine resistance.

S144. STRATEGIES TO IMPROVE ADHERENCE TO PSYCHOTROPIC MEDICATIONS IN DELUSIONAL DISORDER: A SYSTEMATIC REVIEW AND MULTIDISCIPLINARY CONSENSUS

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Background: Non-adherence to psychotropic medications has been associated with poor clinical outcomes in psychosis. Although adherence research is highly developed in schizophrenia, few studies have addressed the important issue of adherence in delusional disorder (DD) patients. Our main goal was to systematically review potential strategies for improving persistent delusions, particularly in those diagnosed with DD. Secondary goals were to classify these strategies by what behaviour they targeted and by factor responsible for non-adherence. These strategies were subsequently discussed and assessed in group meetings of a multidisciplinary mental health team specializing in the treatment of DD.

Methods: We carried out a systematic review based on electronic searches through PubMed and Google Scholar databases from inception until October 2021 according to PRISMA directives. Search terms: ("delusional disorder") AND ("adherence" OR "compliance"). Studies were included if DD patients participated and if strategies to improve adherence to psychotropic medications were noted.

The final set of strategies recommended by the multidisciplinary team of the Community Mental Health Outpatient Clinics - Rambla Terrassa are interventions that received >80% agreement among team members.

Results: From a total of 1185 initial publications, 19 studies met our criteria.

Targets of intervention were identified: (A) Economic and Psychosocial such as a) improving access to mental health services, b) Instituting Assertive Community Mental Health Programs. c) reducing cost barriers to psychotropic medications, d) providing financial incentives, e) providing social skills training to increase to improve social support, f) psychoeducation and (B) Patient-specific such as a) synchronizing timing of medications with schedule of daily activities b) motivational interviewing, including open dialogue, c) psychoeducation geared to the person, d) plasma and urine testing for comorbid substance abuse and (C) Provider-targeted such as a) building trust (establishing a therapeutic alliance), b) decentralizing care by offering home care and day hospital care, c) utilizing reminder devices and supervising/monitoring drug-taking, d) reducing complex medication regimens and offering weekly/monthly blister packs, e) switching to long-acting antipsychotic medications.

From these, 10 strategies were endorsed by the team as essential to improve adherence in DD: Cost reduction, community mental health programs, blister packs and psychoeducation led the list of recommendations.

Discussion: Medication adherence is a complex and multidimensional phenomenon that requires for its implementation multiple and simultaneous strategies. This has not been systematically done in the context of DD. The vast majority of current strategies are focused on patient targets, neglecting other avenues. We found that, by working as a multidisciplinary team, we were able to arrive at a consensus of which strategies were likely to be most effective. Our conclusions need to be tested by further research.

S145. CLOZAPINE-RESISTANT SCHIZOPHRENIA AND WOLFF-PARKINSON-WHITE SYNDROME: A CASE-REPORT

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Background: Ultra-treatment-resistant schizophrenia or Clozapine-resistant schizophrenia (CRS) was defined by the Treatment Response and Resistance in Psychosis Working Group as the maintenance of positive, negative, or cognitive symptoms of at least moderate severity on a patient with schizophrenia submitted to an adequate clozapine treatment. Augmentation strategies are possible with both pharmacological and non-pharmacological therapies, like electroconvulsive therapy (ECT). Augmentation with antidepressants, particularly Selective Serotonin Reuptake Inhibitors (SSRIs), appear to improve negative symptoms.
We hereby present a challenging case of a patient with CRS as well as Wolff-Parkinson-White (WPW) syndrome, that showed a favorable response to augmentation therapy with Sertraline.

Methods: Brief review of the literature on CRS and its augmenting treatment options, concerning a case report.
Results: We present the case of a 41-year-old man, with a history of CRS and WPW syndrome, admitted to the Male Acute Psychiatric Unit for acute clinical decompensation and unwholesome living conditions.
He was admitted two years before the current episode to the Treatment-Resistant Schizophrenia Specialized Unit of our hospital. With the one-year therapeutic program, that included a clozapine protocol, he improved from a PANSS score of 115 to 74. Performing ECT was debated but given the personal history of WPW Syndrome, it was considered that the risks outweighed the benefits. He was discharged to his parents' house with Clozapine 500 mg daily, Sodium Valproate 500 mg once a day, Lorazepam 2,5 mg twice a day and Paliperidone Palmitate 150 mg monthly. Unfortunately, the patient lost both parents, remaining with no social support and had to survive the Covid-19 pandemic on his own.

At the present admission, he exhibited marked negative symptoms and residual erotomanic delusions. A lack of therapy compliance was confirmed by serum levels of Valproate and Clozapine. All the previous medication was restarted. He spent most of the time isolated and showing no interest on the therapeutic planned activities. Eventually, with the development of a doctor-patient relationship, he admitted he still felt sad for his parents' death. Sertraline 100 mg, an SSRI, was started on an upward dose titration scheme. Gradually, he improved negative

symptoms, being more active on social and therapeutic occupations. To date, the patient remains hospitalized, and his social situation is being managed.

Discussion: This case was a challenge, from either a psychopathological, therapeutic, and social perspective.
Concerning psychopathology, he could be suffering a comorbid depressive episode (adverse life events and subjective complains) or a worsening of the negative symptoms (non-adherence to the medication and disease's natural course). Depressive episodes are underdiagnosed in schizophrenia, since are often masked by the negative and cognitive symptoms, that are a part of the disease.

Regarding treatment, the augmenting therapies on CRS are still not defined, and the patient's comorbidity (WPW syndrome) made the case even more difficult to manage. For the choice of the antidepressant, SSRIs are less cardiotoxic than other antidepressants. Since citalopram and escitalopram can cause QTc prolongation, Sertraline seemed like a better choice.

In this patient, most probably, there was a combination of both negative and depressive symptoms. However, and more importantly, both could be treated with antidepressants, and the outcome was very positive.

S146. ARE SELF-REPORTED SIDE EFFECTS OF PSYCHOTROPIC DRUGS IN AGREEMENT WITH CLINICIAN-RATED SIDE EFFECTS?

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Background: Psychotropic medications such as antipsychotics, antidepressants, and hypnotics are essential to treating a wide range of psychiatric disorders. Unfortunately, psychotropic medications are associated with side effects that may reduce patients' adherence to treatment and quality of life. Therefore, systematic screening of side effects is fundamental to optimizing psychopharmacological treatment. Existing self-report questionnaires are limited by a lack of broad coverage across psychotropic drug classes, extended administration time, failure to assess adherence to medication, and distress caused by side effects. Therefore, we developed the Aarhus Side effect Assessment Questionnaire (ASAQ), a self-reported measure comprising nearly all items included in the clinician-rated Udvalg for Kliniske Undersøgelser (UKU) psychotropic side effect scale. In addition, the ASAQ assesses subjective distress caused by side effects as well as self-reported compliance.

The objective of this study was to validate the self-reported ASAQ among a transdiagnostic population of psychiatric patients receiving psychotropic medication using the clinician-rated UKU side effect scale as reference.

Methods: Participants included inpatients and outpatients from the Department of Affective Disorders and Department for Psychosis. Participants completed the ASAQ and the WHO-Five Well-Being Index (WHO-5), and were subsequently rated on the UKU by trained, blinded raters. The criterion validity of the ASAQ was assessed by calculating the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the individual ASAQ items using the corresponding UKU items as reference. The construct validity was evaluated via a Pearson's correlation coefficient analysis of the relationship between the ASAQ and WHO-5 total scores. Predictors of patients who were considering discontinuing psychopharmacological treatment and/or with reduced compliance were assessed using multivariate logistic regression.
Results: A total of 122 patients (males=50%; median age=35 years, psychotic disorders=39%, mood disorders=43%) participated in the study. The median time for completion of the ASAQ was 5 (IQR = 4–6) minutes. Using the UKU as the gold standard reference, the ASAQ demonstrated sensitivity values >75% for 77% of its 30 items ranging from 37% (cutaneous disturbances) to 98% (increased sweating) and specificity values >75% for 47% of its 30 items ranging from 28% (reduced sleep) to 98% (micturition disturbances). PPV ranged from 32% to 97%, and NPV ranged from 29% to 99%. The Pearson's correlation coefficient between the ASAQ and the WHO-5 total score was -0.44, 95% CI: -0.57; -0.28, $p<0.001$). Seventeen percent of participants reported that they were considering discontinuing their psychopharmacological treatment, and 24% had recently not complied with their prescribed medication regimen. None of the explanatory variables (sex, age, duration of illness, psychiatric diagnosis, or ASAQ total score) were associated at the level of statistical significance with patients thinking about discontinuing their medication and/or not taking medication as prescribed.
Discussion: The ASAQ is a sensitive side effect self-report questionnaire with broad coverage across psychotropic drug classes, and is brief enough to ensure clinical feasibility. The relevance of the ASAQ is underscored by the negative association between side effects and well-being and by the large proportion of patients considering discontinuing their medication.

S147. REAL-LIFE EFFECTIVENESS OF TRANSITIONING FROM PALIPERIDONE PALMITATE MONTHLY TO PALIPERIDONE PALMITATE THREE-MONTHLY LONG-ACTING INJECTABLE FORMULATION

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Background: Randomized controlled trials (RCTs) have demonstrated the effectiveness of the three-monthly long-acting injectable (LAI) formulation of paliperidone palmitate (PP3M) in preventing psychotic relapses in patients suffering from schizophrenia. Its real-life effectiveness has been less well documented. This evaluation is essential given that patients for whom this new formulation could prove to be the most useful, e.g. those with poor treatment adherence, are often underrepresented in RCTs or even excluded. To this end, observational studies conducted in naturalistic settings provide the opportunity to examine the effectiveness of antipsychotics in

populations and contexts that may be more clinically relevant than RCTs to many healthcare providers. Hence, the objective of the present study was to evaluate the impact of transitioning from the monthly formulation of paliperidone palmitate (PP1M) to PP3M in terms of treatment discontinuation rate and psychotic relapse in real-life settings.

Methods: This multicentre retrospective observational study was conducted in 4 psychiatric outpatient clinics across Canada. All consecutive patients suffering from a schizophrenia spectrum psychotic disorder (SZSPD) for whom PP3M had been initiated between June 1st, 2016, and March 1st, 2020, were included; there were no exclusion criteria. The primary outcome was a composite of treatment discontinuation and psychotic relapse, defined as an increase of psychotic symptoms requiring either treatment discontinuation, dose increase, supplementation with oral antipsychotic or psychiatric hospitalization. Associations between independent variables and time to composite event were examined using Cox proportional hazard models.

Results: The study population included 178 patients, mostly male (84%) and Caucasian (73%). The most frequent diagnosis was schizophrenia (63%). Forty-eight composite events occurred during the first 12 months following PP3M initiation, including 33 relapses and 19 discontinuations. The composite event-free survival probability at 12-month was estimated at 0.701 (95% confidence interval [CI] = 0.632 – 0.776). Reduced time to event was observed in patients with comorbid personality disorder (hazard ratio [HR] = 3.1, 95% CI = 1.7 – 5.6, p-value = 0.0002), substance use disorder (SUD) (HR = 2.7, 95% CI = 1.5 – 4.8, p-value = 0.0006) and at least one psychiatric hospitalization in the 2 years prior to PP3M initiation (HR = 2.2, 95% CI = 1.2 – 4.0, p-value = 0.010). Patients with a job or at school had increased time to event compared with those not working or studying (HR = 0.5, 95% CI = 0.2 – 0.9, p-value = 0.032).

Discussion: In the present 1-year retrospective chart review of 178 consecutive patients with a SZSPD diagnosis switched from PP1M to PP3M, we observed that 27.0% experienced an a priori composite event, i.e. relapse in 18.5% and discontinuation of PP3M in 10.7%. Furthermore, we found that these rates varied strongly according to the presence or not of comorbid SUD or personality disorder. The very broad inclusion criteria, the absence of exclusion criteria and the fact that a systematic sampling strategy of consecutive cases was used ensure the generalizability of the Results: to the population in which LAIs are typically used. The study that used the design closest from the present one was that reported by Wallman et al. and Clark et al., in which lower relapse rates than those herein reported were found. A first explanation is the difference in relapse definition. Indeed, criteria used in this present study were very broad in order to capture all outcomes that are relevant to clinicians, such as symptoms deterioration requiring medication adjustments. A second explanation is the difference in rates of comorbid disorders across the two studies. Unfortunately, as they did not report on the rates of comorbid clinical psychiatric diagnoses, it is impossible to compare these two samples on that aspect. While the association of the composite issue with SUD was not surprising, since this is already recognized as a very strong predictor of relapse, the one with personality disorder though has not been as well charted in previous research. In fact, personality disorders in SZSPD have been relatively neglected thus far. The present results highlight the pivotal role of observational studies in assessing the effectiveness of clinical interventions in real-life settings.

S148. ANTIPSYCHOTIC ADHERENCE IN PATIENTS INITIATING OR REINITIATING CLOZAPINE: DOES PRIOR POOR ADHERENCE JUSTIFY AVOIDING CLOZAPINE TREATMENT?

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Background: While it is clear in the literature and practice guidelines that clozapine is the treatment of choice for treatment-resistant schizophrenia (SCZ), its use remains inconsistent. The reasons are multifactorial, involving patients, clinicians, and healthcare service organizations. Regular blood sampling early in treatment and potential adverse effects associated with clozapine are often reported as barriers. Moreover, a significant proportion of psychiatrists (from 41% to 82%) mentioned prior nonadherence to AP treatment as a major barrier to the introduction of clozapine. Despite the reported obstacles, recent data on the rates of clozapine continuation after introduction are highly favourable. Thus, the study objective was to determine if prior poor adherence before initiating/reinitiating clozapine predisposed to poor adherence to clozapine or to any APs (including clozapine) after its initiation/reinitiation.
Methods: This cohort study included 3,228 patients living in Quebec (Canada) with a diagnosis of SCZ initiating or reinitiating oral clozapine (index date) between 2009 and 2016. Adherence to AP treatment was measured by the medication possession ratio (MPR) over a one-year period preceding and following the index date. Five groups of patients were formed based on their prior MPR level (independent variable), and two dependent variables were defined after clozapine initiation (good adherence to any APs and to clozapine only). Along with multiple logistic regressions, State Sequence Analysis was used to visualize AP use trajectories over time, before and after clozapine initiation, for each group.
Results: The graphical representation of SSA revealed instantly that AP adherence was significantly improved in all groups regardless of the level of prior adherence to AP treatment. On the other hand, logistic regression showed that poorer adherence level to APs before the index date was significantly associated with an increased risk of poor adherence to any AP treatment after the index date (ORs ranging from 3.61 to 6.65). However, the vast majority of patients (from 84.2% to 97.0%) had good adherence to any APs and to oral clozapine (from 68.4% to 86.8%), regardless of the previous adherence level.
Discussion: Our findings provide a critical insight into the absolute risk vs. relative risk of poor adherence to treatment. Although widely recognized by clinicians as a barrier preventing the use of clozapine, prior poor adherence does not appear to justify avoiding clozapine treatment for patients who would otherwise be deemed eligible to receive it. Further replication of these findings could significantly impact clinical practice for the benefit of treatment-resistant patients.

S149. COGNITIVE REMEDIATION THERAPY IN SCHIZOPHRENIA: EFFECTS ON BDNF GENE METHYLATION

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Background: Cognitive remediation therapy (CRT) is confirmed as an effective treatment as it produces significant improvements on cognitive functioning, symptoms and global functioning in the context of schizophrenia. However, molecular changes underlying cognitive recovery in the process of CRT is poorly understood.
Methods: The main objective of the current study was to test the effect of cognitive improvement that usually follows the implementation of CRT on the methylation levels of the BDNF gene. A randomized and controlled trial was carried out in a sample of participants with schizophrenia (n = 60) with two arms: CRT and treatment as usual (TAU). Outcome measures included DNA methylation of genes central to synaptic plasticity (CpG sites of BDNF promoters) and global scores of a cognitive battery, symptoms scale and global functioning.
Results: CRT group showed significant improvements in cognition (p <0,001) and other variables like symptoms (p= 0.023) and functioning (p <0,001). Interestingly, different methylation patterns were found in 4 CpG sites of the BDNF gene in the two conditions of the trial CRT and TAU. First, the CpG site BDNF_CGI1_CpG_5 showed less methylation in the CRT group compared to TAU (p = 0.007). For the CpG sites BDNF_CGI1_CpG_12, BDNF_CGI1_CpG_24.25 and BDNF_CGI1_CpG_28, the CRT group presented higher levels of methylation compared to the TAU group (p = 0.007, p = 0.039 and p = 0.034, respectively).
Discussion: Current findings provide a neurobiological insight into biological mechanisms of cognitive recovery in terms of DNA methylation of genes that are central to synaptic plasticity. Hopefully, if those data were replicated, methylation patterns and gene expression profiles could be acting as biomarkers of response and they would help clinicians in providing more personalized treatments.

S150. E-NAVIGATE: REAL WORLD EXPERIENCES WITH ADAPTING AND IMPLEMENTING EARLY PSYCHOSIS INTERVENTION SERVICES FOR VIRTUAL DELIVERY

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Background: Comprehensive early psychosis intervention (EPI) services are the standard of care for youth with psychosis. The COVID-19 pandemic required EPI programs and most outpatient mental health services to be delivered virtually, requiring adaptations made to the initial

implementation. This transition to virtual care occurred with limited evidence on how best to administer interventions virtually, and whether treatment outcomes would be similar to in-person delivery. We used structured approaches to identify required adaptations, delivery of core components, and implementation facilitators and barriers for a virtually-delivered evidence-based EPI intervention (NAVIGATE).
Methods: NAVIGATE is a modular form of EPI with specific core components: individualized medication management; psychoeducation and evidence-based psychotherapies (individual resiliency training); supported employment and education; family education; team leadership, training, and practice feedback. The EPI program at the Centre for Addiction and Mental Health has delivered NAVIGATE since 2017, but transitioned to virtual delivery amid the pandemic in March 2020. We adapted a NAVIGATE Practice Profile, detailing how each core component was modified for virtual delivery. Adaptations were identified in structured group meetings with clinicians and coded using the Framework for Reporting Adaptations and Modifications for Evidence-Based Interventions (FRAME). FRAME captures when and how modifications occurred, whether they were planned/unplanned, the impact on fidelity, and the reasons and goals for modification. Barriers and facilitators to implementing NAVIGATE virtually are being explored using structured clinician interviews guided by the Consolidated Framework for Implementation Research (CFIR). The CFIR enables systematic assessment of contextual factors associated with effective implementation in relation to five major domains: intervention characteristics (e.g., complexity); outer setting (e.g., external policy); inner setting (e.g., resources); staff characteristics (e.g., knowledge); and implementation process (e.g., facilitation).
Results: We identified overarching adaptations deemed necessary for the delivery of virtual EPI care affecting all clinicians regardless of their role in NAVIGATE, including process, content, and training/evaluation. We also identified adaptations specifically related to the differing roles (e.g., adding peer-reviewed web-based resources, such as short video clips, to improve engagement in virtual IRT meetings). We documented mitigating strategies that were initiated to address some of the shortcomings of virtual care, for instance, including additional resources to address potential barriers in attending virtual appointments. Contextual factors affecting the implementation of the virtual delivery of NAVIGATE care are currently being investigated. Some key themes from this work that may be used to guide future virtual delivery of EPI services include suggestions on processes, training and technology, health equity factors, and approaches to enhance engagement in a virtual setting.
Discussion: This study identified the key adaptations and mitigating strategies needed to provide outpatient evidence-based EPI services virtually and the barriers and facilitators related to delivering NAVIGATE in a virtual setting. These findings can support the delivery of high-quality virtual services for youth with psychosis during the COVID-19 pandemic and in other situations where virtual care is indicated and warranted.

S151. THE DIGITAL MENTAL HEALTH LANDSCAPE IN THE TREATMENT OF SCHIZOPHRENIA SPECTRUM DISORDERS: A SYSTEMATIC SCOPING REVIEW

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Background: Technologically delivered or supported mental healthcare has the potential to enable illness self-management and improve access to clinically relevant resources outside the clinic. Previous concerns about the relevance and risks of such technologies in serious mental illnesses such as schizophrenia spectrum disorders (SSDs) have limited the growth of this field compared to other mental health conditions. However, recent research has dispelled these notions and has shown that most individuals with an SSD diagnosis have access to such technologies and use them as frequently as the general population. The research and development of digital mental health interventions for SSDs have increased exponentially in recent years. This rapid growth has highlighted the need to summarize the current state of these technologies regarding modalities, scope, and evidence. Previous reviews in this area have focussed on one technical modality such as mobile applications (Firth, 2015) and text messaging (D'Arcey, 2020); thus, there exists a need to examine the field collectively across digital modality/type of technology used.
Methods: The current review aimed to summarize the evidence for digitally delivered interventions and to identify existing gaps in the literature to highlight potential future research as the field progresses toward implementation. To this end, we examined studies that outlined the feasibility and efficacy/effectiveness for various technologies (e.g., smartphones, tablets, wearables, and laptops). Included studies were published after 2010 in English with digital interventions aimed at improving clinical outcomes (e.g., treatment engagement, symptom amelioration, community functioning, and illness self-management). Studies were excluded if the technology did not deliver an intervention if no original research was presented (e.g., editorial or commentary), or if no full text (e.g., conference abstract) was available. Articles were screened by two of the authors using a blinded online review system and conflicts were reviewed by the first and last authors. Extracted data included relevant methodological factors and primary and secondary outcomes.
Results: The search resulted in 805 articles; after careful review of the titles, abstracts, and full-texts, 72 articles were characterized as eligible and included in the review. Most of the included studies were published between 2018 and 2020 (n = 45). Regarding the type of technology studied, most investigated smartphone applications (n = 39), followed by short-message-service (SMS) text messaging (n = 17), internet-based (n = 15), and telemedicine (n = 2). The majority of studies were either development process papers (n =7), pilot or feasibility trials (n = 24), protocol papers for randomized control trials (RCTs; n =18), or completed RCTs (n = 21) with very few real-world effectiveness trials (n=4) and no papers on implementation. Of the studies examining smartphone applications, only eight unique applications had more than one study completed. In terms of other technologies, there were 4 in internet-based, one in SMS text messaging, and none in telemedicine with multiple papers.
Discussion: Overall, there exists strong support for the feasibility of using various technologies in schizophrenia care. However, Results: related to the efficacy show mixed findings. As most of the papers were in the stages of development, feasibility, or pilot trialing, adequately powered RCTs are needed as are trials that include sham conditions. For interventions with significant RCT results, there is a clear need for clinical workflow implementation studies and effectiveness data that are not confounded by artificial clinical trial research environments.

S152. SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS ON FAMILY INTERVENTIONS IN SCHIZOPHRENIA: "LESS IS MORE" FOR RELAPSE PREVENTION?

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Background: Psychotic relapses have a considerable impact on the lives of patients with schizophrenia, their families, and the healthcare system. Different types of family interventions exist may play a role in the prevention of relapses, however, they have never been compared to each other. The purpose of this study is to compare their effectiveness, tolerability, and acceptability.

Methods: We conducted a systematic review of randomized controlled trials (RCT) on patients with schizophrenia treated with family interventions. We searched EMBASE, MEDLINE, PsycINFO, PubMed, BIOSIS, Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, and WHO International Clinical Trials Registry Platform for RCTs published up to 20.01.2020, and in PubMed up to 15.07.2021. The records were screened by two independent researchers for inclusion. Data extraction was performed as well by two researchers independently, and disagreements were resolved by Discussion: or by contacting the study authors. The relapse rate was the primary outcome of the present project and was investigated at one year (primary time-point), 6 months, and more than one year We performed random-effects network meta-analysis to calculate odds ratios (ORs) for dichotomous outcomes and standardized mean differences (SMDs) for continuous outcomes. The study protocol was registered on the PROSPERO platform: CRD42020169951.

Results: 28099 records were screened, of which 24522 records were excluded; 3577 full-text articles were assessed for eligibility, and 284 full-text articles, corresponding to 93 studies, were included in the qualitative synthesis. We included 90 RCTs (10340 participants) in quantitative synthesis, of which 82 provided data for primary outcome relapse at 12 months (involving 9541 participants). All family interventions except crisis-oriented family therapy and one/two family psychoeducation sessions outperformed treatment as usual (TAU) in preventing relapses at 12 months time-point. Pure family psychoeducation was more efficacious than most of the other more complex approaches. The ORs of relapsing compared to TAU with 95% CIs excluding no effect ranged between 0.18 (95% CI 0.12; 0.27) for pure family psychoeducation and 0.63 (95% CI 0.42; 0.94) for community-based care intervention. Results: of other time points and secondary outcomes will be presented in the poster.

Discussion: This is, to our knowledge, the first meta-analytical study comparing family interventions approaches to each other. All family interventions are efficacious with the exception of short interventions (one or two sessions) and the crisis plan-focused ones. Brief interventions didn't perform well, probably because they did not have enough time to be executed appropriately, while crisis plans might not have included valid components implemented in the newer approaches. Simple family psychoeducation is one of the most efficacious interventions. A critical aspect of this study was the classification of different family interventions, which is not straightforward, and for which there is no agreed consensus. We applied a rigorous approach to

categorize each intervention, considering the description provided in each study arm and classifying them according to the therapeutic aspects implemented. The wide range of sensitivity and subgroup analyses corroborated the robustness of our Results: in various scenarios. The present NMA confirms the relevance of family interventions in preventing psychotic relapse. It also suggests that even simple family psychoeducation is efficacious, offering a cost-effective, easily implementable tool.

S153. CLINICAL IMPLEMENTATION OF SMARTPHONE APP ROBIN Z AS AN ADD-ON TREATMENT TOOL TO SUPPORT ADOLESCENTS WITH (ATTENUATED-) PSYCHOTIC SYMPTOMS

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Background: Interest in the development of innovative technologies in the health sector has increased due to their potential to improve accessibility, effectiveness, quality and cost-effectiveness of treatment. Based on these considerations, we have developed App Robin Z to support the treatment of adolescents with attenuated symptoms or full-blown psychotic symptoms. Robin Z aims at supporting medication adherence, real-time symptom assessment and offering help in coping with symptoms and stressful situations in daily life.
Despite initial encouraging research findings supporting the use of smartphone technology in the treatment of psychosis, it remains unclear whether the consistent use of smartphone technology in outpatient clinics outside of research projects is practical. Hence, it is uncertain whether patients will engage with this technology over a longer period of time and whether clinicians are ready to integrate this new technology into their current treatment approaches.

We address these questions in a clinical evaluation of the use of Robin Z in four community-based outpatient services of the Department of Child and Adolescent Psychiatry and Psychotherapy in Zurich, Switzerland.

Methods: From August 2021 on, we have started the implementation and will collect data of at least 20 adolescent patients with (attenuated-)psychotic and their caregivers over a six-week period. At the end, user data about mood logs, symptom trajectories, achieved weekly goals and entries for positive reinforcement will be gathered and analysed. In addition, patients as well as their therapists will complete questionnaires on user-friendliness and satisfaction with Robin Z.
Results: The clinical implementation and evaluation will provide data on feasibility, user-friendliness and satisfaction of patients and therapists with the smartphone app Robin Z. Between regular weekly therapeutic sessions sessions, duration and frequency of general use as well as specific protocols and functions will be available and compared to examine the clinical impact of using the app.
Discussion: The findings of this evaluation are of clinical importance in the field of eMental Health. They will provide initial indications of the clinical benefits of the app. Furthermore, the findings will enhance our understanding of potential barriers and facilitators for the use of Robin Z for both, patients and therapists.

S154. FACEYOURFEARS - VIRTUAL REALITY-BASED COGNITIVE BEHAVIOURAL THERAPY (CBT-VR) FOR IDEAS OF SOCIAL REFERENCE AND PERSECUTION

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Background: The continuum of paranoid ideas and ideas of reference to persecutory delusions are some of the more present symptoms in Schizophrenia Spectrum Disorders.
Cognitive Behavioral Therapy (CBT) has shown beneficial effects on these and other psychotic symptoms. Effect sizes though have only been small to medium so far.

The behavioral part of CBT is important when working with psychotic symptoms but difficult to perform in a real-life setting. Improvement of this aspect in CBT could potentially increase effects of treatment. Preliminary Virtual Reality based CBT (CBT-VR) trials have shown promising Results: but the field needs stronger evidence base.

By using CBT-VR behavioral experiments and exposures can be specifically tailored to the needs of the individual in a safe environment increasing effectiveness in each therapy session. In VR you can e.g. jump from one situation to another, try out worst-case scenarios or create realistic roleplays. The therapist monitors the patients behaviour in VR making realtime observations possible.

The current trial is the hitherto largest randomized, assessor-blinded clinical trial, evaluating the effectiveness of CBT-VR versus 'traditional' CBT in treating paranoid ideas and ideas of reference in patients diagnosed with Schizophrenia Spectrum Disorders and other related psychosis's (ICD-10 F.20-F.29), including Schizotypal Disorder.

The objective is to identify whether CBT-VR can reduce severity and frequency of paranoid ideations, ideas of social reference, clinical symptoms and social avoidance. Thereby improving daily life functioning and quality of life.

The study enroll participants from the outpatient facilities in the capital region of Denmark, (early intervention services (OPUS teams) or Flexible Assertive Community Treatment teams (FACT teams).

Methods:

- A high quality randomized, assessor-blinded parallel-groups superiority clinical trial fulfilling the CONSORT criteria for non-pharmacological treatment.
- A total of 256 patients will be allocated to either CBT-VR plus treatment as usual versus traditional CBT plus treatment as usual.
- All participants will be assessed at baseline and 3- and 9 months post baseline. A stratified block-randomization with concealed randomisation sequence will be conducted. Independent assessors blinded to the treatment will evaluate outcome.
- The primary outcome is level of non-bizarre delusional ideas measured with Green Paranoid Thought Scale, ideas of persecution – which has displayed good reliability and validity.

• Secondary outcomes are ideas of social reference, safety behavior and avoidance, social anxiety, level of function, and emotional recognition.

Results: Inclusion began in April 2021 and primary trial Results: will be available in June 2024. Feasibility Results: and qualitative data will be presented at the SIRS conference.
Discussion: Research on VR-assisted psychotherapy for psychotic disorders is still in it's infancy. Questions regarding effectiveness, tolerability, and feasability need to be explored futher. Results: from the current trial will aid in clarifying these issues. This is key to the potential of scalability of the intervention into clinical practice. Furthermore, health-economic analysis will eludicate on the cost-effectiveness of the VR-assisted therapy.

S155. EFFICACY OF TECHNOLOGY-BASED INTERVENTIONS IN PSYCHOSIS, IMPROVING NEUROCOGNITION. A NETWORK META-ANALYSIS

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Background: Cognitive impairment is a relevant effect in psychosis and could be one of the main aims of the intervention in patients with psychosis. Neurocognition is altered in patients with psychosis in some specific domains such as verbal memory, processing speed, language, and nonverbal memory, and it also directly correlates with functioning, social cognition and employment (Hall et al., 2019). Technology-based interventions (TBIs), complementing treatments as usual (TAUs), including computer and Internet-based interventions, mobile interventions, health applications, social media interventions, and interventions using technological devices, are a useful approach for providing therapy to patients with psychosis and improve neurocognitive malfunction. TBIs have the capacity to reach more people by overcoming accessibility, mobility and stigmatization barriers (Torous et al., 2019) and could become a complement to usual therapy and thus help to improve neurocognitive deficits, functioning and some aspects of quality of life.
The objectives are 1) to compare TBIs, as a complement to TAU, with face-to-face interventions for psychosis focusing on a specific outcome such as neurocognition and 2) to perform a network meta-analysis to investigate which treatment led to a more marked improvement in neurocognition

Methods: The systematic review preceding this work was based on 58 randomized control trials (RCTs) of TBIs for psychosis. And of those, for the specific outcome of neurocognition, we selected the studies that analyzed neurocognition (N = 34). We calculated the standardized mean change (SMC) and applied a three-level model because there were several effect sizes within the same study. In relation to network meta-analysis, we grouped the direct and indirect estimates of the effectiveness of each TBI to obtain a rank of therapies for neurocognition.
Attending to the descriptions of the different RCTs, we categorized TBIs as: 1) Cognitive training; 2) Cognitive training + Vocational therapy; 3) Cognitive training + Social cognition; 4) Cognitive training + Psychoeducation; 5) Cognitive training + CBT; 6) Cognitive training + CBT +

Vocational therapy; 7) Social cognition; 8) CBT; 9) CBT + Vocational therapy; 10) CBT + Mindfulness; 11) Psychoeducation; 12) Mindfulness.

First, we checked the effectiveness of each TBI as a complement to TAU for neurocognition. TAU was any standard intervention that patients were already participating in or receiving. TBI was a complement to this intervention. Second, the overall effect obtained for each TBI and for neurocognition was simultaneously disaggregated according to the type of face-to-face interventions used (control group), so we classified it in 3 groups: 1) Psychotherapy, 2) Technology and 3) Pharmacotherapy only. Psychotherapy refers to any CG that used psychological and psychoeducational techniques and pharmacotherapy intervention; Technology refers to any CG that used non-psychotherapeutic TBIs, such as computer games, computer tasks, or video and television programs, and pharmacotherapy intervention; and Pharmacotherapy refers to any CG that used only drugs, without any other intervention. Finally, we performed a network meta-analysis to study which treatment led to a more marked improvement. Direct and indirect estimates of the effectiveness of each online intervention are pooled together to obtain more precise estimates and we obtained a rank of therapies (P-scores).

Results: Technology-based interventions, complementing treatment as usual, were overall superior to face-to-face for neurocognition (d = 0.13, SE = 0.03, z = 4.14, p = <.0001). Significant effects were observed in the analyses of TBI Cognitive training compared with all the CGs together (d = 0.20, SE = 0.05, z = 4.22, p = <.0001).
Based on the network meta-analysis, the first option for neurocognition was the TBI combining Cognitive training with Vocational therapy (Cognitive training + Vocational therapy) (p = 0.94) and the second option was TBI Cognitive training (p = 0.87). The next options where: Cognitive training_TBI + Social cognition_TBI (p = 0.70); Cognitive training_TBI + Psychoeducation_TBI (p = 0.58); Pharmacotherapy (p = 0.57); Cognitive training_TBI + CBT_TBI + Vocational therapy_TBI (p = 0.56); Cognitive training_TBI + CBT_TBI (p = 0.55); Technology (p = 0.41); Social cognition_TBI (p = 0.35); Psychotherapy (p = 0.25); CBT_TBI + Vocational therapy_TBI (p = 0.20); and CBT_TBI (p = 0.0001).

The effect of TBI Cognitive training for neurocognition differed significantly from zero (d = 0.16; [95% confidence interval (CI): 0.09, 0.23]), whereas the 95% CI of the overall effect estimated for TBIs combining Cognitive training with Vocational therapy included the value of zero (d = 0.29; [95% confidence interval (CI): -0.02, 0.60]).

Discussion: TBI Cognitive training + Vocational therapy and TBI Cognitive training, both added to TAU, can be considered effective interventions to improve neurocognition in patients with psychosis.

S156. TIME MATTERS: A TIME-AWARE DEEP NEURAL NETWORK FOR INDIVIDUALIZED TREATMENT OUTCOME PREDICTION IN FIRST-EPISODE PSYCHOSIS

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Background: Psychotic disorders' clinical representation varies widely among individuals. As of yet, clinicians are not able to accurately predict the prognosis of patients suffering from psychosis. As a consequence, one could potentially treat the patient inefficiently or unnecessarily. Thus, it would be desirable if psychiatrists were able to predict (treatment) outcomes of psychosis. With machine learning, prediction models can be built that are able to predict the outcome at the individual level. This present study has been set up to examine whether a prediction model could be built with a design allowing for potential use in clinical practice. Therefore, the prediction model should at least fulfill the following criteria: high accuracy; clinically relevant outcome measures; insight into how the various (modifiable) predictor variables contribute to an individual's outcome prediction.

Methods: The sample included 446 patients (age: 18-40 years) with first-episode psychosis from the OPTiMiSE study, a multicenter clinical research trial in 27 international sites. The study extensively assessed patients at baseline (T0), after 4 weeks of treatment with amisulpride (T4), and after another 6 weeks of double-blind randomized treatment (T10), either continuing on amisulpride or switching to olanzapine. We selected baseline variables relevant for prediction of remission, including PANSS scores, diagnosis, duration of untreated psychosis, age at onset, sex, and physical health and lifestyle variables. Treatment outcome measures at T4 and T10 were: symptomatic remission (based on PANSS), functional recovery (based on CGI), and personal recovery (based on PSP). We used a deep learning architecture based on long short-term memory (LSTM) units on multimodal data to predict different outcomes. We used not only baseline variables but also clinical data at several time points in between T0 and T10 to improve the performance of the model over time. We trained full models (with all available baseline variables as predictors) and leaner, clinically more feasible, models (with fewer baseline predictors). We used a 10-fold cross-validation design to evaluate the generalization performance of the proposed architecture. In addition, to further test the models' generalizability, we carried out a leave-one-site-out validation. Using counterfactual analysis the importance of the baseline predictors was assessed.

Results: The performance of the prediction models was measured by Area Under the ROC Curve (AUC). Prediction performances for the different outcomes at T4 ranged from 0.64 to 0.71 using only baseline predictors; AUC improved when adding clinical data from week 1, ranging from 0.69 to 0.74. For outcome at T10, using only baseline variables the models achieved AUC ranging from 0.51 to 0.63; when using all available time points in between (week 1, 4, and 6) the Results: improved, with accuracies ranging from 0.63 to 0.76. Variables about diagnosis, occupation and education proved to be the most important sociodemographic baseline predictors.

Discussion: In this study, prediction models were built with a design that can be translated to the real-life clinical practice scenario where a patient with first-episode psychosis receives antipsychotic medication treatment. With the use of LSTM, we made it possible to use clinical patient data over the course of the treatment phase and we demonstrated that adding this extra data over time improves the model's accuracy. In addition, our approach allows for creating leaner, thus clinically more feasible, models and interpreting the importance of predictor variables. We are currently carrying out research to build models with accuracies high enough to be considered for actual use in clinical practice.

S157. AN ANALYTIC ENRICHMENT STRATEGY TO INCREASE CONSTRUCT VALIDITY OF THE MARDER PANSS NEGATIVE SYMPTOM FACTOR: ABILITY TO ENHANCE EFFICACY SIGNAL DETECTION

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Background: In clinical trials of schizophrenia, the Positive and Negative Syndrome Scale (PANSS) is the most widely used measure to assess efficacy. In studies attempting to demonstrate specific efficacy in the treatment of negative symptoms, patients are often selected based on the severity of their Marder PANSS Negative Symptom (MPNS) factor relative to their severity of positive symptoms. However, this "enrichment" strategy can be problematic for a variety of reasons. We present here a pilot study of an alternative enrichment strategy designed to address some of the limitations of standard severity approaches to enrichment in treatment studies targeting negative symptoms.

Methods: In a 5-factor model of the PANSS, the amount of variance explained by the MPNS factor is relatively low (approximately 10-20%). Here we present a method to increase the construct validity of the MPNS factor by (1) defining a Marder Negative symptom Heterogeneity Index (MNHI); (2) rank-ordering patients on the MNHI; and (3) Identifying the MNHI score that maximized the amount of variance explained on the MPNS factor, while minimizing the variance contributed by other Marder symptom domains. Utilizing pooled data from 12 lurasidone clinical trials and one trial of the novel non-D2-blocking TAAR1 agonist, ulotaront (N=4,868), patient-level PANSS item scores between two assessments (screen and baseline) were encoded in a variance-covariance difference (VCD) vector that captured intra-item screen-to-baseline variance of each item on the MPNS factor, the covariance between each 2-item pair on the MPNS, and the between-item differences of PANSS items between two assessment time points (from a single patient).

Results: An MNHI score ≤0.119 was identified as the threshold value that maximized the amount of variance explained on the Marder PANSS Negative Symptom (MPNS) factor, with minimal unexplained variance. The enriched sample (limited to patients with an MNHI threshold score ≤0.119) comprised a subgroup, N=882 (18.1% of the total). In a one-factor model of the total sample (N=4,863), 40% of the variance was explained by the 7 Marder negative symptom items. In contrast, in the enriched subgroup, explained variance increased to 69%. In the enriched subgroup, the resulting MPNS construct had higher construct validity, with improved goodness of fit indices, and therefore was better able to accurately measure the underlying negative symptom domain. We then calculated the endpoint effect sizes in the enriched subgroup after short-term treatment with lurasidone (vs. placebo) and ulotaront (vs. placebo). For ulotaront, the effect size of negative symptom indices was markedly increased in the enriched (vs. non-enriched) subgroup, while enrichment resulted in minimal increase in the effect size observed after treatment with lurasidone. As a result, effect sizes were consistently larger in favor of ulotaront vs. lurasidone on the Marder PANSS Negative Symptom Factor score (0.84 vs. 0.33), the Uncorrelated PANSS Score Matrix (UPSM; Hopkins et al, Schizophr Bull 2018;44:593-602) apathy/avolition score (0.74 vs. 0.05), and the UPSM deficit of expression score: 0.52 vs. 0.30.

Discussion: These Results: suggest that the proposed enrichment strategy was able to successfully identify a subgroup of patients selected (pre-randomization) based on a greater likelihood of having the negative symptom construct that is being measured. These Results: demonstrate that the pre-randomization enrichment strategy does not non-specifically improve negative symptom effect sizes for all treatments but appears to enhance efficacy signal detection in a drug (ulotaront) with a novel TAAR1 mechanism of action that does not block D2 receptors.

S158. UNHEALTHY DIET MAY SUSTAIN PROBLEMATIC BRAIN-GUT VICIOUS CIRCLE IN SCHIZOPHRENIA SPECTRUM DISORDERS: HOW TO ESCAPE THE ENTRAPMENT?

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Background: The high mortality and prevalence of metabolic syndrome in patients with schizophrenia spectrum disorders (SSD) is maintained by poor diet. Poor nutrition is a serious problem for patients with SSD, with multifaceted negative consequences, not only for the somatic but also for the psychological well-being. It is difficult for SSD patients to improve their eating habits due to severe psychiatric symptoms, cognitive problems, and low income. This review summarizes recent literature highlighting current eating habits, dietary preferences, and nutritional status implicated in poor dietary pattern and its contribution to morbidity and symptom severity in SSD. Unraveling these factors provides new insights for potential lifestyle treatment strategies for SSD.
Methods: A narrative review of studies addressing diets in SSD patients that were published in the years 2018-2021.
Results: Only 62% of the SSD patients prepare their food, emphasizing poor eating habits. Results: showed that SSD patients more commonly consume a high pro-inflammatory diet, consisting of high caloric intake including high intake of saturated fat, sugar and sodium, and lack of fruits, vegetables, fish, and wholegrains compared to healthy controls. Furthermore, Results: showed that schizophrenia patients with metabolic syndrome, who followed the dietary intervention, improved on cognitive functioning after three months of dietary intervention, whereas those without the dietary intervention did not. Finally, after two years, the dietic component of the KBIM Xtend lifestyle program increased diet quality of young people with first-episode psychosis, compared to baseline. This improvement was predominantly driven by increased vegetable variety and amounts.
Discussion: Recent findings render poor dietary habits as potential target for treatment of SSD patients. Poor dietary quality affects gut microbiome, which in turn, via the gut-brain-axis, may affect brain psychiatric symptom pathology that may keep SSD patients entrapped in a brain-gut vicious circle. Anti-inflammatory dietary interventions may be necessary to help SSD patients escape from this entrapment. Support is needed to change eating habits and dietary patterns in SSD patients. A more healthy, anti-inflammatory diet should not only be promoted, but also provided as a structured and supervised intervention as only supplementing nutrients probably lacks the impact to significantly improve the risk of chronic physical illnesses/metabolic syndrome. Finally, the efficacy and feasibility of healthy eating patterns, such as the anti-inflammatory diet, in the management of SSD needs to be examined using randomized controlled clinical trials.

S159. EMOTION DYSREGULATION IN PSYCHOSIS SPECTRUM OUTPATIENTS: CORRELATES TO CLINICAL VARIABLES, QUALITY OF LIFE, AND DAILY FUNCTIONING

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Background: Difficulties in emotion regulation (ER) are evident in many psychiatric disorders and can have important implications for illness course and outcome. Individuals with psychosis spectrum disorders often exhibit deficits in ER which have been correlated with positive symptom severity and subjective distress. A paucity of research has investigated the clinical correlates of ER in psychosis, or the impact of these difficulties on quality of life and daily functioning.
Methods: Individuals with psychosis (N = 59) presenting for outpatient CBT treatment completed a detailed intake assessment measuring a range of clinical variables, including ER, psychiatric symptoms, cognitive insight, neurocognition, daily functioning, quality of life, and self-reported personal recovery.
Results: Poor ER abilities as captured on the short-form version of the Difficulties in Emotion Regulation Scale (DERS-18) were positively correlated with positive psychotic symptoms (overall symptoms, delusions), social anxiety, depression, and self-reflectiveness, rs = .285-.515, ps ≤ .029, and negatively correlated with quality of life (r = -0.512, p < .001) and personal recovery (r = -0.423, p < .001). Multiple regression analyses showed that the DERS-18 (B = -0.305, t = -2.804, p = .007) and low mood, measured by the Calgary Depression Scale for Schizophrenia, (B = -0.897, t = -2.597, p = .012) were significant predictors of quality of life. In contrast, daily functioning was significantly predicted by executive functioning neurocognitive performance (B = 5.494, t = 3.142, p = .003) and overall psychiatric symptoms (B = -0.552, t = -2.567, p = .013), but not DERS-18 scores (B = -0.016, t = -0.108, p = 0.915).
Discussion: Findings support the clinical utility of assessing emotion dysregulation in psychosis and add nuance to the understanding of how such difficulties differentially influence recovery, informing both treatment planning and intervention.

S160. GROWING THE HOPE TEAM IN PITTSBURGH: SYSTEMIC, DIAGNOSTIC, AND TREATMENT PERSPECTIVES

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Background: Hope Team is an outpatient mental health clinic at the University of Pittsburgh Medical Center (UPMC) serving young people (10-26 years old) who are at clinical high-risk for psychosis (CHR). The Hope Team was founded in 2017 with initial support from a local Pittsburgh foundation and expanded in 2018 with support from Substance Abuse and Mental Health Services Administration (SAMHSA).

Methods: The services Hope Team currently provides include diagnostic and psychosis risk assessment, community outreach, psychoeducation for families and consultation services for other providers. Hope Team serves as the primary treatment team for currently enrolled participants using a stepped-care approach. We will discuss Hope Team's experiences in service delivery for CHR youth from systemic, diagnostic, and treatment perspectives.

Results: In terms of a systemic perspective, we first review our experiences forming a new specialty CHR clinic within our unique healthcare system. To our knowledge, the Hope Team is the only CHR specialty clinic in the U.S. embedded within a Child Services division of a behavioral health hospital system, which has afforded some unanticipated advantages and challenges for service delivery and community outreach. In particular, it has afforded opportunities for closer collaborations with other youth-serving providers. Our experiences suggest that youth-serving providers—as well as families and young people—typically have insufficient exposure to information about psychosis risk. Thus, affiliation with child services has facilitated access to those who can benefit most from education and outreach. Given that as many as 1/4 of adolescents seeking acute mental health services meet CHR criteria (dePablo, Guinart, Cornblatt, et al., 2020), closer affiliation with youth-serving mental health providers can both enhance recruitment and ameliorate a service gap.

Given Hope Team's experience embedded within Child Services, we argue that developmental expertise should be a core competency of CHR specialty services, which is consistent with recent clinical recommendations (dePablo, Estradé, Cutroni, et al., 2021). In terms of a diagnostic perspective, psychosis is a neurodevelopmental disorder and young people at CHR present with substantial symptom heterogeneity and mental health comorbidities. Furthermore, CHR is inherently a transdiagnostic risk state and requires subtle differential diagnosis (e.g., differentiating an emerging psychotic disorder from a mood disorder). Thus, ensuring CHR providers have developmental competency could enhance early prevention of psychosis and improve quality of life for young people at CHR and their families.

Finally, we present our treatment perspective and review current and future efforts to meet the clinical needs of young people and families served by Hope Team. Our clinic's caseload to date includes higher-than-community base rates of underserved groups, including 45% identifying as LGBTQ+ and 38% as people of color. The majority report adverse events in childhood, and nearly all have comorbid mood, anxiety, and/or obsessive-compulsive disorders. Despite their complex clinical needs, no clear evidence suggests any specific treatment approach is superior for CHR individuals (Fusar-Poli, Davies, Solmi, et al., 2019). We review the stepped care model of treatment adopted by Hope Team, share our DBT-based group therapy program in progress, and provide a brief case example.

Discussion: We conclude by discussing future directions for the Hope Team and CHR services.

S161. EVALUATION OF AN ADAPTIVE IMPLEMENTATION PROGRAM FOR COGNITIVE ADAPTATION TRAINING FOR PEOPLE WITH SEVERE MENTAL ILLNESS: A CLUSTER-RANDOMIZED CONTROLLED TRIAL

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Background: Implementation of many evidence based practices (EBP) in routine care lags behind, despite the established effectiveness of the EBPs. This so called 'science-to-service gap' is a widespread problem in mental health care. One such EBP is Cognitive Adaptation Training (CAT), a psychosocial intervention focusing on reducing the impact of cognitive disorders on daily functioning in people with severe mental illness (SMI). We developed an innovative adaptive implementation program to facilitate implementation of CAT and similar interventions in routine care. The aim of this study is to evaluate the effectiveness of the implementation program and to determine factors that impede or facilitate the implementation process.
Methods: We conducted a multicenter cluster randomized controlled trial comparing the implementation program to a single training program in four mental health institutions (a total of 21 rehabilitation teams) in The Netherlands. Focus groups, semistructured interviews and questionnaires were used at multiple levels of service delivery (service user, professional, team, organization). Assessments took place before, during and after implementation and at follow-up, adding up to a total duration of 14 months. Data were analyzed using multilevel modeling.
Results: Data collection is complete and analyses on the effectiveness of the implementation program are ongoing. Preliminary analyses show that team climate ($p<.008$) and organizational climate ($p<.043$) significantly predict the attitudes of mental health providers toward EBP.
Discussion: The results of this implementation study potentially provide an innovative program to facilitate implementation of effective psychosocial interventions like Cognitive Adaptation Training. We will discuss the effectiveness of the program. Additionally, we will discuss factors on the level of service user, professional, team and organization that facilite and hamper the implementation process of psychosocial interventions in mental health services.

S162. ELEMENTS THAT ENHANCE THERAPEUTIC ALLIANCE AND SHORT-TERM OUTCOMES IN PSYCHOTHERAPY AMONG PERSONS WITH SCHIZOPHRENIA: A SESSION BY SESSION ASSESSMENT

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Background: Preliminary evidence has found metacognitive capacity is associated with therapeutic alliance (TA), and other outcomes in psychotherapy among persons with schizophrenia. The current study explored whether the use of specific therapeutic elements of Metacognitive Reflection and Insight Therapy were followed by higher ratings of TA and short-term outcome in a session-by-session intensive data collection.
Methods: 221 sessions of 10 completers with schizophrenia, who took part in an ongoing integrated design of Randomized Controlled Trial (RCT) of the MERIT and Session by Session

(SBS) assessment at a community clinic at the Bar-Ilan University, were analyzed. Measures of therapeutic alliance (WAI-SR), general outcome (ORS), and metacognition (MAS-A) were used.
Results: Findings showed significant Reliable Change Index in two domains of metacognition, self-reflectivity and mastery, following therapy. In addition, two elements, the introduction of the therapist's mind and reflecting on the progress in therapy, were related to better between-session outcomes. Finally, reflecting on the progress was also followed by higher TA.
Discussion: Metacognitively oriented therapy is beneficial in increasing both TA and short-term outcome. Discussing the therapist's and client's experiences of what is occurring in therapy may positively affect short-term outcome, and could be applicable to other psychotherapy approaches.

S163. IDENTIFYING SEXUAL HEALTH SERVICE NEEDS AND PRIORITIES AMONG WOMEN AND NON-BINARY PEOPLE WITH FIRST EPISODE PSYCHOSIS

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Background: Individuals who experience psychosis are at risk for a wide range of adverse sexual health outcomes including unplanned pregnancy and experiencing sexual assault, and for receiving inadequate sexual health services. Early intervention is important to improve outcomes, yet sexual health is understudied, particularly in the first episode psychosis context. This study explores the sexual health service needs and priorities among women and gender diverse people who experience first episode psychosis to inform service design and delivery.
Methods: We conducted semi-structured individual qualitative interviews with 19 service user participants (age 18-31) who were receiving clinical care in two first episode psychosis programs in Ontario, Canada and who identified as having sexual health needs related to being a women or being assigned female at birth. Service user participants were asked about their experiences with sexual health and priorities for sexual health care. Additionally, we conducted semi-structured interviews and focus groups with 35 clinicians who provide mental health and sexual health care to this population. Thematic analysis was used to analyze the responses among service user participants and the clinician data was used for triangulation.
Results: The service user participants were diverse in terms of gender identity (cis- and trans-women, non-binary individuals), sexual orientation, race and ethnicity, religion, and educational background. The clinician participants were interprofessionally diverse and included case workers, nurses, family physicians, psychiatrists, and therapists in community and hospital settings. Identified themes among service user participants were: (1) Understanding intersections between psychotic illness and sexual health and function (high/low sex drive, impacts of comorbid symptoms and medication); (2) Accessing information and resources for sexual and reproductive health (contraception, menstruation, reproductive planning and pregnancy, sexual trauma, sexually transmitted infections); (3) Intimacy and relationships (impact of illness on relationships and dating, positive impact of relationships, traumatic relationships) and (4) Intersectional influences on sexual health (gender identity, sexual orientation, culture, family, religion, finances, and stigma). Clinician participants discussed specific elements within each of these themes (e.g. risk

associated with hypersexuality, preventing adverse sexual and reproductive health outcomes, supporting clients in traumatic relationships, and sensitivity to cultural influences on sexual health).
Discussion: The women and non-binary service users in our study described wide-ranging sexual health needs, which intersected with their experiences of psychosis in diverse ways and impacted many facets of their lives. There was overlap between service users and clinicians in terms of identified priorities. However, service users presented a more holistic view of sexual health priorities overall compared with clinicians' focus on risk management. These Results: increase awareness of the broad range of sexual health priorities in need of being addressed in clinical settings, and can inform services to proactively meet the needs of this population.

S164. RELIGIOSITY AND BIOLOGY: AN APPROACH TO UNDERSTANDING THE CAUSES OF SCHIZOPHRENIA IN MEXICAN FAMILIES IN WESTERN MEXICO

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Background: In a study conducted in Europe by Ruiz and cols (2012), it was reported that 68% of the participants attributed the causes of schizophrenia to biological factors. A previous research (Townsed, 1975) argued that in studies made in Anglo-Saxon and European societies, people tended to give more importance to the biological factors that explain the disease, unlike Latin or African populations studies where the emphasis was placed mostly on non-medical explanations. In Guadalajara, Jalisco, Mexico in 2003, an ethnopsychiatric study which included 41 relatives of patients with some psychiatric diagnosis from the hospital "Fray Antonio Alcalde", it was reported that 27% of participants attributed the cause of the disease to drug use, 22% referred to "nervousness", 20% pointed to head trauma, and 12% pointed to witchcraft (Villaseñor, et al., 2003).

Lastly, three studies carried out on the African continent, in Ethiopia (Shibre et al., 2001), Nigeria (Ohaeri and Fido, 2001) and Morocco (Kadri et al., 2004), cited by Muñoz et al., in 2009, show that the main causal attributions of schizophrenia were: supernatural factors, drugs, and brain biological causes (Muñoz, Pérez, Crespo, and Guillén, 2009).

Methods: This research used the tools of cognitive anthropology to analyze through semantic structures, the cultural consensus of relatives of people with schizophrenia on the etiology of schizophrenia, and its relation with the EE. It was a mixed study with an analytical method used in ethnographic research. The sample was calculated based on Weller and Romney (1998) proposal, to obtain a level of competence greater than 50%, with a reliability level of 95% and error of 5%. Thus, a total of 40 relatives from 18 different families of users of the "Instituto Jalisciense de Salud Mental" in the Area Metropolitana de Guadalajara, were chosen using convenience sampling of a purposeful selection.
Results: The sample consisted of 40 relatives of individuals with schizophrenia from 18 different families in the Area Metropolitana de Guadalajara. The average age range of the participants was 48.53 years (13-86). 80% were women. Regarding the beliefs about the factors that cause the onset of schizophrenia, it was found that emotional trauma in childhood was identified as the first cause of schizophrenia described by family members (16%). The next factor was the hereditary variable

with 15% and was followed by emotional problems (12%), head trauma (7%), mistreatment (5%), and divine will (5%), among others. It should be noted that variables related to neural problems and brain substances (4%) occupied the last places on the list but were still part of the valid cultural consensus. A single valid cultural consensus was found, with a variability ratio of 39,130 and a statistical significance lower than ($p \leq 0.05$), which included 95.4% of all possible variations of the model items (Figure 1), with a multidimensional diagram with Stress of 0.01.
Participants with adequate cultural competence (good informants) who provided answers attached to the valid cultural consensus on etiology of schizophrenia and people with inadequate cultural competence (bad informants) were categorized in order to analyze a possible association with high EE. Subjects classified with adequate cultural competence had low EE and people with inadequate cultural competence showed a high EE, both with statically significant data ($p = \leq.05$) ($t = -9.15$; 95% CI [64.50-40.66]).

Discussion: Regarding the etiology of schizophrenia, in this study, the environmental and psychosocial causes predominated as the determinant onset of the disorder, according to more than 68% of respondents. Nevertheless, though in this study the biological-hereditary factor took second place in mentions, the medical-scientific understanding of the disease was not discarded and had a predominant place within the cultural consensus: inheritance, neurological problems, brain substances and labor complications were the other biological variables that made up the cultural consensus.
Concerning religious factors, it is to notice that in this study, magical-religious explanations were also part of the cultural consensus about the etiological explanations of the disease. This holds the premise that Mexico remains as a significantly religious country. Studies about religiosity in Mexicans, has reported that religious beliefs, magic, witchcraft, horoscopes, energies or amulets, are common ideas in almost 78% of the population (Sota, 2010). However, it should be clarified that Divine Will was not the most prevalent answer within the cultural agreement.

The Mexican Psychiatric Association (APM) and the Psychiatric Association of Latin America (APAL) argue that religious explanations of mental phenomena such as schizophrenia come from the cultural contexts of the territories in which they occur (APM and APAL, 2014). Some studies from different latitudes suggest that religious beliefs are highly used to cope with the stress that dealing with an illness like schizophrenia can cause.

In this regard, various research has shown that religious interpretations of the disease, help people to find a positive prospective on the lives of individuals and their families.

S165. SCHIZOPHRENIA STIGMA IN PRINT MEDIA IN BRAZIL- A MACHINE LEARNING APPROACH

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Background: Stigma is a broad term that indicates some negative attribute to something or someone as inferior or threatening. It has received attention in diverse ways in psychiatry research and schizophrenia. The consequences of stigma are prejudice, discrimination, and situations of

disrespect.One factor that contributes to stigma is the way that the lexicon "schizophrenia" has been utilized. In one way, the word can represent the disease in a non-metaphorical utilization (denotative way), however "schizophrenia" and its derivatives (other words with the same radical schiz*), is also utilized in a metaphorical way as an adjective (connotative way) to people or things, most commonly used to refer to something negative. Media vehicles have an important role in providing the correct information about schizophrenia but also could contribute to stigma when using the lexicon in a connotative way.
The aim of this study is to identify in a Machine Learning approach the frequency and form of use of the lexicon "schizophrenia" in the last 20 years in printed media in Brazil, first identifying the frequency of denotative (non-metaphorical) and connotative (metaphorical) utilization of "schizophrenia" and then the words more frequently associated with the lexicon.

Methods: First, we selected periodicals that were part every year between 2001 and 2020 of the Communication Verifier Institute (IVC) list of the largest publications in Brazil. Then, we extracted the links from the news that contained the words with the radical "schiz*" (esquiz* in portuguese). 1,125 pieces of news were read and manually classified as metaphorical or non-metaphorical. This database served to train a neural network to classify between denotative and connotative articles in a sentiment analysis approach. After the paragraphs in which the words schizophrenia and its variants were detected, we vectorized them using a CBOW Word2vec model trained with more than a billion Portuguese words. Finally, we trained a multilayer perceptron neural network with 4 dense hidden layers to predict the class that each article belongs to. We obtained an accuracy of about 95% in a test set.
Results: From the list of periodicals with the highest circulation of publications between 2001 and 2020, there were 3 major printed newspapers: “Folha de S. Paulo”, “Estado de S. Paulo” and “O Globo”. Due to the impossibility of extracting data from O Globo, only the first two were used. Of the 4578 texts analyzed, the percentage of metaphorical uses of the searched words according to our model was 27%, varying through the years from 20% to 40%. The most frequent words associated with "schizo*" in the metaphorical context were: government (241), politics (156), country (132), Brazil (127), world (115), public (82), Lula (78), president (74), society (71) and minister (65). In the non-metaphorical context: illness (973), patients (429), treatment (367), mental (317), depression (271), symptoms (268), disorder (266) , study (249), life (249) and brain (238).
Discussion: Our study shows that in the 2 most printed journals in Brazil over the last 20 years, on average 27% of the use of "Schizophrenia" and derivatives have been utilized in a metaphorical way. Most of them are related to politics ("government", "politics, "lula", "president", "minister") and the most common, in a negative context. Several studies have shown that in different languages, the term schizophrenia has been utilized to describe metaphorical and non-metaphorical conditions. This study and methodology could automatically alert journals and other media vehicles to the use of schizophrenia in a stigmatized way.

S166. PERSONAL HEALTH BUDGET AS AN INNOVATIVE REHABILITATION INTERVENTION IN FIRST EPISODE PSYCHOSIS: A 3-YEAR FOLLOW-UP STUDY

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Background: There has recently been increasing interest in offering Personal Health Budgets (PHBs) to people with severe mental illness. However, empirical research on PHB initiatives is still limited. Aim of this observational study was to evaluate the clinical applicability of a PHB intervention model in a sample of Italian adults with first-episode psychosis (FEP) across a 2-year follow-up period.
Methods: Participants (n = 104; 18–50 years) were recruited within the 'Parma-Early Psychosis' program and completed the brief psychiatric rating scale (BPRS), the health of nation outcome scale (HoNOS) and the global assessment of functioning (GAF). Mixed-design analysis of variance (ANOVA) and Kaplan-Maier survival analysis (as drop-out measure) were performed.
Results: A significant effect of time on all BPRS, HoNOS and GAF scores along the follow-up was observed in both the FEP subgroups (i.e., with [n = 49] and without [n = 55] PHB intervention). Mixed-design ANOVA Results: showed a significant 'time x group' interaction effects on BPRS 'Disorganization', HoNOS 'Psychiatric Symptoms' and GAF scores in FEP participants with PHB. Kaplan-Meyer survival analysis showed a longer survival mean for FEP patients with PHB.
Discussion: Our Results: support the applicability of a PHB model within an 'Early Intervention in Psychosis' program in public community mental health services.

S167. THE BURDEN OF CAREGIVERS OF SCHIZOPHRENIA OUTPATIENTS DURING THE COVID-19 PANDEMIC IN SAO PAULO, BRAZIL: A COMPARISON WITH THE PRE-PANDEMIC BURDEN

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Background: The advance of the Covid-19 pandemic in Brazil, which began in February 2020, imposed huge challenges for the general population including social isolation, financial difficulties, and psychological suffering. For those with severe mental disorders these challenges were even greater as they have also to deal with the impact of the pandemic on their disease and lives. (Kosloff et al. 2020). About 3 years ago we evaluated caregiver burden in a sample of outpatients with schizophrenia from a University Hospital in Sao Paulo, Brazil (Di Sarno et al. 2021). Last year we had the opportunity to reevaluate (almost) the same sample and measure the impact of the Covid-19 pandemic on the caregivers' burden. We hypothesized that caregiver burden (both objective and subjective) increased due to the pandemic.
Methods: Of the 60 caregivers previously evaluated, reassessments could be obtained with 50 caregivers who were in contact with the patient for ≥30 hours/week. Ten caregivers could not be contacted or were not the patients' caregivers anymore. Interviews with caregivers were conducted online to respect health protection strategies. Caregivers were assessed using a Sociodemographic Questionnaire, the Family Burden Interview Schedule, Brazilian version (FBIS-BR).
An adaptation of the Clinical Global Impression-Improvement (CGI-I) was made, in which caregivers evaluate their "clinical" impression about the patient during the Covid-19 pandemic in

comparison to pre-pandemic mental status. The study was approved by our local Ethics Committee and informants gave their oral consent after full explanation about the purpose of the study.

Results: All the 50 caregivers were the patients' relatives, aged between 24 and 80 years (mean ± SD: 56.40 ± 11.26 years), 76% were females, 52% mothers of the patients, 54% were married, 58 % had completed high school, and 6% had a bachelor's degree. The time the caregivers spent with the patient during the pandemic ranged from 30 to 140 hours/week (mean ± SD: 88.56 ± 32.89 hours/week) and was not significantly different from the pre-pandemic evaluation. In the view of caregivers 46% of the patients showed no clinical change, 38% were considered minimally worse, and 10% much worse during the Covid-19.
In relation to caregiver burden there was a significant increase in the total subjective burden ($p<0.001$), but not in the total objective burden. The following subjective domains of the burden showed a significant increase: assistance in daily life ($p<0.001$) and worries about patients' present and future life ($p=0.033$).

There was a decrease in the objective burden related to supervision of patients' problematic behaviors ($p=0.031$). Although the caregiver's income did not change significantly during the COVID-19 pandemic, there was an increase in the percentage of caregivers (from 54% to 72%) who perceived the frequency of financial burden imposed by the patient as "very frequent" and "always or almost always"; conversely there was a significant decrease in the subjective perception of the caregiver that the patient imposed financially "no burden" or a "seldom burden" (from 34% to 4%).

Discussion: Although the Covid-19 pandemic did not impose an increase in the objective domains of the burden, there was a significant increase in several aspects of the subjective burden of the caregivers. As all individuals, they had to cope with the many stresses related to the changes in their lives, related to the pandemic. Recognizing their difficulties is a decisive step toward the development of public policies and community care practices that are sensitive to the needs of this population.

S168. THE IMPACT OF PSYCHOSIS IN ADOLESCENT-ONSET BIPOLAR DISORDER: A STRUCTURAL MRI STUDY

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Background: Bipolar Disorder (BD) is a major psychiatric illness defined by episodic mood changes, which in approximately 50% of cases is associated with psychotic features. Over the past decades, a large amount of research has identified brain structural and functional alterations in patients with this mental disorder. Some findings have been found to be specific to patients with

psychotic symptoms, raising suggestions that this could represent a biological subtype of the disorder. Recent interest has been addressed to Early-Onset Bipolar Disorder (EOBD, onset prior to age 18). Latest reviews in EOBD samples have pointed to abnormalities in the frontal lobe and limbic structures, with some inconsistencies in the reported Results: possibly caused by differences in the methodology. In addition, no study so far has examined the neural structural correlates of psychotic symptoms in adolescent-onset bipolar disorder (AOBD).
The aim of the present study is to examine the impact of psychosis on the neurobiological architecture in a sample of patients with AOBD. To our knowledge, this is the first study comparing gray matter structure between AOBD patients with or without psychotic features.

Methods: We conducted a cross-sectional study collecting T1-weighted structural magnetic resonance neuroimaging (3T-MRI) data in patients diagnosed with Bipolar Disorder type I or II between 12 and 19 years old (N=46, mean age (SD)=15.89 (1.94), gender=52.2% females). All patients were recruited from child and adolescent mental health services of the Hospital Clinic of Barcelona, Spain. Diagnoses were confirmed with a semi-structured clinical interview (Kiddie-Sads present and lifetime version) by child and adolescent psychiatrists.
Images were pre-processed employing FreeSurfer 5.3.0,, and data corresponding to Cortical Thickness (CTH) and Subcortical Volumes (SCV) was obtained. Groups were compared according to whether patients had experienced psychotic symptoms at any point during their illness: Non-Psychotic Bipolar Disorder (NPSBD, N=25) and Psychotic Bipolar Disorder (PSBD, N=21). No differences in age ($t=0.498$, $p=0.621$) or sex ($\chi2=0.001$, $p=0.979$). Group effects in relation to both CT and SCV were examined with a general linear model. The main effect of group on CTH and SCV, was performed for the whole brain, performing a correction for multiple comparisons (Montecarlo correction, threshold = 0.05).

Results: Between-group analyses showed smaller CTH in a cluster in the left medial orbitofrontal cortex (cluster size= 1142.58 mm2) in PSBD relative to NPSBD (x, y, z: 25.63, 89.61, -42.74; $p=0.002$). In addition, we observed a smaller right hippocampus volume ($p=0.025$) in PSBD relative to NPSBD. No other statistically significant differences were obtained.
Discussion: PSBD showed smaller cortical thickness in the left medial orbitofrontal cortex, as well as a volumetric reduction in the right hippocampal volume. Similar Results: have been reported in a study comparing adolescent patients with psychotic BD and healthy controls6. These Results: add evidence about the role of these two structures in the genesis of psychotic symptoms in a population diagnosed with AOBD. Interestingly, one study has reported a surface area decreased of the orbitofrontal cortex in adolescent patients with a non-bipolar psychotic disorder, which suggests that they may be a common substrate to psychotic symptoms during adolescence regardless of co-occurring affective symptoms.

In summary, this study points to the existence of a distinct biological nature between bipolar patients according to psychotic symptoms, underpinned by a different neurobiological architecture. Future research should focus on replication and on examining the clinical value of this finding.

S169. NEUROFILAMENT LIGHT (NF-L), GLIAL FIBRILLARY ACIDIC PROTEIN (GFAP), AND S100 CALCIUM BINDING PROTEIN B (S100B) SHOW LITTLE POTENTIAL AS BIOMARKERS FOR FIRST EPISODE PSYCHOSES

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Background: NeuroFilament Light (NF-L), Glial Fibrillary Acidic Protein (GFAP) and S100 calcium-binding protein B (S100B) are well established markers of neuronal (NF-L) and astrocytic-glial (GFAP, S100B) injury.
NF-L is a cytoskeletal intermediate filament protein expressed in neurons. The neurofilaments; light, medium and large, are major components of the neuronal cytoskeleton and are elevated in the blood succeeding neuronal damage. NF-L has been used as a marker for disease monitoring in amyotrophic lateral sclerosis, multiple sclerosis, and Alzheimer's disease.

Glial fibrillary acidic protein (GFAP)is predominantly expressed in astrocytic glial cells in the central nervous system. GFAP is involved in CNS cell communication and in the functioning of the blood brain barrier. Elevated levels of GFAP has been associated to traumatic brain injury, stroke, and brain tumors. Decreased GFAP expression has been reported in schizophrenia, bipolar disorder, and depression.

The protein S100B is involved in several intra- and extracellular regulatory processes and is primarily expressed by astrocytic glial cells in the central nervous system (CNS). S100B peripheral concentration has been correlated to acute head trauma and encephalitis.

In a cohort of antipsychotic-naïve patients with first episode psychoses, we here explore if these biomarkers can inform about the pathophysiology of schizophrenia.

Methods: Serum samples were collected from fasting patients as well as healthy controls. Patients subsequently underwent 6 weeks of aripiprazole monotherapy and fasting serum was collected again. Serum was stored at -80 degrees Celsius before being analyzed. NF-L and GFAP concentrations where obtained through the digital immunoassay Simoa© Human Neurology 2-Plex B assay (N2PB). S100B concentration was determined using Cobas© Elecsys s100 Electrochemiluminescence-immunoassay (ECLIA).
As a part of the clinical examination, patients were interviewed by trained clinicians and rated using the Positive and Negative Symptom Scale (PANSS) both at baseline and after 6 weeks of treatment.

All concentrations were logarithmically transformed to reduce skewness of data. Pearson correlations were calculated to test for correlation. Within patients we tested for correlation with psychopathology.

Results: No differences in NF-L, GFAP or S100B concentrations between patients with firs episode psychoses and healthy controls were found. Neither at baseline nor after 6 weeks of aripiprazole treatment (patients only). No correlations between the NF-L, GFAP or S100B and PANSS measures at baseline and after treatment was found.

We found an age effect of NF-L (r= 0,283 P=0,003) in the full sample. When examined in healthy controls and patients separately, only patients exhibit this age-related effect (r=0,403 P=0,001). No effect of sex or BMI was observed.

Discussion: No group-difference was found; thus we find no clear evidence that NF-L, GFAP or S100B are biomarkers of schizophrenia. The age-related effect observed in the patient subpopulation may reflect an age-related neurodegenerative acceleration amongst the patients suffering from schizophrenia. To further investigate this finding we plan to include longitudinal data from a similar study.

S170. THREAT-BASED MECHANISMS UNDERLYING RISK OF PSYCHOSIS ASSOCIATED WITH DEVELOPMENTAL TRAUMA: AN INTERNATIONAL BEHAVIOURAL STUDY

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Background: There is growing evidence that experiencing developmental trauma, including abuse and neglect during childhood and adolescence, is causally associated with an increased risk of psychosis in adulthood [1]. However, an understanding of the precise mechanisms underlying this is lacking. In light of consistent and compelling evidence for aberrant threat processing in adult survivors of developmental trauma, as well as its involvement in the development of psychotic symptoms that are threatening in nature, aberrant threat processing is a candidate vulnerability mechanism underpinning trauma-induced vulnerability to psychosis [2]. In this international study, we investigated whether, in adult survivors of developmental trauma, alterations in threat attention, threat recognition and threat response - three dissociable components of threat processing – are associated with an increased vulnerability to psychotic symptoms.

Methods: Participants (n=1488) recruited from the United Kingdom (UK) and the Republic of Korea (ROK) were orthogonally assigned to one of four groups depending on exposure to developmental trauma (Childhood Trauma Questionnaire) and presence of psychotic symptoms (Community Assessment of Psychic Experiences). These included adult survivors of developmental trauma with (Psy+DT+; UK n=301, ROK n=351) and without subclinical psychotic symptoms (Psy-DT+; UK n=142, ROK n=234), and adults without experiences of developmental trauma with (Psy+DT-; UK n=45, ROK n=61) and without (Psy-DT-; UK n=151, ROK n=203) subclinical psychotic symptoms. Participants completed separate tasks on an online experimental platform (Gorilla.sc) 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.

Results: In both UK and ROK samples on the emotional recognition task, Psy+DT+ demonstrated significantly lower discriminability for angry faces compared to Psy-DT- (UK t459 = 2.75, p=.029; ROK t717 = 3.49, p=.002) and Psy-DT+ (UK t448 = 3.89, p=.001; ROK t758 = 2.66, p=.044). Also, in both international samples, Psy+DT+ endorsed more negative valence responses for neutral faces than Psy-DT- on the facial affect ratings task (UK t459 = 3.66, p=.001; ROK t717 = 6.41, p=<.001). We observed no differences between groups in the emotional dot probe task. Mediation analyses on the combined sample revealed that both discriminability for angry faces (indirect effect: .012, 95% CI = [.003, .02], p<.01) and valence responses for neutral faces (indirect effect: .023, 95% CI = [.01, .04], p<.01) had a significant mediating effect on the relationship between development trauma and psychotic symptoms.

Discussion: In this large international study, we find that adult survivors of developmental trauma with psychotic symptoms demonstrate impaired emotional recognition of threatening (angry) faces and more negative valence responses to neutral faces. Importantly, these alterations in threat processing partially mediate the relationship between developmental trauma and psychotic symptoms. In sum, the present study provides behavioural evidence supporting the hypothesis that alterations in threat processing contribute to vulnerability to psychotic symptoms in individuals with developmental trauma [3].

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VIRTUAL POSTERS

V1. THE PHENOMENOLOGY OF VISUAL AND OTHER NON-AUDITORY HALLUCINATIONS IN AFFECTIVE AND NON-AFFECTIVE PSYCHOSIS: A MIXED METHODS ANALYSIS

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Background: Non-auditory hallucinations in psychosis have not received as much clinical and research attention to date, relative to voice-hearing experiences. The current paper aimed to quantitatively and qualitatively document the characteristics of visual, tactile and olfactory hallucinations in affective and non-affective psychosis.
Methods: Participants were selected from a primary voice-hearing sample, who had endorsed visual or other non-auditory hallucinations (N=75). A comprehensive, semi-structured phenomenological interview was conducted, followed by mixed methods analysis. For the comparative analysis, participants were subdivided into those with affective (n=33) and non-affective (n=42) psychosis.
Results: Visual hallucinations typically occurred at least than once a day; lasted for a few minutes per episode; localised within one's direct line of sight; with no specific time pattern of occurrence; persons and/or animals being most commonly seen; with low controllability and compliance with perceived commands; and mostly engendered negative affective outcomes. The affective psychosis group reported significantly better awareness and lower functional impairment relative to the non-affective psychosis group. Qualitative thematic analysis revealed notable primary and secondary themes across each of these hallucinations modes.
Discussion: It was concluded that further phenomenological investigations need to be carried out regarding tactile, olfactory, gustatory and other lesser known hallucination modalities, assisted by the development of appropriate assessment tools.

V2. GRAY MATTER CONNECTOME ABNORMALITIES IN NEVER-TREATED SCHIZOPHRENIA

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Background: Convergent evidence is increasing to indicate progressive brain abnormalities in schizophrenia. However, the nature of connectome level changes and the degree to which drug effects contribute to such changes are not clear. Gray matter network has been shown to be highly heritable and may reveal more stable phenotypes related to altered anatomical organization. A systematic evaluation of how the gray matter network changes at the individual level in schizophrenia patients across a large age span without confounding effects of medication would extend our sight of brain changes over the course of the disorder.
Methods: This study was approved by the research ethics committee of West China Hospital of Sichuan University, and written informed consent was obtained from participants or their legal guardians if they were under 18 years old. A total of 237 never-treated patients with schizophrenia (including 202 first episode drug-naïve patients and 35 long-term ill but never-

treated patients) and 254 healthy controls with matched demographic information for these two subgroup of patients were recruited. High-resolution T1 weighted images with a voxel size of 1×1 ×1 mm3 were obtained for all participants with a 3.0T MR scanner. Gray matter networks were constructed individually based on the similarities of regional gray matter measurements, where similarity was determined by the maximal correlation between two cubes over different rotations. The resulted networks were normalized with the Automated Anatomical Labeling (AAL) template, yielding a 90×90 normalized weighted gray matter similarity network for each subject. Network metrics at the global level and the nodal level were compared between patients and healthy controls, and relationships of duration of untreated psychosis (DUP) to network abnormalities were examined. To identify differential relationships between gray matter connectome measures and age in metrics where group differences had been detected, the global and nodal network metrics with significant intergroup differences were exacted for each subject, and modeled with age using a quadratic model for each group. This was done because the age effects on the brain are known to follow a non-linear trajectory. The models that achieved statistical significance in either group were compared across groups to determine whether there exists a significant differential rate of age-related changes between patients and controls.

Results: Nodal centrality abnormalities were observed in patients with untreated schizophrenia, particularly in the regions within central executive (CEN), default mode (DMN) and salience networks (SN). DUP-related declines were observed in global assortativity, and in nodal metrics of right anterior cingulate gyrus and superior temporal gyrus, left thalamus, and bilateral superior temporal pole (STP). In the age-modeled regression analyses, comparison of regression models between age and abnormal network metrics that achieved statistical significance in either participant group revealed significantly accelerated age-related declines in assortativity at the global level ($p=0.040$), and in the betweenness ($p<0.001$), degree ($p=0.013$) and Ne ($p=0.037$) of right ACG, and degree of left STP ($p=0.009$) in schizophrenia patients relative to healthy controls.

It is of interest that some network metrics were increased across all schizophrenia patients (e.g., nodal metrics in bilateral STP and left thalamus), but exhibited DUP-negative changes or age-related decline. Therefore, different pathophysiological processes might be implicated in these altered network metrics at different stages of illness. To further examine the hypothesis, abnormal network metrics were identified separately in short- and long-term patients in the secondary analysis. We found that, the global assortativity that was increased in the whole patient group was higher in the short-term ill patient group than controls, but did not differ between long-term ill patients and matched control subjects. With regards to increased nodal metrics that were found in the overall patient group, relative to healthy controls, nodal properties of left thalamus and right STP were significantly higher in short-term ill patients, but were significantly lower in long-term patients. Nodal properties of the left STP were significantly higher in short-term ill patients, but comparative to long-term patients when compared to healthy controls. These findings indicated potential progressive decline of the gray matter network metrics in left thalamus and bilateral STP in untreated schizophrenia patients.

Discussion: The novel age-related alterations in the anatomic brain connectome, indicated a distinct pattern of effects in temporal cortex and thalamus, which were most typically in the form of increased nodal roles in the brain connectome early in the illness course and declines in nodal connections later in the illness course. The decrease of nodal metrics in CEN, DMN and SN seen at both early and later illness course might represent a disease trait that is maintained over the illness course.

V3. ADAPTING A COGNITIVE BEHAVIORAL SUICIDE PREVENTION TREATMENT FOR ADULTS WITH SCHIZOPHRENIA SPECTRUM DISORDERS

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Background: Suicide is among the leading causes of death for adults with schizophrenia spectrum disorders (SSPDs) and suicide risk estimates are eight times greater than among the general population. There is a gap in evidence-based interventions to reduce suicide among adults with a tailoring need for SSPDs. Cognitive Behavioral Suicide Prevention for psychosis (CBSPp) is an innovative and promising intervention, yet our experience, findings of prior studies, and collaborations with the developer have informed our plan to modify and tailor CBSPp for the US public mental health context, particularly in an outpatient community mental health treatment setting where evidence-informed interventions can be challenging to implement This paper presents on the methodology and process of modifying a cognitive-behavioral suicide prevention treatment for adults with psychosis in a community mental health (CMH) setting using community based participatory research methods.

Methods: Stakeholder data collection and CBSPp modification took place as part of a National Institute of Mental Health (NIMH)-funded pilot effectiveness clinical trial (R34) to modify and preliminarily test a cognitive-behavioral suicide prevention treatment for adults with psychosis in a CMH setting in Michigan. This abstract presents on Aim 1 modification prior to Aim 2 testing in a trial. Stakeholder participants (n=25) included 6 clients, 7 peer advocates, and 12 mental health providers of CMH. All stakeholders were over the age of 18 and clients met criteria for having a SSPD and suicide ideation within 3 months. All completed a survey and qualitative in-depth interview with research staff to explore the need for this treatment, barriers, sustainability facilitators, and areas for improvements. Qualitative interviews were transcribed, coded in Dedoose using an open-coding technique to generate themes across questions, and analyzed using grounded theory methods. Stakeholder findings were presented to a panel of scholarly experts in the fields of suicide and psychosis research, intervention research, and implementation science for input and modification suggestions. Stakeholder data was also shared with stakeholders for accuracy (member checking) and additional feedback prior to modifications. The investigative team decided upon modifications and systematically carried out changes prior to sharing the adapted treatment manual and delivery protocol with expert panel members for additional feedback.

Results: Stakeholder providers were on average 35.67 years of age (SD=6.387), peers 51.71 years of age (SD=7.017), and clients 45.33 years of age (SD=11.02). All providers were trained in the field of social work. Stakeholders agreed there was a need for this treatment in CMH, clients indicated they would want the treatment, and providers expressed interest in being trained to deliver the treatment. Emerging barrier themes included logistic (e.g., time, provider availability, technology access), perceptual (e.g., need for treatment, motivation, and stigma), and clinical (e.g., psychosis symptoms and co-occurring substance use) challenges perceived by clients, peers, and providers. Sustainability facilitator themes included buy-in (i.e., client, provider, and agency), promising client outcome data (e.g., testimonials), and provider support (e.g., ongoing supervision and training). Final modifications include: 1) tailoring CBSPp content and protocol (i.e., shorten treatment to 10 weeks, safety planning, coping cards, ecological approach to assessment, self-esteem, social support, tailoring options for providers with suicide being primary and cognition being variable, assessment of suicide intent given non-suicidal self-injury, and generate new manual), 2) provider training (i.e., cohort-based hybrid training curriculum, supervision, and training boosters), and 3) enhancing client

engagement to boost content and provide added support to clients (i.e., text messages, videos, and treatment website).
Discussion: Findings highlight the logistic, perceptual, and clinical challenges perceived by clients, peers, and providers in the process of introducing this treatment in a CMH setting. Consistent with literature, champions among leadership, provider and organizational buy-in, and provider support in the delivery of a new treatment emerged as important factors in modification, implementation, and sustainability. Collaborations with CMH and involving of stakeholder perspectives, researchers, and scholarly experts using CBPR methods have been essential in navigating implementation barriers with an overall goal of improving access, feasibility, and quality of CBSPp. Continued efforts for researchers to utilize CBPR methods in approaches to modify evidence-based psychosocial treatments are needed to increase the effectiveness of population-focused tailoring and improve delivery so treatment innovations are feasible, acceptable, useful, and scalable in behavioral health settings. CBPR methods are particularly critical in modification efforts for populations alike the current study with serious mental illness and SSPDs in which stigma, marginalization, health disparities, and low service utilization rates are common.

V4. AUDIOVISUAL TEMPORAL PROCESSING IN PEOPLE WITH FIRST-EPISODE SCHIZOPHRENIA AND HIGH-FUNCTIONING AUTISM

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Background: Audiovisual temporal processing is essential for everyday functioning. The neural system processes temporal information of the two sensory modalities, and determines whether the audiovisual stimuli are synchronous or not. Schizophrenia patients exhibited widened audiovisual temporal binding windows (TBWs), which may contribute to aberrant perception and hallucinations. In patients with ASD, the TBWs can be widened or narrowed. Previous studies seldom directly compared schizophrenia patients with ASD patients in TBWs. This study aimed to examine the similarities and differences in TBWs between schizophrenia patients and ASD patients.
Methods: Forty-three patients with first-episode DSM-IV schizophrenia, 35 patients with high-functioning ASD and 48 controls completed two paradigms, i.e., the unisensory Temporal-Order-Judgment (TOJ) task and the multisensory audiovisual Simultaneity-Judgment (SJ) task. The TOJ and SJ tasks generated data for estimating the stimulus onset asynchronies (SOA) threshold and audiovisual TBWs on a participant-by-participant basis. ANOVAs were used to compared the SOA threshold and TBWs (for speech and non-speech stimuli) between schizophrenia patients, high-functioning ASD and controls. Spearman's correlations were conducted to examine the relationship between TBWs and clinical symptoms in schizophrenia patients.
Results: First-episode schizophrenia patients exhibit widened TBW affecting both speech and non-speech processing, relative to controls. The widened TBW in schizophrenia could not be attributable to unisensory deficits, because schizophrenia patients and controls showed comparable SOA thresholds. patients with high-functioning ASD exhibit comparable TBWs

and unisensory thresholds to healthy people. The TBW was not correlated with clinical symptoms in schizophrenia patients.
Discussion: This is one of the pioneer studies investigating audiovisual temporal processing in schizophrenia and ASD. Whilst schizophrenia is associated with widened TBWs, high-functioning ASD patients had comparable TBWs to controls. Low IQ in other ASD samples may be a confound in previous research on TBWs.

V5. QUALITY OF LIFE APPRAISED BY PERSONS WITH SCHIZOPHRENIA AND THEIR PROFESSIONAL CAREGIVERS: A PSYCHOMETRIC NETWORK ANALYSIS IN A NATIONAL COHORT

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Background: Agreement on central aspects of life and treatment between professional mental health caregivers and their patients is regarded as a significant facet of mental health care and closely related to positive treatment outcomes. However, most inter-personal appraisal studies have shown that mental health patients and their professional caregivers tend to disagree on central aspect of life.
Disagreement between patients and professional mental health caregivers is associated with negative implications for treatment outcomes.

The current study will focus on quality of life appraisals, a desirable outcome of mental health care. Studies examining inter-personal appraisals of mental health related quality of life are limited and are mostly focused on small samples of patients diagnosed with schizophrenia. Existing literature shows that disagreement on quality of life between patients and professional mental health caregivers is common.

To date no study has examined the differences in structure of inter-personal appraisals of mental health related quality of life in schizophrenia. The structure of mental health related quality of life may be elaborated on by using psychometric network analysis. Psychometric network analysis can be used to identify an inter-related system of quality of life appraisals and can account for complex interactions between them. It may be used to identify clusters of quality of life appraisals, and highlight the extent that each type of appraisal is central to the general construct of quality of life.

Therefore, the current study aims to examine the structure of mental health related quality of life, focusing on appraisals by persons with schizophrenia and their professional mental health caregivers, using psychometric network analysis.

Methods: The current study inclusion criteria were all participants with a last diagnosis of schizophrenia (N=1639) who received national psychiatric rehabilitation services in Israel. Primary professional caregivers (N=582) were given instruments that mirrored the one designed for self-appraisals.
Mental health related quality of life was measured and validated based on the Manchester Short Assessment of Quality of Life (MSA-QoL). Eight items measured satisfaction with one's work or volunteering activities, financial status, social status and activities, family relations, leisure activities, residential status, physical health condition and mental health condition (one item per life area).

Psychometric network analysis was computed in R with the the qgraph and R libraries using standard guidelines. Two quality of life models were created: one for persons with schizophrenia ('self-appraised', hereafter) and another for their professional mental health caregivers ('caregiver-appraised', hereafter). Networks were then plotted to visually present structure. Communities (defined as clustered groups of nodes) within networks were identified using the Walktrap algorithm. Differences in global strength were computed as the deviation in absolute weighted sum scores of the connections. Node level differences between the self-appraised and caregiver-appraised networks were computed with standardized strength centrality indices.

Results: The self-appraised network comprised of two communities. These were labeled as health conditions (physical and mental health), and socioeconomic system (work activities, residential status, financial status, family relations, social status and activities, leisure activities). The caregiver-appraised network communities differed from those of the self-appraised network. While distinguishing a unique community of social activities (social status and activities and leisure activities), the health related and socioeconomic related communities merged (physical and mental health conditions, work activities, residential status, financial status, family relations).
The self-appraised network and caregiver-appraised network significantly differed ($P<0.001$) in global strength and maximum difference in edge weights ($M=0.26$, $P<0.01$). The caregiver-appraised network (global strength value=3.12) was more strongly connected than the self-appraised network (global strength value=2.90).

Strength centrality was highest for self-appraised social status and activities, followed by mental health condition and physical health condition, while for the caregiver-appraised network strength centrality was highest for residential status, followed by financial status and leisure activities.

Discussion: This national study aimed to examine the structure of mental health related quality of life appraisals made by persons with schizophrenia and their professional caregivers, by using psychometric network analysis. Results contribute to the existing literature by showing that self-appraised and caregiver-appraised quality of life assumed different structures.
The two networks differed in structure (since each network had its own unique quality of life clusters), strength and central elements.

These findings are in line with previous knowledge, which states that quality of life appraisals by mental health patients and corresponding appraisals by caregivers are distinct types of constructs.

V6. ELUCIDATING MECHANISMS OF SOCIAL COGNITIVE DEFICITS THROUGH FMRI AND BAYESIAN LATENT VARIABLE ANALYSIS

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Background: Eye gaze perception is associated with individual differences in social functioning and is impaired in schizophrenia, and social cognitive deficits in schizophrenia have been related to altered functioning in brain networks such as the mirror system (e.g., IPL

and STS) and mentalizing system (e.g., TPJ, mPFC, and PCC). Many of these brain regions are also key nodes of the default network, which has been linked to individual differences in social functioning and psychosis risk. However, few studies have directly investigated neural mechanisms of gaze perception and their relationship to social cognitive functioning and psychopathology. We address this research gap using a combination of fMRI, psychophysics, Bayesian analysis, and latent variable modeling.

Methods: During fMRI, patients with schizophrenia or schizoaffective disorder (N = 75) and healthy controls (N = 71) completed a gaze perception task during which they viewed faces with varying gaze angles and made eye-contact judgments (i.e., whether each face was self-directed). Behavioral responses were modeled as a function of gaze angle; the width of each participants' performance curve was estimated using hierarchical Bayesian modeling and used to index their perceptual sensitivity. Brain activation was compared between the gaze task and a control condition (where participants identified stimulus gender) and parametric modulation was computed, based on participants' endorsement of each stimulus as containing self-directed eye contact or not. Beta values were extracted from regions of interest (ROIs) identified as significantly activated across the full sample, for each of two contrasts (gaze vs. gender and eye-contact endorsement modulation). Next, Bayesian Structural Equation Modeling (BSEM) was used to model a social cognitive ability latent factor, operationalized as shared variance of scores on the gaze perception task, Reading the Mind in the Eyes, Penn Emotion Recognition, Questionnaire for Cognitive and Affective Empathy, and Mayer-Salovey-Caruso Emotional Intelligence Test. Three models were computed to test associations of diagnostic group with 1) social cognition, 2) activation during gaze vs. gender trials, and 3) modulation of activation by eye-contact endorsement. Subsequent models tested full-sample associations of social cognition with 4) activation during gaze vs. gender trials and 5) modulation of activation by eye-contact endorsement.

Results: Modeling social cognition as a single latent factor fit the data well, and all observed variables loaded significantly onto the social cognition factor ($p < .01$). Compared to healthy controls, patients had significantly worse social cognition ($p < .001$). Across participants, significant activation during gaze perception and modulation of activation by eye-contact endorsement was observed in brain regions associated with social cognition (e.g., IPL, STS, mPFC, and PCC). Activation and modulation metrics were not significantly associated with diagnostic group ($p's > .05$). Across the full sample, better social cognition was associated with modulation by eye-contact endorsement in the left and right IPL ($\beta = -.451$, $p = .001$; $\beta = .432$, $p = .003$), as well as by the gaze vs. gender contrast in PCC ($\beta = .490$, $p = .002$) and clusters throughout mPFC ($\beta = -.402$, $p = .004$; $\beta = .435$, $p = .001$; $\beta = -.513$, $p = .001$). ROI activation parameters explained substantial variance in social cognitive ability, using either the gaze vs. gender contrast ($R^2 = .600$, $p < .001$) or modulation by eye-contact endorsement ($R^2 = .659$, $p < .001$).

Discussion: Results link individual differences in social cognition to brain activity during a gaze perception task. This bolsters evidence for the role of default network regions such as the IPL, mPFC, and PCC in social processing and individual differences in social cognitive ability. Results also replicate previous findings of social cognitive deficits in patients with schizophrenia, using multiple tasks and an innovative Bayesian approach to latent variable modeling. This work is in line with initiatives such as the National Institute of Mental Health's Research Domain Criteria (RDoC) and the Hierarchical Taxonomy of Psychopathology (HiTOP), characterizing trans-diagnostic features and neurobehavioral mechanisms of psychopathology and associated functional impairments (i.e., social cognitive deficits). Future work should employ further detailed behavioral phenotyping (e.g., experience sampling), combined with multidimensional computational models of social cognition and analysis of

brain connectivity, to further elucidate mechanisms of social cognition and their impairment in schizophrenia and other forms of mental illness.

V7. THE STRESS-VULNERABILITY MODEL ON THE PATH TO SCHIZOPHRENIA: INTERACTION BETWEEN BDNF METHYLATION AND SCHIZOTYPY ON THE RESTING-STATE BRAIN NETWORK

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Background: The interplay between schizophrenia liability and environmental influences has been considered to be responsible for the development of schizophrenia. Recent neuroimaging studies have linked aberrant functional connectivity (FC) between the default-mode network (DMN) and the frontoparietal network (FPN) in the resting-state to the underlying neural mechanism of schizophrenia. By using schizotypy as the proxy for genetic-based liability to schizophrenia and methylation of brain-derived neurotrophic factor (BDNF) to represent environmental exposure, this study investigated the impact of the interaction between vulnerability and the environment on the neurobiological substrates of schizophrenia.
Methods: Participants in this study included 101 healthy adults and 46 individuals with ultra-high risk for psychosis (UHR). All participants were tested at resting-state by functional magnetic resonance imaging, and group-independent component analysis was used to identify the DMN and the FPN. The Perceptual Aberration Scale (PAS) was used to evaluate the schizotypy level. The methylation status of BDNF was measured by pyrosequencing.
Results: UHR individuals showed reduced DMN-FPN network FC compared to healthy controls. PAS scores significantly moderated the relationship between the percentage of BDNF methylation and DMN-FPN network FC. The strength of the positive relationship between BDNF methylation and the network FC was reduced when the schizotypy level increased.
Discussion: These findings support the moderating role of schizotypy on the neurobiological mechanism of schizophrenia in conjunction with epigenetic changes.

V8. SEMANTIC SPEECH NETWORKS CAPTURE ABNORMAL SPEECH IN PSYCHOSIS

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Background: A core symptom of schizophrenia is formal thought disorder, manifesting in subtle changes of the patient's speech which can appear incoherent and disorganized (Liddle et al., 2002). Deep phenotyping of schizophrenia using speech data could significantly further our understanding of the condition, with the potential to revolutionise healthcare for this debilitating disorder (Bedi et al., 2015).
Graph theoretical tools have been used to measure disorganised syntax in speech transcripts from patients with psychotic disorders (Mota et al., 2012; Mota et al., 2014; Mota et al., 2017). However, existing graph theoretical tools largely ignore the semantic content of speech, which has been shown to be altered in patients with psychotic disorders (Corcoran et al., 2018). We therefore developed an algorithm that maps semantic content of speech as a network and analysed the network using graph theory.

Methods: Our tool uses Natural Language Processing (NLP) to construct semantic speech networks from transcripts of spoken text (e.g. I see a man). Nodes represent entities (e.g. I, man) and edges represent relations between nodes (e.g. see). We have released our tool as an openly available Python package, Networks of Transcript Semantics (netts). The tool is fast, taking approximately 40 seconds to construct a network from 1 minute of transcribed speech. It is also robust against artefacts typical for transcribed speech, such as interjections (Um, Ah, Err) and word repetitions (I think the the man). The algorithm therefore lends itself to the automated construction of speech networks from large datasets.
Here, we used netts to characterise the properties of speech networks from a general population sample (N = 436), as well as to test for group differences in a clinical sample consisting of healthy participants (N = 13), first episode psychosis patients (N = 16) and subjects at clinical high risk of psychosis (N = 24). We then explored whether semantic network properties were related to symptom scores, Thought and Language Index scores and other computational markers of Formal Thought Disorder, for example semantic coherence.

Results: Semantic speech networks from first episode psychosis patients performing a picture description task were more fragmented than those from healthy control subjects: in other words they included more, smaller connected components. The semantic speech networks of participants at clinical high risk showed fragmentation in between first episode psychosis patients and healthy controls: the mean size of connected components was larger in clinical high-risk networks than in first episode psychosis patient networks, whereas the median size of connected components was smaller in clinical high-risk networks than in healthy control networks. A clustering analysis suggested that semantic speech networks captured novel signal not already described by existing NLP measures. We also observed associations between the number and size of connected components in semantic speech networks with symptom scores and scores on the thought and language index, though these did not survive correcting for multiple comparisons.
Discussion: The semantic speech networks proposed here provide a useful framework for mapping the semantic content of speech in more detail than previously possible. Given the richness of information contained in the networks and the low computational cost and free availability, we hope that the tool will inspire other researchers to explore this new perspective on how the core symptom of disorganized speech manifests in psychotic disorders.

V9. TOWARD A CULTURAL, RELATIONAL, AND COMMUNITY-ENGAGED APPROACH TO EARLY PSYCHOSIS INTERVENTION PROGRAMS IN BRITISH COLUMBIA, CANADA

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Background: Previous research has highlighted the importance of engaging people with lived experience of psychosis (PWLEp) in the knowledge creation process and outlined steps researchers can take towards dismantling structural barriers to participation. Community-engaged research (CER) is one such approach, which implements partnerships between community members and academics to design, implement, and sustain interventions that better fit community needs and address the complex health issues of marginalized populations. Using CER, our majority-PWLEp research team aims to address an identified gap in early psychosis intervention (EPI) research and service delivery regarding engagement with young people's cultural beliefs and communities in British Columbia, Canada. The purpose of this presentation will be to discuss our experiences and vision for conducting community-engaged research and how we navigated the challenges and successes that emerged in each phase of this project.
Methods: We will present the first three phases of this ongoing research study and discuss our successes and challenges in conducting CER in each phase. This includes the first phase, where we co-developed our research question and our grant application; the second phase, where we conducted a scoping review of the literature on early psychosis and culture; and the third phase, where we developed our ethics application, survey, and dialogue protocol that will be used in our fourth phase. In the fourth phase of this study, we plan on sharing and validating our review and survey findings in a series of iterative deliberative dialogues with important stakeholders (e.g. mental health providers, researchers, family members, youth with living and lived experience of psychosis).
Results: In phase 1, our successes included initial introductions at peer-led EPI Alumni panel meetings, where discussion happened freely between peers, clinicians, and researchers, formally hiring research assistants who are PWLEp, and building a majority-PWLEp research team. Research questions emerged organically over a 12-month period and relationships were developed such that team members felt comfortable and safe. Barriers included hierarchical structures of research institutions, pay inequity, and funding neither designed for, nor conducive to, peer-led research. In phase 2, not all team members had the same research experience conducting a scoping review, so it was important to support the learning process through frequent team meetings to build these research skills. One example of building these research skills included working closely with a university librarian on how to use Covidence software and reviewing scoping review methodology and best practices. Our team meetings allowed for the team to become more cohesive and for members to synergize ideas from each of our unique points of view. All team members were involved in every step of the review, including co-developing search terms, inclusion/exclusion criteria, and reviewing abstracts and full-text reviews. In phase 3, collaborative creation of the ethics application, survey, and dialogue protocol was one of our successes, but it was also time consuming, and without more substantial funding, we are limited to 1 hour weekly meetings.
Discussion: Our experiences highlight important outcomes for CER, such as the reciprocity of learning between all team members, authentic collaboration with PWLEp in every part of knowledge creation, and empowering communities through the sharing of skills and resources. In CER, people from diverse backgrounds who might otherwise be excluded from research institutions are instead supported to develop skills and experiences that are transferable to different contexts. However, our experiences also revealed ways in which researchers conducting CER may struggle to avoid reproducing systemic inequalities (for example, pay inequity).

V10. A 20-YEAR PROSPECTIVE ANALYSIS OF THE MULTIMODAL DIMENSIONS OF DELUSIONAL REALITY

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Background: Delusions tend to be episodic in nature and vary in prevalence, severity, and dimensionality over the individual's lifespan. Many research groups, including the Chicago Longitudinal Study, have clarified a broad range of relevant features that characterize these temporal dynamics. Less clear, however, is how the individuals switch delusional category in different delusional episodes and which delusional category types are most likely to recur in the same individual over a lifespan. The current study seeks to clarify these features and to probe the common thread of enhanced meaningfulness and the potential sources that underlie these aberrant sensory or perceptual dynamics. Delusions are a transdiagnostic phenomenon that exist along a continuum in the general population, schizophrenia, affective-psychosis (AP), delusional disorder, obsessional disorders, and other neurological conditions. Delusional beliefs are a complex heterogeneous phenomenon that can vary in intensity, stability, and dimensional attributes in which the boundaries between ordinary everyday beliefs and delusional beliefs can be experienced as clearly demarcated, fuzzy, or indistinguishable, highlighting the difficulty in and changing definition of delusional reality.

Methods: All individuals were evaluated at index and at one of six sequential follow-ups over 20yrs in the Chicago Longitudinal Study. We evaluated 16 types of delusions that were further categorized as either thought delusions (thought withdrawal, insertion, broadcasting, dissemination, referential, made feelings, made impulses, and made volitional acts) or thematic delusions (somatic, persecutory, guilt/sin, nihilistic, grandeur, religious, sexual, or fantastic). We also examined the number of delusions at each follow-up and in instances of only one delusion the timepoint was categorized as mono-delusion, whereas the presence of multiple delusions the timepoint was categorized as poly-delusion. We also examined the probability of reoccurrence and the relationship between delusions and hallucinations, depression, anxiety, and negative symptoms.

Results: The sample consisted of a total of 262 individuals with one or more follow-up evaluation and met diagnostic criteria for schizophrenia (n=151) or Affective Psychosis (n=111). The mean values of thought, thematic and all delusions were calculated at each follow-up. We show that thought delusions are significantly different by diagnostic category at all follow-ups except at the 10-year. Thought delusions fluctuate over time showing an overall decreasing pattern, however the test statistic for follow-up was not significant. Thought delusions in individuals with schizophrenia were slightly worse at the 20yr follow-up as compared to baseline, although not statistically significant. Thematic delusions show a decreasing pattern regardless of diagnostic category and the test statistic for follow-up was significant. Group differences were significant at the 2, 4.5 and 15yr follow-up time-points. The prevalence and severity of thought and thematic delusions combined show a similar decreasing trend for both groups yet there was no significant pattern over time. Individuals with schizophrenia experienced increased mono and poly thought-delusions; whereas individuals with AP experienced increased mono-thematic delusions. Next, we calculated the probability of experiencing the same type of delusions at a subsequent follow-up. Within individuals with schizophrenia, referential, persecutory, and thought dissemination show the highest probability of recurrence; whereas made impulses show the lowest probability of recurrence. Individuals with AP show the highest probability of recurrence in delusions of grandeur, thought dissemination, persecutory, and referential; whereas guilt/sin, made impulses, and thought withdrawal show the lowest probability of recurrence. The combined sample show the highest probability of recurrence of referential, persecutory, and thought dissemination; whereas made impulses show the lowest probability of recurrence. The

stickiness of the composite scores show that in individuals with schizophrenia the probability of recurrence of a thought delusion was 33%, thematic delusion was 38%, and any delusion was 45%. In individuals with AP the probability of recurrence of thought delusions was 14%, thematic delusion was 28% and any delusion was 29%. The combined sample show the probability of recurrence of a thought delusion was 35%, thematic delusion was 35% , and any delusion was 38%. Hallucinations are the strongest indicator for thought, thematic, and overall delusions.

Discussion: The formation and maintenance of delusions is a dynamic construct consisting of sensory, perceptual, cognitive, emotional, social, and somatic factors that form the dimensions of delusional reality. Delusional content varied overtime. Given the significant associations between delusions and hallucinations, future participatory research is needed to better define and align subjective and objective perspectives. Our research also points to the need for future clinical interventions that specifically evaluate and target the co-existence and intermingling of delusions and hallucination.

V11. EFFECTS OF CLOZAPINE ON CORTICAL INHIBITION

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Background: Preclinical and clinical studies reported cortical inhibition deficits in schizophrenia. There are few studies evaluating the effects of antipsychotics on cortical inhibition. The purpose of this study is to investigate the effects of 90-120 days of clozapine treatment on TMS parameters and to compare them with healthy controls. There is only one prospective study about the effects of clozapine on cortical silent period (CSP), short interval intracortical inhibition (SICI) and intracortical facilitation(ICF) (Kaster et al., 2015), whereas there is no study investigating effect of clozapine on short-latency afferent inhibition (SAI).

Methods: This study was conducted at Hacettepe University Faculty of Medicine, Ankara, Turkey. Ten patients who were planned to start clozapine treatment by their physicians were included in the study, and eight patients completed the 90-120 days of follow-up period. Eight healthy controls matched with the patients for age and sex were also included. Patients were assessed by Positive and Negative Syndrome Scale (PANSS), Thought and Language Disorder Scale (TALD), World Health Organization Disability Assessment Scale-II (WHODAS-II), a neurocognitive test battery; and the resting motor threshold (RMT), CSP, SICI, ICF and SAI were measured by TMS at baseline and after 90-120 days of clozapine initiation. TMS parameters were also measured once in the controls. The assessments of patients before and after treatment were compared with Wilcoxon signed rank test. TMS parameters of patients and controls were compared with Mann Whitney U test. The relationship between TMS parameters and psychopathological and neuropsychological variables were assessed by Spearman correlation analysis.

Results: RMT, ICF and SAI were lower in the patients compared to healthy controls at baseline, whereas only ICF was lower in the patient group at the follow-up assessment after 90-120 days of clozapine treatment. In the patient group CSP was found to be prolonged compared to baseline after 90-120 days of clozapine treatment. Stroop-2 and RAVLT-5 scores were lower, Stroop-4 scores were higher in patients after treatment. No significant correlation was found between the change in CSP and the change in cognitive tests, however SAI was strongly correlated with ommission errors in Go/No Go task ($r = 0.941$, $p=0.005$) and finger tapping rate of non-dominant hand ($r=1$, $p<0.001$).

Discussion: Prolongation of CSP shows that clozapine is associated with an increase in cortical inhibition which is in line with previous findings (Kaster et al., 2015). CSP is related to

GABA-B mediated neurotransmission (Rossini et al., 2007), and X-ray crystal structure of GABA-B receptor and its molecular docking calculations showed that clozapine could bind to the GABA-B receptor (Nair et al., 2020). These Results: indicate that GABA-B may be an important candidate to understand the mechanism of action of clozapine.
SAI, which is preliminary modulated by cholinergic mechanisms but also by GABAergic mechanisms, was improved and became similar to control groups after clozapine treatment, and was strongly correlated with attention and psychomotor processing speed in patients. SAI was found to be correlated with executive functions in schizophrenia patients previously (Noda et al., 2018).

This is the first study to investigate the effect of clozapine on SAI, and the first follow-up study which compares the effect of clozapine on cortical inhibition parameters together with its effect on cognitive tests. We believe that our findings will contribute to the literature on the pathophysiology and treatment of schizophrenia. Further long term follow up studies involving larger sample sizes are needed to confirm these findings.

V12. RACE MODERATES THE RELATION BETWEEN INTERNALIZED STIGMA AND SUICIDAL THOUGHTS AND BEHAVIORS IN YOUTH WITH PSYCHOSIS-RISK SYNDROMES AND EARLY PSYCHOSIS

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Background: Suicide is a leading cause of death among help-seeking youth, including youth on the psychosis spectrum. Internalized mental health stigma is one well-established risk factor for suicide that may be particularly salient for youth with psychosis-risk syndromes and early psychosis, given that psychosis is one of the most highly stigmatized mental health conditions worldwide. Among this population, youth of color may face exposure to additional forms of stigma such as race-related prejudice and discrimination and other racism-related stressors that may exacerbate the negative effects of internalized mental health stigma.
Methods: The current study examined whether internalized stigma and race interact to predict suicidal thoughts and behaviors (STB) in a help-seeking sample of Black and White adolescents with psychosis-risk syndromes and early psychosis (N = 34). Race was reported by participants and/or their caregivers, internalized stigma was assessed via the Internalized Stigma of Mental Illness Inventory (ISMI), and STB was assessed via the suicide screener from the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS) clinical interview.
Results: Results demonstrated that, even after controlling for a mood disorder diagnosis, internalized stigma had a significant effect on STB for Black youth (with higher levels of internalized stigma predicting higher levels of STB; $p = .002$, $f2 = 0.40$), but no significant effect on STB for White youth ($p = .504$, $f2 = 0.02$).
Discussion: Findings suggest that compared to their White peers, Black help-seeking youth with early psychosis spectrum disorders may be particularly vulnerable to the negative effects of internalized stigma as they pertain to STB. Internalized stigma may therefore represent an important treatment target in suicide prevention efforts among this population.

V13. PATIENT AND HEALTH CARE PROFESSIONAL PREFERENCES AND TREATMENT EXPERIENCES WITH TV 46000, A LONG-ACTING SUBCUTANEOUS ANTIPSYCHOTIC (LASCA) RISPERIDONE FORMULATION

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Background: Patient and healthcare professional (HCP) preferences concerning characteristics of antipsychotic agents are important to understand for shared decision making about medication choice. TV-46000 is a long-acting subcutaneous (SC) antipsychotic (LASCA) agent that combines risperidone and an innovative copolymer-based drug delivery technology in a suspension suitable for subcutaneous use. The opportunity to examine patient and HCP preferences regarding long-acting injectable antipsychotic agents (LAIs) arose in the context of a study of TV 46000 for the treatment of schizophrenia.

Methods: Patients with schizophrenia and HCPs participating in the Safety in Humans of TV-46000 SC Injection Evaluation study (SHINE, NCT03893825) had the opportunity to participate in a prospective, cross-sectional companion study to assess preferences for LAI treatment. TV-46000 was administered by HCPs once monthly (q1m) or once every 2 months (q2m) in the upper arm or abdomen to patients. Surveys were completed following ≥2 experiences prescribing/administering or receiving TV-46000 at week 8 or 12. Patients and HCPs rated injection and dosing characteristics, treatment comparison, and determinants of satisfaction from 1 (least) to 7 (most).

Results: At 15 sites, there were 49 HCP respondents, comprised of 25 nurses and 24 physicians (42 specialized in psychiatry). Of the 102 clinical trial patients, 63 patients enrolled (62%) in the companion study. Among HCPs, 23 nurses (92% of nurses) and 7 physicians (29% of physicians) administered TV-46000. Mean patient age was 35 years; 75% were male; 51% black, 35% Hispanic, 13% white.

Patients rated 'a short needle' (68% of patients), having a 'choice of once monthly or once every 2 months dosing interval' (59%), and 'injection instead of oral tablet' (59%) as the most important features of the clinical trial medication. HCPs rated a 'single injection to initiate treatment' (61%), a 'flexible dosing interval' (q1m or q2m; 84%), and 'injection instead of oral tablet' (59%) as the most important features. A SC injection was rated 'easy to receive' by 62% of patients; 17% rated it difficult, and the remainder rated as neutral. 84% of HCPs believed SC delivery was easy, and preferred (65% of HCPs) it over intramuscular injection because it caused less discomfort. No loading dose requirement when initiating or switching medications was preferred by 90% of HCPs and 86% of patients. It was important to most HCPs (78%) to have 4 dose strength options. Most HCPs felt that having a prefilled syringe (96%) and no need for reconstitution (90%) were advantages. Most patients (75%) preferred q1m treatment. Compared with returning to previous treatment, 90% of patients with prior antipsychotic treatment (n=57) would remain on TV-46000.

Discussion: LAI antipsychotic formulations differ in their product attributes. These data suggest that HCPs valued having dosing options, flexibility of injection type (subcutaneous versus intramuscular) and injection frequency, and prefilled syringes that do not require reconstitution. A majority of patients preferred an injection over oral delivery of antipsychotic

medication, a flexible dosing interval, and a short needle when selecting a LAI. TV-46000 was preferred by most patients over their prior antipsychotic treatment.

V14. THE CORRELATES OF SELF-STIGMA AMONG PEOPLE WITH SCHIZOPHRENIA SPECTRUM DISORDERS ACROSS CULTURES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Individuals with schizophrenia spectrum disorders are at heightened risk of experiencing self-stigma compared to people with other mental illnesses. Thus far, one systematic review of personal stigma published in 2013 focused specifically on schizophrenia spectrum disorders (Gerlinger et al., 2013). Since then, a large body of research has been conducted on self-stigma among people with schizophrenia spectrum disorders. However, there are no recent meta-analysis that examined the correlates of self-stigma among individuals with schizophrenia from a cross-cultural perspective. This is important to investigate given that research suggests that the prevalence and severity of stigma towards individuals with schizophrenia differs across countries and cultures. These differences may, in turn, result in variations in the manifestation of self-stigma among individuals with schizophrenia spectrum disorders. The first purpose of this systematic review and meta-analysis was to provide an up-to-date review on the relationship between self-stigma and various outcomes. The second purpose of this review was to examine the cross-cultural correlates of self-stigma among individuals with schizophrenia spectrum disorders.

Methods: Studies were identified following the PRISMA guidelines, through conducting searches in several electronic databases, including PubMed, PsycINFO, and Web of Science from June 2021 to September 2021. Studies were included if they reported quantitative correlational measures pertaining to the statistical relationships between self-stigma and at least one selected outcome variable. The Internalized Stigma of Mental Illness (ISMI) is one of the most used measures of self-stigma and assesses feelings of alienation, stereotype endorsement, discrimination experience, social withdrawal, and the ability to resist stigma. The results for the meta-analysis were analyzed using R programming and mean effect sizes were calculated by transforming Pearson correlation coefficients using Fisher's r-to-Z-transformation.

Results: Sixty-one articles (N = 8555) were included in the systematic review and thirty-eight articles (N = 5732) were included in the meta-analysis. Overall, the results from the systematic review revealed that the correlates of self-stigma are similar across countries (N = 19 countries, including United States, China, and Czech Republic). The findings from the meta-analysis revealed that self-stigma had a strong, negative correlation with quality of life ($r = -.53$, $p < .001$) and self-esteem ($r = -.57$, $p < .001$). In addition, self-stigma had a moderate, negative correlation with functioning ($r = -.43$, $p = .003$) and a moderate, positive correlation with severity of psychotic symptoms ($r = .35$, $p < .001$) and depressive symptoms ($r = .48$, $p < .001$). On the other hand, self-stigma had a small, positive correlation with positive symptoms ($r = .21$, $p = .003$) and negative symptoms ($r = .24$, $p < .001$).

Discussion: Research indicates that some countries/cultures are more stigmatizing towards individuals with schizophrenia compared to other countries/cultures. Nevertheless, this review suggests that self-stigma is correlated with various psychosocial and psychiatric outcomes among people with schizophrenia spectrum disorders and these relationships were similar across countries/cultures. Future longitudinal research is needed to examine the potential mechanisms explaining the relationship between self-stigma and various outcomes, thereby

allowing for the development of effective programs and interventions aimed at reducing self-stigma.

V15. THE RELATIONSHIP OF GUT MICROBIOME DYSBIOSIS WITH SYMPTOM SEVERITY IN SCHIZOPHRENIA

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Background: The connection between the gut microbiota and schizophrenia has become a fertile area of research. The relationship is bidirectional and quite complex, but is likely to lead to practical clinical applications. For example, the commensal microbiota can produce metabolites that cross the blood-brain barrier and trigger neuroinflammation, which is believed to be a neurobiological precursor of psychosis. On the other hand, life-style in schizophrenia, such as high-calorie/high-fat food, smoking and sedentary living can be disruptive to the normal microbiome diversity. In addition, the antimicrobial properties of antipsychotic drugs can lead to microbiota dysbiosis.
Methods: We conducted a literature review using specific key words including schizophrenia, psychosis, microbiome, dysbiosis and antipsychotic drugs, to identify controlled studies published on PubMed. We specifically focused on the relationship of the gut microbiota with symptom severity in schizophrenia.
Results: Multiple clinical differences emerged in this search including 1) differences in microbiota diversity in drug-naïve first-episode psychosis vs healthy controls, 2) the positive effect of antipsychotic therapy on the gut microbiota diversity, 3) the relationship of the microbiome with overall symptom severity in schizophrenia and, 4) microbial profiles which correlate to more specific clinical features, such as negative symptom severity, among patients with schizophrenia.
Discussion: The evolving literature on schizophrenia and the microbiome reveal several promising areas of investigation that may have important clinical implications. Further studies are warranted to explore the possible association of microbiota dysbiosis with other clinical features of schizophrenia such as the severity of negative and cognitive symptoms, comorbid depression or anxiety, functional outcomes and early mortality. The microbiome may generate useful biomarkers, before and after the onset of psychosis.

V16. POLYGENIC RISK SCORES DIFFERENTIATING SCHIZOPHRENIA FROM BIPOLAR DISORDER ARE ASSOCIATED WITH PREMORBID INTELLIGENCE IN SCHIZOPHRENIA PATIENTS AND HEALTHY SUBJECTS

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Background: Impairments in intelligence are more severe in patients with schizophrenia (SCZ) than in patients with bipolar disorder (BD) despite clinical and genetic similarities between the disorders. Genetic loci differentiating SCZ from BD, i.e., SCZ-specific risk, have been identified. Polygenetic [risk] scores (PGSs) for SCZ-specific risk are higher in SCZ

patients than in healthy controls (HCs). However, the influence of genetic risk on impaired intelligence is poorly understood. Here, we investigated whether SCZ-specific risk could predict impairments in intelligence in SCZ patients and HCs.
Methods: Large-scale genome-wide association study (GWAS) datasets related to SCZ vs BD, childhood intelligence (CHI) and adulthood intelligence (n=12,441-282,014) were utilized to compute PGSs. PGSs derived from the GWASs were calculated for 130 patients with SCZ and 146 HCs. Premorbid and current intelligence and the decline were measured in SCZ patients and HCs. Correlations between PGSs and intelligence functions were investigated.
Results: High PGSs for SCZ-specific risk were correlated with low premorbid intelligence in SCZ patients and HCs (β=-0.17, p=4.12×10-3). The correlation was still significant after adjusting for diagnostic status (β=-0.13, p=0.024). There were no significant correlations between PGSs for SCZ-specific risk and current intelligence or intelligence decline (p>0.05). PGSs for CHI were lower in SCZ patients than in HCs (R2=0.025, p=0.025), while the PGSs for CHI were not significantly correlated with premorbid and current intelligence, the decline or the PGSs for SCZ-specific risk (p>0.05).
Discussion: These findings suggest that genetic factors differentiating SCZ from BD might affect the pathogenesis of SCZ and/or pathological differences between SCZ and BD via the impairment of premorbid intelligence, i.e., crystallized intelligence, while genetic factors for CHI might affect the pathogenesis of SCZ not via impaired impairments in intelligence.

V17. ATTENTION AND DYSEXECUTIVE BEHAVIOURS IN FIRST EPISODE OF SCHIZOPHRENIA

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Background: Dysexecutive syndrome is a prominent and functionally significant cognitive feature of schizophrenia. This research studies correlations between attentional abilities, executive function and dysexecutive behaviors in first episode of schizophrenia (FES) patients.
Methods: We evaluated 22 FES patients, from 17 to 29 years of age with a recent history of a single psychotic outbreak only treated with atypical neuroleptics. We also evaluated twenty healthy persons matched by sex, age and educational level with FES patients as a control group. Attention was estimated using ANT (Attentional Network Test); executive function using Modified Wisconsin Card Sorting Test (MWCST) and Frontal Assessment Battery (FAB) and dysexecutive conducts applying the questionaries DEX and Behavioral Dysexecutive Syndrome Inventory (BDSI) in both groups. DEX scores are: DEX self-rating (DEX-S), "significant other" (DEX-SO) and the difference between DEX-S and DEX-SO scores reflects awareness of the deficit (DEX-A).
Results: the increase in the mean reaction time in Executive Attention (EA) is significantly higher in FES with respect to controls without significant differences between groups in Alerting or Orienting (*). We found that FES patients had marked executive function impairments and dysexecutive behavior as compared to controls (**). We correlated performances of FES in EA with MWCST, FAB, BDSI and DEX. Correlations between EA and FAB and WCST, showed only a significant correlation with FAB go-no go sub-item (r = -0.430, p = 0.046). EA did not show significant correlations with BDSI total score and DEX total scores. However, statistically significant correlations were found with the DEX-SO perseverative alterations sub-item (r = 0.428, p = 0.047). Significant correlations were also found between EA and DEX-S in positive affect factor (r = -0.499, p = 0.018), knowing-doing dissociation sub-item (r = -0.457, p = 0.033) and motivation sub-item (r = -0.573, p = 0.005).

* Orellana G, Peña M, Slachevsky A. “Executive attention impairment in first episode Schizophrenia”. BMC Psychiatry 2012 Sep 22; 12:154.

** Orellana G, Slachevsky A, Henriquez F. “Dysexecutive behavior in first episode of schizophrenia”. BMC Psychiatry. Submitted 2021.

Discussion: Dysexecutive behavior is common during FES and may be a primary impairment throughout disease progression. The present results could help clinical practice by providing information on some specific characteristics of dysexecutive behavior in FES. Understanding the associations between attention, executive function and dysexecutive behavior helps to explain the social adjustment disorders associated with schizophrenia. This knowledge may be used to improve diagnostic and therapeutic tools; for example, clarifying the implications of specific DEX and BDSI dimensions could increase the efficacy of individual or family psychotherapy interventions.

V18. LONGITUDINAL TRAJECTORIES OF BRAIN NETWORK CONNECTIVITY AFTER 16 WEEKS OF ANTIPSYCHOTIC TREATMENT IN MEDICATION-NAïVE FIRST EPISODE PSYCHOSIS PATIENTS

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Background: Connectome studies have provided rich data consistent with the hypothesis that dysconnectivity is predominant in psychosis spectrum disorders. Nonetheless, very few have examined the impact of antipsychotic medication on functional connectivity (FC) in medication-naïve first episode psychosis patients (FEP). The present study measured resting state FC from brain networks deemed crucial for higher-order cognition: default mode (DMN), salience (SN), dorsal attention (DAN), and executive control network (ECN). Patients were scanned prior to treatment (baseline), 6 weeks (W6), and 16 weeks (W16) following antipsychotic treatment. A group of healthy controls (HC) was also scanned. We hypothesized that FEP would show differential FC compared to HC at baseline, but these effects would normalize after exposure to antipsychotic treatment.

Methods: Data from 87 HC (age = 24.02; 52M/35F) and 88 antipsychotic-naïve FEP (age = 23.49; 56M/32F) were preprocessed using a standard preprocessing pipeline. Within- and between-network FC was assessed for each group. A series of linear mixed models (random factor = subjects; fixed effects = group | time) were done to assess longitudinal effects of antipsychotic treatment on FC between groups. Partial correlations between response to treatment (changes in positive symptoms after 16 weeks of antipsychotic treatment) and FC were performed. Post-hoc analyses splitting FEP into responders (≥50% decrease in positive symptoms) and non-responders (<50% decrease in positive symptoms) were also performed. All analyses were controlled for age, sex, and in-scanner motion.

Results: FEP showed reduced ECN FC compared to HC at baseline. Significant group × time interactions were found in the DAN (baseline = none; W6 = HC > FEP; W16 = marginal HC > FEP) and ECN (baseline = HC > FEP; W6 = HC > FEP; W16 = none). We also found another group × time interaction in DMN-SN FC (baseline = none; W6 = HC > FEP; W16 = HC > FEP) and in DMN-DAN (baseline = none; W6 = HC > FEP; W16 = none) Post-hoc analyses showed significant group × time interactions in DAN, ECN, and DMN-SN where both responders and non-responders had reduced FC compared to HC. Finally, correlations between response to treatment and baseline SN and SN-DAN FC were found in responders, but these were absent in non-responders.

Discussion: Changes in both within- and between-network FC were observed following 16 weeks of antipsychotic treatment in medication-naïve FEP patients. The largest change in FC occurred in the ECN, where aberrant FC has been a consistent finding in the FEP literature. While no correlations were found between treatment response and FC across all FEP patients, when these were split, correlations were found in the responder group, but not in the non-responder group. Overall, our findings suggest that antipsychotics can impact brain network connectivity in FEP and this effect varies across responders and non-responders to medication. This has clinical significance as this may help develop more targeted interventions for those who do not respond to traditional medication.

V19. HALLUCINATIONS AND DELUSIONS AS ABERRATIONS OF BELIEF

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Background: Hallucinations and delusions are viewed as aberrations of perception and belief respectively. However, the distinction between perception and belief and their alignment with hallucination versus delusion may not be clear cut.
Methods: I will show the impact of beliefs on perception through a laboratory task that encourages hallucinations. These conditioned hallucinations are driven by strong prior perceptual beliefs, and they are more likely in people who hallucinate outside of the lab. On the other hand, paranoid persecutory delusions seem related to more promiscuous beliefs. This instability can be recreated in experimental animals treated with methamphetamine, and it has been fomented in the general population by the evolving pandemic and attendant challenges to conditional cooperation.
Results: Hallucinations then appear to entail strong priors, and delusions, weaker ones. We reconcile these differences by focusing on symptom contents. In a large scale phenomenological study we found certain delusions (passivity) travel with hallucinations, whereas others (persecution, grandiosity) do not.
Discussion: These finer grained distinctions may better illuminate psychosis, perception, and belief.

V20. RANGE ADAPTATION TO INCENTIVE AND OUTCOME VALUE IN INDIVIDUALS WITH SOCIAL ANHEDONIA

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Background: Amotivation is evident in individuals with social anhedonia and has a negative impact on their social functioning. Incentive and outcome value representation plays an important role in the process of motivation. Evidence suggests that individuals would represent the values as its relative place in its range, i.e., range adaptation, in order to insure the value discrimination. Range adaption has been shown to correlate with individuals' motivation levels. However, the interaction between range adaptation with incentive and outcome values in individuals with social anhedonia is largely unclear. The present study aimed to examine (1) the range adaptation performance to incentive and outcome values and (2) explore the

relationship between range adaptation to incentive and outcome values with motivation in individuals with social anhedonia.
Methods: The Effort Expenditure for Reward Task-adaptive (EEfRT-adaptive) task was administered to 31 pairs of participants with high (HSoA) and low (LSoA) social anhedonia. Participants were required to choose between a high and low effort task with different values. The reward value was fixed to ￥5 in the low-effort task. The high-effort task has two potential values ranging between ￥5.4–￥6.4 and ￥5.4–￥7.4. Participants need to execute the chosen task and would receive the actual outcome from the trial. Then they need to rate on their consummatory pleasure during the outcome presentation. We defined the range adaptation ability as the difference between the response slopes of the two different ranges for high-effort task. Moreover, all participants also completed the Motivation and Pleasure-self reported (MAP-SR) and the Anticipatory and Consummatory Interpersonal Pleasure Scale(ACIPS). We also recruited an independent sample of 29 pairs of participants with HSoA and LSoA to verify and replicate the findings with a wider value range of the EEfRT-adaptive task.
Results: The HSoA and LSoA group did not exhibit significant differences in the slope difference between the response ranges for the incentive and outcome values. However, the LSoA group exhibited significant negative associations between range adaptations to incentive value with the MAP-SR. On the contrary, the HSoA group exhibited a significant negative correlation between range adaptation to outcome value with the ACIPS. These correlations were replicated in the validated sample.
Discussion: We found negative associations between range adaptation to incentive and outcome values with individuals' motivation performances. Range adaptation to incentive and outcome value seems to have a unique role in affecting motivation for individuals with HSoA and LSoA.

V21. STAGE-SPECIFIC BRAIN AGING IN FIRST EPISODE SCHIZOPHRENIA AND TREATMENT RESISTANT SCHIZOPHRENIA

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Background: Brain age is a popular brain-based biomarker that offers a powerful strategy for using neuroscience in clinical practice. We investigated the brain-predicted age difference (PAD) in patients with schizophrenia (SCZ), first-episode schizophrenia spectrum disorders (FE-SSDs), and treatment-resistant schizophrenia (TRS) using structural magnetic resonance imaging data. The association between brain-PAD and clinical parameters was also assessed.
Methods: We developed brain age prediction models for the association between 77 average structural brain measures and age in a training sample of controls (HC) using ridge regression (RR), support vector regression (SVR), and relevance vector regression (RVR). The trained models in the controls were applied to the test samples of the controls and three patient groups to obtain brain-based age estimates. The correlations were tested between the brain-PAD and clinical measures in the patient groups.
Results: Model performance indicated that, regardless of the type of regression metric, the best model was SVR and the worst model was RVR for the training HC. Accelerated brain aging

was identified in patients with SCZ, FE-SSDs, and TRS compared to the HC. A significant difference in brain-PAD was observed between FE-SSDs and TRS using the RR algorithm. Symptom severity, the Social and Occupational Functioning Assessment Scale, chlorpromazine equivalents, and cognitive function were correlated with the brain PAD in the patient groups.
Discussion: These findings suggest additional progressive neuronal changes in the brain after SCZ onset. Therefore, pharmacological or psychosocial interventions targeting brain health should be developed and provided during the early course of SCZ.

V22. IDENTIFYING THE BARRIERS TO HELP SEEKING FOR EARLY PHASE PSYCHOSIS AMONG CANADIAN AFRICAN NOVA SCOTIAN YOUTH

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Background: Mental illness experienced by Black Canadian populations is an understudied topic, including limited research to understand the pathways to care for early intervention services for psychosis for Black Canadians. In Nova Scotia, even fewer studies have focused on access to care by African Nova Scotians (ANS) and ANS youth. In discussing mental health with ANS communities and ANS healthcare providers there are several reasons noted why there may be a reluctance in this community to seek help: stigma, lack of culturally appropriate services, and the lack of mental health providers from the ANS community, however this has not been formally studied. The aim of this study was to collect qualitative data on the experiences of ANS youth in seeking help for psychosis, thru the lens of ANS youth, community leaders, families and ANS healthcare providers.
Methods: Following qualitative methodology, data was collected from 14 focus groups with a total sample size of 75 participants enrolled. Participants were recruited for one of five focus groups: ANS youth already in early intervention services for psychosis, ANS youth, ANS caregivers, ANS community leaders, and service providers. The participants resided in the predominant ANS communities in the Halifax Regional Municipality.
The focus groups were led by trained ANS facilitators who were familiar with/connected to these ANS communities, to maximize engagement and discussion. Participants were asked to share their experience and knowledge regarding help seeking for psychosis and provide their suggestions regarding the content and format of communication/information that is needed to increase awareness of psychosis and promote youth help seeking. This study used an interpretive, narrative approach to collect and analyze the data around how ANS youth define and understand metal illness/psychosis and help seeking.

Results: The data indicated that perceptions and beliefs about mental illness among ANS youth reflect the perceptions and beliefs in the broader ANS community, including stigma and the labelling of people with mental illness as “crazy” and weak. It was suggested, that in general, the ANS community tends to avoid the topic of mental illness or deny its prevalence in the community. It was also noted by the focus groups that there is a considerable lack of knowledge and understanding of mental illness, which can be attributed to lack of education on the topic in schools or in conversations at home. The participants identified the church as a first contact for health issues and a reliance on faith and religion to address these issues. Other contributing factors identified by this study that impede an ANS youth seeking mental health care include: fear of police involvement in their care, general lack of trust in the healthcare system and healthcare providers, and lack of cultural competency demonstrated by mental health professionals.

Discussion: The findings of this study will serve as a guide for early intervention programs to engage in outreach locally and nationally to Black youth. This data will also be used to design educational resources that will decrease and remove barriers ANS youth face in accessing and utilizing mental health services, with the goal of encouraging help-seeking, self-care, and decreasing stigma.

V23. THE ASSOCIATION BETWEEN SUBSTANCE USE AND ENROLLMENT STATUS THROUGHOUT NEW JOURNEYS: A COORDINATED SPECIALTY CARE PROGRAM

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Background: Approximately 50% of individuals experiencing early psychosis have a co-occurring alcohol or cannabis use disorder. Among those with early psychosis, substance use is associated with lower functioning and quality of life, medication nonadherence, symptom relapse, and disengagement relative to non-substance users. While substance use has been associated with disengagement from coordinated specialty care (CSC) programs, there is a paucity of literature identifying associations between substance use and other status outcomes (e.g., referral to another service). In the present study, we assessed the association between recent substance use, cannabis use, and alcohol use at intake and enrollment status over time.
Methods: Between 2015 and 2021, 481 service users were enrolled and completed an intake across New Journeys, programs located in the Pacific Northwest, US. At intake, 248 service users reported on their substance use (e.g., cannabis, alcohol, sedatives, stimulants) in the past 30 days. We first computed and plotted the probability of being in each of the New Journey's enrollment statuses (i.e., active, referred, graduated, disengaged) across time in the program using the Aalen-Johansen estimate. In order to obtain statistical estimates of the effect of substance use, New Journeys program progress was analyzed using a competing risks model. Cause-specific Cox models were fit with enrollment statuses as competing outcomes. Service users who were still active two-years post intake date were censored. Separate models were fit for different breakdowns of substance use. These include: any substance/no substance, alcohol/no alcohol, cannabis/no cannabis, and alcohol and/or cannabis/neither alcohol nor cannabis use. All models were adjusted for age, gender, and duration of untreated psychosis. Multiple imputation was used to handle missing values in the independent variables. Coefficients are presented as hazard ratios (HR) along with 95% confidence intervals.
Results: At intake, the mean age was 20.7 (±3.7) years, 71.0% (n = 176) identified as male, and the mean DUP was 173.5 (±188.2) days. In the previous month, 25.5% (n=51) of the 200 service users who answered alcohol use questions had consumed alcohol, 32.5% (n=64) of the 197 service users who answered cannabis use questions had used cannabis, and 52.4% (n=130) of the 248 who at least partially completed the substance use measure had used at least one substance. Based on the Cox model results, service users who reported 'any substance' at the time of intake, had a 60% lower chance (HR = 0.41, 95% CI = (0.20, 0.82), p = 0.01) of graduating compared to service users who reported no substance use at intake. Services users who reported using alcohol and/or cannabis at time of intake had a 56% lower chance (HR = 0.44, 95% CI = (0.20, 0.98), p = 0.04) of graduating from New Journeys. Services users who reported only cannabis were more likely (HR = 3.28, 95% CI = (1.09, 9.87), p = 0.04) to be referred to other services over time. All other associations between substance use and status outcomes in the CSC program were determined to be not significant.

Discussion: Service users who reported any substance use and those who reported alcohol and/or cannabis use were significantly less likely to 'graduate' from New Journeys. Moreover, recent cannabis use resulted in more referrals to other services. There needs to be an additional focus on evidence-based interventions for substance use within CSC programs to improve care and retention among service users.

V24. PREFRONTAL-CEREBELLAR DYNAMICS DURING POST-SUCCESS AND POST-ERROR COGNITIVE CONTROLS IN MAJOR PSYCHIATRIC DISORDERS

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Background: Difficulty in cognitive adjustment after a conflict or error is a hallmark for many psychiatric disorders, yet the underlying neural correlates are not fully understood. We have previously shown that post-success and post-error cognitive controls are associated with distinct mechanisms particularly related to the prefrontal-cerebellar circuit (Cao and Cannon, 2021), bringing the possibility that altered dynamic interactions in this circuit may underlie mental disorders characterized by cognitive deficits.
Methods: A total of 136 patients with three diagnosed disorders (48 schizophrenia (SZ), 49 bipolar disorder (BD), 39 attention deficit hyperactivity disorder (ADHD)) and 89 healthy controls were drawn from the Consortium for Neuropsychiatric Phenomics and completed a stop-signal task during the fMRI scan. Brain activations for post-success and post-error conditions were analyzed and compared between groups. Dynamic causal modelling was applied to investigate effective connectivity patterns for the prefrontal-cerebellar circuit during post-success and post-error processing in the studied groups.
Results: Consistent with the previous findings (Cao and Cannon, 2021), both post-success and post-error conditions significantly activated the frontoparietal network (in particular prefrontal cortex and posterior parietal cortex) and posterior cerebellum. No significant group differences were observed for brain activations and overall effective connectivity structures during post-success and post-error conditions. However, significant group difference was shown for the modulational effect on top-down connectivity from prefrontal cortex to cerebellum during post-error trials (PFWE = 0.01), which was particularly driven by reduced modulation in patients with ADHD and SZ. Moreover, we also found significant group difference in the modulational effect on bottom-up connectivity from cerebellum to prefrontal cortex during post-success trials (PFWE = 0.03), which was driven by decreased modulation in patients with ADHD.
Discussion: These findings suggest that patients with SZ and ADHD are associated with insufficient neural modulation on the prefrontal-cerebellar circuit during post-success and post-error cognitive processing, a phenomenon that may underlie cognitive deficits in these disorders.

V25. EFFECTS OF PERCEIVED SOCIAL THREAT ON SELF-OTHER BOUNDARY IN SCHIZOPHRENIA: A VIRTUAL REALITY (VR) STUDY OF PERIPERSONAL SPACE

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Background: A coherent sense of the bodily self with a clearly defined boundary is a prerequisite for adaptive social interactions. The multisensory-motor buffer zone between the body and the external world is known as peripersonal space (PPS), a protective defensive space that, when breached, triggers alarm signals. A weakened self-boundary would make it difficult to differentiate one's own behaviors from those of others, leading to maladaptive social interactions. We examined parameters of PPS in social contexts to further understand self-disturbances in individuals with schizophrenia (SZ).
Methods: 23 SZ and 25 control subjects (CO) participated in a visuotactile response time (RT) task in immersive VR. The task required participants to detect tactile vibration while watching an avatar approach them at walking speed. Vibrations were delivered at different times corresponding to various distances from the avatar. The avatars represented varying degrees of threat: non-threatening and threatening humans and a monster. PPS was estimated from a sigmoid function generated by RTs; when a stimulus enters the PPS, there is a sharp drop in RT. Both the PPS size and the "slope" (the uncertainty of self-other boundary) were estimated. False alarm (FA) rates (responding ahead of the tactile vibration), clinical symptoms, paranoia, social phobia, and loneliness were also examined.
Results: SZ showed higher FA rates than CO, which was exacerbated by perceived social threat. PPS size did not differ between SZ and CO, However, for PPS slope, a group-by-slope interaction was found such that perceived social threat sharpened the self-boundary in CO, whereas it increased the uncertainty of the self boundary in SZ. In SZ, shallower PPS slope was associated with delusion, persecution, and loneliness but not in CO.
Discussion: Sharper self-boundary in response to threat in CO is considered adaptive. However, perceived threat resulted in a weakened self-boundary in SZ. Anomalous self-other boundary would result in maladaptive interactions. Increased FA rates in SZ suggest heightened anticipation. The associations of PPS slope and relevant clinical variables merit further investigation towards a better understanding of the role of self-disturbance in social outcome in SZ.

V26. METACOGNITIVE TRAINING FOR PSYCHOSIS (MCT): A SYSTEMATIC REVIEW AND META-ANALYSIS OF EFFICACY, MAINTENANCE EFFECTS, AND MODERATORS

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Background: Background: The majority of those with psychosis experience persistent positive symptoms despite antipsychotic treatments. Metacognitive training for psychosis (MCT) mitigates such symptoms in a non-confrontational manner by promoting an awareness of cognitive biases. MCT is a brief group-or-individual intervention, available in 37 languages at no cost. Results from previous meta-analyses support its acceptability and efficacy in reducing cognitive biases, delusions and positive symptoms, and in improving cognitive insight. Two meta-analyses failed to observe significant effects for MCT; cursory search strategies and overly-strict exclusion criteria may have been contributing factors. Given the weight meta-analyses receive in treatment guideline recommendations, it is essential to rigorously address inconsistent findings. Further, several trials have been published since the prior meta-analyses focused on psychotic symptoms, and to our knowledge, no meta-analysis has investigated both

participant and treatment -related moderators that may influence outcomes. This comprehensive review and meta-analysis provides an important update and novel results regarding the immediate and sustained efficacy of MCT on proximal (directly targeted) and distal (indirectly influenced) intervention outcomes, and an examination of moderators.
Methods: Method: The search included 11 electronic databases and ranged from 2007 to June 3, 2021 (alert until September 10, 2021). Reference lists of prior meta-analyses and all included studies were screened. Studies examined MCT and included participants with a schizophrenia spectrum disorder. There were no age, sex, gender, language, or study design restrictions and the PRISMA guidelines were followed. Two reviewers performed study selection. Data were extracted by three reviewers and pooled using random effects models. Hedges' g effect sizes were computed and the Mixed Methods Appraisal Tool assessed study quality. Proximal outcomes were global positive symptoms, delusions, hallucinations, and cognitive biases. Distal outcomes were self-esteem, negative symptoms, quality of life (QoL), wellbeing, and functioning. Pre- to post-treatment and maintenance effects were examined, and meta-regressions, subgroup, and sensitivity analyses assessed moderator effects.
Results: Results: Forty reports were synthesized in meta-analysis (1045 identified; 281 assessed; 46 included (40 in meta-analysis, 6 in narrative review); N=1816 participants). MCT was effective on positive symptoms (g = 0.50 [95% CI, 0.34-0.67]), delusions (g = 0.69 [95% CI = 0.45-0.93]), hallucinations (g = 0.25 [95% CI = 0.11-0.40]), cognitive biases (g = 0.16 [95% CI = 0.03-0.29]), self-esteem (g = 0.17 [95% CI = 0.03-0.31]), negative symptoms (g = 0.23 [95% CI = 0.10-0.37]), and functioning (g = 0.41 [95% CI = 0.12-0.69]). All significant effects were maintained up to one-year follow-up. A non-significant effect was observed for QoL (g = 0.20 [95% CI = -0.07-0.47]) and wellbeing was assessed by only one study. Year of study publication moderated hallucinations (β = .04, [95% CI = 0.00 - 0.07]).
Discussion: Discussion: This rigorous systematic review and meta-analysis establishes the immediate and sustained efficacy of MCT on multiple proximal outcomes, including reductions in delusions, hallucinations, and cognitive biases. The intervention also significantly reduces negative symptoms and improves self-esteem and functioning. Results indicate that MCT is an accessible and durable intervention deliverable by a variety of mental healthcare professionals. MCT is now ready for large-scale implementation and warrants inclusion in guideline recommendations for the treatment of schizophrenia.

V27. AN EXPLORATORY FACTOR ANALYSIS OF THE PTSD CHECKLIST FOR DSM-5 IN PSYCHOTIC DISORDERS

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Background: Background: The PTSD Checklist for DSM (PCL) is the most widely used screener to assess posttraumatic stress disorder (PTSD) and related symptoms in those with psychotic disorders. However, there is debate regarding the scale's validity for use as a brief screener in this population. Considerable symptom overlap between the two disorders (e.g., intrusions that may aggravate or be misinterpreted as hallucinations, emotional numbing, avoidance, concentration difficulties, etc.) likely contribute to the general underdiagnosing of PTSD in psychosis. These important issues speak to the need to better understand the underlying presentation of PTSD dimensions in psychosis. This hypothesis-generating study

is, to our knowledge, the first to explore the PCL-5 (its most recent iteration) factor structure in psychosis to examine whether a more valid underlying structure may exist.
Methods: Methods: One hundred and two male and female participants completed an exhaustive clinical research intake interview at a centre proving specialized psychological follow-up to individuals with psychotic disorders. Of these, 65 participants reported a valid DSM-5 PTSD criterion A traumatic event and subsequently completed the PCL-5. Exploratory factor analysis was then conducted to estimate the number of latent constructs underlying the 20 items of the PCL-5 in psychosis, using Principal Axis Factoring employing an oblique (oblimin) rotation. Factors with eigenvalues exceeding one were retained and then confirmed via scree plot. Factor selection cut-off was at the point of inflection of the scree plot curve and solutions were verified against the parallel analysis of randomly generated eigenvalues. Other indices of fit were analysis of inter-factor correlation magnitudes and factors with at least three-item solutions. Factors with communalities of at least .5 and a gap of at least .2 between cross-loadings were kept. Cronbach's alpha (α) was estimated for each factor, with the 'scale if item deleted' option selected. Output was examined to verify that individual items did not decrease the overall α.
Results: Results: Cronbach's α for the total scale was .95. Factorability complied with recommended standards: all items had inter-correlations exceeding r = .3, all correlations in the anti-image correlation matrix exceeded r = .5, the Kaiser-Meyer-Olkin measure of sampling adequacy = .87, and Bartlett's test of sphericity was significant ($\chi 2$ (190) = 896.17, $p < .05$). After extraction, communalities all exceeded .5, except for one item in factor one. Principal axis factoring revealed four factors that individually explained 50.00%, 7.12%, 6.52%, and 5.05% of the variance, or 68.69% of the cumulative variance. Parallel analysis confirmed the four-factor solution. All cross-loadings had a gap of at least .3 and all factors had at least three-item solutions. No factor correlation exceeded r = .58. A four-factor solution differing from the DSM-5 four-factor model thus emerged as the best fitting model. Resulting PCL-5 dimensions in psychosis were labelled (1) Re-experiencing/Negative Affect; (2) Depressive; (3) Externalizing Anxious Behaviors; and (4) Avoidance/Physiological Reactivity.
Discussion: Discussion: Results guide the hypothesis that the latent structure of the PCL-5 may be unique in psychotic disorders. Given robust findings, albeit using a small sample size, more research is needed to confirm the proposed model in larger samples. This study makes a novel contribution toward validating the PCL-5 for use as a brief screener in psychotic disorders. We offer a starting point toward understanding how psychotic symptoms may influence the subjective experience of posttraumatic stress symptoms and PTSD (and vice versa) in individuals with psychosis.

V28. THE IMPACT OF SEROPOSITIVITY TO TOXOPLASMA GONDII ON COGNITION AND RESPONSE TO NEUROSCIENCE-INFORMED COGNITIVE TRAINING IN SCHIZOPHRENIA

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Background: Studies indicate that neuroscience-informed digital cognitive training can remediate cognitive impairments in schizophrenia. However, it is unclear which factors contribute to deficits and response to cognitive remediation in this population. Toxoplasma

gondii (T. gondii) is a neuroinvasive protozoan parasite that has been linked to poorer cognitive performance, with a higher prevalence in schizophrenia subjects. Here, we investigated whether seropositivity to T. gondii is associated with poorer cognitive performance and more severe symptoms in schizophrenia and whether it affects their adherence and response to 40 hours of neuroscience-informed cognitive training.

Methods: We measured IgG titers for T. gondii, assessed cognition and symptoms from 60 schizophrenia subjects. Quantile Regression and General Linear Models were used to compare seropositive (TOXO+; n=25) and seronegative (TOXO-; n=35) patients at baseline, as well as their changes after 40 hours of neuroscience-informed cognitive training.

Results: At baseline, TOXO+ subjects presented lower global cognition when compared to TOXO- ($F=3.78$, $p=0.05$). Specifically, TOXO+ subjects showed worse verbal memory and learning ($F=4.48$, $p=0.03$), social cognition ($F=5.71$, $p=0.02$), and their antibodies concentration was associated with negative ($r=0.42$, $p=0.04$) and total ($r=0.40$, $p=0.04$) schizophrenia symptoms. After training, the TOXO+ group showed higher adherence to intervention ($X^2=9.31$, $p=0.01$), and larger improvements in attention ($\beta=0.64$, $p=0.02$) and social cognition ($\beta=0.40$, $p=0.03$).

Discussion: Seropositivity to T. gondii was associated with worse baseline cognition, higher adherence, and larger responses to cognitive training. These findings highlight the potential of neuroscience-informed cognitive training to remediate the poorer cognition of subjects with schizophrenia who are seropositivity to T. gondii.

V29. DEVELOPMENT AND VALIDATION OF A PREDICTIVE MODEL FOR DETECTING UNDIAGNOSED CASES OF TYPE 2 DIABETES FOR PEOPLE WITH SEVERE MENTAL ILLNESS. CROSS-SECTIONAL STUDY BASED ON THE PRIMARY CARE DATA IN A MULTI-ETHNIC EAST LONDON POPULATION.

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Background: Type 2 diabetes mellitus (T2DM) and its complications are among the leading causes of excess mortality in people with severe mental illness (SMI), which includes schizophrenia, bipolar disorder, and other non-organic psychoses. People with SMI are 2-3 times more likely to be diagnosed with T2DM, and a third of people with SMI older than 55 have diabetes. Yet, existing diabetes risk scores rarely adjust predictions to the presence of a mental illness, and none of the models, to the best of our knowledge, have been developed specifically for people with SMI.

In the present study, we utilised a large cross-sectional data of a multi-ethnic East London population and developed predictive models to estimate probability of a person with SMI to have a T2DM diagnosis. Based on a cross-sectional data, such models cannot predict future chances of developing T2DM, however they can be used as a screening tool to identify undiagnosed T2DM cases. Our primary aim was to assess whether the primary care data can provide enough information for predictive models of T2DM targeted for people with SMI.

Methods: The data was extracted from the primary care electronic health records (EHRs) in March 2013 and contains anonymized records of 674,000 participants aged 18-75. Participants with SMI (N=10,159) formed our analytical sample. The outcome was a prior T2DM diagnosis; risk factors included age, gender, ethnicity, body mass index, treated hypertension,

cardio-vascular diseases, prescribed antipsychotics, all derived from relevant coded clinical terms; socio-economic status was measured by the area-based deprivation index based on the participants' postcodes mapped to the Index of Multiple Deprivation (IMD-2010). Missing data was handled by multiple imputations (n=20).
We fitted two models to predict presence of the T2DM diagnosis from individual risk factors: a regularised logistic regression and a machine-learning alternative, Gradient Boosted Decision Trees (GBDT), chosen for its ability to automatically handle non-linear and interaction terms and fast convergence. The data was randomly split into derivation and test sets (80%/20%), the models were fitted using a derivation set and internally validated on the test set. Models were assessed for discrimination and calibration. Discrimination, which is the ability to identify high-risk individuals, was measured by the area under the receiver-operating area under the curve (ROC-AUC). Calibration quality, that is how well predicted probabilities tie with the observed outcome rates, was assessed with calibration-in-the-large and calibration slope statistics, with the ideal values of 0 and 1.

Results: Out of 10,159 adults in the SMI sample 1,513 had T2DM (14.9%). T2DM prevalence varied across self-reported ethnicities (27.7% among Bangladeshi to 9.8% in White British) and age groups (3.3% in 18-35y, 14.3% in 35-55y, 29.9% in 55-75y).
Regularised logistic regression performed well in the test set while detecting T2DM presence for people with SMI, ROC-AUC was 0.83 (95% CI 0.81-0.86), calibration statistics were nearly perfect: calibration-in-the-large, -0.09 (95% CI -0.23-0.06), calibration slope, 1.00 (95% CI 0.9-1.02). GBDT performed equally well, with ROC-AUC of 0.825 (95% CI 0.80-0.85).

Discussion: Predictive modelling has advanced greatly in the past decade, and it is important to apply these cutting-edge methods to vulnerable groups. Our study is one of the first to investigate prediction of T2DM diagnosis for people with SMI. We showed that primary care data, the setting where such models could be most fruitfully used, can provide enough information for well-performing predictive models to screen for undiagnosed T2DM cases among people with SMI. Both classical and machine learning algorithms can be employed.

V30. MATERNAL QUERCETIN SUPPLEMENTATION IMPROVES WORKING MEMORY IMPAIRMENT AND INFLAMMATORY RESPONSE IN AN ANIMAL MODEL OF SCHIZOPHRENIA

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Background: Schizophrenia is a neuropsychiatric illness affecting one percent of the world population. Among the multiple factors, maternal exposure to immunogenic agents such as lipopolysaccharide (LPS) is known as a significant environmental risk factor that increases the risk of schizophrenia or other neurodevelopmental disorders in the next generation. Quercetin (QE) is a natural flavonoid with multiple forms of desirable biological activity,
including anti-inflammatory and antioxidant properties. In the present study, we utilized maternal LPS injection on gestational days (GD) 15 and 16 as a model for schizophrenia to investigate whether QE supplementation can prevent LPS-associated alterations.

Methods: Pregnant rats (n=24) were randomly assigned into four experimental groups with six litters per group. Control and LPS groups: pregnant dams were received two consecutive intraperitoneal (i.p.) injections of either saline or LPS (0.5 mg/kg) dissolved in saline at

GD15/16, respectively. Both control and LPS groups were also gavaged with vehicle (water) throughout their pregnancy. LPS+QE and QE groups: pregnant dams were treated with LPS (0.5 mg/kg, i.p.) or saline on GD15/16 and meanwhile were daily supplemented with QE (50 mg/kg, suspended in water) throughout the gestational period. At postnatal day 60, Y-maze was used to evaluate the working memory performance of male offspring (n=12). After behavioral assessment, qPCR analysis was carried out to measure the expression levels of several pro-inflammatory mediators, including IL-6, IL-1β, TNF-α, NF-κB, and GFAP in the prefrontal cortex (PFC) of male pups (n=6). Furthermore, immunostaining was performed for the evaluation of astrocyte and microglia density on brain sections. The data analysis was conducted using two-way analysis of variance (ANOVA), with taking prenatal treatment (saline vs. LPS) and maternal supplementation (vehicle vs. QE) as between-group variables, followed by Bonferroni post hoc tests.

Results: Male offspring prenatally exposed to LPS showed a significant working memory impairment compared to the corresponding control ($F(1, 36) = 13.13$, $P = 0.0009$; LPS group vs control group Bonferroni post hoc analysis, $P < 0.001$), that returned to the control level upon maternal QE supplementation in LPS+QE group (LPS+QE vs LPS Bonferroni post hoc analysis, $P>0.05$). Furthermore, a significant effect of prenatal treatment was also detected for mRNA levels of IL-6 ($F(1, 20) = 6.060$, $P = 0.0230$), IL-1β ($F(1, 20) = 27.90$, $P < 0.0001$), TNF-α ($F(1, 20) = 12.44$, $P = 0.0021$), NF-κB ($F(1, 20) = 8.968$, $P = 0.0072$), and GFAP ($F(1, 12) = 23.86$, $P = 0.0004$), that was prevented by QE supplementation in LPS+QE group. These findings were accompanied by increased microglia ($F(1, 12) = 5.929$, $P = 0.0314$) and astrocyte ($F(1, 12) = 23.86$, $P = 0.0004$) density with unchanged neurons number ($F(1, 12) = 0.6726$, $P = 0.4281$) in the PFC of adult offspring. Interestingly, quercetin supplementation could reverse the mentioned deficits induced by LPS (LPS+QE vs LPS Bonferroni post hoc analysis, $P>0.05$).

Discussion: These results support the idea that the deleterious effects of prenatal LPS exposure could be attenuated by natural flavonoids such as quercetin. It is of interest to suggest early therapeutic intervention as a helpful approach to prevent neurodevelopmental deficits, following maternal infection.

V31. CORTICAL AND SUBCORTICAL STRUCTURAL MORPHOMETRIC PROFILES IN INDIVIDUALS WITH NON-AFFECTIVE AND AFFECTIVE EARLY ILLNESS PSYCHOSIS

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Background: Research has found strong evidence for common and distinct morphometric brain abnormality profiles in nonaffective psychosis (NAff-P) and affective psychosis (Aff-P). However, illness chronicity and prolonged medication exposure can confound the relationship between structural brain morphometry and pathophysiological processes underlying these disorders. Given these potential confounds, as well as the importance of early psychosis intervention, the current study analyzes Human Connectome Project-Early Psychosis (HCP-EP) morphometric brain profile data from NAff-P and Aff-P patients who are within five years of psychosis onset, as well as healthy controls (HC).

Methods: Multivariate profile analyses were implemented to examine regional profiles for cortical thickness, cortical surface area, subcortical volume (basal ganglia and other subcortical regions), and ventricular volume in healthy control (HC; n=56) and early illness NAff-P (n=83) and Aff-P (n=30) groups after accounting for normal aging effects. Associations with symptom severity, functioning, and cognition were also examined.

Results: Group regional profiles were significantly non-parallel and differed in overall level for cortical thickness (ps<.002), with NAff-P having widespread cortical thinning relative to HC and Aff-P and some regions showing greater deficits than others. Significant non-parallelism of group regional profiles was also evident for cortical surface area (ps<.018), with Aff-P and N-Aff-P differing from HC but not from each other. For basal ganglia volume, there was significant profile non-parallelism, with NAff-P having an enlarged left pallidum relative to HC and with Aff-P not differing from either HC or NAff-P. For other subcortical volumes (accumbens, hippocampus, amygdala, and thalamus), group regional profiles were significantly non-parallel and differed in overall level (ps<.032). In two-group comparisons, the NAff-P group had smaller subcortical volumes relative to HC (p=.022), driven primarily by smaller accumbens and hippocampus volumes (ps<.050). The Aff-P group had a smaller accumbens and amygdala relative to HC (ps<.005) and a smaller amygdala relative to NAff-P (p=.050). Further, NAff-P had enlarged ventricular volumes compared to HC and Aff-P (ps<.037). Regional morphometric measures were not significantly correlated with clinical and cognitive measures within groups.
Discussion: Overall, participants with early psychosis had structural morphometric brain abnormalities relative to HC, with more pronounced and widespread abnormalities in the NAff-P group than in the Aff-P group. Moreover, direct comparison of NAff-P and Aff-P groups revealed differences in both the overall level of abnormalities and/or the pattern of their regional profiles, depending on the type of morphometric measure (i.e., thickness, surface area, or volume) and whether cortical or sub-cortical regions were considered. Despite these group differences, which largely reflect differential manifestations of structural brain abnormalities in the early course of schizophrenia spectrum disorders versus bipolar and unipolar affective disorders, clinical and cognitive measures were not significantly associated with structural morphometric measures within either group. Thus, our results suggest that distinct underlying pathophysiological processes in schizophrenia spectrum and mood spectrum psychoses give rise to different levels and non-parallel profiles of brain dysmorphologies in the early stages of these disorders.

V32. ADAPTING THE METHOD OF ADMINISTERING THE MATRICS CONSENSUS COGNITIVE BATTERY (MCCB) TO ASSESS COGNITION IN OLDER, UNDEREDUCATED INDIVIDUALS WITH SCHIZOPHRENIA IN RURAL CHINA

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Background: Community-dwelling individuals with schizophrenia who are elderly and those with low levels of education – many of whom live in rural areas of low- and middle-income countries – are excluded from most studies about cognition in schizophrenia. As a result, currently available research is unable to provide insights about the trajectory of cognitive changes in elderly, undereducated patients and, thus, it is not possible to develop appropriate intervention for these vulnerable individuals. One problem of conducting cognitive research in these under-represented cohorts is the difficulty many of them have in understanding the expectation of standardized neuropsychological tests developed in Western countries for younger, better-educated populations. This report describes our experience of adapting 8 of the 10 tests in the MATRICS Consensus Cognitive Battery (MCCB) – the most widely used cognitive battery for assessing cognition in schizophrenia -- for use with community-dwelling individuals with schizophrenia living in rural parts of China.

Methods: Based on province-wide registries of community residents with severe mental illness, we enrolled 134 individuals with schizophrenia who had never been treated (UT) and 134 matched individuals currently being treated for schizophrenia (TC) in Ningxia and Guangxi, China; 134 matched healthy controls (HC) were identified from local health clinics. Groups were matched for gender, age, years of schooling, ethnicity, residence and [for the patient groups] duration of illness. The mean (sd) age of the 402 respondents was 49.2 (9.2) years (16.2% were 60 years of age or older); 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 the patient groups was 20.5 (9.5) years.
While maintaining the formal testing part of each MCCB test, the instructions provided prior to each test were expanded and repeated with the goal of ensuring that respondents understood the expectations of each test to the greatest extent possible. Interviewers assessed respondents' comprehension of the requirements of each test (on a 4-level 'comprehension' measure) and classified results of each test as 'incomplete' or 'successfully completed'. Based on two independent raters' assessment of tape recordings of 125 individuals (42 UT, 26 TC, 56 HC) administered the adapted MCCB, the mean inter-rater reliability (kappa) of the comprehension measure for the 8 tests was 0.83 (range: 0.73-0.92) and that for the completion measure was 0.94 (range: 0.86-0.98).

Results: The mean successful completion rate among all 402 respondents for the 8 MCCB tests was 88.1% (range: 73.4% to 92.3%); for all 8 tests the successful completion rate was greatest in HC, intermediate in TC and lowest in UT. The mean proportion of respondents requiring multiple explanations (more than provided in the standard administration of the MCCB) to understand the requirements of the 8 tests was 52.9% (range: 38.3-76.9%). Among those who required multiple explanations – that is, those who would be dropped from studies using the standard MCCB – a mean of 78.1% (range: 66.0-88.9%) successfully completed the test. Multivariate logistic regression analysis found that after controlling for group status, years of schooling remained significantly associated with successful test completion for all tests except for the verbal learning and visuospatial memory tests.

Discussion: It is feasible to expand the use of MCCB to assess undereducated, older individuals with schizophrenia who are typically excluded from studies of cognition in schizophrenia. This requires standardized expansion of the instructions for each of the MCCB tests and providing additional training to test administrators. Even after expanding the instructions, there are higher rates of incomplete tests and higher proportions of basement values in the successfully completed tests in undereducated, older respondents than reported in younger, more educated respondents, but the majority of these respondents can, nevertheless, successfully complete the tests. An estimated 40-50% of individuals with schizophrenia worldwide do not meet the standard age and education inclusion criteria for MCCB, so adaptation of the methods presented here to expand the use of MCCB to such individuals merit assessment in other locations.

V33. IS GENETIC PREDISPOSITION TO SCHIZOPHRENIA ASSOCIATED WITH A HIGHER INCIDENCE OF TYPE 2 DIABETES MELLITUS AMONG ADULTS WITH NO SCHIZOPHRENIA DIAGNOSIS? A LONGITUDINAL STUDY OF THE UK POPULATION.

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Background: People with a diagnosis of schizophrenia are 2-3 times more likely to suffer from type 2 diabetes (T2DM) than general population. Although there are factors known to be associated with a higher risk for T2DM, such as poor diet or low physical activity, recent evidence suggests that common genetic variants that are shared between T2DM and schizophrenia diagnoses may be potent in increasing risk for T2DM onset. Indeed, using polygenic risk scores, which measures genetic propensity to a disease, it was shown that high genetic propensity to schizophrenia was associated with poor glycemic control and insulin resistance.

These results, however, have not been consistently replicated, leaving a degree of uncertainty of the importance of the shared genetic between T2DM and schizophrenia for influencing T2DM onset. Studies of the relationship between schizophrenia genetic liability and T2DM in undiagnosed individuals are even less consistent and scarce, although they provide a methodological advantage, in which schizophrenia-specific environmental factors are minimal limiting their confounding effect on the findings. Therefore, in the present study we investigate whether the polygenic predisposition to schizophrenia is associated with a higher risk of T2DM onset in the general population of adults without schizophrenia diagnosis.

Methods: The analysis is based on a large, population-representative sample of adults (aged ≥50) residing in the UK with no reported diagnosis of schizophrenia from the English Longitudinal Study of Ageing (ELSA). We investigated longitudinal association between the PGS for schizophrenia (PGS-SZ) and T2DM onset using a proportional hazards model with interval censoring. The outcome included diagnosed and undiagnosed incidences of T2DM, which were identified by self-report or by the study blood tests respectively. PGS-SZ were computed based on the 2020 GWAS by Schizophrenia Working Group of the Psychiatric Genomics Consortium. Power calculations were performed: we have a 80% power to detect a hazard ratio larger than 1.15 per 1 standard deviation in PGS-SZ at an alpha level 0.05 in our sample; weaker associations can be falsely reported as insignificant.

Results: Our sample comprised 5968 adults with mean observation time of 8.7 years. We identified 493 incident cases of T2DM, 379 self-reported and 117 from the blood tests. The association analyses showed that there was no significant association between PGS-SZ and incidence of T2DM during the follow-up, neither while adjusting for age, gender, and genetic ancestry, nor while additionally accounting for the polygenic score for T2DM and T2DM risk factors such as body mass index, hypertension, cardiovascular disease, stroke, exercise regime, smoking, depression.

Discussion: Our results do not support a notion that an aggregated risk of minor genetic variations linked with schizophrenia accelerates T2DM risk in older adults from the general population in the UK. This suggests that the link is weak in this population, limiting clinical relevance of the genetic predisposition to schizophrenia in relation to T2DM risks to the individuals with schizophrenia. The results might indicate a confounding role of schizophrenia-related environmental factors, in the absence of which in population-wide samples like ours the observed effect is minimal. Another possibility is that PGS-SZ were not effective in representing schizophrenia-related genetic risks underlying T2DM development, in which case different methods introducing genetic risk to the analysis may be needed to clarify and quantify the impact of schizophrenia genetic factors on the risk of T2DM.

V34. A NETWORK ANALYSIS ON SCHIZOTYPAL FEATURES, PSYCHOPATHOLOGY AND SOCIAL FUNCTIONING IN A YOUTH EPIDEMIOLOGICAL SAMPLE

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Background: Schizotypy is conceptualised as a set of personality characteristics which reflect the vulnerability to schizophrenia. Schizotypy is an important construct for elucidating psychopathology-personality connection in subclinical populations. Schizotypal features could be captured using various self-report rating scales, such as the Schizotypal Personality Questionnaire (SPQ), the Community Assessment of Psychic Experiences (CAPE) and the Prodrome Questionnaire (PQ), and are manifested early in late adolescent and early adulthood. Epidemiological sampling is a robust method to identify representative samples. However, very few research have been conducted to investigate schizotypal features in epidemiological youth samples.

Methods: A total of 864 youth participants aged 15-24 were recruited using epidemiological sampling in Hong Kong Special Administrative Region, China, and completed the brief versions of the SPQ, the CAPE and the PQ. Participants also completed the 21-item Depression Anxiety Stress Scale (DASS), the Social and Occupational Functioning Assessment Scale (SOFAS), the 12-item Social Functioning Scale (SF-12), and the Connor–Davidson Resilience Scale (CDSS). Network analysis using Fruchterman-Reingold algorithm was performed using R software, with variables of SPQ-cognitive perceptual, SPQ-Interpersonal, SPQ-Disorganised, CAPE-Distress, CAPE-Feeling, PQ-Distress, PQ-Endorsement, SF-12, SOFAS, DASS-Depression, DASS-Anxiety, DASS-Distress, CDSS as nodes.

Results: The resultant network found that the nodes of SPQ clustered together, and the nodes of PQ and CAPE formed another cluster. The psychopathological nodes also clustered together. Notably, the nodes of SPQ-Interpersonal and the CAPE-Distress linked the clusters of schizotypal traits with the node of SOFAS. The nodes of DASS-Depression and DASS-Anxiety also linked with the SOFAS. The PQ-Endorsement and CAPE-Distress are nodes having the highest expected influence. The resultant network showed high stability.

Discussion: Our preliminary study investigated the complex interplay between schizotypal features, psychopathology, resilience and social functioning in an epidemiological sample of youth. Our findings supports that schizotypal personality features play a role in social functioning in the youth populations.

V35. PATIENT-REPORTED EXPOSURES AND OUTCOMES LINK THE GUT-BRAIN AXIS AND INFLAMMATORY PATHWAYS TO SPECIFIC SYMPTOMS OF SEVERE MENTAL ILLNESS

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Background: A number of studies now identify gut dysbiosis in persons with psychiatric disorders, but information on underlying factors, such as other inflammatory conditions, allergies, health factors, diet, and lifestyle is lacking. This cross-sectional study employed a comprehensive self-report questionnaire on conditions and exposures related to the microbiome gut-brain-axis (GBA) in psychiatric cases and controls to examine the association of GBA factors with psychiatric symptoms and illness features.
Methods: The 82 study subjects included 40 with psychosis (mean age=38.1 (11.1), 50% female), 18 nonpsychotic affective disorder cases (mean age=39.7 (11.2), 72% female), and 24 healthy controls (mean age=33.4 (9.39), 54% female). Each completed the self-report scale, underwent research diagnostic interviews with the Diagnostic interviews for Genetic Studies (DIGS) and Diagnostic Interview for Psychosis and Affective Disorders (DI-PAD). Symptoms were rated using the Positive and Negative Syndrome Scale, with symptoms quantitated in the original and 5-factors solutions. Logistic and linear regression examined associations of self-reports with clinical data.
Results: Subjects self-reported psychiatric diagnoses matched those from structured interviews. The severity of activation symptoms was robustly associated with numerous immune and inflammatory conditions, including gastroesophageal reflux disease ($p=0.014$), skin conditions ($p=0.000$), and lactose intolerance ($p=0.050$), as well as with the number of comorbid psychiatric and medical conditions ($p's<0.009$). Activation is characterized by hostility, poor impulse control, excitement, uncooperativeness, poor rapport, and tension. Gluten sensitivity, on the other hand, predicted general psychopathology and total symptom scores ($p's<0.040$), whereas bowel habits, mode of birth and infant feeding were variably related to dysphoria, negative symptoms, and general psychopathology ($p's<0.045$). Compared to controls, both psychotic and non-psychotic affective disorder groups had worse health and dietary habits (e.g., smoking, less exercise, frequent ready-made meal consumption: $p's<0.045$) and increased consumption of filtered rather than tap water ($p's<0.014$). The psychotic cases were distinguished from the nonpsychotic cases by being significantly less likely to take probiotics or other supplements ($p's<0.038$).
Discussion: We demonstrate the value of patient reported measures, specifically those related to the GBA, in psychiatric research. The clear association of activation factor severity with inflammatory conditions suggests its utility to identify disorders with an inflammatory basis and as a treatment target. Other findings replicate previous associations of poor nutrition, food intolerance, inflammatory conditions, and early life exposures with psychiatric disorders.

V36. SCREENING FOR EARLY PSYCHOSIS IN A COLLEGE COUNSELING CENTER: PROCESS OUTCOMES AND IMPLEMENTATION CHALLENGES

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Background: Although evidence on community-based early detection (ED) programs aimed to reduce prolonged durations of untreated psychosis (DUP) is large and growing, very little is known about the effectiveness of ED services on college campuses in the United States. This gap in the literature is problematic because, with the first symptoms of psychosis being most likely to surface among college age young adults, college campuses are hubs for individuals at an age of increased risk of first episode psychosis (FEP). The objective of our study was to determine the feasibility of an ED program that aimed to: (i) identify college students at clinical

high risk (CHR) of psychosis or with FEP, and (ii) efficiently link them to coordinated specialty care (CSC) services for a 2nd stage screen, a clinical assessment, and appropriate treatment.
Methods: To identify whether case identification is an important target for ED programs on college campus, the Prodromal Questionnaire Brief (PQ-B) was included in the battery of screening tools completed by students during triage when seeking mental health services at a local university's college counselling center. Since August 1st, 2020, the following process outcomes have been tracked: (1) number of PQ-B's; completed at triage, (2) number of students who met the cut-off score on the PQ-B ($\geq$ 20), (3) number of referrals to CSC, (4) number of students who received a phone screen and second stage assessment, (5) number of students enrolled in CSC, and (6) basic demographic characteristics of those who completed the PQ-B (i.e., age, gender, ethnicity, level of education and PHQ-9). Among those students who met cut-off criteria on the PQ-B but not referred to CSC, we also tracked reason for not being referred. Among students who were referred and who contacted the CSC program referral line, we also tracked reasons for not being enrolled in CSC.
Results: Between August 1st 2020 and September 30th, 2021, 1,096 students completed the PQ-B. Students identified predominantly as either Hispanic/Latino (38%) or White non-Hispanic (42.9%) female students (61.5%) with an average age of 24.40±6.59 years (range = 17 to 65 years). The majority (50.3%) of students were either sophomore (13.8%), junior (16.4%), or seniors in college (20.1%) and had a mean PHQ-9 score of 11.92±5.95 (range = 0.00 to 29.00). Of those 1096 students who completed the PQ-B, 334 students met the cutoff of $\geq$ 20. Of those, 239 students were referred to CSC. Of those, 171 students contacted the CSC referral line. Of those, 160 students completed a phone screen. Of those, 53 students were referred to CSC for CHR and 11 were referred to CSC for FEP. Of the 53 students referred to CSC for CHR, 36 completed the SIPS and 16 were enrolled. Of the 10 students referred to CSC for FEP, 2 students were enrolled.
Discussion: The implementation of the PQ-B at a college counseling center has thus far identified more students at CHR of psychosis rather that students with FEP. It is likely that those students with FEP have either dropped out of college or show up at points of care that serve higher acuity levels, including psychiatric emergency services and inpatient units. Many challenges with the implementation of universal screening for CHR and FEP within a collegiate health setting were identified and will be discussed in this presentation, including the identification of the appropriate PQ-B cut-off for this population, the need for ongoing communication with and training for the counseling center counselors to address their concerns and increase their psychosis literacy, and implementation of a universal screening tool during COVID when all services at the college counselling center shifted from in-person to remote.

V37. NO EVIDENCE FOR MODULATION OF NEURONAL NETWORKS OF AUDITORY HALLUCINATIONS BY TRANSCRANIAL DIRECT CURRENT STIMULATION

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Background: Transcranial direct current stimulation (tDCS) is being investigated as treatment for auditory verbal hallucinations. The theory behind the treatment is that tDCS increases

activity in cognitive control areas in the prefrontal cortex, which are assumed to be hypoactive, and simultaneously decreases activity in speech perception areas in the temporo-parietal lobe, which are assumed to be hyperactive during auditory-verbal hallucinations. We tested this hypofrontal/hypertemporal reversal theory in two ways: (1) A randomized clinical trial (RCT) in patients with medication resistant, auditory-verbal hallucinations that received tDCS treatment and (2) in healthy individuals that received a single session of tDCS. Anatomical, neurotransmitter, brain activity, and network connectivity changes in both patients and healthy individuals were examined.

Methods: 1) Twenty-one patients (mean age 35.5 years, 14 males) with auditory-verbal hallucinations participated in a double-blind RCT, receiving either sham or real tDCS treatment (2mA) twice daily for 5 days (double-blind). All patients experienced auditory-verbal hallucinations at least five times a week and received unsuccessful treatment with at least two different antipsychotics. The majority was diagnosed with schizophrenia (15) as diagnosed by their independent psychiatrist according to ICD10. The anode was placed over the left dorsolateral prefrontal cortex (DLPFC) and the cathode over the left temporo-parietal cortex (TPC). Multimodal neuroimaging (fMRI, MRS, resting state MRI, structural MR) as well as clinical and neurocognitive functioning assessment were performed before, immediately after, and three months after treatment.

2) We ran two studies with healthy individuals. In experiment 1, 20 participants received two sessions of tDCS (sham and 2mA, within-design, double-blind) for 10 min with the anode placed over the TPC and the cathode placed over the contralateral orbitofrontal cortex. MR spectroscopy in the TPC region was measured before, during, and after stimulation. In Experiment 2, 32 participants received two sessions of tDCS (sham and 2mA) for 20 min (double-blind) with the anode placed over the TPC and the cathode placed over the left DLPFC. Task-related fMRI as well as MR spectroscopy in the DLPFC and TPC was measured before, during, and after tDCS. Additionally, the electrical current was modeled based on anatomical scans.

Results: 1) Real tDCS led to a reduction of hallucinations as compared to sham with d=0.14 to 0.47, based on patients' self-report. No reductions in hallucinations or other clinical measures were reported by clinicians who had assessed patients (e.g., with PANSS). Moreover, tDCS did not lead to measurable effects in the neuroimaging data.

2) Neither experiment in healthy individuals revealed robust changes in GABA, glutamate or in functional activity measures. Modelling of the tDCS electrical currents suggested that with the DLPFC/TPC montage that is used in most tDCS treatment studies, the activation is strongest in Broca's area, not the DLPFC or the TPC itself.

Discussion: Our findings suggest that the currently leading theory behind tDCS treatment of AVH may need to be revised: Neither in patients after typical tDCS treatment (and typical treatment effects), nor in healthy individuals after a single session of tDCS (with the same intensity and length as in the tDCS treatment), we observed meaningful neuroimaging effects in the two target regions DLPFC and TPC. In line with other studies our modelling data suggests that Broca's area might play a critical role for the underlying neuronal mechanisms of the tDCS treatment. However, the interpretation of the findings is limited by the small sample sizes.

V38. CHILDREN'S HOSPITAL OF PHILADELPHIA (CHOP) ELECTRONIC HEALTH RECORD (EHR) ANALYSIS OF INDIVIDUALS WITH 22Q11.2 DELETION SYNDROME AT RISK FOR PSYCHOSIS SPECTRUM DISORDERS

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Background: 22q11.2 deletion syndrome (22qDS) is the most common microdeletion syndrome, found in 1/2148 neonates and 1/992 unselected pregnancies. Because nearly 1/3 of individuals with 22q11.2 deletion syndrome (22qDS) develop schizophrenia, this patient population is a natural focus of early risk factors for psychosis. The 22q and You Center at the Children's Hospital of Philadelphia (CHOP) is a world leader in multidisciplinary care for patients with 22qDS supporting patients locally and from a distance (>50% reside >100 miles from CHOP). The present study retrospectively mined the CHOP EHR of patients with 22qDS to identify potential biomarkers enriched in individuals who subsequently develop psychosis prior to onset of symptoms.

Methods: The study used Clinical Text Analysis and Knowledge Extraction System (cTAKES), an open-source Natural Language Processing (NLP) system to extract clinical information from EHR unstructured text, based on healthcare notes, in the form of 3,812 Human Phenotype Ontology (HPO) terms. A cohort of 1,008 patients with 22qDS and 50,801 total notes were identified based on billing records, of whom 127 had evidence of psychosis-related HPO terms (mean age of first psychosis-related HPO term, 10.6 years; mean age of first encounter, 5.5 years). A case-control approach was used to compare HPO terms in these individuals (prior to documentation of psychosis) compared to the remaining cohort in age-matched bins. Penalized logistic regression (ridge regression) was performed with 5-fold cross validation in independent test sets. Pairwise phenotypic similarity between individuals was also calculated based on the information content of the least common subsumer (Lin's semantic similarity), and a permutation test was used to compare phenotypic similarity between groups.

Results: The association between documented psychosis and psychosis predicted by ridge regression models in independent data was weakly statistically significant (r=0.07, p=0.02). Individual HPO terms enriched in the psychosis sample (prior to any documentation of psychosis) included "Impulsive behavior", "Impaired cognition", "Self harm", "Sleep Apnea Syndromes", "Tooth problem", and "Sinusitis". Phenotypic similarity in the group without psychosis (0.65) was higher than phenotypic similarity in the group with psychosis (0.61, p=0.006, 1,000 permutations).

Discussion: This study provides evidence for both the opportunities and challenges in employing the EHR to develop predictive models of psychosis risk. The results are consistent with a heterogeneous spectrum of phenotypic presentations prior to onset of psychosis in individuals with 22qDS.

V39. GENERATIVITY AMONG PEOPLE RECEIVING PEER SUPPORT: A MIXED METHODS STUDY

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Background: Generativity refers to the contributions that people make towards the betterment of others, communities, and future generations. Engaging in generativity may add purpose and meaning to one's life, elements which people who experience psychosis feel is relevant for their recovery. Findings from a scoping review suggest that providing peer support may facilitate generativity among peer support workers (Jordan et al., 2021). However, no

qualitative or quantitative study has examined if receiving peer support is associated with generativity. Addressing this knowledge gap using mixed methods may highlight the importance of peer support in people's recovery; inform the development of recovery-oriented interventions; and may help shift stigmatizing views that people with mental illnesses are a burden on society. To address this knowledge gap, we employed mixed methods to 1) determine if people who received peer support endorsed higher average generativity scores relative to people who did not receive peer support; and 2) ask participants to help interpret and elaborate on the quantitative results

Methods: The objectives were evaluated using a mixed methods sequential design over two phases. During the quantitative phase, 43 participants completed questionnaires measuring generativity and the receipt of peer support over the past month. During the qualitative phase, 5 participants interpreted and elaborated upon the quantitative results by drawing on their own lived experiences. Participants of the quantitative component were recruited from a public mental health hospital serving the needs of marginalized people with mental health challenges in the United States. Participants of the qualitative component were recruited from community-based peer support organizations and professional societies staffed by people with lived experience of mental health challenges based in the United States

Results: No difference in average generativity scores was observed between people who received ($M = 4.2$, $SD = 1.7$) or did not receive ($M = 3.9$, $SD = 1.5$) peer support over the past month $F(1,38) = .55$, $P = .46$. When asked to interpret the quantitative results participants in the qualitative component expressed that the null result could be explained by the fact that peer support was delivered in a hospital-based setting, where peer support often centres around clinical activities to the exclusion of doing "what makes peers really powerful", such as building relationships and fostering generativity. When reflecting on their own experiences, participants in the qualitative component reflected on how being part of community-based peer support groups helped them find ways to "give back" to their communities, in turn fostering recovery, as expressed by one participant: "All the small ways that I'm giving back, and the stuff that I've acquired…I used to be very isolated and I used to reach out to nobody and I used to think that I didn't like people. But when I started to volunteer, it was like things led to things. People can be completely transformed by being part of something bigger than themselves."

Discussion: Findings from this study suggest that peer support may facilitate generativity among recipients of such support; however, it may be important for such support to be based in the community and in group settings where mutuality and relationship-building among members is experienced.

V40. COMPARING PSYCHOSIS RISK DURING COVID IN HISPANIC/LATINO AMERICANS, NON-HISPANIC/LATINO AMERICANS, AND HISPANIC/LATINOS LIVING IN LATIN AND CENTRAL AMERICAN COUNTRIES

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Background: Ethnic minority status is associated with societal disadvantages and is noted as a significant risk factor for the development of psychosis (Selten et al., 2019). Concurrently, the COVID pandemic has been associated with increased risk for psychosis across cultures but especially among ethnic minority groups, such as Hispanic/Latino Americans (HLA; Griffith et al., 2021). To further understand how minority status might be linked to psychosis risk, we compared the psychosis risk rate among a prominent ethnic minority group (HLA) with rates among two majority groups: non-Hispanic/Latino Americans (n-HLA) and Hispanic/Latinos

living in Latin and Central American countries (HL). We predicted that HLA would have the greatest number of high-risk respondents compared to n-HLA and HL. Several cross-cultural studies of mental wellbeing during COVID have also identified universal markers associated with high psychosis risk: younger age, social isolation, and trauma (Lee et al., 2020; Dean et al., 2020; Tso and Park, 2020). Based off these findings, we predicted that these markers would be consistent among high-risk participants across HLA, n-HLA, and HL.

Methods: We assessed psychosis risk across HLA, n-HLA, and HL, and assessed characteristics of high- vs. low-risk individuals across cultures. 45 HL participants, 34 n-HLA respondents, and 30 HLA respondents completed an anonymous, online survey in English or Spanish. Respondents self-reported demographic information (including racial and/or ethnic background), physical health, and past trauma. The Depression, Anxiety, and Stress Scale (DASS); the UCLA Loneliness Scale, and the Prodromal Questionnaire-16 (PQ-16) assessed mental health. Social isolation was assessed by the Social Network Index (SNI).

Results: 30% of HLA participants met criteria as high-risk for psychosis on the PQ16. In HLA, high-risk individuals were younger, had less education, more depression, more days disabled, more days physically ill, and were lonelier than low-risk individuals. The HLA group had fewer male respondents than n-HLA and HL, but the groups matched on all other demographic variables.

8.8% of n-HLA respondents were noted as high-risk for psychosis. High-risk participants had worse general health, fewer social networks, more trauma, fewer days happy or hopeful, and were lonelier than low-risk respondents.

26.7% of HL participants were classified as high-risk for psychosis. High-risk participants were younger, had more trauma, fewer social networks, and fewer high-contact social roles than low-risk people.

In sum, HLA had the greatest number of high-risk respondents, closely followed by HL. HL also had the most distress related to psychotic-like experiences. Multiple linear regression analysis showed group membership predicted the number of psychotic-like experiences and related distress, as well as trauma and number of high-contact social roles – two factors related to elevated psychosis risk.

Discussion: Our results support our primary hypothesis and echo previous findings there are disparities across groups in proportion of high-risk individuals based on ethnic minority status, with HLA having the most high-risk respondents. Results also support our secondary hypothesis that younger age, trauma, and social isolation are markers for high psychosis risk across groups. Of note, each group also demonstrated specific additional markers for high-risk status, which suggests additional risk factors may be culturally distinct. A thorough understanding of these distinctions and group-specific markers is crucial for culturally informed research, especially in Hispanic/Latino populations, which are historically underrepresented in psychological research.

V41. ALTERED NEURAL MECHANISM OF SOCIAL REWARD ANTICIPATION IN PATIENTS WITH SCHIZOPHRENIA

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Background: Social motivation is the ability to form and maintain the social relationships. Patients with schizophrenia (SCZ) are characterized by a wide range of severe social dysfunctions including diminished motivation for social rewards. Altered social reward anticipation has been recently emphasized as a transdiagnostic phenotypic marker of psychopathology. However, previous studies have been mainly limited to behavioural performances. The underlying neural mechanisms of the altered social reward anticipation remain largely unclear in psychiatric disorders such as SCZ. On the other hand, several specific social brain regions have been found to engage in social motivation processing. However, it is still not clear whether the general social brain network (SBN) may support the complex social interaction on the social reward anticipation processing. In the present study, we examined the potential abnormality of the neural processing of social reward anticipation in patients with SCZ. We also explored the SBN during the social reward anticipation in SCZ patients.
Methods: Twenty-three SCZ patients and 17 healthy controls (HC) were recruited in the present study. All the participants completed a Social Incentive Delay (SID) functional magnetic resonance imaging paradigm while they were undertaking a brain scan in a 3T Siemens scanner. They also completed a set of social network (SN)-related questionnaires after the brain scans. We used the group contrast to explore the potential abnormal bold signal changes and functional connectivity (psychopathological interaction analysis, PPI) during the social reward anticipation. A SBN was built based on the meta-analysis results of multiple social processes from NeuroSynth. Then, we used the regions in this SBN as regions of interest and constructed the functional SBN for each participant using the Beta series correlation. The partial least squared regression (PLSR) analysis was further applied to examine the functional connectivity (FC) within SBNs to predict the SN characteristics.
Results: Compared to HC, SCZ patients exhibited decreased activation in the left medial frontal gyrus (MFG, peak MNI at -3 -6 60, cluster size = 54 voxels, t = -4.63, cluster-level pFWE < .01) and showed the negative FCs between the left MFG and the left parietal regions (including the cuneus, post cingulate cortex and postcentral gyrus) while they were anticipating social rewards. For the beta-series SBNs, SCZ patients exhibited increased cerebellum-temporal FCs during the social reward anticipation. The FCs of SBN during the social reward anticipation did not predict SN characteristics in SCZ patients ($R2 = 0.09$, $F(1,20) = 1.60$, $p = .22$), but significantly predicted the SN characteristics in the HC ($R2=0.28$, $F(1,14) = 5.01$, $p = .04$).
Discussion: The altered BOLD signals changes and the FCs in SCZ patients suggest that SCZ patients exhibited decreased local frontal-parietal neural connection during social reward anticipation. These findings are consistent with previous evidence showing that SCZ patients were sensitive to social processing. For the beta-series SBNs, our findings also suggest that there might be disassociation between the SBNs with the social functioning performance in SCZ patients. Taken together, these findings highlight the altered neural mechanism associated with social reward anticipation in SCZ patients.

V42. 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-four antipsychotic-naive FEP patients, aged 19 or more and less than 45, were enrolled, along with 23 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 69.3, 47.5, and 42.7, respectively. All FEP patients showed treatment response after 6-week treatment of amisulpride, while 2 FEP patients had worsening of psychotic symptom afterwards. The change in kicer value over time significantly differed between FEP patients and healthy controls.
Discussion: Significant change in dopamine synthesis capacity were found after 1-year amisulpride treatment but not after 6-week treatment in FEP patients. These results suggest that the effect of antipsychotics treatment on dopamine neurotransmission might be related to delayed decrease of striatal dopamine synthesis capacity. Longer prospective study is needed to confirm the antipsychotic effect on the dopamine synthesis capacity in FEP.

V43. PLASMA MARKERS INDICATING OXIDATIVE STRESS IN RECENT ONSET PSYCHOSIS

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Background: Findings of increased skin levels of advanced glycation endproducts (AGEs) in patients suffering from recent onset psychosis compared to controls indicate excessive oxidative stress. The investigation of plasma markers of oxidative stress and inflammation, and their determinants can further elucidate the role of oxidative stress in the pathophysiology of psychosis. Also, investigation of activity of the kynurenine pathway (a possible link between immune-activation and neurotoxic effects) will contribute to our understanding of the neurobiological processes underlying psychotic disorders.
Methods: 150 patients aged 18 to 35 years of diverse ethnic backgrounds suffering from recent onset psychosis are matched to 150 controls based on age, sex and ethnicity. EDTA plasma samples will be analyzed for parameters indicating oxidative stress (chlorotyrosine, bromotyrosine, nitrotyrosine and malondialdehyde) and activity of the kynurenine pathway, and a set of pro- and anti-inflammatory cytokines. Plasma concentrations will be compared in patients versus controls through linear regression analyses and best predictors of disease status will be selected through a lasso-penalized regression analysis. Also, disease-related and non-disease related determinants of individual of the biomarkers identified as best predictors will be assessed. Finally, association of skin AGE levels and plasma indicators of oxidative stress will be investigated through linear regression analyses.
Results: Biomarkers are being analyzed as of now, results are expected in December 2021.

Discussion: The size and representability of the sample, our matching strategy and the careful investigation of plasma markers indicating oxidative stress will enable us to draw reliable conclusions about the association between psychosis and oxidative stress, inflammation, activity of the kynurenine pathway. If results confirm our hypothesis of excessive oxidative stress in recent onset psychosis, this would emphasize the need to further investigate the effect of interventions aimed to lower oxidative stress or treat its determinants.

V44. MORTALITY, CARDIAC PROCEDURES AND CARDIOPROTECTIVE PHARMACOTHERAPY AFTER ACUTE CORONARY SYNDROME IN PATIENTS WITH SEVERE MENTAL ILLNESS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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[1]Li Ka Shing Faculty of Medicine, University of Hong Kong**Background:** People with severe mental illness (SMI) including schizophrenia, bipolar disorder and their related spectrum disorders have a life expectancy 15 – 20 years shorter than that of the general population. A vast majority of premature mortality was attributable to natural causes, including acute coronary syndrome (ACS). Notably, recent investigation further indicated that people with SMI were less likely to undergo cardiac procedures such as catheterization and revascularization, and receive prescriptions of cardioprotective medications for any cardiovascular diseases relative to the general population, thereby indicating inequitable medical care in this vulnerable group of patients. This study aimed to conduct an updated comprehensive meta-analysis to quantitatively synthesize estimates of post-ACS mortality risk and adequacy of cardiac treatment in patients with SMI relative to the general population.
Methods: We performed a comprehensive search of EMBASE, MEDLINE, PsychoINFO and WOS databases without language restrictions up to 31 July 2021. Three reviewers evaluated evidence that compared mortality risk and likelihood of receipt of cardiac procedures and cardioprotective medications in ACS patients with and without SMI, and performed formal assessment of the methodological quality of the studies using the Newcastle-Ottawa Scale. Adjusted relative risk (RR) and odds ratios (OR) were pooled across studies using the random-effects models. Heterogeneity was assessed by the chi-square Cochran's Q-test and I2 statistic and publication bias was examined using the funnel plot and Egger's regression asymmetry tests.
Results: Twenty-two studies were included in the review, comprising 12,235,501 patients with ACS (of whom 503686 had SMI). Patients with SMI had increased risk of mortality (RR=1.40 [95% CI: 1.21–1.62]; I2=97.3%, P<0.001), and were less likely to receive cardiac procedures (OR=0.52 [0.47–0.58]; I2=99.1%, P<0.001) and cardiovascular medications (RR=0.89 [0.85–0.94]; I2=89.4%, P<0.001), relative to the general population. Subgroup analyses demonstrated that SMI was associated with higher 30-day (RR=1.38 [95% CI: 1.16–1.65]) and 1-year mortality (RR=1.68 [1.42–1.98]), lower receipt of cardiac catheterization (OR=0.49 [0.39–0.60]) and revascularization (OR=0.57 [0.49–0.67]), and reduced ACEI/ARBs (RR=0.92 [0.88–0.97]), beta-blockers (RR=0.92 [0.88–0.95]) and statins (RR=0.76 [0.61–0.94]) prescriptions, relative to the comparison population.
Discussion: Our finding confirms the elevated mortality risk and insufficiency of cardiac care in people with SMI following ACS and thus underscores the urgent need to address underutilization of therapeutic procedures and under-prescribing of cardiovascular medications among patients with SMI. Future studies should also assess moderators and mediators for the

differential mortality gap and thus more information can be gathered to guide healthcare resources allocation to optimize the cardiac outcomes in treatment planning.

V45. TREATMENT RESISTANCE IN FIRST EPISODE PSYCHOSIS: EARLY INDICATORS AFTER ONE YEAR IN TREATMENT

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Background: Identification of early indicators of treatment non-response is an important step for the achievement of personalized treatment options for first episode psychosis (FEP) patients. The response to established treatments is heterogeneous and studies indicate that approximately 1/3 of patients appear to be treatment-resistant (TR) to standard antipsychotic treatment. A recently introduced consensus definition of TR include 1) the presence of symptoms that are sustained at moderate levels or higher and 2) markedly reduced functioning in the context of 3) at least two adequate trials of antipsychotic medications. Studies indicate that TR can manifest already during the first years of treatment. The aim of the current study was thus to investigate the prevalence of TR at one-year follow-up (FU), and to examine pre-treatment, baseline, and early treatment characteristics of TR.

Methods: This study is part of the naturalistic "Thematically Organized Psychosis" (TOP) research study. Patients meeting DSM-IV criteria for a schizophrenia spectrum disorder at baseline and recruited within their first year of treatment were eligible to this prospective one-year FU study. TR was defined based on the Treatment Response and Resistance in psychosis working group (TRRIP) criteria, with reduced global functioning defined as GAF-F score ≤ 60. Symptomatic remission was defined based on the Remission in Schizophrenia Working Group (RSWG) criteria for remission.

Results: A total of 211 FEP patients with a schizophrenia spectrum diagnosis participated, 125 (60 %) were males and the mean age at baseline was 27.2 (SD 7.7) years. At FU, 99 (47%) FEP met RSWG criteria for remission. Out of the 101 patients not currently in remission, 98 (46% of all participants) also had a GAF functioning score below 60 and thus met the symptom- and function criteria for TR. However, only 36 (17%) of all FEP patients met the additional TRRIP treatment criteria of either two adequate antipsychotic trials or use of Clozapine. A total of 65 patients met the symptom- and function criteria but had not received two adequate antipsychotic trials. A total of 12 (18.5% of this group or 5.5% of the total) were in an ongoing trial of antipsychotic medication with less than 12 weeks observation time at FU. In the group that had achieved symptomatic remission, 25 (23% of this group) had received two adequate trials while 46 (42% of this group) were using the same medication throughout the follow-up period. The corresponding figures for continuous use was 9 (25% of those meeting the TR criteria) and 14 (21,5% of the remaining non-remitted patients) ($p < 0.001$). A total of 69 (33% of total) were not using any antipsychotic medication at all at follow-up, distributed as follows:

41 (37%) of the remitted group, 1 (3%) of the TRRIP group and 27 (41.5%) of the remaining non-remitted group ($p< 0.001$).
Discussion: In line with previous studies, we found a significant proportion of FEP patients meeting consensus criteria for treatment non-response already at one-year FU. The prevalence is however slightly lower than in more long-term studies. One reason may be the relatively short observation time, were a large proportion of those meeting the symptom and function criteria for TR had not completed two adequate trials. Our findings thus also underline the complexities of studying apparent non-response in naturalistic samples, as many also did not receive adequate antipsychotic treatment at this point of time. Use of TRRIP criteria identified different potential backgrounds for lack of clinical response. These backgrounds have to be addressed correctly to identify early predictors of treatment resistance.

V46. FRONTOSTRIATAL BRAIN WIRING ORGANIZATION IN NON-AFFECTIVE EARLY PSYCHOSIS PATIENTS AND HEALTHY CONTROLS USING A NOVEL DIFFUSION IMAGING FIBER CLUSTER ANALYSIS

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Background: Alterations in brain connectivity may underlie neuropsychiatric conditions such as schizophrenia. We here assess the geometric pattern of structural connectivity between the frontal cortex (FC) and caudate (Cd) in 56 healthy controls (HCs) and 108 Early Psychosis Non-Affective Patients (EP-NAs) from the Human Connectome Project (HCP); mean age: 22.9+ 3.7 years years; sex: 48 females and 116 males. We used our novel method of fiber cluster analysis of whole brain diffusion Magnetic Resonance Imaging (dMRI) tractography to assess the organization of frontostriatal brain wiring, which allows us to quantify the degree of deviation from a topographic, parallel, arrangement.
Methods: The data used in this study come from the shared data set from the Human Connectome Project for Early Psychosis (HCP-EP) study (MPI: Shenton, Breier). Diffusion MRI Data from 3 HCP sites (University of Indiana, Massachusetts General Hospital and McLean Hospital) were harmonized using our harmonization methodology (Cetin-Karayumak S et al, 2019). From this harmonized data set we generated whole brain tractography using our unscented Kalman filter (UKF) 2-tensor tractography methodology (Malcolm JG et al, 2010). To enable the identification of fiber tract parcels from the frontal cortex (FC) and the caudate (Cd), we used a data-driven fiber clustering atlas (Zhang et al, 2018) that allows for a whole brain tractography parcellation into 2000 fiber clusters according to the white matter (WM) anatomy (i.e., fiber geometric trajectory). Then, fiber clusters of interest (i.e., from FC to Cd) from the whole brain WM were identified for each subject in each subject group, according to their connected anatomical brain regions. We studied multiple Freesurfer FC regions including orbital, lateral and medial FC regions and the Cd. We identified 17 WM fiber clusters that connect FC and Cd in both left and right hemispheres in each subject group. To quantify the topographical relationship of these fiber clusters, we measured the intercluster mean distances between the endpoints of the fiber clusters within the FC (i.e., cortical distance) and the mean

distances between the endpoints of the corresponding fiber clusters terminating in the Cd (i.e., caudate distance).
Results: We have performed the following preliminary analyses. For each group (HC and EP-Non-affectives subjects) in each hemisphere, we generated plots (not shown) based on the 17 fiber clusters (with 136 pairs of fiber clusters, yielding 136 data points), showing the relationship between the inter-cluster cortical and corresponding Cd distances of the obtained fiber cluster pairs that connect the FC and the Cd. First, for the left hemisphere (LH) we found a non-linear relationship between intercluster cortical distances and caudate distances in HCs in both HC and EP-NAs groups driven by the results from 10 cluster pairs. For the right hemisphere (RH), we found a similar non-linear relationship driven by the results from 10 cluster pairs in HCs with a fiber cluster, originating in the inferior frontal gyrus (IFG), pars triangularis, significantly over-represented in these 10 cluster pairs. Of note, we found the curve correlating intercluster cortical and caudate cluster pair distances showed a qualitatively different non-linear relationship in the EP-NA patient group vs HCs, visually suggesting that the wring pattern in the RH differed between groups. Second, we quantitatively explored this observation in 2 ways. First, we categorized the mean difference in cluster endpoint distances (EP-NA – HC) between groups in each hemisphere using the signs of the differences in Cd and FC for each cluster pair, and demonstrated that there was a significantly greater number of cluster pairs with positive Cd and negative FC differences in the RH, but not in the LH, suggesting a more convergent pattern of intercluster endpoint distances in 58 out of 136 pairwise cluster comparisons, using a chi-square test with p-values determined by permutation (RH p=.03; LH p=.23). Second, using a mixed model regression analysis, we showed a significant group by fiber cluster interaction for 2 RH fiber clusters originating in the rostral middle frontal gyrus (rMFG), frontal pole, and IFG, pars orbitalis which withstood significance correction for multiple tests (p =.00087; p=.00015).
Discussion: Using a novel dMRI tractography analysis, we find 1) PFC-caudate brain wiring in both HCs and EP-NAs deviate from a strictly topographic organization due to similar regionally specific patterns of fiber cluster convergence; 2) this is a replication and an extension of our previous reported findings in healthy subjects (Levitt, et al., 2021); and, 3) against, a backdrop of wiring similarity, we also show 1) a generally more convergent PFC-caudate wiring pattern in the RH in HCS compared to EP-NAs; and, 2) a group by fiber cluster interaction in the wiring pattern in the RH. Specifically, we show that streamlines contained in 2 specific fiber clusters projecting from the RH rMFG, frontal pole and IFG, pars orbitalis to the caudate show significant group by fiber cluster interaction differences between EP-NAs and HC subjects. These brain regions subserve cognitive functions, such as executive function, which are characteristically impaired in schizophrenia.

V47. THE ROLE OF THE INSULA IN INTEROCEPTION, EMPATHY, AND SELF-PATHOLOGY IN SCHIZOPHRENIA

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Background: Insular dysfunction plays a vital role in the neurobiology and clinical phenomenology of Schizophrenia (SZ). The insula is central to many tasks and brain networks, notably interoception and the ability to discriminate self from other (internal from external), which is foundational to concepts of the self and identity. Insular pathology has been implicated in the interoceptive deficits and self-pathology of SZ, as well as Theory of Mind/empathy.
Methods: This selective review used PubMed to identify controlled trials that examined the association between the structure and function of the insula with the symptom domains of SZ.

49 reports met our inclusion and exclusion criteria. We further selected studies that focused on core schizophrenia symptoms associated with neuroimaging structural and functional insular pathology.

Results: Of the studies reporting insular abnormalities associated with the major domains of positive, negative, and cognitive symptoms, 10 studies found deficits in interoception, self-pathology, and empathy.

Data across several studies showed that alterations in the insula contributed to disturbed perceptions of the self, meaning disturbances in the internal representation of self and impairments in perceiving the self as the agent that produced one's actions. These included 1) the Default Mode Network connectivity was altered and implicated in hallucinations and delusions, 2) difficulties in distinguishing "internal and external sensory events", 3) reduced gray matter volume in the insula was implicated in "disrupted internal representations", 4) malfunctions in the mismatch detection network (that involves the insula) contributed to a patient's inability to understand the "sensory consequences of one's actions", 5) insular impairments were associated with deficits in insight, both into one's emotions and into one's abnormal clinical symptoms, 6) one study identified a right-sided network (including the insula) as the "neural basis of insight", implying that insular pathology would lead to impaired insight, 7) anosognosia was associated with right insula abnormalities, 8) the insula was linked with facial recognition and ability to appraise and process emotions in others, contributing to empathy, 9) hypoactivation of the insula was associated with impaired emotional regulation, 10) cortical thickness was related to "empathy-related neural regions", with a reduced capacity for the insula to respond to facial expression of others.

Discussion: Abnormalities of the insula structures and functions appear to have a central role in generating a host of key clinical features of SZ, including difficulty in understanding the self as the originator of action; difficulty in differentiating internal from external stimuli, and reduced ability to read and process emotions in others that can lead to empathy deficits. Recognizing the insula's role in these symptoms could lead to targeted interventions and perhaps using insular volumetric atrophy and reduced cortical thickness as a biomarker for susceptibility to converting to psychosis in individuals at risk for SZ.

V48. PROFILE VALIDITY OF THE PERSONALITY ASSESSMENT INVENTORY (PAI) WITH AN ETHNICALLY DIVERSE ACUTE INPATIENT POPULATION WITH SERIOUS MENTAL ILLNESS (SMI)

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Background: Given the short length of stay typical of acute inpatient settings, measures such as the PAI have been regarded as efficient tools, often in combination with other data sources (e.g., interview, behavioral observations), for obtaining diagnostic impressions in a time efficient manner. Self-report measures like the PAI carry their own set of limitations including the risk of idiosyncratic understanding and responding of items, poor insight of the respondent, and attempts by the respondent to portray themselves in an overly positive or negative light. Consequently, it is not uncommon for patients to produce invalid or cautionary PAI profiles. The rise of multiculturalism in the United States has made it imperative to continue understanding the role of culture and ethnicity in symptom endorsement and overall psychiatric presentation. This carries particular importance for psychological assessments as lack of relevant normative data and validation studies can increase the risk for misdiagnosing cultural

and ethnic minorities. This study aims to examine the frequency of invalid profiles of the PAI among ethnically diverse patients with serious mental illness (SMI) to better inform utility of this measure as diagnostic tool for future clinical work.
Methods: The present study utilized retrospective data collected during the course of clinical care. All patients above the age of 18 were included in the study, regardless of age, gender, race, or phase of illness. 280 patients who completed the PAI between 2014 and 2020 were identified. Subjects who identified as Asian American, Biracial, or "Other" were excluded from sample given the small sample size of these groups. The sample size for analysis was 264 completed PAIs. Invalid and cautionary PAI profiles were determined using the PAI Interpretation Manual. Profiles considered invalid included at least one of the following severe elevations: ICN t-score: 73+; INF t-score: 75+, and/or PIM t-score: 68+. Cautionary profiles included at least one moderate elevation: ICN t-score: 64-72; INF t-score: 60-74; NIM t-score: 73+; and/or PIM t-score: 57-67.
Results: From this sample, 62 (23.5 %) PAI profiles were invalid and 147 (55.7%) PAI profiles' validity scales indicated to interpret with caution. Subjects were grouped by ethnicity; White (n= 105), African American (n= 82) and Hispanic (n= 77). A chi-square test of independence was conducted to examine the relationship between ethnicity and severe elevations on the IFC, ICN, PIM and NIM validity scales. The relationship was significant, χ^2 (4, N =264) = 9.831, p = .007 when assessing the IFC scale. Furthermore, the relationship was significant, χ^2 (2, N =264) = 5.919, p = .052 when assessing the ICN scale. On both scales, African American patients were more likely to score within the severe elevation ranges than other ethnicities examined. No significant differences were noted when examining the relationship between ethnicities and severe elevations on the NIM and PIM scales.
Discussion: Results raise questions regarding the utility of the PAI in the accurate assessment of SMI in acute inpatient populations given the disproportion of valid versus invalid profiles found in our sample. Further, results suggest that there is a significant difference between ethnicities, our sample indicates African American patients more consistently have severe elevations on ICN and INF scales, deeming their profiles invalid. These findings have important implications as they suggest PAI may not be a reliable measure for obtaining valid diagnostic impressions within acute inpatient settings. Further research exploring additional factors affecting the validity of PAI profiles is needed.

V49. EMPATHY AND THEORY OF MIND IN ULTRA-HIGH RISK FOR PSYCHOSIS

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Background: Social cognition impairment is the key features found in patients with schizophrenia. In individuals at ultra-high risk (UHR) for psychosis, deficits in theory of mind (ToM) skills were found in previous studies, but empathic tendencies remain unclear. UHR have also shown high schizotypy and compromised executive function, and these factors can affect ToM skills and empathic tendencies. This study examined ToM skills and empathic tendencies in UHR and investigated their relationship with schizotypy and executive function.
Methods: A total of 56 participants (UHR individuals, N=28; age- and sex-matched healthy controls (HC), N=28) were recruited and completed clinical assessment, Wisconsin schizotypy scale and Wisconsin card sorting test. ToM skills were assessed by the performance of ToM Pictures Stories Task (ToM-PST) and empathic tendencies were examined using a self-reported empathic scale (Interpersonal Reactivity Index, IRI). We examined the differences of

ToM skills and empathic tendencies between UHR individuals and HCs using a multivariate analysis of variance (MANOVA), and post-hoc comparisons were conducted using one-way analysis of variance (ANOVA). In individuals at UHR for psychosis, the relationships between IRI and ToM-PST with schizotypy were assessed by stepwise multiple linear regression.
Results: For empathic tendencies, there was a significant difference at the trend level between UHR and healthy controls [UHR vs. HC; $F(4,49)=2.3$, $p=0.070$] while no difference was observed in ToM skills [$F(2,47)=2.4$, $p=0.104$]. Of the four subscales of the IRI, only empathic concern contributed to the group difference. In UHR individuals, empathic concern was solely associated with negative schizotypy [$F(1,25)=5.2$, $p=0.032$, adj. $R2=0.14$].
Discussion: Consistent with previous studies, UHR individuals showed relatively preserved cognitive empathy but compromised emotional empathy. Empathic concern of IRI was associated with negative schizotypy but not with executive function. Considering that social anhedonia, the negative schizotypy, is decreased pleasure derived from social origins, decreased empathic concern in UHR would reflect lower emotional reactivity to others' experiences.

V50. STUDY VALIDATION OF THE UPDATED VERSION OF THE CLIENT ASSESSMENT OF STRENGTHS, INTERESTS, AND GOALS

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Background: A major model in psychiatry that influences service delivery is the recovery model which emphasizes personal goals and overcoming obstacles to meet them. The Client Assessment of Strengths, Interests, and Goals-CASIG (Wallace, Lecomte, Wilde, and Liberman, 2001) is a well-known functional assessment, that was not only presented deficits and obstacles for psychiatric rehabilitation, but also included short and long-term goals. It included goals, and skills essential to community living, it was used for treatment planning, and repeatedly administered to assess progress over time. Its psychometric properties have been documented within both American and French-Canadian samples. The CASIG has however aged, with items that are not close enough to the recovery model and that reflect treatment paradigms more present in the late 90's. Hence, this new French version aims to 1) adapt the current version with non-stigmatizing and skills-oriented terms, 2) add new dimensions recognized as important factors for recovery (i.e., sleep, physical exercises), and 3) evaluate its psychometric characteristics: convergent validity, internal consistency, and test-retest reliability.
Methods: The self-report was administrated to 201 individuals with serious and persistent mental illness across four French speaking countries (Canada, France, Switzerland and Belgium). The sample included 69.5% females and participants all reported an history of mental disorder: Major depression=90, psychotic disorder=12, eating disorder=3, anxiety disorder=55, bipolar disorder=15, neurodevelopmental disorder=7, and substance use disorder=3. We examined the factor structure, internal consistency, concurrent, and convergent validities of the current version. Instruments for convergent validity were: The Recovery Assessment Scale (Corrigan, Salzer, Ralph, Sangster, and Keck, 2004), The psychological well-being scale (Ryff and Keyes, 1995), and the World Health Organization disability assessment schedule 2.0 (Ustun et al., 2010).

Results: Internal consistency for the resulting subscales ranged from acceptable to good (Kuder Richardson= 0.76 to 0.89). All subscales were significantly, positively associated with established measures of theoretically relevant constructs, demonstrating concurrent and convergent validities. The test-retests also demonstrated stability over times at the two follow-ups: one month, and six months.
Discussion: The French CASIG is a reliable and valid instrument assessing individual needs, and the use of those data is structured to determine treatment planning and evaluation, as well as producing aggregate data for research and program purposes. More extensive validity will be presented. These results should be repeated, with an English-speaking sample as well.

V51. DOPAMINE D2/D3 RECEPTOR PARTIAL AGONISTS EFFICACY AND TOLERABILITY IN SCHIZOPHRENIA WITH PROMINENT NEGATIVE SYMPTOMS - A LITERATURE REVIEW

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Background: Schizophrenia with prominent negative symptoms is characterized by significant functional impairment, lower quality of life, and high risk of partial recovery due to the frequently treatment-resistant nature of these manifestations [1,2]. Aripiprazole, brexpiprazole and cariprazine are new generation antipsychotics with D2 and D3 receptors partial agonistic properties, therefore they could be useful for the treatment of persistent negative symptoms in schizophrenia, with lower risk of hyperprolactinemia, sedation, or weight gain [2,3]. However, the data derived from clinical trials regarding the efficacy and tolerability of these agents in schizophrenia with prominent negative symptoms are scarce, and the beneficial properties of D2/D3 receptor partial agonists, especially of newer agents like cariprazine, are yet to be demonstrated.
Methods: This systematic literature review focused on finding evidence for efficacy and tolerability of D2/D3 receptor agonists in schizophrenia with prominent negative symptoms is based on searching the main electronic databases (PubMed, Thomson Reuters/Web of Science, PsycInfo, CINAHL) for papers published between January 2015 and October 2021. The search paradigm was “schizophrenia” AND “negative symptoms” AND “aripiprazole” OR “brexpiprazole” OR “cariprazine” OR “dopamine D2/D3 partial agonists”. Clinical trials, systematic reviews and meta-analyses corresponding to the inclusion and exclusion criteria were included in the secondary analysis.
Results: A number of 257 papers surfaced after primary search, but only 18 remained after filtering them according to pre-defined inclusion/exclusion criteria. According to the data found in the secondary analysis, aripiprazole was the most extensive studied atypical antipsychotic with D2/D3 partial agonism, and it has been associated with decrease of negative symptoms vs. placebo, while its overall tolerability was good. Cariprazine also led to favorable results regarding the evolution of the negative symptoms in schizophrenia, but these data are derived mainly from industry-sponsored trials. Brexpiprazole gathered significantly less data to support its use for schizophrenia with prominent negative symptoms, but it possesses a good tolerability profile. Trials that followed patients with schizophrenia switched from other atypical antipsychotics to brexpiprazole or aripiprazole reported positive effects over metabolic parameters, prolactin levels, or extrapyramidal symptoms. These observations regarding the switch to D2/D3 partial agonists are based on small sample sizes, short-term monitoring and open-label methodology, therefore better designed trials are needed to support such conclusions.

Discussion: Antipsychotics with D2/D3 partial agonistic properties may be useful in patients with schizophrenia presenting prominent negative symptoms, and their tolerability profile may be advantageous. However, a definitive conclusion cannot be drawn from this systematic review due to high degree of clinical samples heterogeneity, mainly industry-sponsored trials, and limited number of studies.

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V52. EFFICACY AND TOLERABILITY OF LUMATEPERONE IN SCHIZOPHRENIA SPECTRUM DISORDERS

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Background: Lumateperone is a second generation antipsychotic agent used in the treatment of schizophrenia, which interacts with serotonin, dopamine, and glutamate neurotransmission [1,2]. This antipsychotic presents 5HT2A receptor- and D2 receptor- antagonistic properties, low affinity for histamine-1 and alpha adrenergic-1 receptors, and partial serotonin reuptake inhibitor properties [1]. Due to this pharmacodynamic profile, lumateperone can alleviate positive and negative symptoms of schizophrenia, and it may be useful where other antipsychotics were not efficient [1,3]. Also, a better tolerability profile has been suggested for lumateperone, based on its highly selective nature for D2 receptors in specific brain regions [4].

Methods: A systematic literature review focused on finding evidence for efficacy and tolerability of lumateperone in schizophrenia included a search through the main electronic databases (PubMed, Thomson Reuters/Web of Science, PsycInfo, CINAHL) for papers published between January 2020 and October 2021. The search paradigm was "schizophrenia" AND "lumateperone" AND "efficacy" OR "tolerability". Clinical trials and systematic reviews were included in the secondary analysis.

Results: A number of 25 papers surfaces after primary search, but only 8 were included in the secondary analysis. Lumateperone improves symptoms of schizophrenia and it is comparable to risperidone as efficacy, although it may be better tolerated. Mild and transient elevations of ALT were detected in controlled trials, but the mechanism underlying this adverse event is not known. Somnolence, sedation and fatigue have also been reported in patients receiving lumateperone, but these have been of mild severity, also. The rate of extrapyramidal symptoms and metabolic impairments have been low during lumateperone administration. More patients on lumateperone than on risperidone improved from having metabolic syndrome at baseline to no longer meeting criteria for this disease at the end of the study. Higher affinity for 5HT2A receptors compared with D2 receptors, and lower affinities for other receptors may explain lumateperone's favorable efficacy and tolerability. Lumateperone is not recommended for use in pregnant or breastfeeding women, children, adolescents, or elderly patients with dementia-related psychosis, where a risk for cerebrovascular diseases has been identified, in patients who

use inducers or inhibitors of CYP4550 3A4, and in cases where alcohol or other sedating agents are being used.
Discussion: Lumateperone may be recommended in patients who developed extrapyramidal symptoms or metabolic dysfunctions during other antipsychotics administration, or who may have not responded well to other drugs. Most of the trials have been industry-sponsored, and head-to-head trials are lacking (except for trials comparing lumateperone and risperidone), so the evidence supporting lumateperone in patients with schizophrenia are still beginning to accumulate.
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V53. THERAPEUTIC MANAGEMENT IN SCHIZOPHRENIA AND SUBSTANCE USE DISORDERS DUAL DIAGNOSIS

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Background: Schizophrenia and substance use disorders (SUDs) are frequently co-morbid, and according to several estimates almost half of the patients diagnosed with schizophrenia may suffer from a concomitant drug or alcohol use disorder [1]. Younger age, male gender, and lower educational attainment have been associated with greater risk for substance dependence, while patients with schizophrenia and comorbid addiction tend to have an earlier onset of psychosis than those without comorbid SUD [1]. A common vulnerability for psychosis and SUDs has been suggested, and patients with dual diagnosis are difficult to treat because they have low adherence, frequent psychotic relapses and higher re-hospitalization rate [2,3]. Integrated management programs should focus on long-term outpatient regimens and include a combined, pharmaco-therapeutic and psychotherapy-based approach [3,4].
Methods: This review selected papers published between January 2000 and October 2021 that have been found in the main electronic databases (PubMed, Cochrane, EMBASE, CINAHL). The search paradigm used was “schizophrenia” AND “substance use disorder” OR “substance abuse” OR “substance dependence” AND “treatment” OR “therapy” OR “case management”. All clinical trials, systematic reviews, and meta-analyses found using the paradigm search were included in the primary analysis. Research that did not specified a therapeutic outcome were excluded, and those not reporting clinical changes for psychotic and addiction severity using structured methods were not included.
Results: A number of 577 papers surfaced, but only 26 remained after the inclusion/exclusion criteria were applied. The need to integrate substance abuse treatment in the case management of schizophrenia is underlined in all the papers found, and the close monitoring of the variables

related to both psychotic and substance use severity was recommended by authors. A combined approach, consisting of pharmacotherapy and motivational enhancement, psychoeducation, cognitive-behavioral therapy and/or family interventions was mentioned as the main strategy for these dual diagnosis patients. Collaborative goal setting is also considered a key to the therapeutic strategy success. No significant difference in effectiveness was found between antipsychotics (either from the first- or second-generation). Naltrexone, disulfiram or acamprosate may be recommended for alcohol use disorder and schizophrenia dual diagnosis. Varenicline and bupropion benefits in nicotine use disorder comorbid with schizophrenia are supported by multiple clinical trials. In opioid use disorder diagnosed in patients with schizophrenia no significant data about efficacy of a certain pharmacological intervention have been found. Clinical trials reporting decreased SUD severity in patients diagnosed with schizophrenia by the antipsychotics administration exist, but their methodology is of low quality. Significant improvements in the patients' functionality and social adjustment were reported after integrated treatment programs.
Discussion: A collaborative, integrated, multi-modal treatment is recommended for patients with schizophrenia and SUDs, and it is supported by evidence derived from multiple clinical trials. There are few data about the optimal duration of the combined treatment, or about the most efficient or best tolerated antipsychotics in this population.
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V54. THERAPEUTIC CHALLENGES IN PATIENTS DIAGNOSED WITH SCHIZOPHRENIA DURING COVID-19 PANDEMIC

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Background: The negative impact of the COVID-19 pandemic over mental status in patients diagnosed with schizophrenia has been moderated by multiple variables, e.g., isolation due to quarantine restrictions, limited access to mental health services during the lockdown, economic pressure over caregivers that may be perceived also by the patients, hospitalization for COVID-19-related problems etc. [1]. Patients with schizophrenia who had been in quarantine for almost a year showed similar levels of concern as their caregivers regarding health and social life [1]. Also, patients diagnosed with schizophrenia have high co-morbidity rates of medical illness, impaired insight and judgement, barriers to obtain health care, trouble understanding and implementing preventive measures for COVID-19, which represent negative prognosis factors in their evolution [2,3]. An increased susceptibility to COVID-19 in patients diagnosed with schizophrenia, and a higher risk of adverse outcomes from COVID-19 in this population, independent of age and comorbidity, have also been reported [4]. Dysregulation of the immune response, antipsychotic use and coexisting organic diseases in patients with schizophrenia have

been invoked as potential explanations for poor prognosis in patients with schizophrenia who are infected with SARS-CoV-2 [4].
Methods: A literature review was conducted through main electronic databases (PubMed, Cochrane, EMBASE, CINAHL, Thomson Reuters/Web of Knowledge) using the search paradigm "schizophrenia" AND "COVID-19" AND "treatment" OR "case management" OR "therapy". All papers published between January 2020 and October 2021 were included in the primary analysis.
Results: Based on the found data (n=12 papers) the main therapeutic challenges reported during the management of patients with schizophrenia in times of COVID-19 pandemic were: an increased risk for mortality (as opposed to patients with mood or anxiety disorders) that suggest schizophrenia might be a risk factor for mortality in COVID-19 positive individuals; an increased incidence of COVID-19 among people diagnosed with schizophrenia or depression, with a possible mediation by socioeconomic and environmental factors being suggested; a higher rate of adverse events related to COVID-19 treatment has been reported in patients with severe mental disorders; a possible diminished immune response in patients with schizophrenia compared to general population, which indicates the need for an early therapeutic intervention in case of SARS-CoV-2 infection; no evidence-based recommendations regarding vaccination, pharmacological interventions, or education focused on the prophylaxis of COVID-19 in this vulnerable population have been identified; patients with schizophrenia may be vulnerable to the psychological effects of the COVID-19 pandemic; addressing risk factors (psychosocial and illness-related) for COVID-19 by the mental health specialists should be considered an important objective within the case management plan.
Discussion: Higher mortality rate has been reported in patients diagnosed with schizophrenia and COVID-19, which should trigger the implementation of active prophylactic and monitoring techniques targeting SARS-CoV-2 contamination in this population. Long-term studies regarding the impact of COVID-19 over psychological and somatic status of schizophrenia-diagnosed patients are needed.
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V55. THERAPEUTIC STRATEGIES FOR TREATMENT-RESISTANT SCHIZOPHRENIA - A CASE SERIES

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Background: Schizophrenia is associated with a high rate of partial response and treatment resistance, a phenomenon leading to severe impairments and low quality of life on long term [1]. Although clozapine is efficient in TRS, an important proportion of patients do not respond to optimal doses of this antipsychotic, which leads to the need of finding various augmentation strategies [2]. Therapeutic adherence to clozapine treatment is crucial, since the risk of serious

adverse events is important and regular monitoring of the clinical status and biological variables is necessary on long-term basis [3].

Methods: The first patient was a 52-year old male, with a history of schizophrenia for 15 years, who received clozapine 600 mg/day in the last 2 years. However, he still presented prominent negative symptoms and severe impairment of his daily social and professional functioning. He had no other psychiatric or somatic comorbidities and presented a good therapeutic adherence. The second patient was a 45-year old male, diagnosed with schizophrenia 22 years ago, and currently on treatment with the maximum dose of clozapine he could tolerate, namely 450 mg/day. He also did not have any significant psychiatric or somatic comorbid conditions and presented to his psychiatrist for negative symptoms with severe impact on his daily functionality. The third patient was a 37-year old female, diagnosed with schizophrenia for 18 years, currently on clozapine 400 mg/day and sodium valproate 1200 mg/day. She was also treated episodically with naltrexone for alcohol-related disorder and presented to the psychiatrist for residual positive symptoms and prominent negative clinical features. All patients were initiated on amisulpride 200 mg/day, with increased doses up to 600 mg/day, if needed. They were monitored using monthly Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression- Severity (CGI-S), Global Assessment of Functioning (GAF) and EuroQoL-5D for 6 months. Body mass index, body weight, blood pressure, electrocardiogram, blood tests for metabolic, renal, hepatic functions and complete blood count were also performed.

Results: Two patients presented improvement during augmentation with amisulpride as reflected by the evolution of global and negative PANSS, CGI-S and GAF scores ($p<0.001$) after 24 weeks. In one case however the amisulpride did not improve the patient's status after 12 weeks and she was switched on aripiprazole 20 mg/day, as add-on to clozapine. After week 24 her clinical status improved on global PANSS and GAF scores at a significant level compared to baseline ($p<0.001$), while the CGI-S also improved but non-significantly. The EuroQoL-5D scores were slightly improved in all cases, without significant difference between week 24 and baseline, or between amisulpride-treated patients and aripiprazole-treated patient. No significant changes in biological variables were reported.

Discussion: Adding another atypical antipsychotic to clozapine, with a different mechanism of action, may be useful on medium-term in order to control positive and/or negative symptoms. Patients should be careful monitored using clinical scales and biological variables during the entire period of treatment.

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V56. REWARD MOTIVATION DURING THE EFFORT-REWARD IMBALANCE AND ITS RESTING-STATE NEURAL CORRELATES

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Background: Reward motivation refers to the desire towards potential rewards ('wanting') and pleasure for obtained rewards ('liking'), which could be adaptive to situational factors by trading off effort and reward. Such adaptivity of reward motivation is important to individual's survival, development and effective everyday functioning. For the neural basis, 'wanting' involves the prefrontal, orbitofrontal cortices and dopaminergic brain regions, while 'liking' mainly involves the pallidum and amygdala. The functional connectivity of these brain regions are closely related to the adaptive adjustment of reward motivation. Reward motivation in individuals with high levels of negative schizotypal traits (NS) has been reported to be lower than individuals with low schizotypal traits. But it is unclear whether individuals with high NS are also impaired in the ability to adjust reward motivation in response to environmental changes. It is also not known for the association of the corresponding resting-state functional connectivity (rsFC) and their reward motivation. The present study aimed to explore: 1) whether reward motivation of NS individuals would adapt to effort-reward balance (ERB) and imbalance (ERI) conditions; 2) the association between reward motivation and rsFCs in individual with NS.

Methods: Thirty-five individuals with high levels of NS and 44 individuals with low levels of NS were recruited. All the participants undertook resting-state functional brain scan in a 3T scanner. They also completed the ERI behavioural paradigm after the brain scans. The paradigm was manipulated with ERB and ERI conditions. 'Wanting' and 'liking' for rewards were measured under each condition. We conducted the seed based voxel-wise rsFC analysis to explore which rsFCs would be associated with the 'wanting' and 'liking' ratings in individuals with NS.

Results: Participants with NS reported significantly lower 'wanting' and 'liking' ratings in both ERB and ERI conditions. From ERI to ERB conditions, their reward motivation was difficult to increase or recover. Under the ERB condition, the reward motivation was negatively correlated with rsFC between the ventromedial prefrontal cortex and superior frontal gyrus. Under the ERI condition, reward motivation was negatively associated with rsFCs between the orbitofrontal cortex/substantia nigra and the thalamus, between the ventral tegmental area/cerebellum_crus 2 and the cerebellum_9, between the substantia nigra and the caudate nucleus.

Discussion: The present preliminary findings suggest that individuals with NS exhibit reward motivation reduction in ERI situation. Resting-state functional findings also suggest that their reward motivation was negatively associated with brain connections between the prefrontal cortex, dopaminergic regions, thalamus and cerebellum.

V57. THE USE OF TELETHERAPY IN THE TREATMENT OF PEOPLE WITH PSYCHOTIC DISORDERS DURING COVID-19 LOCKDOWN - ACCEPTABILITY, FEASIBILITY AND CHALLENGES

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Background: COVID-19 has greatly affected the lives of everyone on the planet, with people with schizophrenia and psychotic disorders being uniquely affected by the fear, isolation and disruption that has emerged in response to the pandemic. The suspension of many social and community services exacerbated the social isolation of this population, thus increasing emotional distress and relapse in psychotic symptoms. To reduce the risks of psychotic relapses and disorganization, regular contact with case managers, clinical teams, and peer support workers became essential. Clinical teams have struggled to offer services while social distancing. Most clinical teams have turned to teletherapy. Despite several concerns about this population, studies have shown that people with psychosis respond well to teletherapy. While a lot of research on teletherapy focuses on the impacts and challenges for the clients, few have looked at the challenges faced by the clinicians. Teletherapy can bring new challenges for clinicians used to in-person treatment, many of them being reluctant to try teletherapy, and experiencing anxiety and self-doubt. Since little is known about the clinicians' and health care workers' application and usage of teletherapy, more research is needed to reflect on service offer for this population in the context of the pandemic and its resulting restrictions.

Methods: Clinicians from diverse backgrounds working with people with psychosis were recruited to fill an online survey on Limesurvey, which was shared across Canada on French- and English-speaking social media platforms and through organizations such as the Canadian Network for Research in Schizophrenia and Psychoses. The 24-item survey collected information about their use of webconferencing platforms or phone therapy during the pandemic. The frequency and method of usage, the challenges, and the advantages and limits for the clinicians and the clients were assessed.

Results: A total of 201 clinicians participated in the study, with 80% identifying as female. The age ranged from 23 to 71 years old, with a mean age of 39.8 years. The sample included occupational therapists (25%), social workers (16%), psychologists (12%), nurses (10%), psychiatrists (10%), case managers (8%), psychosocial workers (7%), peer helpers (4%), psychoeducators (3%), special educators (2%) and pharmacists (1%). Only 20% of clinicians had ever used teletherapy before the pandemic, compared to 86% during the pandemic. Teletherapy was mostly conducted using phone calls, both before and during the pandemic (88% and 92% of clinicians, respectively). Still, 90% of clinicians conducted teletherapy by webconference during the pandemic, compared to 32% before. Even if only 45% of clinicians consider that webconferencing could be a good alternative for outpatients, 84% of clinicians considered continuing to use teletherapy after the pandemic. The data also showed that 65% of clinicians believed that a mixed model of in-person and teletherapy provides the same quality of care for clients. Clients' bad internet connection and difficulty logging on were the two main technical difficulties associated with teletherapy, whereas the main difficulties for clinicians were not being able to see non-verbal cues and experiencing screen fatigue.

Discussion: The goal of this study was to examine clinicians' experience with teletherapy with people with psychotic disorders during the pandemic. The study showed an increase in

clinicians' use of teletherapy during the pandemic, as well as clinicians' desire to keep providing teletherapy in the future. These findings may lead to changes in treatment offers for people with psychotic disorders during pandemics, and for people with limited mobility or living in remote areas.

V58. NETWORK ANALYSIS OF PSYCHOPATHOLOGICAL SYMPTOMS AND SOCIAL FUNCTIONING IN PATIENTS WITH SCHIZOPHRENIA

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Background: Although the relationship between psychopathological symptoms and social functioning in schizophrenia patients has been widely examined, only few studies investigated the complex interrelationships among symptoms, illness-related characteristics and social functioning. The present study aimed to investigate the interrelationships between psychopathological symptoms and social functioning using network analysis in a sample of schizophrenia patients.
Methods: Two hundred and sixty-nine patients who met DSM-IV criteria for schizophrenia were included in this study. We administered the Positive and Negative Syndrome Scale (PANSS) and the Clinical Assessment Interview for Negative Symptoms (CAINS) to evaluate psychopathological symptom domains, the Social and Occupational Functioning Assessment Scale (SOFAS) to assess social functioning, the Simpson-Angus Extrapyramidal Side Effects Scale (SAS) and the Barnes Akathisia Rating Scale (BARS) to assess the antipsychotic side effects. We conducted network to construct symptom domains and social functioning variables as nodes and the partial correlations between nodes as edges. Furthermore, the relative importance analysis was also conducted to examine the specific contribution of each symptom domain to social functioning.
Results: Network analysis showed that motivation/pleasure domain was negatively and strongly correlated with social functioning. However, other symptom domains such as positive symptoms, disorganized symptoms, expression domain exhibited very weak correlation with social functioning. As for the relative importance analysis, 72.97% variance of social functioning was explained by these symptom domains and illness-related characteristics. Compared with other symptom domains, motivation/pleasure domain explained significantly larger proportion of variance of social functioning.
Discussion: The present findings suggest that different psychopathological symptom domains may have different impact on social functioning. More importantly, among these symptom domains, the motivation/pleasure domain plays an important role in social functioning of patients with schizophrenia. The motivation/pleasure domain may be a potential intervention target for improving the social functioning of schizophrenia patients.

V59. ALTERATIONS IN THE DORSOLATERAL PREFRONTAL CORTEX DURING REPRESENTATION MAINTENANCE OF REWARD VALUE: RELATIONSHIPS TO SCHIZOTYPAL TRAIT

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Background: Individuals with schizotypy demonstrate dysfunctional hedonic processing, thereby hindering their psychosocial outcomes. One possible explanation is due to the difficulties in the representation of value in schizotypy. However, few studies have addressed the relationships between schizotypal trait and reward representation maintenance and its relevant neural substrates. The present study aimed to investigate behavioral and neural mechanisms of representation maintenance in individuals with schizotypy.
Methods: We recruited 26 individuals with high level of schizotypal trait (HS) and 27 individuals with low level of schizotypal trait (LS) with well-matched age and gender. Individuals with HS and LS were identified by using Schizotypal Personality Questionnaire. All the participants underwent functional magnetic resonance imaging scans while performing the Reward Representation Maintenance task (RRMT), which was designed to assess the process of representation maintenance of rewarding value as well as anticipation of upcoming reward. Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS) and Chapman Social Anhedonia Scale (CSAS) were administrated to all the participants after scanning. We used three-way (Maintenance x Price x Group) flexible factorial analysis to determine group difference in the neural activation associated with representation maintenance and reward anticipation. Psychophysiological interaction analysis (PPI) was carried out to characterize the influence of maintenance level on functional connectivity between dorsolateral prefrontal cortex (DLPFC) and other regions. Group differences were determined by performing independent T-tests on the beta value of PPI items across entire brain.
Results: Individuals with HS reported higher scores on the CSAS ($t(51) = 5.146$, $p < .001$) and tendency of low score on the anticipatory ($t(51) = -1.893$, $p = .064$) and consummatory ($t(51) = -2.004$, $p = .050$) sub-score of ACIPS as compared to LS group, indicating high schizotypal trait demonstrated social-related anticipatory anhedonia. For RRMT, there was no significant interaction effect of Group or main effect of Group with regard to mismatch rate during representation maintenance or counting number of button-press during reward anticipation (ps > .05). However, imaging data shows that individuals with HS displayed heightened brain activity in the dorsal lateral prefrontal cortex (DLPFC, BA 46, $F = 13.49$, pFWE-corrected (cluster level) < .05) compared to LS group while maintaining the representation of reward value. PPI analysis revealed that HS individuals had a tendency of decrease in the functional connectivity between DLPFC and ventral medial prefrontal cortex ($t = 4.07$, p uncorrected < .001, cluster size = 15 voxels) during maintaining the representation of low reward.
Discussion: In line to findings of working memory in schizotypal personality disorder and genetically high risk people, our findings suggest that hyper DLPFC activation may play a compensatory role that preserve the function of reward representation maintenance, which shed a new light on the underlying nature of anhedonia in schizotypy.

V60. WHEN SCHIZOPHRENIA RESEARCH SAVES LIVES: THE STORY OF COVID-19 INCREASED MORTALITY IN SCHIZOPHRENIA

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Background: The first wave of Covid-19 had a strong impact on healthcare systems. It was unknown if schizophrenia was a risk factor for covid mortality, as these patients were more isolated but also more institutionalized.
Methods: For the first study, we have analyzed the population-based data in France (>50,000 patients hospitalized for Covid-19).
For the second study, we have carried out a comprehensive meta-analysis of all population-based studies published in the 6 months following ours in collaboration with American and Korean teams.

Results: In summer 2020, we have published in Schizophrenia Bulletin the first data showing increased Covid-19 mortality in patients with schizophrenia, especially in those aged 65-80 years. We have also shown that schizophrenia patients had lower chance of being admitted to intensive care units, suggesting loss of chance in these patients.
Since, 6 other countries have published their population data. We have included them in a meta-analysis in collaboration with 2 other teams who published their population-based data.

This meta-analysis recently published in the JAMA psychiatry has shown that schizophrenia patients had the highest risk of mortality among all psychiatric patients.

Discussion: Following the publication of the first article, patients with schizophrenia have been listed in priority patients for vaccination in feb 2021 in France.
Following the publication of the meta-analysis, the CDC (centers for diseases control and prevention) has listed mental disorders in the individuals at high risk of Covid-19 mortality (quoting our meta-analysis in reference).

This case illustrates how quick population-based research and international collaborations may address timely issues to protect our patients with schizophrenia.

V61. ASSESSMENT AND REPORTING OF TREATMENT RESISTANT SCHIZOPHRENIA IN CLINICAL PRACTICE

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Background: Treatment-Resistant Schizophrenia (TRS) is a heterogenous disorder and defining it in a consistent way has been a major challenge in both research and clinical practice. In response, The Treatment Response and Resistance in Psychosis (TRRIP) group published consensus guidelines that operationalize criteria for TRS. We recently evaluated the quality and consistency of TRS definitions across studies investigating therapeutic response to Non-Invasive Brain Stimulation (NIBS) in relation to the TRRIP guidelines. To this end, we generated a scoring algorithm that can be used at the level of a single case report to quantify the extent to which TRIPP-based TRS definitions are captured in the literature. We now assess the applicability of this algorithm to clinical practice to assess the quality of assessment of treatment-resistance in patients receiving long term treatment for schizophrenia (>18 years).
Methods: The algorithm assigns a score from 0-1 for each of the 11 criteria for TRS established by TRRIP guidelines. We compared the data routinely collected for patients with schizophrenia in adult psychiatry and forensic units at Ontario Shores to the algorithm criteria. We are in the process of extracting the available data including, Brief Psychiatric Rating Scale-6 scale scores, Clinical Global Impression-Schizophrenia scale scores, Mini-Functional Remission of General Schizophrenia Scale scores, medication trials tracking and clozapine trial length and maximum

dose, for those patients >18 years targeting a data set of 200 patients. We will then trial our algorithm in assessing the quality of TRS assessment and reporting as an indicator of its applicability to clinical practice.
Results: Preliminary results indicate only 3/11 criteria are captured by validated rating scales used to assess illness severity and functional impairment. Data for the 4/11 criteria pertaining to past medication trials are not reliably recorded for every patient, but may be deduced if medication trials tracking was completed or if clozapine trial parameters can be determined from previous orders. The data for the remaining 4 criteria including resistant symptom domain, timing of resistance onset, adherence to medication, and illness duration are not recorded. Nonetheless, illness duration >12 weeks can be inferred based on expected illness chronicity in patients seeking tertiary care.
Discussion: There are similarities between criteria excluded from routine data collection in clinical practice and those that received the lowest scores in our quality of assessment of TRS reporting in NIBS studies, specifically timing of resistance onset and medication adherence. The timing of resistance onset defined as whether a patient was resistant from illness onset or developed resistance over time can aid in elucidating illness pathophysiology. Assessment of adherence to medication is critical in differentiating true treatment resistance from pseudo-resistance, and can therefore also aid in elucidating pathophysiology. Research on novel treatment modalities must aim to characterize and target illness pathophysiology, which requires standardization of TRS assessment and reporting to include key determinants of pathophysiology such as, timing of resistance onset and medication adherence. The goal of our algorithm is to facilitate standardization of TRS assessment and reporting in research and thus the clinical translation of novel treatment modalities. As such, it must be applicable to clinical practice to ensure TRS research study populations are representative of TRS patient populations so clinical practice guidelines may be reliably distilled from research evidence.

V62. COMORBID MAJOR DEPRESSIVE DISORDER IN SCHIZOPHRENIA: A SYSTEMATIC REVIEW AND META-ANALYSIS.

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Background: Background. Comorbid major depressive disorder (MDD) in schizophrenia (SZ) (SZ-MDD) has been identified as a major prognostic factor. However, the prevalence and associated factors of SZ-MDD have never been explored in a meta-analysis.
Methods: Methods. All studies assessing the prevalence of SZ-MDD in stabilized outpatients with a standardized scale or with structured interviews were included. The Medline, Web of Science, PsycINFO and Google Scholar databases were searched. Using random effects models, we calculated the pooled estimate of the prevalence of SZ-MDD. We used meta-regression and subgroup analyses to evaluate the potential moderators of the prevalence estimates, and we used the leave-one-out method for sensitivity analyses.
Results: Findings. Of the 5633 potentially eligible studies identified, 18 studies (N=6140 SZ stabilized outpatients) were retrieved in the systematic review and included in the meta-analysis. The pooled estimate of the prevalence of SZ-MDD was 32.6% (95% confidence interval: 27.9 – 37.6); there was high heterogeneity (I2=92.6%), and Egger's test did not reveal publication bias (p=0.122).
Discussion: The following factors were found to be sources of heterogeneity: publication in or after 2015, the inclusion of patients from larger studies, the assessment tools, the inclusion of patients with substance use disorder or somatic chronic diseases, age, education level, the

lifetime number of hospitalizations, antidepressant use. Two thirds of the extracted variables could not be explored due to an insufficient amount of published data.

V63. MANUALIZED GROUP COGNITIVE BEHAVIORAL THERAPY FOR SOCIAL ANXIETY IN FIRST EPISODE PSYCHOSIS: A RANDOMIZED CONTROLLED TRIAL

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Background: Social anxiety (SA), a prevalent comorbid condition in psychotic disorders with a negative impact on functioning, requires adequate intervention relatively early. Using a randomized controlled trial, we tested the efficacy of a group Cognitive-behavioral therapy intervention for SA (CBT-SA) that we developed for youth who experienced a first episode of psychosis (FEP). For our primary outcome, we hypothesized that compared to the active control of group cognitive remediation (CR), the CBT-SA group would show a reduction in SA that would be maintained at 3- and 6-month follow-ups. For secondary outcomes, it was hypothesized that the CBT group would show a reduction of positive and negative symptoms and improvements in recovery and functioning.
Methods: Ninety-six patients with a FEP and SA, recruited from five different FEP programs in the Montreal area were randomized to 13 weekly group sessions of either CBT-SA or CR intervention.
Results: Linear mixed models revealed that multiple measures of SA significantly reduced over time, but with no significant group differences. Positive and negative symptoms, as well as functioning improved over time, with negative symptoms and functioning exhibiting greater reduction in the CBT-SA group.
Discussion: While SA decreased over time with both interventions, a positive effect of the CBT-SA intervention on measures of negative symptoms, functioning, and self-reported recovery at follow-up suggests that our intervention had a positive effect that extended beyond symptoms specific to SA.

V64. REAL-WORLD EFFECTIVENESS OF ANTIPSYCHOTIC TREATMENTS IN 1,011 ACUTELY HOSPITALIZED PATIENTS WITH SCHIZOPHRENIA: A ONE-YEAR FOLLOW-UP STUDY

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Background: To compare the real-world effectiveness of antipsychotic treatments focusing on long-acting injectable antipsychotic medications (LAIs) and antipsychotic polytherapies except polytherapy involving clozapine (APEC) for patients with schizophrenia.
Methods: This prospective study was conducted over a 19-month period in 12 psychiatric emergency hospitals in Japan. Patients who were newly admitted to psychiatric emergency wards between September 2019 and March 2020 because of acute onset or exacerbation of Schizophrenia and Other Psychotic Disorders as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, were included. All patients were followed for one-year after discharge or until March 31, 2021. The primary outcome was the risk of treatment failure defined as psychiatric rehospitalization, discontinuation of medication, death, or continuation of hospitalization for one year. Cox proportional hazards multivariate regression was used for analyses.
Results: A total of 1,011 patients were enrolled (women, 53.7%; mean [SD] age, 47.5 [14.8] years). During follow-up, 588 patients (58.2%) experienced treatment failure including rehospitalization (513 patients), discontinuation of medication (17 patients), death (11 patients), and continuation of hospitalization for one-year (47 patients). Switching to LAIs (hazard ratio [HR] 0.810, 95%CI 0.659-0.996) and APEC (HR 0.829, 95%CI 0.695-0.990) were significantly associated with a low rate of treatment failure.
Discussion: Switching to LAIs and APEC in early non-responders seems to be beneficial for the prevention of treatment failure in acutely admitted patients with schizophrenia. The risk of treatment failure was about 19% and 17% lower in patients treated with LAIs and APEC, respectively, than in patients treated without them.

V65. ALTERED DYNAMIC RESTING-STATE BRAIN NETWORK ORGANIZATION IN SCHIZOPHRENIA PATIENTS AND UNAFFECTED FIRST-DEGREE RELATIVES

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Background: Schizophrenia is defined as a severe mental disorder with disorganization of functional brain networks. There have been a large number of evidences suggesting atypical resting-state functional connectivity (FC) in schizophrenia as compared to healthy controls. However, this standpoint comes from those studies investigating static FC which overlooks constantly changing patterns of brain network. From the framework of dynamic FC, the present study aims to quantify the neural flexibility at the level of individual regions as well as functional networks such as default mode network (DMN), executive control network (ECN), Salience network (SAN). Moreover, the neural flexibility associated with developmental psychopathological and genetic diathesis of schizophrenia is explored.
Methods: We recruited 46 patients who met DSM-IV diagnosis for schizophrenia, 38 unaffected first-degree relatives and 39 healthy controls. All subjects underwent resting state functional Magnetic Resonance Imaging (rs-fMRI), and were required to finish the Temporal Experience of Pleasure Scale (TEPS) and Emotional Expressivity Scale (EES). Rs-fMRI data was pre-processed using GRETNA toolbox. Sliding window approach was carried out to estimate dynamic functional connectivity patterns among 90 brain regions (defined in the AAL atlas) for each subject with a window width of 20 TRs = 56 s and in sliding steps = 1 TR. We further calculated the Shannon entropy of dynamic FC patterns for each region and each of

three networks including DMN, ECN, SAN to reflect the level of neural flexibility. Finally, a series of one-way ANOVAs were performed to determine the group difference in the values of entropy at the level of individual regions and functional networks, respectively.
Results: There was a significant difference in the average flexibility of the entire brain among the three groups ($F_{2,121} = 2.789$, $P = 0.060$), with schizophrenia patients showing higher neural flexibility than that of healthy controls. At the network level, only significant difference was observed for the neural flexibility in the SAN ($F_{2,121} = 4.126$, $p = 0.018$), with patients showing higher neural flexibility than that of healthy controls. To our expectation, those patients with early-onset schizophrenia (onset age < 18) displayed higher value of flexibility than healthy controls. In addition, unaffected first-degree relatives demonstrated higher level of neural flexibility compared to HC in the subnetwork of DMN, namely posterior DMN ($F_{2,121} = 6.410$, $p = 0.002$). Correlation analyses showed that neural flexibility of ECN($r = 0.314$, $p < 0.05$),and posterior DMN($r = 0.368$, $p < 0.05$) were positively correlated with total scores on the TEPS in patients with schizophrenia, indicating that inconstant neural organization over time may be associated with dysfunctional affective experience in schizophrenia.
Discussion: Our findings suggested abnormal changes in the dynamic reconfiguration of functional brain networks in schizophrenia and unaffected first-degree relatives. Aberrant neural flexibility of the brain may reflect the inconstant emotional processing in schizophrenia.

V66. REWARD DYSFUNCTION IN SCHIZOPHRENIA AND THE ROLE OF THE CEREBELLUM: A NEUROIMAGING META-ANALYSIS FOR MULTIPLE REWARDING COMPONENTS

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Background: Lack of pleasure and motivation is a key dimension of negative symptoms in schizophrenia (SCZ) and it is associated with reward dysfunction. Extensive research has sought to explore the brain alteration relating to such reward dysfunction in SCZ. However, with the notion that reward processing is a circulation of multiple components, studies focusing on specific components cannot fully reflect the overall damage pattern of SCZ. The present meta-analysis aimed to examine the altered brain functional activation patterns of SCZ covering multiple reward components, in particular associating with the involvement of the cerebellum.
Methods: We conducted a systematic search on Pubmed and Web of Science databases for studies investigating brain function deficits associated with reward or motivational processing in SCZ from 1990 to June 16, 2021. The inclusion criteria covered four domains, namely reward anticipation, reward consumption, reward learning, and reward approaching motivation. We performed the whole-brain ALE meta-analyses for studies in each domain by Ginger ALE. For the exploration of cerebellar abnormalities, we also recorded the frequencies of cerebellar significant results in each domain and compared them with the chi-square test.
Results: Two hundred and ninety-six studies were identified by preliminary literature search, and 72 studies (1922 SCZ patients and 1924 healthy controls) meeting the inclusion criteria

were included in the subsequent meta-analysis. The results showed that the brain function of SCZ was intact during reward consumption, while there were distinct altered patterns in the other three domains. Regarding the reward anticipation, SCZ patients exhibited weakened activation in the left dorsal striatum. Regarding the reward learning, SCZ patients exhibited hypoactivation in the right superior temporal gyrus and cerebellar I-IV and declive areas, and hyperactivation in the midbrain red nucleus. Regarding the reward approaching motivation, SCZ patients exhibited lower activation in the right superior frontal gyrus than healthy controls. The comparison analysis on cerebellum significance showed that cerebellum dysfunction was more consistently presented in reward learning studies than other domains (Chi-square = 13.82, df = 3, p = 0.003).

Discussion: The present finding demonstrated that patients with SCZ exhibit various brain alteration patterns associated with reward anticipation, reward consumption, reward learning, and reward approaching motivation. Our finding of SCZ cerebellar abnormalities during reward learning supports the SCZ cerebellar hypothesis and also suggests the involvement of the cerebellum in the normal reward functions.

V67. HEALTHY CHOICES, HEALTHY CHANGES: USING INCENTIVES TO PROMOTE FITNESS AMONG PEOPLE WITH SCHIZOPHRENIA AND OTHER SERIOUS MENTAL ILLNESSES

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Background: People with schizophrenia and other serious and disabling mental illnesses represent the nation's most dramatic health disparity population, with a life expectancy that is 25-30 years less than the general population, mainly from high rates of cardiovascular disease (CVD). Combined exercise and healthy eating interventions produce significant CVD risk reduction, but only among 50% of participants in highly standardized, controlled clinical trials. This study assessed whether cash incentives for participation would improve the outcomes of healthy lifestyle programming provided free-of-charge to participants over 12 months.

Methods: Incentives Counselors recruited and enrolled 1,348 people with schizophrenia or a disabling mood disorder who were overweight or obese and receiving services at one of the 10 community mental health centers participating in this study, funded by the Medicaid Incentives for the Prevention of Chronic Disease program. Participants were randomly assigned using equipoise stratified randomization to 1 of 4 healthy lifestyle interventions, including a gym membership, the InSHAPE fitness program for people with serious mental illness, a Weight Watchers membership, or InSHAPE+Weight Watchers. Participants were simultaneously randomly assigned to receive cash incentives for going to the gym ($5 each, up to 3 times per week) and/or Weight Watchers ($10 for 1 meeting each week), with baseline and quarterly assessments for 12 months. We examined main effects of the interventions and of incentives on three primary outcomes: weight loss, improvement in cardiovascular endurance based on 6-Minute Walk Test (6MWT) distance, and decrease in mortality risk based on Framingham Risk Score, using generalized linear models.

Results: Study participants were at substantial risk of CVD; mean body mass index (BMI) of the group was 37.6 (SD=8.8) and 30% had severe obesity (BMI>40). Incentives significantly increased gym attendance only in the InSHAPE+Weight Watchers group (estimate = .27, X2 = 10.08, p=.0015). Incentives increased attendance at Weight Watchers meetings both for the Weight Watchers (estimate = .53, X2 = 26.01, p<.0001) and the InSHAPE+Weight Watchers group (estimate= .42, X2 = 6.04, p =.01). Main effects of randomization to receive cash incentives was not significant for any outcome; however, total amount of incentives received

was significantly associated with weight loss (estimate = 0.002, p = 0.000), 6MWT distance (estimate = 0.129, p = 0.000), and Framingham Score (estimate = -0.001, p = 0.027). The InSHAPE+Weight Watchers participants who could earn cash incentives for attendance at the gym and Weight Watchers were the most successful, with superior improvement on all 3 primary outcomes.
Discussion: Simply offering the opportunity to earn rewards for participation was not enough to produce significant improvement in outcomes. However, when cash rewards for participation in free healthy lifestyle programming were earned, at the highest levels, improvement in all 3 primary outcomes was achieved. The superior outcomes for the InSHAPE+Weight Watchers group who could also earn cash incentives, suggest that intensive support is necessary to effect significant improvements in health outcomes among overweight and obese individuals with schizophrenia and other serious and disabling mental illnesses. Policy changes are needed to increase access to healthy lifestyle programming for people with schizophrenia and other disabling mental illnesses, and to establish mechanisms to offer incentives for participation. More research is required to establish the optimal amount of incentives needed to encourage participation in healthy lifestyle activities.

V68. LEVELS OF BRAIN GLUTAMATERGIC METABOLITES IN PATIENTS WITH NMDA RECEPTOR ENCEPHALITIS RELATIVE TO PATIENTS WITH SCHIZOPHRENIA AND HEALTHY VOLUNTEERS: A 12 MONTH FOLLOW-UP STUDY

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Background: The N-methyl-D-aspartate receptor (NMDAR) hypofunction model of schizophrenia suggests that dysfunction of these receptors leads to an excess release of glutamate and could explain the clinical manifestations characterising these patients. In NMDAR encephalitis (NMDARE), which holds clinical similarities with schizophrenia, autoantibodies target NMDARs, leading to increased levels of glutamatergic metabolites in brain tissue (Manto et al., 2010). However only two case report studies so far have measured neurometabolites in patients with NMDARE, and have found decreased Glutamate + Glutamine (Glx) and N-Acetyl Aspartate (NAA) in the frontal lobe and subcortical structures (Endres et al., 2015; Kataoka et al., 2009). In schizophrenia, there is also evidence of lower levels of glutamatergic metabolites in the frontal cortex, while higher levels of metabolites in both the frontal and medial temporal lobe have been associated with greater illness severity (Merritt et al., 2021). No study so far has examined these disorders comparatively.
Methods: Thirty patients with NMDARE in the post-acute phase, 22 patients with schizophrenia and 27 healthy controls (HC) were recruited within a tertiary setting and scanned with a 3T Siemens scanner and received a psychiatric and neurological assessment. Sixty three percent of patients with NMDARE, 50% of patients with schizophrenia and 59% of healthy controls underwent a follow-up scanning session at 12 months. Magnetic resonance

spectroscopy was performed using a 2x2x2 cm3 voxel (VOI) placed in the middle frontal region and of 3x2x2 cm3 in the medial temporal lobe. Ratios of glutamate (Glu), and glutamate + glutamine (Glx) and n-acetyl aspartate were quantified using LCModel and compared between groups. Between group differences in metabolites were assessed with multivariate GLM controlling for age and sex at each time point. Relationship between metabolite levels and symptoms (Rankin Scale, General Assessment of Functioning and Positive And Negative Symprom Scores, PANSS) were assessed with spearman correlations within each of the two patient groups.

Results: Multivariate models revealed significant group effects for Glu, Glx and NAA (ps<.002) at baseline in the prefrontal VOI, whereby patients with NMDARE displayed decreased levels of metabolites in relation to both HC and schizophrenia. At follow-up, NMDARE patients continued to display lower levels of glutamate and Glx (ps<.026), but not NAA than HC and than patients with schizophrenia in the prefrontal cortex. For NMDARE patients, higher levels of Glu in the medial temporal lobe at baseline were associated with more severe neurological symptoms (rs>.59, ps<.013), yet higher NAA was associated with better current psychosocial functioning (r=.73, p=.001). For patients with schizophrenia, higher levels of Glx and of Glu in the medial prefrontal cortex at baseline were associated with higher levels of PANSS general symptoms (r=.49, p=.033) and with poorer general assessment of functioning (r=-.47; p=.042), respectively, and higher levels of NAA in the prefrontal cortex were associated with better working memory performance (r=.60, p=.007). Also, in patients with schizophrenia, baseline levels of Glu and Glx in the medial temporal cortex were associated with higher ratings in working memory (rs>.69; p<.027).

Discussion: Our findings support observations of limbic and extra-limbic impact of NMDARE, and include the frontal lobe as a target region within the illness. NAA may act as a marker of clinical recovery while changes in glutamate and Glx may be more enduring. While metabolites in the hippocampus did not differ between groups, our findings suggest that they may distinguish patients symptomatically, across diagnoses. The comparative study of these conditions has the potential to help increase understanding of the impact of NMDA receptor hypofunction to the manifestations of psychosis.

V69. "'THE MORE THINGS CHANGE…'? STABILITY OF DELUSIONAL THEMES ACROSS 12 YEARS OF PRESENTATIONS TO AN EARLY INTERVENTION SERVICE FOR PSYCHOSIS"

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Background: While the prevalence of delusional themes is relatively consistent across geographic settings, there is little known about the prevalence of such themes over time. We therefore investigated the change or stability in prevalence of delusional themes across 12 years of presentation to a single early intervention service for first episode psychosis (FEP).

Methods: Systematically collected data from 500 patients at an early intervention program for FEP were analyzed. Four three-year periods, spanning from 2006-2017, were constructed to compare the frequency of delusion themes across cohorts at baseline and over time. Sociodemographic factors such as gender, age, and highest level of education, as well as clinical factors such as anxiety, depression, suicidality, hallucinations, and primary diagnosis (affective or non-affective) were reported.

Results: Sex and education level were found to be stable across cohorts, while patient age varied ($p = 0.047$). Clinical anxiety, depression, and suicidality were also found to be stable. Across cohorts, the proportion of patients with affective versus non-affective diagnosis differed ($p = 0.050$), with no difference in global rating of delusion severity or theme prevalence except for delusions of guilt or sin ($p = 0.001$). This single theme difference did not persist once the potential effects of age, cohort, and primary diagnosis on frequency of guilt or sin delusions were adjusted for.
Discussion: Our study indicates a relatively stable presentation of delusions themes over a 12-year span, demonstrating the potential utility of studying thematic content for understanding delusions and prospects for early intervention in clinical populations. Future explorations of the longitudinal course of delusions, the relationships between delusion themes, as well elaborating current work on their phenomenology will be discussed.

V70. PSYCHOTIC AND HAVING A "SAFE NIGHT" AT THE ACUTE PSYCHIATRIC WARD WITH A RADAR SENSOR ON THE WALL

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Background: Patients with psychosis admitted to the acute psychiatric department are often unable to inform of own somatic health. Many need medications to calm down. Psychotropic medications can suppress vital functions of the heart and respiration and is a constant stress to staff. Continued monitoring by ECG is not possible due to the patients` state. Currently there is no medical device that provide such continued information of the vital functions for use in acute psychiatry. Also, psychotic patients may suddenly wake up at night due to deterioration of their mental state with agitation or suicidal plans. These changes can go undetected between routine visits and situation may escalate and become dangerous. The project "Safe Night" aims at bringing into use a non-invasive sensor installed in the wall with multi modal function for use in all patient rooms. The aim of the pilot study was to confirm detection by the sensor of changes in respiration and movements.
Methods: The sensor is based on ultra-wide-band impulse-radar (UWB-IR) technology that is unique in its detection of millimetric precision of movements. Four healthy persons spent the night in a patient room at the acute ward at the Oslo University Hospital.
Results: All reporting is in real time. The sensor reported respiration rate through-out the night with a clear change from wake to sleep. It also detected with high precision movements out of bed.
Discussion: The sensor is in commercial use as a sleep pattern device and in prisons to signal changes of respiration. No sensor in use detect both respiration and movements. To be of use for a Safe Night in the hospital several sensors need to operate together. The next step is to test four sensors. The sensor has a great potential not only in acute psychiatry but for other medical disciplines to assess sleep disorders, sleep apnea and seizures. The regular use for all patients, especially psychotic non-consenting patients, needs to be legally explored.

V71. SYNTACTIC COMPLEXITY IN THE DIAGNOSIS OF SCHIZOPHRENIA: A BELIEFS PROPAGATION MODEL

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Background: In psychiatry, speech represents an important source of information that clinicians rely upon to diagnose mental disorders and track their evolution in time. A large body of research has underscored the importance of syntactic complexity —the ability to group words phrases and embed clauses in a recursive, hierarchical fashion, to produce coordinated and subordinated structures during speaking— as a key linguistic variable in psychotic disorders. A diagnosis of schizophrenia is generally possible only after several months of assessment of subjects experiencing a first episode of psychosis (FEP). In the current study, we apply automated analysis of syntactic complexity, in particular, the progressive changes in complex-clause grammar, to determine if the trajectory of its change allows us to improve our diagnostic confidence in identifying schizophrenia in the first 6 months of FEP.
Methods: We acquired language data from 38 subjects (12 healthy controls and 26 patients with FEP) at the baseline 0 month, and approximately at 6 months for a follow-up. Based on a diagnostic consensus procedure, 18 out of 26 were diagnosed with schizophrenia and 8 with affective psychosis. All participants performed a 3-minutes speech-elicitation task describing with three pictures from the Thematic Appreciation Test at both the baseline and the follow up. Multiple fine-grained measures of clause complexity were extracted using open source TAASSC, and a Bayesian-network model was fit to the data (26 clause complexity indices, group membership at time of first assessment, and group membership at consensus diagnosis time six months later).
Results: The complexity index 'noun subject per clause' (a group of words that acts like a noun in a sentence) had the best probability for a Bayesian causal association with the consensus diagnosis. While healthy control subjects had100% probability of increasing the clause complexity of their speech when the same pictures were presented 6-months later, I patients with diagnosis of schizophrenia were highly likely (70 %) to show a decrease in clause complexity across time. A lower probability of reduction in clause complexity (29 %) was estimated in patients diagnosed with affective psychosis. The belief-propagation model revealed that the probability of being diagnosed with schizophrenia increases when clause complexity in speech production decreases across time.
Discussion: Schizophrenia is distinctly associated with a progressive change in the syntactic-clause-complexity of spoken language. The probability of being diagnosed with this illness increases longitudinally when patients use fewer nominal subjects-per-clause. Both features comprise the bulk of the morpho-syntactic machinery of human language deteriorating from the onset of the illness. Tracking progressive changes in speech syntax using automated natural language processing methods in a Bayesian framework may improve our diagnostic confidence.

V72. EFFORT-BASED DECISION-MAKING PERFORMANCE IN PEOPLE WITH HIGH VERSUS LOW SCHIZOTYPY

Poster Presentation

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Background: Schizotypal personality is a trait that putatively suggest one's proneness towards schizophrenia. Literature indicates that people with schizotypal personality traits exhibit

similar abnormalities in various cognitive functions with, albeit in a milder degree than, patients with schizophrenia. Recent research has shown altered effort-based decision-making in schizophrenia patients who display reduced effort exertion, especially in response to high-value/high-probability reward as compared to healthy controls, with such abnormality being related to higher levels of amotivation. The current study aims to explore whether individuals with psychometrically-defined high schizotypy would also exhibit aberrant effort allocation relative to those with low schizotypy.

Methods: Two thousand four hundred participants were screened for schizotypy using Schizotypal Personality Questionnaire-Brief (SPQ-B) from Hong Kong Youth Epidemiology Study of Mental Health, an ongoing population-based study examining mental health conditions of youths. Forty participants were randomly recruited with top 10% SPQ-B score (high schizotypy) while another 40 demographically-matched participants were also recruited with bottom 10% SPQ-B score (low schizotypy). Participants with lifetime diagnosis or family history of psychotic or bipolar disorder, or history of antipsychotic treatment were excluded. A well-validated computerized Effort-Expenditure for Reward Task (EEfRT) was administered to quantify physical effort allocation (hard vs easy task based on button pressing) for monetary reward (low, medium and high) of varying magnitude and probability levels (12%, 50% and 88%). In addition, participants were assessed with Brief Negative Symptom Scale (BNSS), Social and Occupational Functioning Assessment Scale (SOFAS) and a brief standardized battery of cognitive tests.

Results: Mixed ANOVA revealed a significant main effect of reward ($F_{1.57,122.32}=131.72$, $p<0.001$), probability ($F_{1.76,137.14}=138.06$, $p<0.001$) and reward by probability interaction ($F_{3.62,282.09}=18.52$, $p<0.001$) but not any group-related effect. Correlation analysis was also performed on four EEfRT performance indices, including percentage of hard choice in 88% probability and high reward, and difference in percentage of hard choice between 88% and 12% probability, and high and low reward. There were no significant correlations between performance indices and BNSS measures and SOFAS scores. Performance indices were also not correlated with cognitive functions after correction for multiple comparisons.

Discussion: Our preliminary analysis suggests that there was no difference in performance between high and low schizotypy groups on effort allocation paradigm. Effort task performance indices were not significantly associated with any clinical and cognitive measures in the study cohort. Further research is required to clarify whether negative schizotypy might be more related to the effort-based decision-making construct.

V73. INDIVIDUALS WITH HIGH LEVEL SCHIZOTYPY EXHIBIT ALTERED EMPATHIC ACCURACY BUT NOT SELF-REPORTED COGNITIVE EMPATHY

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Background: Empathy, the ability to understand and experience other's emotions, is an important aspect of social cognition. The extant literature suggests that the construct of empathy includes both affective and cognitive components that have been shown impaired in schizophrenia spectrum disorders. However, most of these studies have been limited to self-reported measures rather than performance-based tasks. The concept of empathy accuracy (EA)

has been introduced to capture how accurately an individual understands thoughts and emotions of others. The present study aimed to investigate empathy in individuals with high schizotypy using the Chinese version of Empathic Accuracy Task (EAT) and self-rating scales of empathy.

Methods: Based on an online survey of 1530 college students who finished the Schizotypal Personality Questionnaire (SPQ), 40 individuals with high schizotypy (HS group, top 10% on SPQ, 14 males) and 40 low schizotypy (LS group, below average on SPQ, 13 males) were recruited. All participants completed the Chinese version of EAT as well as the Interpersonal Reactivity Index (IRI) and Questionnaire of Cognitive and Affective Empathy (QCAE). The Chinese version of EAT consists of 8 videos (4 positive and 4 negative events). Participants were asked to continuously rate the target's emotional valances when watching videos in which a target is telling his or her autobiographical event. Empathic Accuracy (EA), correlation coefficients between emotional ratings of target and participants for each video were calculated. In addition, stability of EA for each participant was measured by calculating intra-individual variability across videos. All EA coefficients were fisher-z transformed, and variances of EA were log-transformed before further analysis. Two-sample t tests and Pearson correlation analyses were performed respectively to examine group differences in EA and relationships with schizotypal traits.

Results: Compared to LS group, HS group reported lower EA scores ($t = -3.14$, $p = .002$). The HS group exhibited significantly more variability of EA for positive videos ($t = 2.18$, $p = .03$) but comparable EA variability for negative videos ($p > .1$). Moreover, the HS group only reported higher personal distress subscore of the IRI ($t = 4.08$, $p < .001$) and emotion contagion subscore of the QCAE ($t = 3.06$, $p = .003$) than the LS group. However, no significant differences were found on subscales capturing cognitive empathy between HS and LS groups. In LS group, interpersonal subscore of SPQ was negatively correlated with total EA ($r = -.42$, $p = .008$) and EA for negative videos ($r = -.43$, $p = .006$) , whereas total score of SPQ was positively correlated with EA variability for negative videos ($r = .36$, $p = .02$). In high HS group, SPQ total scores was negatively correlated with EA variability for positive videos ($r = -.40$, $p = .010$).

Discussion: Our findings showed that HS individuals exhibited reduced EA for both positive and negative videos, and larger variance of EA for positive videos. However, HS individuals did not show significantly changes on self-report cognitive empathy. These findings suggest that HS individuals exhibit difficulties in cognitive empathy but with relatively intact subjective awareness. Moreover, total score of SPQ associates with EA variability for negative events in LS but associates with more stable EA for positive videos in HS group. These findings suggest that emotion valences should be considered in future studies to investigate cognitive empathy in schizotypy. Taken together, our findings suggest altered cognitive and affective empathy in HS individuals and highlight a dissociation between self-report empathy and performance-based EA.

V74. CLINICAL, BRAIN, AND MULTILEVEL CLUSTERING IN EARLY PSYCHOSIS STAGES

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Background: Clinical high risk (CHR) and recent onset psychosis (ROP) stages are biologically and clinically heterogeneous, which reduces research and clinical precision. Such multilevel heterogeneity needs to be parsed in order to better explain premorbid risk factors, baseline differences, illness courses, and genetic underpinnings. Our objective was to use machine learning to cluster, clinically and biologically compare, and combine subgroup solutions derived from clinical questionnaire data and brain structural imaging data using a pooled sample of CHR, ROP, recent-onset depression (ROD), and healthy control (HC) individuals.

Methods: A multisite, longitudinal cohort study (10 sites in 5 European countries; 3-month follow-up intervals for 18-months) with a sample of CHR, ROP, ROD, and HC totalling 1352 individuals was used (discovery, n=742; validation, n=610). A consensus-based, nonnegative matrix factorisation technique separately decomposed clinical (287 variables) and parcellated brain structural volume (204 grey, white, and cerebrospinal fluid regions). Premorbid functioning, clinical baseline differences, brain differences, longitudinal courses, and polygenic risk for schizophrenia (scz-PRS) were compared.

Results: A clinical four-subgroup solution was found separating individuals based on positive symptoms, negative symptoms, depression, and functioning. Distinctive signatures were found across premorbid functioning, baseline variables, longitudinal functioning, and scz-PRS. A negative symptoms subgroup was particularly relevant as it contained individuals from all illness categorisations (i.e., CHR, FEP, ROD) and exhibited poor premorbid, baseline, and longitudinal functioning. Brain clustering revealed a two-subgroup solution including a decreased brain volume subgroup associated with negative symptoms, reduced performance IQ, and scz-PRS, but brain subgroups did not exhibit distinctive premorbid functioning or longitudinal illness courses. HC were included in the decreased brain volume subgroup. Clinical and brain solutions did not substantially overlap. The multilevel solution enhanced clinical differences in the decreased brain volume subgroup. All solutions crossed stage and diagnostic boundaries. Results were validated in the external sample.

Discussion: Early psychosis stages were reconceptualised in this study using data-driven clinical, brain, and multilevel approaches as demonstrated by distinctive premorbid, baseline, longitudinal, and genetic signatures. Clinical subgroups follow canonical symptoms, but cross illness stages and diagnoses. Brain subgroups demonstrate how substantial heterogeneity can be parsed into a simple two-subgroup solution, which may represent subgroups of brain risk and resilience. Clinical and brain subgroups did not substantially overlap, which demonstrates different sources of heterogeneity that need to be considered in future research. Overall, the

results question whether the current stage- and diagnosis-based classifications are optimal and suggest that such data-driven approaches may reveal enhance research precision to facilitate the development of more targeted treatments.

V75. RECLASSIFICATION AND MONITORING PROGRAM (RAMP) FOR CLINICAL HIGH RISK FOR PSYCHOSIS: A STUDY PROTOCOL FOR A PROSPECTIVE NATURALISTIC OBSERVATIONAL STUDY

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Background: Alterations of dopaminergic and glutamatergic systems are thought to play a pivotal role in the pathophysiology of schizophrenia. The neurodevelopmental hypothesis postulates that these abnormalities arise at the genetic, molecular, and cytological levels in early life and are also evident in the high-risk state prior to the onset of psychosis. With the development of molecular neuroimaging techniques, it became feasible to identify dopamine and glutamate imbalances in vivo, making it critical to diagnose and predict the onset of psychosis in addition to structural, diffusion, and functional magnetic resonance imaging (MRI).
Methods: We started a prospective observational cohort of high-risk individuals for psychosis in the Psychosis Clinic of the Pusan National University Yangsan Hospital. Participants will be assessed by the Structured Interview for Prodromal Syndromes, the MATRICS Consensus Cognitive Battery, inflammatory markers in the blood, and neuroimaging including MRI, diffusion MRI, resting-state function MRI, neuromelanin-sensitive MRI, and MR spectroscopy.
Results: We will examine neuromelanin and glutamate in people at high risk for psychosis and plan to use them to biotype high-risk groups for psychosis. Moreover, we will develop a predictive model for their clinical outcomes and provide personalized intervention guidelines.
Discussion: This study will establish biological evidence for predicting the onset of psychosis and remission from high-risk states based on the dopamine and glutamate hypotheses. In addition, it will facilitate the understanding of the pathophysiology of the onset of psychosis and contribute to discovering novel therapeutic targets.

V76. PSYCHOSIS BRAIN SUBTYPES VALIDATED IN FIRST-EPISODE PSYCHOSIS AND RELATED TO ILLNESS REMISSION

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Background: Brain heterogeneity reduces the precision of psychosis research and practice. To address this problem, we recently used a data-driven approach and discovered two main neuromorphological subgroups within a large chronic schizophrenia sample— a 'reduced brain volume' subgroup (SG1) and an 'increased striatal volume' subgroup (SG2). In this follow-up study, we investigated the validity of such subgroups within a first-episode psychosis sample to assess their presence at illness, and their relationships with transdiagnostic psychotic disorders. In addition, we contextualized clinical signatures separating the subgroups, and probed the relationship with the presence of illness remission over periods of 1-, 3-, 5-, and 10-years. We also applied the same control-schizophrenia subtype models to healthy controls to probe the relationships with normative brain variation and to investigate hypotheses of brain-risk and -resilience.

Methods: Participants were included from the PHENOM consortium, including 572 FEP patients and 424 healthy controls from 4 international sites (Brazil, Spain, UK, Australia). Our previously developed pipeline for volumetric T1-weighted brain MRI subgrouping was applied to the full sample including healthy controls. Subgrouping models defined four categories: subgroup 1 (SG1), subgroup 2 (SG2), no subgroup membership ('none'), and mixed subgroups. Volumetric images from the SG1 and SG2 subgroups were compared. Multiclass machine learning analyses employing L1-regularised support vector machine (SVC) were used to investigate baseline and remission signatures across sites.

Results: Volumetric MRI validated the original brain subgroups across study groups by demonstrating similar patterns of 'reduced brain volume' in SG1 and 'increased striatal volume' in SG2. The SG1 membership included healthy controls in addition to a higher proportion of individuals with FEP diagnoses, lower level of functioning, longer duration of untreated psychosis, and a family history of psychosis. SG2 membership included healthy controls and those with FEP diagnoses who had higher educational attainment, employment, longer duration of illness, and increased remission frequency. A predictive remission signature included SG2 membership, female gender, and reduced schizophrenia diagnoses. Additional analyses controlling for site and schizophrenia diagnosis supported the association of SG2 membership with remission. Further analyses indicated that the effect of SG1 and SG2 membership on remission was partly dependent on female gender.

Discussion: The study validated the two-subgroup solution and extends our previous work by demonstrating their presence already at illness onset and healthy controls. Enrichment of first-episode cases in the 'reduced brain volume' subgroup may indicate premorbid brain risk factors or illness-related changes. Multivariate brain signatures indicated that the 'increased striatal volume' subgroup may be representative of a brain-resilience phenotype related to increased symptom remission. The results highlight how brain heterogeneity potentially reduces precision in research and indicates directions for future investigations of brain risk and resilience factors.

V77. COGNITIVE AND AFFECTIVE THEORY OF MIND IN PATIENTS WITH EARLY-STAGE PSYCHOTIC BIPOLAR DISORDER

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Background: Previous research has indicated that patients with bipolar disorder (BD) exhibit abnormalities in theory of mind (ToM), which refers to the ability to detect the mental state of others. Nonetheless, most prior studies focused on chronically-ill samples and the study results would be confounded by illness chronicity and clinical heterogeneity, with study samples mixed in varying proportions of different mood states (euthymia, mania or depression), disorder subtypes (type I or II), and history of psychosis. Few studies have been conducted to specifically examine ToM in patients with early-stage bipolar disorder with psychosis (BD-P).
Methods: This study cognitive and affective ToM abilities in 31 euthymic early-stage BD patients aged 16-40 years who were treated within three years from their first-episode mania with psychotic features and 33 demographically-matched healthy controls using Faux-pas task and RMET (Reading the Mind in the Eyes Test). Relationships of ToM task performance measures with symptoms, self-reported impulsivity, cognitive functions, and treatment characteristics were also assessed
Results: There were no significant differences between BD-P patients and controls in age gender or education level. Comparison analyses revealed that patients exhibited significantly lower scores in inference of emotion in Faux pas task ($t = -2.24$, $p = 0.029$) and identification of neutral emotions in RMET ($t = -2.59$, $p = 0.012$). The two groups did not differ from each other in any other ToM measures. No significant correlations were noted between ToM measures and ratings on symptom and functioning scales as well as cognitive functions.
Discussion: Our findings suggested that early-stage euthymic BD-P patients demonstrated subtler ToM deficits relative to those reported by previous studies focusing on chronic BD samples. Further longitudinal investigation is warranted to clarify development and trajectories of ToM impairment along the early stage of illness.

V78. ANTIPSYCHOTIC UTILIZATION PATTERNS IN PREGNANT WOMEN WITH PSYCHOTIC DISORDERS

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Background: There is a growing concern about reproductive safety of antipsychotics. Most, if not all, previous studies examining antipsychotic use during pregnancy did not take into consideration specific psychiatric diagnoses or indication of use. There is a paucity of research specifically assessing prenatal antipsychotic prescribing practices for psychotic disorders.
Methods: This population-based cohort study identified women aged 15-50 years with diagnosis of psychotic disorders, who delivered their first and singleton child between 2003-2018 in Hong Kong, with an aim to examine temporal trends and predictors of prenatal antipsychotic use as well as antipsychotic utilization patterns before and during pregnancy. Data were retrieved from territory-wide medical-record database of public healthcare services.
Results: Of 804 women, 519 (65%) redeemed at least 1 prescription for antipsychotics during pregnancy. Older age at conception (25-34 years: OR 2.12 [95% CI 1.22–3.67]; 35-50 years: 2.52 [1.38–4.61]; 15-24 years as reference category) and antipsychotic treatment within 12 months pre-pregnancy (24.22 [16.23–36.16]) were significantly associated with prenatal antipsychotic use. Second-generation-antipsychotic (SGA) use during pregnancy increased over 16-year study period, while prenatal first-generation-antipsychotic (FGA) use showed declining trend. Overall antipsychotic and SGA use progressively decreased across pre-pregnancy and trimesters of pregnancy. Further analyses on antipsychotic use trajectories revealed that 87.4% (n=459) of 529 women receiving antipsychotics in 12 months pre-pregnancy redeemed antipsychotic prescription during pregnancy, and 63.4% (n=333)

continued antipsychotic treatment throughout pregnancy. Only 7.5% of the cohort (n=60) commenced antipsychotics in pregnancy.
Discussion: This is one of the few studies evaluating real-world prenatal antipsychotic utilization among women with psychotic disorders. Future research delineating risk conferred by illness-related factors and antipsychotic exposure on adverse maternal and fetal outcomes is warranted to facilitate treatment guideline development.

V79. DIETARY INTAKE LEVELS OF OMEGA-3 FATTY ACIDS FROM SEAFOOD ARE ASSOCIATED WITH BETTER COGNITIVE FUNCTIONING IN PATIENTS WITH A RECENT ONSET OF SCHIZOPHRENIA

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Background: Cognitive dysfunction is a core feature prevalent in individuals diagnosed with schizophrenia. This manifestation of the disorder impairs individuals' attention, memory, learning, concentration, and processing abilities. Past studies investigating whether broad dietary trends or interventions are relevant for attenuating schizophrenia-induced cognitive impairment have found mixed results, but show some potential benefits of omega-3 fatty acid consumption for cognition.
Methods: To analyze the possible impact of omega-3 fatty acid intake on cognition, this study explored associations between the consumption of omega-3 fatty acids found in seafood and cognition scores in first-episode schizophrenia patients (N = 54). The patients were participants in a study of cognitive training and aerobic exercise conducted at the University of California, Los Angeles, Aftercare Research Program. Patients were randomly assigned to an aerobic exercise or non-exercise group. The Automated Self-Administered 24-Hour (ASA-24) Dietary Assessment tool was used for patients to recall their food and beverage consumption from a 24-hour period at baseline and every six months throughout the 12-month longitudinal period. Cognition was assessed at baseline and after three, six, and twelve months using the MATRICS Consensus Cognitive Battery (MCCB). The ASA-24 recall data was averaged from at least two administrations during the follow-through period. The relationships between cognition and various omega-3 fatty acids, including eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and docosapentaenoic acid (DPA), were also explored.
Results: We found that consuming seafood high in omega-3 fatty acids was significantly associated with overall neurocognition in the aerobic exercise condition at baseline ($r = .40$, $p = .03$), 3 months ($r = .39$, $p = .03$), and 6 months ($r = .44$, $p = .02$), but nonsignificantly at 12 months ($r = .41$, $p = .06$). For patients in the non-exercise, healthy living condition, there were no significant correlations found between omega-3 fatty acid consumption and overall neurocognition. EPA consumption was associated with better overall neurocognition in the aerobic exercise group at baseline ($r = .39$, $p = .03$), the 3-month follow-up ($r = .36$, $p = .048$), and the 6-month follow-up ($r = .44$, $p = .02$), but nonsignificantly at 12 months ($r = .41$, $p = .06$). DPA was also found to be significantly correlated with better overall neurocognition in the aerobic exercise group at baseline ($r = .43$, $p = .02$), the 6-month follow-up ($r = .43$, $p = .03$), and the 12-month follow-up ($r = .45$, $p = .04$) . DHA was found to be significantly correlated with overall neurocognition in the aerobic exercise group at baseline ($r = .37$, $p = .04$) and 6 months ($r = .39$, $p = .05$).

Discussion: The consumption of seafood and other foods high in omega-3 fatty acid content was associated with better neurocognitive outcomes in patients with a recent onset of schizophrenia who were participating in a cognitive training program. Although the direction of causality cannot be confirmed with correlational analyses, these findings suggest that an intervention study to increase consumption of omega-3 fatty acids may help reduce the cognitive decline seen in the early phase of schizophrenia. Further, given the context of a cognitive training study with half of the participants also assigned to the aerobic exercise condition, the synergistic effect of cognition-enhancing interventions and omega-3 fatty acid supplementation believed to benefit neuronal maintenance needs to be explored. Both exercise and omega-3 fatty acids reduce inflammation, and the two together might enhance this reduction.

V80. DEEP BRAIN SHAPE FEATURES DIFFERENTIATE COGNITIVE SUBTYPES IN SCHIZOPHRENIA

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Background: Cognitive dysfunction is a prominent feature of schizophrenia; however, a spectrum of impairment type has long been recognized as occurring across the illness, with individuals ranging from very impaired to relatively intact performance. Studies of brain integrity in cognitively-derived subtypes continues to expand in an attempt to identify meaningful substrates for each behavioral profile. The aim of this study was to characterize the morphology of deep brain structures using high-dimensional brain mapping in cognitive subtypes of schizophrenia. It was hypothesized that the cognitively "intact" group would demonstrate structural characteristics similar to healthy comparison individuals, but be disparate from a typically impaired subgroup.

Methods: Schizophrenia participants were clustered into neuropsychologically impaired (NPI=34) and neuropsychologically near-normal (NPNN=45) subgroups using a k-means algorithm; matched healthy comparison subjects were also included (COM=56). Neuropsychological functioning was assessed with a comprehensive battery, and MR scanning included T1-weighted images. Shape features of the caudate (CD), putamen (PU), globus pallidus (GP), nucleus accumbens (NA), thalamus (TH), hippocampus (HPC), and amygdala (AM) were derived using surface-based processing pipelines. Statistical analyses included MANOVA models of shape vectors, then follow-up vertex-wise contrast maps to test specific group differences.

Results: Results revealed significant main effects for group status in both the left and right hemisphere of all structures ($F=1.63$ to 3.77, all $p<0.05$), except the right HPC ($F=1.15$, $p=0.30$). Examination of vertex-wise contrast surface maps revealed significant abnormal shape in NPI relative to COM in PU, NA, TH, AM, and HPC. For the NPI-NPNN contrast, a similar but slightly more extensive pattern of abnormal shape in NPI was also observed in the same structures. Finally, the NPNN-COM contrast revealed no significant differences between groups, except for outward deformation in lateral aspects of the PU in NPNN.

Discussion: Findings provide support for neurobiological heterogeneity that matches the cognitive presentation of empirically-derived schizophrenia subtypes. The impaired subgroup demonstrated abnormal surface shape that was consistent across multiple structures relative to both the healthy and intact groups, revealing a distinct deep brain presentation. The relative

absence of abnormalities in the intact subgroup suggests alternative brain mechanisms are acting in the clinical expression of the illness. Unique pathophysiological processes may be involved for each schizophrenia group, which implicates separate forms of the illness or the involvement of biological protective factors to reduce disease burden.

V81. PREMORBID SOCIAL FUNTIONING AND AFFECTIVE SYMTPOMS ARE RELATED TO SUBJECTIVE OUTCOME AMONG PATIENTS WITH SCHIZOPHRENIA

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Background: Improving the subjective outcome of patients is an important target in the treatment of schizophrenia. Accordingly, the aim of the present study was to examine the association of factors deemed relevant in this context, i.e. premorbid functioning, residual symptoms, and side effects of antipsychotic medication, with subjective outcome.
Methods: 70 clinically stable outpatients with schizophrenia were included into a cross-sectional study. Premorbid functioning, psychopathology, and side effects were assessed by using the Premorbid Adjustment Scale, the Positive and Negative Syndrome Scale, and the Udvalg for Kliniske Undersogelser Side Effect Rating Scale, respectively. Subjective outcome was measured in terms of life satisfaction (Life Satisfaction Questionnaire), self-esteem (Index of Self-Esteem), and needs for care (Berliner Bedürfnisinventar).
Results: Both premorbid social functioning and affective symptoms predicted life satisfaction, self-esteem, and patients' basic needs, whereas positive and negative symptoms predicted needs in the health, social, and functional domains. Concerning side effects, parkinsonism and akathisia showed a significant negative correlation with self-esteem.
Discussion: These findings highlight the complex nature of subjective outcome in patients suffering from schizophrenia. Evidently, premorbid social functioning plays a prominent role in the experienced subjective outcome during the course of the illness. Furthermore, these preliminary findings underscore that constant efforts are essential to treat residual symptoms of the disorder and to avoid extrapyramidal motor side effects of antipsychotic medication. Longitudinal studies are needed to investigate this latter point in more detail.

V82. USING POLYGENIC SCORING TO TEST SHARED VULNERABILITY AND SEX EFFECTS IN PSYCHOTIC DISORDERS

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Background: Psychotic disorders affect approximately 3% of the general population (Perälä et al 2007) and are among the leading causes of disability worldwide (Vigo et al 2016). There is increasing evidence for shared genetic susceptibility between psychiatric disorders. The latest study of the PGC cross-disorder group has provided molecular evidence for this common genetic architecture clustering schizophrenia (SZ), bipolar disorder (BD) and major depressive disorder (MDD) in the mood and psychotic disorders group (Lee et al. 2019).
Sex differences in psychotic disorders have long been reported but sex genetic differences have been an under-explored area (Riecher-Rössler et al 2018). To our knowledge, sex-stratified polygenic score (PGS) analyses examining the genetic contribution to psychotic disorder risk have not been previously reported.

The aim of this study was to evaluate whether PGSs specific for SZ, BD and MDD, are associated with psychotic disorders in our sample of patients with broadly defined psychosis. In addition, we examined these associations in the sample stratified by sex.

Methods: Our study included 1826 patients (1220 males and 606 females) with a range of psychotic disorders (DSM-IV criteria) and 1372 healthy controls (744 males and 628 females). All patients and controls are part of the Spanish CIBER of Mental Health (CIBERSAM). All participants provided written informed consent, and the study was approved by the different ethical committees at the hospitals.
Samples were genotyped with the Infinium PsychArray from Illumina. PGSs were calculated using PLINK 1.9 (Chang et al 2015) and the PRS-CS tool (Ge et al 2019), based on the results of the following GWAS: SCZ (Ripke et al 2020), BD (Mullins et al 2021) and MDD (Wray et al 2018).

Logistic regression models were used in order to associate psychotic disorder diagnosis with SCZ-PGS, BD-PGS and MDD-PGS including sex and the first 10 PCs as covariates. In order to quantify the increased risk, the sample was divided into quartiles based on SCZ-PGS, BD-PGS and MDD-PGS and the odds ratios (ORs) were calculated for affected status in each quartile using the first quartile as reference.

Results: We found association between all PGSs and broadly defined psychosis in our sample. The variance explained at the observe scale was 17.21% (p-value<2x10-16) for SCZ-PGS, 5.06% (p-value<2x10-16) for BD-PGS, and 0.47% (p-value=2.73x10-4) for MDD-PGS.
When dividing the sample into PGS quartiles, we observed an increase in the case-control ratio in progressively higher quartile categories using all PGS. Compared with individuals in the first quartile, those at the highest quartile had an OR for psychotic disorder risk of 7.95 (95% CI 6.34-9.97) for SCZ-PGS, 2.67 (95% CI 2.18-3.28) for BD-PGS and 1.36 (95% CI 1.12-1.66) for MDD-PGS.

Sex-stratified analyses showed no differences between males and females with similar variances explained in each group than the ones obtained when running analyses with all individuals together

Discussion: Our results show that SZ-PGS, BD-PGS and MDD-PGS are associated with broadly defined psychosis in an independent Spanish sample from CIBERSAM. The variances explained by the SCZ-PGS and the BD-PGS are in line with a previous study (Calafato et al 2018). No sex differences were found. Our results emphasize the shared genetic bases between SCZ, BD and MDD.

V83. ASSESSING NOVEL AND NOT-SO-NOVEL COGNITIVE STRATEGIES TO IMPROVE EPISODIC MEMORY PERFORMANCEIN SCHIZOPHRENIA

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Background: Episodic memory (EM) impairment is well documented in the schizophrenia literature. Relational memory (RM), a component of episodic memory that refers to one's ability to make associations between items, events and context, is particularly impaired. Considering the relationship between memory performance and clinical and functional outcomes in schizophrenia, there is an important need to remediate those impairments. Interventions to improve cognitive capacity in schizophrenia are more effective when strategy use is explicitly addressed. Adapting those strategies to individuals according to their cognitive profiles can improve therapy outcomes. The present work includes the results of four studies aimed to increase our understanding of the use of cognitive strategies to improve EM, and in particular RM performance in schizophrenia.
Methods: In Study 1, we investigated whether a well-known and highly effective visuospatial mnemonic, the Method of Loci (MoL), could improve EM recall in schizophrenia. Study 2 explored the sociodemographic, clinical, neuropsychological and task-specific factors - including strategy use - associated with relational learning of a RM-dependent task in schizophrenia. Study 3 examined the feasibility and acceptability of a brief intervention using unitization to circumvent RM impairments in schizophrenia. Unitization, a cognitive strategy that provides a way to combine disparate information into a functional unit, has been effective to improve RM performance in clinical populations with a similar pattern of RM impairment to that found in schizophrenia. The question of whether unitization can generalize to closer-to-real-life contexts was addressed in Study 4. Participants were instructed to use unitization in the Relational Trip Task (RTT), a task developed to mimic the learning of associations in real-life situations, such as those between people and places, and people and objects.
Results: In study 1, MoL seemed to require high levels of cognitive function in domains in which individuals with schizophrenia experience impairment, making it suboptimal for this population in the context of cognitive remediation therapy. Study 2 suggested that RM performance is associated with better non-relational memory cognitive dimensions, as well as superior awareness of task elements, including engaging more often and elaborating more, on cognitive strategies during learning. Study 3 suggested that the unitization intervention has moderate feasibility and good acceptability, and unitization training was effective in improving RM performance in schizophrenia. Study 4 results showed an overall improvement in the intervention group after unitization training. The findings suggest that unitization can be successfully generalized with real-life stimuli, an important indicator that this strategy can be transferred to participants' daily lives.
Discussion: In sum, the four studies identified factors associated with relational learning in schizophrenia, explored for the first time two different strategies to improve episodic memory in schizophrenia, and expanded the application of one of these strategies to a close-to-real life context previously unexplored. These findings extend our understanding of the mechanisms

behind relational learning, and the effective and ineffective use of cognitive strategies to improve episodic memory performance or circumvent impairments in relational learning in this population.

V84. LUVADAXISTAT, AN INVESTIGATIONAL D-AMINO ACID OXIDASE INHIBITOR, SHOWED SIGNALS OF EFFICACY IN COGNITIVE IMPAIRMENT ASSOCIATED WITH SCHIZOPHRENIA BUT NOT NEGATIVE SYMPTOMS: RESULTS FROM THE INTERACT STUDY

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Background: Deficits in glutamatergic signalling are hypothesized to play an important role in the negative symptoms and cognitive impairment associated with schizophrenia (CIAS). The D-amino acid oxidase inhibitor luvadaxistat may increase glutamatergic neurotransmission by increasing D-serine, which activates the NMDA receptor co-agonist site. Luvadaxistat has been shown to improve social interaction and cognition in rodent behavioral models. Here we report efficacy and safety results from INTERACT, a phase 2 study of adjunctive luvadaxistat in adults with schizophrenia (NCT03382639).

Methods: INTERACT was a randomized, placebo-controlled, dose range finding study that included participants with symptomatically stable schizophrenia, a baseline Brief Negative Symptom Scale score of ≥28 (12-item, excluding item 4), and who were receiving primary antipsychotic therapy. The study comprised a 28-day screening period, a 14-day single-blinded placebo run-in period and a 12-week double-blind treatment period.

The primary endpoint was the 12-week change from baseline in the Positive and Negative Syndrome Scale – Negative Symptom Factor Score (PANSS NSFS). Secondary endpoints included the changes from baseline (CFB) to Week 12 in the Brief Assessment of Cognition in Schizophrenia (BACS) composite score and the Schizophrenia Cognition Rating Scale (SCoRS) score; measures of neurocognition and day to day cognitive function, respectively. Safety endpoints included assessment of treatment-emergent adverse events (TEAEs).

Results: Of the 256 participants randomized 3:2:2:2 to receive placebo, luvadaxistat 50 mg, 125 mg and 500 mg, respectively, 228 (89.1%) completed the study. Baseline demographics and characteristics were evenly distributed across treatment groups.

No significant improvements in PANSS NSFS versus placebo were observed with luvadaxistat 50 mg, 125 mg or 500 mg at Week 12 ($p = 0.426$, $p = 0.362$ and $p = 0.808$, respectively). The least squares (LS) mean CFB to Week 12 in PANSS NSFS were –3.3 (95% confidence interval [CI]: –4.3, –2.2), –3.4 (95% CI: –4.4, –2.3) and –2.5 (95% CI: –3.6, –1.5) with luvadaxistat 50 mg, 125 mg and 500 mg, respectively, and –3.1 (95% CI: –4.0, –2.3) with placebo.

Significant improvements were observed with luvadaxistat 50 mg versus placebo in the BACS composite score and the SCoRS interviewer total score (nominal $p = 0.031$ and $p = 0.011$, respectively), but not with luvadaxistat 125 mg or 500 mg. For the BACS composite score, LS mean CFB to Week 12 were 4.6 (95% CI: 2.7, 6.5) with luvadaxistat 50 mg and 2.3 (95% CI: 0.7, 3.9) with placebo. For the SCoRS interviewer total score, LS mean CFB to Week 12 were 3.8 (95% CI: –5.3, –2.3) with luvadaxistat 50 mg and –1.6 (95% CI: –2.9, –0.3) with placebo.

Overall, 76 participants (29.7%) experienced ≥1 TEAE (mild, n = 49 [19.1%]; moderate, n = 24 [9.4%]; severe, n = 3 [1.2%]); 23 (9%) were considered drug related by the investigator. TEAEs occurring in ≥5 participants were headache, insomnia and weight gain, which occurred at similar frequencies in the four treatment groups. Two participants taking luvadaxistat experienced drug-related TEAEs of psychiatric disorders resulting in discontinuation.

Discussion: Luvadaxistat did not significantly improve negative symptoms of schizophrenia at the three doses studied. However, the 50 mg dose did show a signal of efficacy in both the BACS composite score and the SCoRS interviewer total score vs placebo.
The efficacy signal seen with luvadaxistat 50 mg warrants further clinical research in participants diagnosed with CIAS. In line with past clinical experience, luvadaxistat was generally well tolerated.

V85. NEURAL CORRELATES OF MENTAL TIME TRAVEL IN PARTICIPANTS WITH HIGH SCHIZOTYPY

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Background: Mental time travel (MTT) is the ability to recall past personal events (autobiographic memory, AM) and to imagine possible future events (episodic future thinking, EFT) through mental simulation. Empirical findings suggest that AM and EFT share similar neural mechanisms. However, most of the empirical findings were generated from healthy volunteers and it is still not clear for the neural correlates of AM and EFT deficits in participants with high schizotypy. The present study aimed to examine this issue.
Methods: We recruited 38 participants with high schizotypy and 35 low schizotypy with the use of the Schizotypal Personality Questionnaire. All the participants also undertook a MTT functional imaging paradigm inside a 3T GE scanner. Three conditions were included in the task: AM, EFT, and Control. During AM and EFT, participants were instructed to generate specific past or future events related to cue words. In the control condition, participants were instructed to generate three exemplars of a category. Group comparisons were conducted to examine brain activation differences. Psychophysiological interaction (PPI) analysis was applied to unveil the functional connectivity using brain regions activated during MTT (AM+EFT-Control) in all participants as seed regions. A cluster-level FWE correction ($p < 0.05$, cluster size >20) was adopted in all analyses.
Results: Participants with high schizotypy exhibited reduced activation in the bilateral anterior cingulate cortex (ACC) and the right medial superior frontal gyrus (SFG) during MTT (vs. Control) compared to participants with low schizotypy. During AM (vs. Control), participants with high schizotypy exhibited decreased activation in the left ACC; during EFT (vs. Control), they exhibited decreased activation in the left medial frontal gyrus (MFG) relative to participants with low schizotypy. PPI analyses did not reveal significant group difference. However, there was significant functional connectivity between bilateral PCC and right precuneus as seed regions with other brain areas in participants with low schizotypy during MTT, but participants with high schizotypy did not exhibit significant functional connectivity.
Discussion: These findings suggest that decreased activations and altered functional connectivity may underlie MTT deficits in participants with high schizotypy.

V86. ASSOCIATION OF EPIGENETIC MARKERS IN PERIPHERAL BLOOD AND SUICIDAL ATTEMPTS IN BIPOLAR DISORDER

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Background: Suicidal behavior (SB) is a serious public health problem involving approximately one million annual deaths worldwide, with 90% of them being related to mental disorders such as bipolar or psychotic disorders (Plans et al., 2019). SB is determined by multiple factors emerging because of the interaction of socio-demographic, clinical, neurocognitive, environmental, and genetic factors and new evidence points to an important role of epigenetic factors. The aim of the present study is to compare genome-wide methylation patterns at a peripheral level between bipolar disorder (BD) patients with and without suicide attempts.

Methods: A sample of 79 BD patients assessed following DSM-IV-TR criteria (APA, 2000) were recruited from the Bipolar Disorder Program of the Hospital Clinic of Barcelona and Mental Health Services in Oviedo. All patients gave their written informed consent and approval from each institution's ethics committees was obtained. SB was assessed using the Columbia Suicide Severity Rating Scale (C-SSRS) (Al-Halabí et al., 2016; Posner et al., 2011). Individuals presenting one or more suicide attempts were categorized as suicide attempters (SAs) (N=44; 75% females) and individuals presenting no suicide attempts were classified as non-SAs (N=35; 65.7% females).

Peripheral-blood DNA extractions were done using nucleic acid isolation technology (Chemagic, PerkinElmer). Genome-wide DNA methylation was assessed using the Infinium MethylationEPIC BeadChip (Illumina).

R program was used to analyze methylation status between SAs and non-SAs. Raw Illumina microarray data was processed with ChAMP (Tian et al., 2017) by following quality control standards (e.g., filtering of probes with low detection p-value ($p>0.01$), probes with <3 beads in at least 5% per probe, etc.). Normalization and batch correction were done using BMIQ and Combat, respectively. Blood-cell type proportions were calculated using refbase.

Differentially methylated positions (DMPs) and regions (DMRs) between SAs and non-SAs were calculated using Limma and DMRcate, respectively (Peters et al., 2015; Ritchie et al., 2015). Blood cell counts, sex, smoking score (based on methylation data) (Bollepalli et al., 2019), methylation principal components (mPCs) (Barfield et al., 2014), and age were used as covariates. For both, DMPs and DMRs, Benjamini-Hochberg multiple-testing correction was used to correct the false discovery rate (FDR) and a p-value of 0.05 was considered for significance.

Results: A total of 8 CpG sites (p-value<5.62E-7; FDR adjusted p-value<0.05) and 1 DMR (FDR adjusted p-value= 4.92E-16) were significantly differentially methylated between SAs and non-SAs.
From all the DMPs differentially methylated between groups, three of them have been found to be mapped to genes: LAMC1, MSX2, and FAM20A. Lastly, the DMR observed in our sample was mapped to several genes: VWA5B2, MIR1224, and ALG3.

Discussion: From the genes mapped to DMPs or DMRs, LAMC1 has been previously associated with Alzheimer's disease (Palu and Liesi, 2002). Additionally, VWA5B2, MIR1224, and ALG3 genes have been found to be located close to rs1969253, which has been related to major depressive disorder, though results not reaching genome-wide significance (Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium, 2013).
All in all, our results show DNA methylation differences in peripheral blood between SAs and non-SAs BD patients pointing to the importance of considering epigenetic markers when studying SB. These results should be replicated in larger samples and further studied for a better understanding of SB and ultimately help in suicide prevention and treatment.

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V87. WEIGHT GAIN AND COMORBIDITIES ASSOCIATED WITH OLANZAPINE: ANALYSIS OF REAL-WORLD DATA FOR PATIENTS WITH SCHIZOPHRENIA OR BIPOLAR I DISORDER

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Background: Olanzapine is an effective antipsychotic, but its clinical use has been limited due to clinically significant weight gain (CSWG). Using real-world data, we describe CSWG and comorbidities in patients with schizophrenia (SZ) or bipolar I disorder (BD-I) after initiating olanzapine treatment.
Methods: Percent change in weight, CSWG (≥7% weight increase), and incident comorbidities within 12 months of olanzapine initiation were assessed with medical records/claims (OM1 Real-World Data Cloud). Outcomes were stratified by baseline body mass index and reported descriptively.
Results: Among patients (SZ=1,455; BD-I=1,515), three-quarters were overweight/obese at baseline. During olanzapine treatment (mean duration, weeks [SZ=24.7; BD-I=25.9]), average change in weight was highest for underweight/normal weight patients (SZ=5.9%; BD-I=6.5%), followed by overweight (SZ=3.7%; BD-I=4.9%) and obese patients (SZ=2.5%; BD-I=3.2%). Within 3 months of olanzapine initiation, 17.3% (SZ) and 18.7% (BD-I) of patients experienced CSWG. Among patients with CSWG who subsequently discontinued olanzapine, most patients (SZ=73.6%; BD-I=64.7%) did not return to baseline weight during follow-up (mean follow-up, weeks [SZ=156.8; BD-I=161.5). A total of 15.3% (SZ) and 13.5% (BD-I) of patients developed coronary artery disease, hypertension, dyslipidemia, or type 2 diabetes within 12 months of initiating olanzapine; rates were highest among overweight/obese patients and those with CSWG.

Discussion: CSWG and comorbidities associated with olanzapine were independent of disease state. Weight gained during olanzapine treatment persisted for most patients even after discontinuation. Patients' overall health should be considered when selecting treatments. New

treatments are needed for patients who would benefit from olanzapine's efficacy but with a reduced risk of CSWG.

V88. PATIENT PERCEPTION OF COGNITIVE ADAPTATION TRAINING AND TREATMENT PREFERENCE BETWEEN REMOTE AND IN-PERSON DELIVERY

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Background: The pandemic revealed one of many barriers in provision of psychological interventions for people with SMI, one of which is flexible and feasible formats of treatment delivery. However, limited data is found on acceptability, desirability and barriers of remote-delivered interventions in this group. This project aimed to assess patient perception of remote and electronic delivery of CAT(R-CAT) in comparison to standard in-person delivery(CAT). We obtained qualitative reports on both hypothetical and actual acceptability of two deliveries from patients who experience difficulties with medication follow-through.

Methods: CAT is an evidence-based psychosocial treatment using environmental supports such as signs, alarms, pill containers, and the organization of belongings established in a person's home on weekly visits to cue adaptive behaviors and establish healthy habits. R-CAT uses the same active ingredients with adjustments in how they are delivered. It involves weekly video visits, plus text or phone contact. Treatment supplies are mailed to their home and coaching is provided over the phone or via video chat about how to best use them.

The research team conducted surveys in which a description of CAT or R-CAT was randomly provided to patients. Following the initial introduction, the description of the other intervention was given. After that, they were invited to participate in a study examining CAT and R-CAT during which their preference was recorded.

Results: Out of a total of 2569 referrals, the research team successfully connected with 368 Medicaid recipients and obtained responses from 204 individuals(55%) from 38 counties in Texas. Results of binomial regression for mixed models examining the order of offer (first or second), type of treatment (CAT or R-CAT), and acceptance of the offer (yes or no) revealed a significant Order X treatment interaction ($F(1,89)= 6.41$ $p <0.02$). Participants were more likely to accept the first treatment offered when that treatment was R-CAT with 90% accepting R-CAT and 72% of individuals accepting CAT. Overall, R-CAT was significantly more likely to be accepted than CAT ($F (1,89)= 4.55$; $p<0.04$) with 86% accepting the telemedicine R-CAT and 78% accepting in-home CAT. Qualitative data showed several themes of benefits reflected by participants' reports, supporting supplies, remote platform, coping support, convenience, companionship, and medication assistance.

Discussion: Individuals with SMI readily identified their needs for more services to maintain their wellness.

CAT and R-CAT offer individualized support that appears to be appealing to this population, such as medication assistance, frequent check-ins, and problem-solving assistance. Acceptability of both CAT and R-CAT is supported by high acceptance rates. R-CAT is more adaptative given patients' concerns related to COVID-19, in the meantime, a comparable number of patients prefer live interaction in CAT.

V89. DISENTANGLING THE RELATIONSHIPS BETWEEN THEORY OF MIND AND THE FIVE DIMENSIONS OF CLINICAL SYMPTOMS IN SCHIZOPHRENIA AND RELATED PSYCHOTIC DISORDERS: A META-ANALYSIS

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Background: Theory of mind (ToM) refers to the ability to infer other people's mental states, including their intentions, emotions, or beliefs. ToM is impaired in people with schizophrenia and related psychotic disorders (SSD) and has detrimental effect on everyday functioning. ToM is a multidimensional construct influenced by several aspects including clinical symptoms of SSD. Previous authors have suggested the contribution of several dimensions of clinical symptoms such as positive or negative symptoms to ToM impairments. However, it remains unclear whether some dimensions or specific symptoms are more strongly associated with ToM. This might be partly explained by the large heterogeneity of ToM measures and by the classification of clinical symptoms into two or three dimensions that do not optimally represent the structure of clinical dimensions. A meta-analysis was conducted to determine the associations between ToM and the five dimensions of clinical symptoms, including positive, negative, cognitive/disorganization, excitability/hostility and depression/anxiety.

Methods: Inclusion criteria were 1) participants with a diagnosis of SSD, 2) published or Epub before July 2021 and 3) reporting at least one correlation between ToM and one of the five dimensions of clinical symptoms. The correlations between the clinical symptoms and ToM were transformed into an effect size Zr and weighted means were calculated for 1) the overall association between ToM and the clinical symptoms, 2) between ToM and the five dimensions of symptoms, and 3) between ToM and the individual symptoms within each dimension. Focused tests were used to assess the differences between the associations.

Results: A total of 127 studies were included (7 864 participants, mean age of 31.2 years, 64.9% men). The overall association between ToM and clinical symptoms was moderate (k sample=131; r=0.27). The results revealed a significant difference between the dimensions of clinical symptoms ($\chi2(5)=81.43$, $p<0.001$). Pairwise comparisons revealed that the negative (k=109; r=0.27) and the cognitive/disorganization (k=45; r=0.29) dimensions were significantly more strongly related to ToM than the positive (k=102; r=0.22), excitement/hostility (k=24; r=0.17) and depression/anxiety (k=24; r=0.15) dimensions (all $p<0.001$). Further, the positive dimension showed a significantly stronger association with ToM compared to the excitement/hostility ($p=0.04$) and depression/anxiety ($p<0.001$) dimensions. Finally, a significant difference emerged regarding the associations with ToM, within the positive dimension ($\chi2(9)=38.02$, $p<0.001$). The pairwise comparisons revealed that the symptom thought disorder (k=8; r=0.44) was more strongly associated with ToM compared to all other individual positive symptoms (all $p<0.01$). No significant difference was observed for the individual symptoms within the other dimensions of symptoms (all $p>0.05$). Sensitivity analyses revealed no significant effect of the type of mental state assessed in the ToM tasks on the overall association between ToM and clinical symptoms ($\chi2(4)=2.87$, $p=0.411$).

Discussion: The current results revealed a moderate overall association between ToM and clinical symptoms, with a stronger association with negative and cognitive/disorganization symptoms. Pelletier-Baldelli and Holt (2021) have suggested the hypothesis of a close relationship between negative symptoms and the "real-life" manifestation of ToM deficits. Further, these results support the well-recognized contribution of neurocognition to ToM in

SSD. A better understanding of the relationships between ToM and the clinical symptoms is useful for the development of treatment interventions for ToM in SSD.

V90. ECOLOGICAL MOMENTARY ASSESSMENT OF SOCIAL MOTIVATION AND SOCIAL AVOIDANCE IN SERIOUS MENTAL ILLNESS: CONNECTIONS TO SYMPTOMS AND SUICIDAL IDEATION

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Background: Despite a high rate of suicidal behavior in serious mental illness (SMI; i.e., schizophrenia, schizoaffective disorder, bipolar disorder with psychotic features, or major depressive disorder with psychotic features) the understanding of suicide in psychosis is sparse. Though social contributors to suicidal ideation (SI) have received little study in psychosis, diminished motivation is central to understanding the social dysfunction in SMI. As social motivation and avoidance are linked to social functioning, and social isolation is a risk factor for suicide, studying these factors in relation to SI is important. To our knowledge, there are no studies that have examined diminished motivation and increased avoidance in relation to SI among people with SMI. Ecological momentary assessment (EMA) provides a way to evaluate the diminished motivation and avoidance in the context of daily life. The aim of this study is to understand the interplay of motivation and avoidance in relation to positive symptoms and SI.

Methods: Participants (N=128) with a diagnosis of SMI (see above) completed assessments of SI (Columbia-Suicide Severity Rating Scale; Modified Scale for Suicidal Ideation) and symptoms (Positive and Negative Syndrome Scale) at baseline. They then completed EMA 3 times daily for 10 days at stratified random intervals. EMA surveys included questions about social motivation, social avoidance, and psychotic symptoms (mistrust of others, hearing voices) on a 1-7 Likert scale, where higher scores represent greater values. Independent t-tests were performed to compare mean levels of motivation and avoidance between people with and without current SI, and correlations were performed with these variables and symptom measures. Participants were split in to four groups based on the median scores of social motivation and avoidance: low motivation/high avoidance (LM/HA); low motivation/low avoidance (LM/LM); high motivation/low avoidance (HM/LA); and high motivation/high avoidance (HM/HA), and levels of symptoms were compared using an ANOVA.

Results: An independent samples t-test comparing participants with and without baseline SI revealed that participants with SI had higher mean avoidance, $t(126)=2.84$, $p=.003$, Cohen's $D=.49$, and lower mean social motivation, $t(126)=-2.44$, $p=.008$, Cohen's $D=.43$, than participants without current SI. Greater baseline positive symptoms were related to greater mean avoidance, $r=.231$, $p=.009$. However, baseline positive symptoms was not related to motivation. An ANOVA with post-hoc Tukey tests revealed that the LM/HA group had significantly higher current SI than those with HM/LA ($p<.001$). Overall, the LM/HA group reported greater severity of EMA-measured voices than the LM/LA group ($p<.001$), as well as the HM/LA group ($p<.001$). However, the LM/HA group did not report significantly more voices than the HM/HA group ($p=.374$). Similarly, the LM/HA group reported more EMA-

measured suspiciousness than the LM/LA group (p <.001) and the HM/LA group (p <.001), but not the HM/HA group (p=.018).
Discussion: The combination of motivation and avoidance related to differences in SI and EMA-measured positive symptoms. The results of this study point not only to the additive role of social motivation and avoidance in relation to SI and psychotic symptoms, but also to the importance of avoidance processes relating to SI and psychotic symptoms within this population. Clinically, exposure therapies may help people to become comfortable around others, confronting avoidance and potentially increasing motivation. Additionally, cognitive behavioral therapy may help clients to gain a greater understanding of their avoidance processes and challenge thinking surrounding them.

V91. CORRELATIONS BETWEEN WISCONSIN CARD SORTING PERFORMANCE, GLOBAL COGNITIVE PERFORMANCE, AND ACCURACY OF SELF-ASSESSMENT

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Background: Inaccurate self- assessment of performance on cognitive and functional tasks is a critical feature of schizophrenia (SCZ) and bipolar disorder (BD). Challenges in self-assessment are also consistently associated with disability above and beyond performance deficits. Part of the challenge appears to be utilizing feedback from the environment to adjust self-assessments. As successful performance on the Wisconsin Card Sorting Task (WCST) requires responding to external feedback, it is an optimal test to evaluate incorporation feedback and response biases.
Methods: A modified WCST was used to examine accuracy, accuracy judgments, and confidence in those judgments in participants with schizophrenia (n=99) and bipolar disorder (n=67). Participants were also assessed with a shortened version of the MCCB and asked to generate self-assessments of their overall cognitive performance with the Cognitive Assessment Inventory (CAI).
Results: Participants with bipolar disorder generated more correct sorts (p<.001), but both groups over-estimated their performance on a momentary basis to an equal extent (~30%). Participants with schizophrenia performed more poorly on the MCCB composite (p<.001) but reported less cognitive impairment than the bipolar participants on the CAI (p<.001). Participants with bipolar disorder were significantly more likely to correctly determine if their sorts were right or wrong than the schizophrenia participants (p<.001). In both groups MCCB performance was significantly correlated with correct sorts and being correct about the accuracy of their sorts(p<.001), but MCCB performance was not correlated with incorrect accuracy determinations (all p>.16). Self-reported cognitive performance was uncorrelated with WCST sorts and MCCB global scores in the participants with schizophrenia, but the correlations between self-reported cognitive performance and MCCB composite scores was significant in participants with bipolar disorder (p<.05).
Discussion: Momentary biases in self-assessment were seen in both the SCZ and BD groups, overestimating the correctness of their sorts. However, the BD participants were more likely to be correct in evaluating the accuracy of their sorts overall. Inaccurate self-assessments were

not due to impairments in global cognitive performance. These data suggest that participants with SCZ manifest challenges in incorporating external feedback, as well overestimating both their momentary cognitive performance and their global abilities. Interventions targeting momentary self-assessment and incorporating feedback would seem to be the best strategy to reduce these response biases.

V92. THE ASSOCIATION OF MOMENTARY SAD MOODS AND CONCURRENT PRODUCTIVE BEHAVIOR: A 30-DAY ECOLOGICAL MOMENTARY ASSESSMENT STUDY OF PEOPLE WITH SCHIZOPHRENIA AND BIPOLAR ILLNESS

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Background: Previous research using weekly sampling has suggested that persistent sad moods are associated with disability in bipolar illness. We examined the momentary quality of activities (productive, unproductive, and passive recreation) in a 30-day ecological momentary assessment study and related the level of sadness to the quality of activities.
Methods: Participants with bipolar illness (N=71) or schizophrenia (n=102) were sampled 3 times per day for 30 days. At each survey, participants were queried as to where they were, with whom, what they were doing, and as to their mood state. Activities were characterized according to predetermined criteria and related to momentary sadness rated on a 1 (not at all) to 7 (extremely sad) scale.
Results: A total of 11608 surveys were collected. Participants with bipolar disorder reported greater sad moods and their mood state was more variable than participants with schizophrenia. For the participants with schizophrenia, the level of sadness did not differ across concurrent activities. For the participants with bipolar illness, sadness reported was associated with activities, with unproductive activities associated with the most sadness, followed by passive recreation, and productive activities associated with the least sadness ($p<.001$).
Discussion: The current study expands upon studies examining the course of sad moods in people with bipolar illness to momentary assessments. Our results suggest that momentary sadness correlates with the quality of concurrent activity. Although we cannot determine the causal direction, these findings support the idea that sadness predicts less productivity. In participants with schizophrenia, their sadness was less variable and the association of sadness and quality of activities was considerably smaller.

V93. ASSOCIATIONS BETWEEN THE TRANSCRIPTION LEVEL OF HUMAN-ACCELERATED GENES, HIPPOCAMPAL VOLUME, AND COGNITIVE ABILITY IN SCHIZOPHRENIA

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Background: Cognitive decline is the core symptom of schizophrenia. Magnetic resonance imaging (MRI) has great power to display the brain phenotype at the macroscopic level, demonstrating multiple abnormalities in brain structure and function in relation to cognitive impairments in patients with schizophrenia. Likewise, genetic factors play an important role in the pathogenesis of schizophrenia. Transcriptome analysis can probe the functional genes and the mechanisms of gene expression regulation by directly measuring the RNA sequences in blood. This approach makes it possible to explore the functional changes in molecules and cells from a microscopic perspective. The human accelerated regions (HAR) genes are thought to be closely associated with neurodevelopment. Previous studies have found that HAR genes are more differentially expressed in higher-order cognitive networks in humans compared to chimpanzees and macaques. At the same time, the transcription level of HARs genes shows correlations between higher cognitive networks functional activity, intelligence, social competence, and schizophrenia. However, the associations between transcription level of HAR, brain volume, and cognitive ability of this disorder are quite complicated and remains unknown.
Methods: Structural MRI, cognitive ability, and blood sample were collected from a total of 103 participants (43 patients and 60 healthy controls). Screening of brain regions with significant changes in gray matter volume based on whole brain analysis using voxel-based morphometry. Wechsler Adult Intelligence Scale revised in China (WAIS-RC) was used to assess the cognitive abilities of the subjects. Transcriptome-wide analysis was performed to detect the expression differences of genes. Data were analyzed between Jun 2021 and Oct 2021. There was no intervention in addition to routine therapy determined by their clinicians on the basis of standard clinical practice.
Results: We began with brain structure to explore differences in gray matter volume between patients and healthy individuals. The results showed that patients had a significantly lower volume in the right hippocampus and parahippocampal gyrus compared to healthy controls. Right hippocampus and parahippocampal gyrus was positively correlated with information ($r = 0.3382$, $p = 0.0265$) and digit symbol coding test ($r = 0.3202$, $p = 0.0363$). We next used Allen Human Brain Atlas to screen for genes that were highly expressed in the hippocampus and parahippocampal gyrus. We created three gene sets, namely the HAR gene set, the transcriptome gene set, and the hippocampal and hippocampal paracentral gene sets. Intersection of the above three gene sets eventually get five genes: NECTIN1, ADCY9, GFRA2, TENM4, SMPD3.
Discussion: Our integrated approach implicates the associations between altered transcription level of HAR genes, decreased volume of hippocampus and parahippocampal gyrus, and cognitive impairments in schizophrenia. Multi-omics technology can provied a more comprehensive perspective to explore the pathogenesis of schizophrenia. We hope to further investigate the neurobiological mechanisms behind the brain phenotypes and clinical manifestations of schizophrenia patients with the help of trans-scale and multi-omics techniques.

V94. MULTIMODAL MRI DEPICTS WIDESPREAD AND SUBREGION SPECIFIC ANOMALIES IN THE THALAMUS OF EARLY-PSYCHOSIS AND CHRONIC SCHIZOPHRENIA PATIENTS

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Background: Anomalies associated with the thalamus have a central role in schizophrenia pathophysiology, contributing to sensory, cognitive and sleep alterations. In this study, a multimodal approach is proposed to locate and assess thalamic microstructural alterations along the course of the disorder, from early psychosis (EP) to chronic schizophrenia (SCHZ) patients.

Methods: Forty-two patients with schizophrenia (SCHZ, 38.6±9.2yo; 31 males), 97 patients with early psychosis (EP, 24.7±5.6yo; 66 males) and 139 healthy controls (HC, 31.3±6.5yo; 97 males) were recruited from the Service of General Psychiatry (Lausanne University Hospital, Switzerland). MRI was performed on a 3-Tesla scanner with T1w and Diffusion Weighted Imaging (DWI) sequences. T1w images were employed to divide each thalamus in seven subregions and to estimate gray matter tissue concentrations (GMc). Spherical Mean Technique (SMT) was applied over the DWI images to obtain several microstructure parameters (intra-neurite volume fraction (VFINTRA), intra-neurite diffusivity (DIFFINTRA), extra-neurite mean diffusivity (MDEXTRA) and extra-neurite transversal diffusivity (TDEXTRA)). GMc and SMT-derived parameters (VFINTRA, DIFFINTRA, MDEXTRA, and TDEXTRA) for the seven thalamic subregions and whole thalamus of both hemispheres were tested for group difference in EP versus age-matched HCs (HCEP) and in SCHZ versus age-matched HCs (HCSCHZ). Pair-wise comparisons between HCs and patients groups for GMc and SMT metrics were conducted. Pearson partial correlation was performed to explore the direct associations among GMc, VFINTRA, MDEXTRA and TDEXTRA inside each region of interest. GMc and SMT parameters in the thalamic subregions with significant group differences were tested in both EP and SCHZ patients for correlation with the duration of illness, symptom severity, and global functioning (GAF).

Results: Compared to age-matched HCs, the thalamus of EP but not SCHZ patients displayed widespread microstructural alterations (VFINTRA decrease, TDEXTRA increase) that were similar to and correlated with alterations in whole brain white matter. In addition, local and heterogeneous changes (either GMc decrease, MDEXTRA increase, or DIFFINTRA decrease) in mediodorsal, posterior, and ventral anterior parts of the thalamus in both EP and SCHZ patients were found. Partial correlation analysis revealed that the relationship between diffusion-derived parameters and GMc differed across thalamic sub-regions, and most remarkably between EP patients and HCEP. Thus, while mostly absent in HCEP, partial correlations between VFINTRA (or TDEXTRA) and GMc exist in most subregions of EP patients. Finally, GMc and DIFFINTRA in the whole thalamus correlated with global functioning, while DIFFINTRA in the subregion encompassing the medial pulvinar was significantly associated with negative symptoms in SCHZ patients.

Discussion: The widespread alterations in VFINTRA and TDEXTRA throughout the whole thalamus in EP patients may capture microstructural alterations of the fiber tracts entering and/or projecting out of the thalamus. On the other hand, the local and heterogenous anomalies in mediodorsal, posterior, and ventral anterior parts of the thalamus suggests that local microstructural alterations vary from one thalamic subregion to another. The preponderance of thalamic microstructural alterations reported in EP as compared to SCHZ patients suggests that

these anomalies are more important in the early stages of psychosis and could represent neurobiological vulnerabilities and potential early biomarkers.

V95. EFFORT ALLOCATION FOR REWARDS IN FIRST-EPISODE PSYCHOSIS, ULTRA-HIGH-RISK FOR PSYCHOSIS AND FAMILIAL-HIGH RISK FOR PSYCHOSIS

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Background: Patients with schizophrenia are more reluctant to expend efforts for reward. This reluctance is important since it could affect the social and occupational functioning of the individuals. The degree of decision-making effort in chronic samples with schizophrenia patients varies according to the size of the reward value and probability. There is limited evidence of motivational deficits in earlier phases of psychotic disorders. Few studies investigated motivational deficits in subjects with first-episode psychosis (FEP), ultra-high-risk psychosis (UHR), and familial-high-risk for psychosis (FHR) individuals. This study aimed to evaluate the effort for reward in subjects who had the first episode of psychosis, the variation of this effort according to the size and probability of reward; and to compare the changes in the effort for the reward with the FHR, UHR, and healthy control groups. We also aimed to assess whether these deficits in the willingness to expend effort for rewards are related to negative symptoms, cognition, and medication.

Methods: In this study, effort-based decision-making and global cognition were compared in patients with the FEP (n=44), UHR individuals (n=51), FHR individuals (n=37), and healthy controls (n=13). The ages of the participants ranged from 13 to 29. Risk groups were determined according to the Structured Interview for Prodromal Syndromes (SIPS). Effort-based decision-making has been evaluated using Effort-Expenditure for Rewards Task (EEfRT). This test evaluates individuals' efforts based on reward magnitude and probability. Global cognition scores were calculated by a factor analysis based on a comprehensive neurocognitive battery. Negative symptoms were assessed with the Brief Negative Symptom Scale (BNSS). Chlorpromazine equivalent doses were calculated for people having medical treatment.

One-way ANOVA was used to compare global cognition among the groups. For EEfRT, the data were analyzed using a mixed model repeated measures ANOVA with the group as a between-subject factor and both probability and reward level (low, medium, high) as within-subjects factors. Correlations with global cognition, negative symptoms, and chlorpromazine equivalents have been tested using Pearson’s product-moment correlations.

Results: There were significant differences in global cognition between groups (F=23,916, p<0,01). The main effect for interaction between probability, reward, and the group was significant in EEfRT (F=3,798 p<0,001). Post hoc tests for the repeated measures ANOVA showed significant differences between patients with FEP and other groups for EEfRT. In terms of the likelihood of hard task choices, conditions that differed between groups were medium probability-high reward (F=4,519,p=0,005), high probability- medium reward (F=8,911 P<0,001), and high probability-high reward (F=16,361 P<0,001). The likelihood of choosing the hard task in these three situations was correlated with global cognition and negative symptoms (p<0,05). Chlorpromazine equivalent doses were associated with reduced effort in high reward magnitude and high probability status (p=0,008).

Discussion: Deficits in the willingness to expend effort for rewards were evident in FEP but not in risk groups. Impairment in reward processing was associated with negative symptoms severity, cognitive deficits, and the use of antipsychotics. These findings suggest that the motivational disorder was not evident in most individuals with genetic and clinical risk for psychosis. Our study provides additional evidence for the impairment in effort for a reward could not be considered as an endophenotypic marker for psychosis.

V96. LONGITUDINAL ASSOCIATIONS BETWEEN SOCIAL ANXIETY AND FUNCTIONING IN FIRST-EPISODE PSYCHOSIS

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Background: Social Anxiety Disorder is a common condition in people recently diagnosed with psychosis, with up to 50% meeting criteria. Social anxiety is negatively associated with both occupational and social functioning; therefore targeting it in first-episode psychosis may improve functional outcomes. In a recent longitudinal study of social anxiety group treatments in first-episode psychosis, both Computer-Assisted Cognitive Remediation Therapy (CACRT), and a manualized group CBT treatment (CBT-SA) saw significant reductions in social anxiety at the end of the 13-week treatment, and at 3- and 6-month post-treatment. Decreases in positive and negative symptoms and increases in functioning were also observed across this time period. As all measures improved, we leveraged the longitudinal nature of the study to evaluate whether improvements in social anxiety symptoms earlier in the study predicted functional improvements later in the study, controlling for changes in other clinical variables.
Methods: 96 clinically stable participants who met criteria for Social Anxiety Disorder on the SCID were recruited from First-Episode Psychosis clinics in Montreal. Participants were randomized to one of two 13-week interventions, CBT-SA or CACRT. Measures of social anxiety (Social Interaction Anxiety Scale, Social Phobia Inventory, Brief Social Phobia Scale), functioning (Recovery Assessment Scale, Social and Occupational Functioning Scale), and the SANS and SAPS were collected at baseline, post-intervention (Time 1), 3 months post-intervention (Time 2), and 6 months post-intervention (Time 3). 52% of participants completed the intervention. Non-completers were significantly younger and had lower scores on the Social Interaction Anxiety Scale than completers; there was no difference in any other clinical measure. Analyses were based on the 36 participants who completed the entire study (from baseline to Time 3). Supervariables were created for change in social anxiety and change in functioning by averaging Z-scored percent changes across the measures in each domain.
Results: As the intervention groups did not differ in clinical variables or functioning at baseline nor in percent change to Time 3, the groups were combined for the analyses. Changes in functioning between baseline and Time 3 were predicted by changes in social anxiety between baseline and Time 2, $r=-53$, $p<.001$. To ensure the association was not driven by generalized improvements in all areas, we then ran the analysis controlling for changes in positive and negative symptoms from baseline to Time 3; the association remained significant, $r=-56$, $p=.001$. Finally, to ensure the association was not driven by patients at one end of the severity spectrum responding, we additionally controlled for baseline SAPS and SANS, and the association remained significant, $r=-.61$, $p<.001$.
Discussion: In many cases, full recovery in first-episode psychosis has been difficult to attain despite adequate treatment of psychotic symptoms. Targeted interventions for social anxiety could increase social contact and social support and facilitate return to school and work, thus enabling functional recovery. Our findings suggest that longitudinal changes in social anxiety do impact functional recovery, above and beyond changes in positive and negative symptoms

and across the illness severity spectrum. However, the high attrition rate suggests that barriers to effective treatment delivery need to be identified and addressed.

V97. SYNERGY BETWEEN VMAT2 INHIBITORS AND ANTIPSYCHOTICS IN ANIMAL MODELS OF SCHIZOPHRENIA

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Background: Vesicular monoamine transporter 2 (VMAT2) inhibitors and antipsychotics have the potential to act synergistically as both target dopaminergic (DA) signaling in the central nervous system. While antipsychotics block postsynaptic DA receptors, VMAT2 inhibition lowers synaptic DA levels by preventing uptake into presynaptic secretory vesicles. The effects of a coadministered antipsychotic and VMAT2 inhibitor were evaluated using animal models of schizophrenia while also assessing potential for lack of concomitant weight gain (primary side effect of antipsychotics).
Methods: In one animal model of schizophrenia (conditioned avoidance response [CAR]), rats were dosed with an antipsychotic (risperidone or olanzapine), [+]-alpha-dihydrotetrabenazine, [+]-α-HTBZ, an inhibitor of VMAT2), and/or vehicle and tested in 20 trials of foot-shock avoidance. Antipsychotic effects were defined as CAR suppression or "escape" (failure to avoid foot shock despite prior conditioning). Synergy was defined as CAR suppression when antipsychotic and [+]-α-HTBZ were co-administered at subthreshold doses (ie, doses with no CAR suppression when administered individually). Synergy was also evaluated based on shifts in the antipsychotic plasma concentration-response (C-R) curve (with response defined as number of escapes) with [+]-α-HTBZ coadministration. Changes in weight were assessed for olanzapine, [+]-α-HTBZ, and both combined.
Results: At subthreshold doses, the mean number of escapes for [+]-α-HTBZ alone (0.8 [0.15 mg/kg]) and risperidone alone (0.7 [0.1 mg/kg]) were comparable to vehicle (0.4). CAR suppression increased when subthreshold doses of [+]-α-HTBZ and risperidone were combined (range, 6.5-7.1 escapes), and the results were comparable to the effects at threshold doses for [+]-α-HTBZ alone (4.8-11.4 escapes [0.3 mg/kg]) and risperidone alone (7.2-8.0 escapes [0.3 mg/kg]). This synergistic effect was not due to a drug-drug interaction, as the combination of drugs did not significantly affect the plasma concentration of either agent. Subthreshold [+]-α-HTBZ also increased the potency of risperidone for CAR suppression, as evidenced by a leftward shift of the C-R curve. Similar CAR suppression and C-R curve results were observed with the coadministration of [+]-α-HTBZ and olanzapine. Weight gain was observed with olanzapine, but coadministration with [+]-α-HTBZ did not further increase weight.
Discussion: The observed synergistic effect is consistent with a reduction of presynaptic DA resulting from VMAT2 inhibition, which in turn decreases the level of postsynaptic DA receptor blockade required for an antipsychotic effect. VMAT2 inhibition therefore mitigates the counterproductive presynaptic stimulation of DA by antipsychotics. These results suggest that combining VMAT2 inhibition with antipsychotic treatment will provide favorable clinical outcomes for efficacy without potentiation of a side effect of weight gain.

V98. SAME-GENDER AND SAME-RACE AMYGDALA ACTIVATION IN PSYCHOSIS-SPECTRUM COMMUNITY YOUTH WITH INTERPERSONAL TRAUMA EXPOSURE

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Background: Abnormal amygdala activation in response to threatening facial stimuli is associated with psychosis-spectrum (PS) and trauma symptoms. We previously confirmed this finding in PS youth from the Philadelphia Neurodevelopmental Cohort (PNC) (Wolf et al., 2015). We also showed PNC youth with trauma exposure show emotion identification impairments (Barzilay et al., 2019). These findings suggest social-emotional deficits may be a transdiagnostic mechanism across psychosis and trauma. However, the relationship between trauma and amygdala activation during facial processing has not yet been studied in PNC PS youth. Additionally, in- vs. out-group perceptions may also moderate social-emotional processing. Such effects may be altered in individuals with interpersonal trauma exposure, as salient social identities associated with perpetrators or protectors may be activated, though literature regarding in- vs. out-group activation is mixed. Here we examined the relationship of participant and stimulus gender and race to amygdala activation in PNC youth. We hypothesized amygdala activation would be greater for in-group faces compared to out-group faces, and that this effect would vary based on psychosis symptoms, trauma experiences, and demographic variables.

Methods: The analyzed sample comprised 1301 PNC youth, ages 8-21, with clinical and imaging data (including 365 PS, 332 TD; ~50% female and ~43% Black). PS symptoms and trauma severity were measured dimensionally. 3T fMRI BOLD data from a facial emotion identification task was examined with group-level regression analyses, focusing primarily on same-race>opposite-race and same-gender>opposite-gender contrasts within the amygdala ROI.

Results: Female participants exhibited stronger amygdala activation in response to same-gender vs. opposite-gender faces compared to males (female $t=4.25$, $p<.001$; male $t=-.63$, $p=.53$; female>male $t=3.34$, $p<.001$). Black participants showed increased activation in response to same-race vs. other-race faces than White participants (Black $t=8.62$, $p<.001$; White $t=.81$, $p=.42$; Black>White $t=5.47$, $p<.001$). The same-race effect was significant both in Black males and females, though stronger in Black females (sex*race interaction $p=.04$). The same-race effect was significant in all females ($t=2.76$, $p=.006$) but not males ($t=1.04$, $p=.30$) with a similar trend in Black and White females. PS youth did not show significantly greater same-race or same-gender effects than TD participants. Dimensional PS symptoms related across the full sample with the same-gender effect ($t=2.21$, $p=.027$) but not the same-race effect ($p>.05$). In females only, physical trauma severity related to the same-gender effect ($t=2.76$, $p=.006$); trauma did not relate to the same-race effect. Examining amygdala activation regardless of the stimulus demographic identity, only Black females showed an association between physical trauma exposure and amygdala activation ($t=2.67$, $p=.008$; other demographic groups $p>.05$).

Discussion: Participants who identify with a minoritized group (female, Black) exhibit neural responses in the amygdala consistent with enhanced in-group identification. Relationships with trauma and psychosis varied across contrasts and demographic groups, but where significant, the associations reflected greater in-group responses in those with greater trauma or psychosis. This suggests the possibility that stronger in-group responses may be a consequence of experiencing discrimination-based adversities, possibly due to great affiliation to in-group members associated with safety. These results may have important clinical implications for personalized treatment strategies with these unique groups.

V99. EXPLORING THE COGNITIVE PROFILES OF UNIMODAL AUDITORY HALLUCINATIONS, AND MULTISENSORY HALLUCINATIONS, IN SCHIZOPHRENIA-SPECTRUM DISORDERS

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Background: Hallucinations can be experienced across multiple different sensory modalities. Investigation of potential etiological factors of these experiences in schizophrenia-spectrum disorders, however, has been somewhat restricted to the auditory domain. The current study aimed to explore the cognitive profiles of individuals experiencing multisensory hallucinations in psychosis, and specifically whether these differed from those who experienced unimodal auditory hallucinations or no hallucinations.

Methods: Clinical participants with schizophrenia-spectrum diagnoses were divided into three groups based on current hallucinations status. Groups were as follows: no hallucinations (n = 56), unimodal auditory hallucinations (n = 35), multisensory hallucinations (n = 27). Hallucination status was determined using scores from hallucination items in the Scale for the Assessment of Positive Symptoms (SAPS). These referred to current (i.e. previous two weeks) experiences. Three auditory hallucination items (auditory hallucinations, voices commenting, voices conversing) were considered as a reference for auditory hallucination experiences and items for the other hallucination modalities (visual, somatic/tactile, olfactory) where used to determine the presence of multisensory hallucinations. Clinical groups and non-clinical controls (i.e. no past or current diagnosis of a psychiatric disorder or known first-degree relative with a psychotic disorder; n = 22) were compared for their performance across a battery of tasks of broad cognition (MATRICS consensus cognitive battery (MCCB)) and inhibition (Hayling Sentence Completion task and the Delis–Kaplan Executive Function System (D-KEFS) Colour-Word Interference Test). Group differences for demographic and clinical variables were calculated using chi-square tests of independence for categorical variables, and one-way analyses of variance (ANOVA) for continuous variables. Subsequently, ANOVA were conducted to determine group differences for cognitive variables.

Results: Analyses of demographic-clinical data revealed that individuals who experienced multisensory hallucinations scored significantly higher than both the no hallucinations and the auditory hallucinations groups, on severity rating levels for hallucinations, delusions, positive symptoms, general symptoms, and total symptom scores. With regards to cognition, non-clinical controls performed significantly better than all clinical groups on the reasoning and problem solving, verbal learning, and speed of processing domains. The clinical groups did not differ across these domains. Working memory was significantly more impaired in both the multisensory and the auditory hallucination groups, compared to the nonclinical controls. Individuals who experienced multisensory hallucinations exhibited significantly poorer performance on the visual learning domain, than both the no hallucinations group and the non-clinical controls. The auditory hallucinations group likewise displayed poorer performance than the non-clinical controls on this domain. Individuals who experienced multisensory hallucinations were also significantly slower than the nonclinical group on the inhibition condition of the DKEFS colour-word inference test.

Discussion: Firstly, multisensory hallucinations are not uncommon in schizophrenia-spectrum disorders. Individuals who experience multisensory hallucinations may report greater psychopathology than those who experience unimodal auditory hallucinations, and no hallucinations. These experiences should therefore receive greater attention in both clinical and research settings. Moreover, an impairment in visual learning may be specifically associated with multisensory hallucinations in schizophrenia-spectrum disorders, and this cognitive domain could therefore be a potential target for interventions. Other cognitive deficits associated with multisensory hallucinations, over and above a global schizophrenia-wide deficit, are not clear-cut. Future research should endeavour to investigate other cognitive impairments that might be implicated in these experiences. For example, existing models of auditory hallucinations should be explored for their applicability to multisensory experiences.

V100. THE IMPACT OF NEGATIVE SYMPTOMS ON LANGUAGE USE DURING A NOVEL SOCIAL INTERACTION TASK

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Background: Negative symptoms, defined as deficits in motivation, pleasure, and expressivity, are common in psychotic disorders and significantly contribute to social impairment (Kalin et al., 2015; Kring et al., 2013; Ventura et al., 2014). More severe negative symptoms are related to poorer social skills (Blanchard et al., 2015). Lexical analysis has also shown that negative symptoms manifest in word choice, with those higher in negative symptoms using more negative emotional words (Cohen et al., 2009; Vakhrusheva et al., 2020) and fewer social words (Minor et al., 2015). Importantly, to our knowledge no previous studies have explored how negative symptoms relate to word choice during social interactions.

Methods: Using a novel social interaction task (McCarthy et al., 2017), the current study seeks to explore the relation between negative symptoms, word choice, and social skills. We hypothesize that 1) Those with greater negative symptoms will use fewer total words, social words, positive emotional words, and more negative emotional words; 2) Those with poorer observed social skills will use fewer total words, social words, positive emotional words, and more negative emotional words; and 3) the relation between negative symptoms and word choice will remain after controlling for positive symptoms.

Data were collected from a transdiagnostic sample of adults with psychotic disorders and non-clinical participants living in Baltimore and Washington D.C. areas. Negative symptoms were measured using the Clinical Assessment Interview for Negative Symptoms (CAINS; Kring et al., 2013) which assessed both motivation and pleasure (MAP) and expressive (EXP) deficits. Positive symptoms were assessed using the Brief Psychiatric Rating Scale (BPRS). Participants completed a novel social interaction task with a highly affiliative partner which included a 3-minute affiliative conversation (McCarthy et al., 2017). Linguistic Inquiry Word Count (LIWC; Pennebaker et al., 2015) was used to assess speech content from transcripts of these conversations. Participant responses were also rated by undergraduate and master's level graduate students on their behavioral skills including overall nonverbal skills, overall affiliation skills, and overall social skills (Garcia et al., 2018).

Results: Analyses (N = 100) indicated that greater MAP deficits were related to fewer total words ($r = -.28$, $p = .006$) and fewer social words ($r = -.21$, $p = .03$) but were unrelated to positive or negative emotional words. EXP deficits were also related to fewer total words ($r =$

-.38, p < .001) but were unrelated to social or emotional words. Regarding social skills, greater nonverbal skills, overall affiliation skills, and overall social skills were all related to more total words (rs. .42-.47) but were unrelated to social and emotional words. After controlling for positive symptoms, the relation between total words and both MAP (pr = -.28, p = .004) and EXP (pr = -.38, p < .001) remained. However, MAP deficits and social words were no longer related (pr = -.20, p = .053).

Discussion: As hypothesized, during a highly affiliative social interaction task, negative symptoms were related to using fewer total words and fewer social words and poorer social skills were related to using fewer total words. Results also indicated that the relation between negative symptoms and total word count remained when controlling for positive symptoms. Individuals high in negative symptoms may behave in ways which discourage meaningful social interaction, due to their brevity of language, word choice, and poor social skills. This may reduce opportunities to improve social skills, contributing to further isolation and social impairment. Results will be discussed further at the time of presentation.

V101. PRELIMINARY ANALYSIS OF ACALP AND NEURAL SOURCE ACTIVITY OF PITCH AND DURATION MMN IN FIRST EPISODE PSYCHOSIS AT BASELINE, 3, 6, AND 12 MONTHS

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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 schizophrenia, and if MMN shows progressive impairment with early disease course.

Methods: We investigated scalp-recorded pMMN and dMMN with EEG and their neural generators with MEG concurrently in first episode psychosis patients (FE) and healthy controls (HC) at baseline and 3-, 6- and 12-month follow-ups. For this preliminary analysis we compared FE and HC cross-sectionally at each time point: 30 FE and 28 HC at baseline, 18 FE and 26 HC at 3mo, 19 FE and 28 HC at 6 months, and 12 FE and 23 HC at 12 months. We projected MEG inverse solutions to participant's individual MRI-based cortical surfaces, parcellated using the Human Connectome Project Glasser quasi-functional parcellation, and examined MMN activity in left and right primary auditory cortices (A1).

Results: Despite no significant baseline scalp EEG pMMN or dMMN reduction at FCz, analysis of MEG A1 source-resolved dMMN indicated reduction in the left hemisphere in FE at baseline (t(39) = -2.261, p = .023). Further, left hemisphere dMMN was reduced at 6 months (t(40) = -2.676, p = .011). Right hemisphere pMMN A1 source activity was only reduced in FE at 12 months (t(26) = -2.295, p = .030).

Discussion: Our results indicate that source-resolved MEG-based MMN activity may be more sensitive to initial auditory cortex pathophysiology, indicating deficits in dMMN not apparent in the EEG scalp MMN. Further, pMMN may show progressive deficits with psychosis duration. However, the power of this preliminary analysis may not be large enough to indicate significant changes at each timepoint, and the cross-sectional design of this preliminary analysis is not optimal to track progressive changes. We continue to test participants longitudinally for this project to increase the sample sizes and power. Our next steps will

include a true longitudinal analysis comparing the same subjects at each time point and a more conservative statistical approach (ANOVA with time x hemisphere as repeated measures).

V102. EVALUATING ROMANTIC AND SEXUAL FUNCTIONING AMONG PERSONS WITH A PSYCHOTIC DISORDER DIAGNOSIS: VALIDITY OF THE MULTIDIMENSIONAL SEXUALITY QUESTIONNAIRE AND THE ROMANTIC RELATIONSHIP FUNCTIONING SCALE

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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., 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. However, this tool has never been empirically validated in this population. While romantic relationship functioning is often limited among people with psychotic disorders, 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 of these two instruments among French Canadian individuals with a psychotic disorder diagnosis.

Methods: A total of 79 participants were recruited through several clinics specializing in psychotic disorders, as well as ads posted online (e.g., Facebook groups for people with psychosis, community mental health social media platforms, etc.). Individuals were included if they were 18 years of age or older, could read and understand French, and had been formally diagnosed with a schizophrenia-spectrum disorder (i.e., schizophrenia, schizoaffective disorder, schizophreniform disorder, etc.). The MSQ is a 60-item self-report questionnaire that measures several tendencies associated with human sexuality across 12 subscales: sexual consciousness, sexual self-esteem, sexual preoccupation, sexual self-monitoring, internal sexual control, external sexual control, sexual anxiety, sexual depression, sexual motivation, sexual assertiveness, fear of sex, and sexual satisfaction. The RRFS is a 22-item questionnaire assessing various aspects of romantic competence, including beliefs and attitudes about intimate relationships, perceived social skills, and self-confidence. It contains the following three subscales: Risks, Resources, and Stigma. The MSQ and the RRFS were completed online through the Qualtrics platform. The MSQ has been divided into two dimensions: positive and negative.

Results: Confirmatory factor analyses were performed using AMOS in order to evaluate the construct validity of the MSQ and the RRFS subscales in French. The fit indexes are insufficient which indicate that the hypothesized factor structures were not robust for both the

MSQ negative dimension, 2M(390, N = 79) = 732,48, p < .001; CFI = .77; TLI = .77; RMSEA = .11 (90% CI=.09, .12); SRMR = .12, and the MSQ positive dimension 2M(174, N = 79) = 251,42, p < .001; CFI = .90; TLI = .88; RMSEA = .08 (90% CI=.05, .10); SRMR = .07, as well as the RRFS, 2M(209, N = 79) = 407,26, p < .001; CFI = .63; TLI = .55; RMSEA = .11 (90% CI=.09, .13). In order to get better fitted models, items from each model were removed. The MSQ negative dimension and the RRFS remained insufficient even after a model adjustment was performed. The MSQ positive dimension was almost acceptable following a model adjustment, but still failed to suit the minimum requirements of an acceptable fitted model.
Discussion: The MSQ and the RRFS did not meet the minimum requirements of an acceptable fitted model. The small sample size may have negatively influenced the confirmatory factor analysis results. Therefore, future studies with a larger sample size are needed to validate the MSQ and the RRFS in individuals with a psychotic disorder. Since the questionnaires were completed online and without the supervision of any research assistants, it was impossible to confirm that the questionnaires were filled up adequately. This factor may have negatively impacted the results.

V103. CLINICAL AND PSYCHOSOCIAL CORRELATES OF MEDICATION ADHERENCE BEHAVIOR AND ATTITUDES IN ADULT PATIENTS WITH EARLY PSYCHOSIS IN HONG KONG

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Background: Treatment adherence is an important factor in predicting clinical and functional outcomes in patients with psychotic disorders. Yet, poor adherence to antipsychotic medications and negative attitudes towards medication treatment remain prevalent. This study aimed to identify clinical and psychosocial correlates of medication adherence behavior and attitudes in a cohort of Chinese patients with early psychosis.
Methods: The current analysis was based on a study which compared clinical and functional outcomes between patients who had received 3-year extended early intervention (EI or extended EASY programme) service and those managed by 3-year standard psychiatric care for their first-episode psychosis. Interviewed assessments on premorbid adjustment (PAS), onset profiles, symptom severity (by PANSS, CDSS, BNSS), functional levels (SOFAS), treatment characteristics as well as self-rated questionnaires on self-stigma, service satisfaction and subjective quality of life were administered 3 years after their presentation to psychiatric services. Systematic record review was also conducted to examine past psychiatric hospitalizations and prescription of antipsychotics over the 3-year period. Patients were classified into good versus poor medication adherence, and positive versus negative attitudes towards medication treatment based on the ratings on the modified Medication Compliance Questionnaire (MCQ). A series of univariate binary logistic regression analyses were conducted, with medication adherence status and medication attitude status as dependent variables, and an array of clinical and psychosocial variables (including intervention type i.e., EI or standard care) as candidate predictors. Those variables that were found to be statistically significant in preceding analyses were then included in multvariate binary logistic regression models to identify independent correlates for good adherence behavior and positive medication attitude.
Results: A total of 208 early psychosis patients completed the study assessment on MCQ, and were categorized into good (n = 122) versus poor (n = 84) medication adherence groups (2 subjects with missing data), as well as positive (n = 109) versus negative (n = 99) medication

attitude groups. Final mutlivariate logistic regression model revealed that good adherence behavior was significantly associated with lower positive symptom severity (OR=0.873, 95% CI [0.806,0.946], p=0.001) and lower level of self-stigma (OR= 1.108, 95% CI [1.038, 1.183], p=0.002). Alternatively, positive medication attitude was associated with older age (OR=1.099, 95% CI [1.050, 1.151], p<0.001), schizophrenia-spectrum diagnosis (OR=0.412, 95% CI [0.212, 0.802], p=0.009), secondary education level or below (OR=0.336, 95% CI [0.157, 0.716], p=0.005), better insight (OR=0.681, 95% CI [0.559, 0.828], p<0.0001), lower level of self-stigma (OR=1.084, 95% CI [1.007, 1.167], p=0.031), greater service satisfaction on staff communication (OR=1.065, CI [1.004, 1.129], p=0.038) and better subjective quality of life (OR=1.051, 95% CI [1.012, 1.091], p=0.009).
Discussion: Our results indicated that a patient's attitude towards medication and medication compliance were associated with different clinical and psychosocial variables. In particular, self-stigma is significantly related to both attitude and adherence behavior towards antipsychotic treatment. Further research could be conducted to evaluate the efficacy of self-stigma reduction strategies in improving medication treatment adherence among patients with early psychosis.

V104. DROPOUT PREDICTORS OF COGNITIVE TREATMENTS FOR SOCIAL ANXIETY IN EARLY PSYCHOSIS

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Background: Premature treatment termination (i.e., dropout) is a significant issue in psychological interventions, estimated to occur in up to one-third of psychosis patients. Despite the high dropout rates observed, few studies have investigated dropout predictors. Identifying these predictors can inform intervention monitoring and personalization, thus improving patient retention. This is crucial in early psychosis as individuals experience greater functional outcomes and quality of life post-intervention. The present study evaluated predictors of dropout in two cognitive interventions for social anxiety (SA) in early psychosis.
Methods: A multisite randomized controlled trial was conducted in 5 First Episode Psychosis clinics in Montréal. Early psychosis patients who met criteria for a diagnosis of SA disorder using the SCID were randomized to either a 13-week manualized group CBT treatment for SA (CBT-SA) or Computer-Assisted Cognitive Remediation Therapy (CACRT), serving as the active control (n = 96). Each intervention was delivered weekly for 1.5 hours by a trained clinician. Baseline sociodemographic and clinical scales were measured at baseline, post-intervention, and at 3 and 6-months follow-up. Across both interventions, 48% of participants dropped out of either intervention (n = 46), characterized by the completion of less than 7 of 13 sessions. Intervention type did not impact dropouts, thus the two interventions were grouped together. The highest dropout rate was either before or after the first session, representing 26% and 28% of total dropouts, respectively. Clinical, sociodemographic and group preference variables were evaluated as predictors of dropout status (dropped out or completed intervention). Dropout predictors were investigated using a logistic regression model. Predictor variables were selected if they were statistically significant in a t-test. Clinical variables included positive and negative symptoms (Scale for Assessment of Positive Symptoms and the Scale for Assessment of Negative Symptoms) , depression (Calgary Depression Scale) and social anxiety, assessed using a composite of three complementary SA scales (Social Interaction Anxiety Scale, Social Phobia Inventory and Brief Social Phobia Scale). Sociodemographic variables included socioeconomic status, age, years of education, number

of hospitalizations and duration of illness. The group preference variable assessed whether the participant was randomized to the intervention they expressed a preference for.
Results: Four of the twelve variables were significantly correlated with drop-out status. Dropouts tended to be younger, have a higher number of hospitalization, fewer years of education and lower SA scores. Lower baseline SA (M = 48.3) compared to higher baseline SA (M = 55.5) was the only significant predictor of dropout in the logistic regression model (B = -0.040, p = 0.013).
Discussion: Lower baseline SA predicted treatment dropouts, suggesting the importance of personalizing interventions (e.g. intensity or duration) to retain participation in those with lower symptom severity. Contrary to other interventions targeting different symptoms in first-episode psychosis, sociodemographic or clinical factors did not predict dropout, suggesting that dropout predictors may differ based on the targeted symptom of the intervention. Future studies should also evaluate therapist-level predictors of dropout. Given the importance of continuity of care in early psychosis, it is important to continue exploring dropout factors to retain patients in early interventions.

V105. NEUROPHYSIOLOGICAL EVIDENCE OF COROLLARY DISCHARGE DYSFUNCTION IN INNER SPEECH IN SCHIZOPHRENIA

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Background: Inner speech, also known as auditory imagery or verbal thoughts, refers to the action of silently producing words in one's mind. Prominent neurocognitive models (Feinberg, 1978; Frith, 1992) suggest that auditory verbal hallucinations (AVHs) in schizophrenia arise from failure of corollary discharge mechanisms to correctly identify and suppress self-initiated inner speech, thus leading it to be misattributed to external sources. While strong empirical evidence of sensory suppression deficits of overt speech in schizophrenia has been provided (Ford et al., 2001), such deficits in inner speech, a purely mental action, have long been regarded as untestable. Recent neurophysiological studies using a novel electroencephalographic (EEG) paradigm showed that inner speech is associated with a time-locked and content-specific corollary discharge that can suppress cortical response to overt speech, suggestive of shared neural generators and functional equivalence between inner and overt speech (Jack et al., 2019; Whitford et al., 2017). Here, using the same paradigm, we tested the long-held notion that schizophrenia with current AVHs exhibit deficits of inner speech suppression.
Methods: Hallucinating (n=23) and non-hallucinating (n=30) patients with schizophrenia spectrum disorders, along with matched healthy controls (n=22), were asked to imagine a single phoneme while, precisely at the same time, to listen to the same (match condition) or a different auditory probe (mismatch condition) through the headphones, while EEG was recorded. A passive condition where participants were asked to passively listen to the auditory probes was also presented (passive condition). The amplitude of the auditory-evoked potential (AEP) component N1 was examined.

Results: Healthy controls showed reduced N1 amplitude in the match condition (-3.97 μV, SD = 3.04) compared to the mismatch (-4.25 μV, SD = 2.95) and passive (-4.31 μV, SD = 2.82) conditions, replicating previous results of N1-suppression to self-generated stimuli. Critically, hallucinating patients showed a larger N1 amplitude in the match condition (-3.83 μV, SD = 2.91) compared to the mismatch (-3.33 μV, SD = 2.63) and passive (-3.33 μV, SD = 3.10) conditions. On the other hand, non-hallucinating patients showed reduced N1 amplitude in the mismatch condition (-3.63 μV, SD = 2.96) compared to the match (-4.01 μV, SD = 3.47) and passive (-4.13 μV, SD = 3.31) conditions. No statistical tests were performed given the small sample size and on-going data collection. The study is expected to be completed in early 2022 with a sample size of 30 per group.
Discussion: The preliminary results of this study indicated that cortical suppression of inner speech in schizophrenia was disrupted. While the production of inner speech resulted in N1-suppression in healthy controls when the content of inner speech matched with the content of the auditory probe, hallucinating patients exhibited markedly abnormal N1-suppression to inner speech, with a sharpened N1 amplitude in the match condition, compared to the other conditions. Intriguingly, non-hallucinating patients also exhibited an intermediate level of abnormal N1-suppression, with no difference in N1 amplitude between the match and passive conditions. If these results are validated after the study concludes, these would suggest specificity of inner speech suppression deficits with AVHs, and provide early evidence in support of atypical inner speech monitoring in patients with AVHs.

V106. CORTICAL MYELIN MAPPING IN ANTIPSYCHOTIC MEDICATION-NAIVE FIRST-EPISODE PSYCHOSIS PATIENTS WHO DO OR DO NOT DISPLAY CLINICAL FEATURES OF THE DEFICIT SYNDROME

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Background: Several lines of evidence suggest that dysfunctional myelination may signify abnormal brain maturation and may be relevant in the pathophysiology of schizophrenia. The deficit syndrome is a clinical subtype of schizophrenia characterized by enduring negative symptoms and is thought to reflect an early-onset developmental process whereas the non-deficit form of the illness may be characterized by attenuated neuroplasticity. Here, we used myelin mapping to test the hypothesis that dysfunctional myelination as a proxy of abnormal brain maturation in antipsychotic medication-naïve patients is present in those who display clinical features of the deficit syndrome, but is not present in those who do not.
Methods: We recruited 90 medication-naïve, first-episode psychosis (FEP) patients and 109 healthy controls. 28 FEP met clinical criteria for the deficit syndrome and 62 did not, based on the Schedule for the Deficit Syndrome (SDS). Images were obtained using a 3T whole-body Siemens MAGNETOM Prisma MRI scanner (Siemens AG, Erlangen, Germany) equipped with a 20 channel head coil. Structural images were acquired using a high-resolution T1-weighted scanner (TR= 2400 ms; TE= 2.22 ms; TI= 1000 ms; flip angle = 8 degrees; GRAPPA factor = 2; voxel size = 0.8 mm^3) and T2 weighted images likewise (TR= 3200 ms; TE= 563 ms; GRAPPA factor = 2; voxel size = 0.8 mm^3). Bias maps were also acquired (TR= 8000 ms; TE= 66.0 ms; flip angle = 90 degrees; echo spacing = 0.58 ms; voxel size = 2.0 mm^3). Preprocessing was performed using the Human Connectome Project minimal preprocessing pipelines (version 4.3.0), to align T1 and T2 images in native space, perform bias correction, registration to MNI space, segmentation, surface registration and calculate the T1w/T2w ratio for myelin quantification. After removing poor quality scans, 81 patients (54 non-deficit, 27 deficit) and 108 controls were included in analysis. Mean global cortical myelin content was

assessed. We performed an analysis of co-variance (ANCOVA) to compare average global myelin content between groups using sex and age as covariates.
Results: We compared three groups: healthy controls (mean age: 23.8, SD: 5.3, 54.6% male), non-deficit patients (mean age: 23.4, SD: 6.0, 57.4% male), and deficit patients (mean age: 23.4, SD: 6.0, 77.8% male). There was no difference in overall cortical myelin content between healthy controls or either patient group in the whole brain, $F(2, 186) = 1.056$, $p = 0.35$, left hemisphere, $F(2, 186) = 0.706$, $p = 0.495$, or right hemisphere, $F(2, 186) = 0.967$, $p = 0.382$.
Discussion: Our results suggest that no global differences in cortical myelination are present in either schizophrenia subgroup. Voxel-wise analysis will be employed next to identify specific brain regions that may show differences in cortical myelin content.

V107. THE EFFECT OF ANTICHOLINERGIC BURDEN ON COGNITIVE FUNCTIONS IN TREATMENT RESISTANT AND NON-TREATMENT RESISTANT SCHIZOPHRENIA PATIENTS

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Background: Antipsychotic and other psychotropics medications for schizophrenia often possess anticholinergic properties, which are associated with cognitive impairment. Anticholinergics medications are often used to reduce extrapyramidal symptoms such as akathisia and tardive dyskinesia that are induced by antipsychotic medications. Long-term intake of medication with anticholinergic properties may exacerbate underlying cognitive impairment in schizophrenia patients, especially in treatment resistant schizophrenia (TRS) patients who have poorer cognitive functioning compared to non-treatment resistant (NTRS) patients. Understanding the attribution of anticholinergic burden on cognitive function can help to improve patients' functional outcomes. Thus, the objective of this study was to examine the association between anticholinergic burden and cognition in TRS and NTRS.
Methods: A total of 464 first episode schizophrenia (FES) patient who took part in our previous nested case-control was included in the current study, in which 307 and 157 were classified as NTRS and TRS respectively based on the operational definition. Clinical ratings and cognitive assessments of Wechsler Adult Intelligence Scale-Revised were collected from patients. Medication data was acquired from our centralised hospital database and anticholinergic burden score was calculated using the Anticholinergic Drug Scale. Exploratory factor analysis was used to established cognitive domains and structural equation modelling was used to establish relationship between anticholinergic burden and cognitive domains.
Results: Four cognitive domains were identified using an exploratory factor analysis based on the cognitive assessments. Logical memory immediate and delay recall loaded on domain 1; arithmetic, information, digit span forward and back loaded on domain 2; visual pattern and digit symbol loaded on domain 3 and modified card sorting test on domain 4.TRS performed poorer on domain 1 ($U=5560.00$, $p=.002$), 2 ($U=5501.00$, $p=.001$) and 4 ($U= 5413.00$, $p=.001$) compared to NTRS after conducting a Mann-Whitney U test. Significantly higher anticholinergic load was also found in TRS compared to NTRS ($U=9278.00$, $p<.001$). Multiple group structural equation modelling was conducted in TRS and NTRS separately with the four cognitive domains and anticholinergic load in the model. Results indicated a direct effect of anticholinergic burden on the cognitive domain 3 ($\beta=-.413$, $p<.001$) in TRS, where the higher the anticholinergic burden, the poorer their cognition performance specifically in visual pattern and digit symbol. However, such association was not found in NTRS.

Discussion: Anticholinergic burden on cognitive functioning in schizophrenia is commonly reported various studies but limited have focused on TRS and NTRS. Our results indicated a direct effect of anticholinergic burden on cognitive functioning in TRS but not in NTRS. However, the aggregate effect of one's medication on cognitive functioning in a clinical practice remains unknown.

V108. SELF-REFERENTIAL GAZE PERCEPTION IN INDIVIDUALS WITH AT-RISK MENTAL STATES FOR PSYCHOSIS

Poster Presentation

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Background: Self-referential gaze perception (SRGP), referring to the perception of others' gaze directing towards oneself, has been considered as a crucial component of social cognition. Hypersensitivity in SRGP may lead to misinterpretation of others' intentions in social interaction, which is associated with ideas of reference and paranoid delusions in schizophrenia. While deficits of social cognition have been consistently reported in psychosis, eye gaze perception has yet to be comprehensively studied in those with at-risk mental states. This study aims to examine the SRGP bias and its association with clinical and cognitive functioning in individuals with at-risk mental states for psychosis (ARMS) and healthy controls (HCs).

Methods: Thirty-two ARMS subjects were identified and recruited from the psychiatric out-patient clinics at Queen Mary Hospital, Hong Kong between April 2017 and January 2021. The status of ARMS was confirmed using CARRMS. Suitable ARMS subjects and their age- and gender-matched healthy individuals (N=32) completed a set of standardised clinical and cognitive assessments as well as a computerized gaze perception task which required ones to judge whether averted gaze with various levels of ambiguity (centre: 0° and 5°; ambiguous gaze: 10° and 15°; unambiguous gaze: 20°, 25° and 30°) were directed towards themselves. Rate of SRGP was calculated for each gaze condition.

Results: When judging averted eye gaze, ARMS (mean age 23.22 ± 7.41 years old) displayed a greater SRGP bias than HCs (mean age 22.34 ± 3.96 years old). ANCOVA tests revealed that group differences in SRGP bias were observed in both ambiguous ($F(1,59) = 11.65$, $p = .001$) and unambiguous gaze ($F(1,59)=7.75$, $p=.007$) judgment even after adjusting for age, gender and years of education. Poorer task performance in digit span ($t(61)=-2.87$, $p=.006$) and comic strip tasks ($t(61)=-3.71$, $p<.001$) were found in ARMS when compared against HCs. In ARMS, digit span performance and scores of Schizotypal Personality Questionnaire (SPQ), Liebowitz Social Anxiety Scale (LSAS) and Peter's Delusional Inventory (PDI) were significantly associated with both ambiguous- and unambiguous- SRGP rates. Positive correlations were observed between LSAS ($r=0.510$, $p=.003$) and PDI ($r= 0.438$, $p=.014$) and ambiguous-SRGP rate and between SPQ ($r=0.408$, $p=.023$), LSAS ($r=0.609$, $p<.001$) and PDI ($r=.583$, $p=.001$) and unambiguous-SRGP rate, while negative correlation was only shown between digit span performance and unambiguous-SRGP rate ($r=-0.372$, $p=.036$). Ambiguous-SRGP rate was positively correlated with the SPQ scores ($r=0.658$, $p<.001$) among HCs, showing that HCs with a greater level of schizotypal personality were more likely to perceive ambiguous gaze as referencing to themselves.

Discussion: ARMS subjects exhibited SRGP bias in response to ambiguous and unambiguous gaze, which is consistent with previous studies examining eye gaze perception in patients with

schizophrenia. The deficits in gaze perception were also related to more severe symptoms and poorer cognitive performance in ARMS. Our findings demonstrated that impairment in abnormal gaze perception occurred even before the onset of psychosis, providing evidence for early detection of psychosis through the use of eye gaze perception tasks. However, further longitudinal studies are recommended to assess the predictive value of eye gaze perception for the transition to psychosis.

V109. AEROBIC EXERCISE ENHANCES THE IMPACT OF COGNITIVE REMEDIATION ON POSITIVE SYMPTOMS IN FIRST-EPISODE SCHIZOPHRENIA

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Background: It is a well replicated finding that schizophrenia patients who engage in systematic cognitive training improve in basic cognitive abilities. Our research has shown that adding aerobic exercise to the cognitive training intervention can further improve cognition and work/school functioning beyond intervention with cognitive training alone. Here, we further explore further the effect of this combination of interventions as an adjunctive treatment for first-episode patients. Specifically, we examined the effects of combining cognitive training plus aerobic exercise versus cognitive training alone on positive symptoms in first-episode schizophrenia patients.

Methods: Sixty-one participants were randomly assigned to Cognitive Training Plus Exercise (CT and E, N=33) or Cognitive Training alone (CT, N=28). All participants were also prescribed either oral risperidone or paliperidone palmitate (PP1M) in a concurrent antipsychotic medication RCT. Participants had a first psychotic episode within two years of study entry. Seventy-four percent were male. Mean age (study entry) was 22.7 (3.8) years and the average age of onset of first psychotic symptoms was 21.8 (4.3) years. All participants were provided four weekly sessions of internet-based cognitive training conducted in a group format, and half were concurrently randomized to receive an aerobic exercise program over a 6-month period, followed by six additional months of treatment with half the frequency of the group interventions. Trained raters administered the Brief Psychiatric Rating Scale (BPRS) every 2 weeks to assess a range of psychiatric symptoms, including the positive symptoms examined here. BPRS items are rated on a scale from 1 = “not present” to 7 = ”extremely severe.”

Results: The mean of BPRS Unusual Thought Content and BPRS Hallucinations, averaged over all available BPRS administrations during the 12-month protocol, was used as the Reality Distortion dependent variable in a General Linear Univariate Model (GLM). Oral versus PP1M was included as a factor in the model, and baseline Reality Distortion from the BPRS at the randomization baseline point was entered as a covariate. Reality Distortion during the 12-month trial was lower for the CT and E group (mean = 1.9, SD=1.3) compared to the CT group (mean = 2.4, SD=1.6), $F(1,54)=6.8$, $P = .02$). The medication groups were not significantly different ($P = .17$) in Reality Distortion, although there was a nonsignificant tendency toward an interaction between the psychosocial and medication interventions ($F(1,54)=3.6$, $P = .07$). In a separate Repeated Measures GLM with Reality Distortion averaged over the first and

second six-month periods as the dependent measure, there was a nearly significant tendency for the two groups to diverge from the first to second 6-month periods, with the CT group worsening and the CT and E group improving on Reality Distortion ($F(1,41)=3.9$, $P = .055$).
Discussion: Our findings suggest that the enhancing effect of adding aerobic exercise to cognitive training appears to extend beyond cognitive gains, and includes positive psychotic symptoms. Previous studies that included at least 90 minutes per week of at least moderately intense exercise (without cognitive training) also found reductions in positive symptoms (Firth et al., 2015). It is noteworthy that we found this effect in an intent-to-treat analysis, whereas Scheewe et al. (2013) did not find reductions in symptoms for their intent-to-treat analyses for the exercise intervention, but only among participants who attended > 50% of the exercise sessions. Our average attendance among our participants was over 50%, which may have strengthened our effect. Additional exploration will be needed to understand the underlying mechanisms of the impact of exercise on psychotic symptoms.

V110. PROSPECTIVE MEMORY PERFORMANCE IN INDIVIDUALS WITH HIGH SCHIZOTYPY AND ITS IMPROVEMENT: EYE TRACKING STUDIES

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Background: Schizotypy is a personality trait susceptible for schizophrenia, and prospective memory (PM) is one of the cognitive deficits observed in individuals with high schizotypy. However, the underlying cognitive processing of PM impairment in individuals with high schizotypy are still not fully known. Implementation intention is an encoding strategy and has been found to improve PM performance in healthy volunteers and patients with schizophrenia. This study aimed to examine PM performance in individuals with high schizotypy and whether implementation intention could improve PM performance in these individuals and the underlying mechanisms using eye-tracking.
Methods: Two experiments were conducted. In experiment 1, 30 participants with high schizotypy and 30 participants with low schizotypy completed PM tasks with eye movements recorded. In the PM task, participants underwent visual search task, and if specific words appeared, they need to make PM responses. In experiment 2, 50 individuals with high schizotypy were randomly assigned to the implementation intention group and typical instruction group. Participants finished the same PM task as in experiment 1 but received different instructions. The implementation intention group received PM instructions in the "if… then…" format and were required to repeat the instructions three times aloud and imagine themselves performing the PM task for 30 seconds, while the typical instruction group received PM instructions not in the "if… then…" format and without repetition or imagination.
Results: In experiment 1, individuals with high schizotypy had a lower PM accuracy and lower total fixation counts on distractor words than those with low schizotypy. In experiment 2, implementation intention significantly improved PM accuracy and total fixation counts on distractor words in individuals with high schizotypy compared to the high schizotypy group with typical instruction.
Discussion: Individuals with high schizotypy were impaired in PM compared to individuals with low schizotypy, and this deficit may be caused by their lack of continuous monitoring of PM cues. Implementation intention improved PM performance in individuals with schizotypy through facilitating cue monitoring.

V111. ANNOTATION OF SCHIZOPHRENIA RISK GENES IN 270 LOCI FROM PGC3 GWAS FOR ISCHEMIA-HYPOXIA RESPONSE

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Background: The risk of schizophrenia (SCZ) is thought to involve gene-environment interactions during neurodevelopment. Obstetric complications (OCs) are associated with the risk of SCZ as environmental factor, and OCs can cause ischemia-hypoxia in the developing brain. We previously annotated the SCZ risk genes in 145 loci of the GWAS dataset of Pardinas et al. (2018) for a known role in the ischemia-hypoxia response using gene sets (Schmidt-Kastner et al., 2020). We here isolated the protein coding genes from the 270 loci defined in PGC3 GWAS (Ripke et al., medRxiv, Sept. 13, 2020) and repeated the annotation for a role of ischemia-hypoxia.

Methods: Protein-coding genes were extracted from the list of 270 loci reported in the pre-print of the PGC3 GWAS. Subsets of SCZ risk genes with a link to loss-of-function (LoF) or synaptic functions (SynGO) were formed using gene sets. The gene set of "ischemia-hypoxia response" (IHR) gene (n=1,629) was used to annotate the complete set and subset of SCZ risk genes. A RNAseq study of focal brain ischemia (gene set BHATT; n=2,449) was used for confirmation. A data collection for putative targets of hypoxia-inducible factors (HIFs; n=2,345) was used to annotate SCZ risk genes that was supplemented with a literature search. Enrichment in gene sets was tested by chi-square tests ($p<0.01$) whereby a total number of 18k genes was assumed to be expressed in the developing brain.

Results: The total set of SCZ risk genes extracted from PGC3 GWAS consisted of n=1,490 protein coding genes, whereby n=322 were listed for LoF and n=115 in SynGO. Considering protein coding genes only, n=307/372 (83%) of the SCZ risk genes analyzed before (S.-K. et al., 2020) reappeared in PGC3 GWAS. IHR genes were not enriched in the total set (n=146; p=0.45), but in SCZ risk genes listed for LoF (n=55; p=0.0023) and in SCZ risk genes in SynGO (n=34; p=0.0001). N=24/25 of IHR genes listed before were reproduced. A separate gene set for brain ischemia (BHATT) was not enriched for in total set (n=189; p=0.28) whereas enrichment was found for SCZ risk genes listed for LoF (n=77; p=0.0013) and for SynGO (n=32; p=0.0092). N=27/33 genes of high interest for HIF regulation were reencountered, and more than 100 additional SCZ risk genes were classified as candidates for hypoxia regulation.

Discussion: The 270 loci of the PGC3 GWAS in SCZ contained four times as many protein coding genes as the 145 loci annotated before (S.-K. et al., 2020). Despite this strong expansion for SCZ risk genes, the results for annotation for ischemia-hypoxia response were broadly replicated in that subsets of SCZ risk genes related to LoF and synaptic functions were enriched for IHR genes and the BHATT dataset. The pool of SCZ genes related to ischemia-hypoxia through annotation has been more than doubled by the analysis, and these expanded subsets can now be used in targeted investigations including OCs as environmental factor. Further analyses of HIF regulation of SCZ genes may provide experimental targets in which genetic variation in regulatory regions can be linked to the strength of the hypoxia response.

V112. VALIDATION OF THE KOREAN VERSION OF THE ANTICIPATORY AND CONSUMMATORY INTERPERSONAL PLEASURE SCALE (ACIPS) IN NON-HELP-SEEKING INDIVIDUALS

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Background: Anhedonia, defined as the loss or reduction of the capacity for pleasure, is a prominent feature of several forms of psychopathology, especially schizophrenia-spectrum disorders. The Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS; Gooding and Pflum, 2014) is a psychometric instrument that has been used as an indirect measure of social anhedonia in many cross-cultural contexts, such as Western (U.S.), European (French, Spanish), and Eastern (Chinese) samples. However, little is known about the psychometric properties of the ACIPS among the Korean population. The purpose of this study was to validate the Korean version of ACIPS among non-help seeking individuals.
Methods: The sample consisted of 307 individuals who had no current or prior psychiatric history aged from 17 to 35. The study was conducted with the questionnaire packet consisting of the following measures: ACIPS, the Behavioral Inhibition and Behavioral Activation Scales (BIS/BAS), and Beck Depression Inventory (BDI). We examined the internal consistency for the total ACIPS scale, BAS/BIS, and BDI using reliability analysis. We also explored the factor structure of the Korean translation of the ACIPS. External validation was assessed by examining the association of the total ACIPS scores with the other measures.
Results: The total ACIPS showed good internal consistency. Factor analysis yielded a three-factor structure that accounted for 50.1% of the variance. Eight ACIPS items were loaded onto Factor I (Interaction in the context of communication). Factor II (casual interactions) contained four items, and Factor III (intimacy related interactions including family members) had 5. The score of BDI was negatively correlated with the total score of ACIPS. Additionally, the scores of the BIS and BAS scale were also significantly correlated with the total score of ACIPS, respectively.
Discussion: Our results indicated that ACIPS showed good construct validity in the Korean population. Future directions include using the Korean translation of the ACIPS to elucidate the varying degrees of hedonic capacity in psychiatric patients.

V113. WIDESPREAD THINNER CORTEX ASSOCIATES WITH EXCESSIVE GLUTAMATE IN A SUBGROUP OF FIRST-EPISODE PSYCHOSIS

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Background: Several observations indicate that patients with first-episode psychosis have a decreased cortical thickness profile and dysregulated glutamate levels. However, the relationship between the two is unclear. Several thickness-based, cluster analytic studies have reported a subgroup in schizophrenia marked by widespread cortical thinning. Glutamate-mediated excitotoxicity may underlie the mechanistic pathway of cortical thinning in this subgroup. In this study, we pursue the relationship between the suspected neurobiological heterogeneity in structural deficits and varying levels of glutamate at the time of the first presentation with psychosis.
Methods: Patients with first-episode psychosis (n = 66) were recruited from the Prevention and Early Intervention for Psychosis Program at London Health Sciences Centre in London, Ontario, Canada. Healthy Controls (n = 36) were recruited with matched age and gender. Neuroanatomical images and neurometabolic concentrations in the dorsal anterior cingulate cortex were collected with an ultra-high-resolution (7T) MRI scanner. We applied hierarchical cluster analysis to Freesurfer preprocessed cortical thickness values based on the Destrieux

atlas, and compared subgroup differences in demographic, clinical, neurochemical, functional, and linguistic data collected at the time of scanning.
Results: The clustering procedure produced two subgroups. Around 70% of patients (n = 46) were clustered with the majority of healthy controls. The remaining 30% of patients (n = 20) were placed in a subgroup with only 3 healthy individuals, and this subgroup showed lower thickness values in 124/148 regions with age as a covariate. ANOVA showed that this subgroup had significantly older age ($p < 0.0001$), higher glutamate levels ($p = 0.03$), higher lifetime exposure to antipsychotics medications ($p = 0.036$), and a trend towards higher formal thought disorder [Thought and Language Index (TLI) scores ($p = 0.09$)]. A positive correlation between negative symptom severity and resting glutamate concentration ($R = 0.47$, $p = 0.05$) was also limited to this subgroup. The two subgroups did not differ in overall symptom severity (PANSS-8), functioning (SOFAS) and processing speed (symbol substitution).
Discussion: In line with previous studies, cortical thinning is strongly age-related and neurobiological heterogeneity in cortical thickness exists. Patients with a globally reduced thickness may represent a mechanistically distinct subtype in first-episode psychosis characterized by excessive glutamate levels as well as more severe thought and language disorders. This finding supports the role of glutamate-mediated neurotoxicity in cortical thickness reduction and this mechanism may only operate in around one-third of patients. The lack of differences in symptom severity, social functioning and cognitive functioning implies that different neuropathological pathways can lead to similar clinical profiles, a phenomenon called phenocopying.

V114. ANTIDEPRESSANT USE AND PSYCHIATRIC REHOSPITALIZATION IN PATIENTS WITH SCHIZOPHRENIA

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Background: Antidepressants are often used by persons with schizophrenia. These medications are used in variety of symptoms, such as depressive or negative ones. Effectiveness of antidepressant use in persons with schizophrenia have been rarely studied in the real-world setting. The aim of this study was to investigate the risk of psychiatric rehospitalization related to antidepressant use in patients with schizophrenia.
Methods: This cohort study utilized data combined from several nationwide Finnish registers. The study cohort included all persons treated in inpatient care due to schizophrenia (defined as International Classification of Diseases, ICD, version 10 codes F20 and F25) during 1972–2014 in Finland (N=61,889). National Prescription register data was utilized to obtain drug purchase data, which was then modelled into drug use periods with PRE2DUP (From Prescriptions to Drug Use Periods) method, developed by our research group. The follow-up covered the years from 1996 to 2017. Antidepressants (Anatomic Therapeutic Chemical classification system ATC code N06A) were categorized by mechanism of action (non-selective monoamine reuptake inhibitors (TCAs, ATC-codes N06AA), selective serotonin reuptake inhibitors (SSRIs, N06AB) and serotonin-norepinephrine reuptake inhibitors (SNRIs, including venlafaxine, milnacipran and duloxetine), and on drug-substance level. Main outcome was psychiatric rehospitalization (hospitalization due to ICD-10 diagnoses F20-F29) as the main diagnosis. Within-individual design was used to compare the risk of outcome

between the time periods of antidepressant use and non-use within the same person to minimize selection bias. Stratified Cox regression analyses were used to calculate adjusted hazard ratios (aHR) with 95% confidence intervals (CIs). The effect of all time-invariant covariates (such as sex) is eliminated by the within-individual design and only time-varying factors needed to be adjusted for. These analyses were then adjusted for sequential order of treatments, time since cohort entry, use of antipsychotics, mood stabilizers, benzodiazepines, and Z-drugs.
Results: The mean age of the study cohort was 46.2 (standard deviation, SD 16.0) years at cohort entry, and 50.3% of were males. Altogether 49.3% (N=30,508) of the study cohort used antidepressants during the follow-up (median 14.8 years, IQR 7.5-22.0), with citalopram and mirtazapine being the most used antidepressants. The risk of psychiatric rehospitalization was lower during antidepressant use as compared to non-use (aHR 0.93, 95% CI 0.92-0.95). Use of SSRIs was associated with the lowest risk (aHR 0.91, 95% CI 0.89-0.93), followed by SNRIs (aHR 0.92, 95% CI 0.88-0.97) and TCAs (aHR 0.93, 95% CI 0.89-0.98). Of the most used antidepressants, use of sertraline (aHR 0.87, 95% CI 0.83-0.91), fluoxetine (aHR 0.88, 95% CI 0.83-0.91), citalopram (aHR 0.92, 95% CI 0.90-0.95), venlafaxine (aHR 0.93, 95% CI 0.88-0.97), and escitalopram (aHR 0.93, 0.88-0.99) were associated with the lowest risk of psychiatric rehospitalization. However, not all commonly used antidepressants were associated with decreased risk, e.g. mirtazapine (aHR 1.01, 95% CI 0.96-1.05), the second most frequently used antidepressant.
Discussion: Use of antidepressants was common in the study cohort, and it was associated in 7% lower risk of hospitalization due to psychosis. This trend was observed also with antidepressant subgroups, SSRIs, TCAs and SNRIs.

V115. SURFACE-BASED BRAIN MORPHOMETRY CORRELATES OF COGNITIVE DECLINE IN SCHIZOPHRENIA

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Background: Cognitive impairment is a prominent aspect of the psychopathology in schizophrenia considered to contribute to social impairments and treatment outcomes [1,2]. Brain structural alterations have been well-documented in individuals with schizophrenia, most consistently in prefrontal, temporal and parietal regions, areas found to be involved in high-order cognitive functions [3,4,5]. Previous research has found reduced cortical thickness in schizophrenia patients in relation to specific impaired cognitive domains such as working memory [6] or verbal learning [7]. However, it is not well established whether and to what extent the evidence for cognitive decline in schizophrenia – ie the discrepancy between estimated premorbid and current IQ that has reliably been found in patients with the disorder – is associated with brain structural abnormalities.
Methods: One hundred fifty-nine adults meeting DSM-IV-TR criteria for schizophrenia or schizoaffective disorder were included. All subjects were assessed using WAIS-III as a measure of general IQ and the Word Accentuation Test [8] as a measure of estimated premorbid IQ. The patients were then divided into two groups based on the presence or absence of cognitive decline, defined as a reduction ≥15 points (ie 1SD) in the current IQ score relative to

the estimated premorbid IQ. The patients underwent 3T fMRI scanning and individual cortical thickness, area and volume maps were reconstructed using FreeSurfer software. Group analyses were conducted with general linear models using age, sex, and intracranial volume as covariates in all analyses. For each metric, we examined the correlation with global IQ as a measure of general cognitive functioning. We also compared the groups with and without cognitive decline with a two-sample t-test in all metrics. Statistical inference was carried out with FreeSurfer tools based on non-parametric permutation testing, using a cluster-wise correction method for multiple comparisons with initial cluster-forming threshold of sig = 2.6 (i.e., $p < 0.0025$, two tails) and 5000 iterations. In these analyses, only those clusters with a corrected value of $p < 0.05$ were considered significant.

Results: Global IQ for all the schizophrenia patients was positively correlated with cortical thickness bilaterally in the middle frontal cortex and the precentral and postcentral cortices, the right superior frontal cortex and right supramarginal gyrus, and the left middle frontal and middle and superior temporal cortices. Global IQ was also correlated with cortical volume in the left precentral and middle temporal cortices. However, no correlations were found with surface area.

The cognitive decline group (n=46; 56.52% female) had a mean IQ of 76.3 (SD=9.93) while for the preserved group (n=113; 29.2% female) the mean IQ was 97.8 (SD=12.49). Both groups were equivalent in terms of age and premorbid IQ.

Results showed significant differences between groups in cortical thickness bilaterally in the precentral cortex, right superior frontal gyrus, and cuneus. Regarding cortical volume, groups showed differences in left precentral and superior frontal cortices and in the left inferior temporal gyrus. The cognitive decline group showed lower cortical thickness and volume than the preserved group. No differences were found in surface area between groups.

Discussion: This study found a pattern of cortical thickness and volume reductions associated with cognitive decline in schizophrenia patients involving frontal and temporal regions, areas previously found to be involved in high-order cognitive function. This pattern was found to be directly correlated with global IQ in the total sample but with a larger extension. Contrary to previous research [9] the cognitively impaired group was composed by a majority of women in comparison to the preserved group. These findings may help to understand brain correlates of cognitive decline in schizophrenia. However, further research would be needed to clarify if a previous reduced volume could determine the subsequent cognitive impairment characteristic of schizophrenia.

V116. LONG-TERM OUTCOMES IN PATIENTS WITH PSYCHOTIC DISORDER NOS - A 10 YEAR FOLLOW-UP STUDY

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Background: The DSM-IV diagnostic category “Psychotic disorder not otherwise specified” (PNOS) is intended to be used as a temporary diagnosis in cases of limited or unclear information, but studies indicate that for some patients the diagnosis is retained over time. While a diagnosis of PNOS is commonly used in first episode psychosis, our knowledge of these unspecified conditions is limited. We here examined diagnostic stability, symptom

severity, global functioning and rates of clinical recovery (defined as stable symptomatic remission with regained functioning) 10 years after an initial diagnosis of PNOS.
Methods: A total of 32 participants diagnosed with PNOS at their first treatment for psychosis were reassessed 10 years later. The assessments included SCID-I for DSM-IV, Positive and Negative Syndrome Scale (PANSS) and Global Assessment of functioning (GAF, split version), at baseline and 10-year follow-up. We investigated diagnostic stability and compared those who retained the PNOS diagnosis in the long term (PNOS-retained) with those who had a subsequent change of diagnosis (PNOS-change) at 10-year follow-up regarding sociodemographic factors, symptom severity, global functioning and recovery.
Results: Of the 32 participants included, 17 (53%) retained the diagnosis at 10-year follow-up assessment, while seven participants (22%) were diagnosed with schizophrenia, 6 (19%) with an affective psychotic disorder and 2 participants (6%) with a substance-induced psychotic disorder at 10-year follow up. The PNOS-retained group had higher mean baseline scores for the PANSS Excited factor (F=10.4, p=0.004) and the PANSS Depressive factor (F=4.5, p=0.042) compared to the PNOS-change group. There were no other significant differences for other PANSS factors and GAF-scores, at baseline or at 10-year follow-up. There were also no significant differences in rates of clinical recovery.
Discussion: Our findings indicate that the category of DSM-IV PNOS is not just a temporary diagnostic category, but also comprises conditions that retain the same symptomatic characteristics over time. This is in line with the DSM-5 decision to divide this group into the two groups called “Other specified schizophrenia spectrum and other psychotic disorder”, which applies to presentations where symptoms characteristic of a psychotic disorder is present without meeting the full criteria for a specific disorder, and “Unspecified schizophrenia spectrum and other psychotic disorder” which applies to cases without sufficient information.

V117. ANTIPSYCHOTICS AND IMPULSIVITY IN SCHIZOPHRENIA

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Background: Impulsivity has been repeatedly identified as a major problem in schizophrenia. It was implicated in the increased suicidal risk of schizophrenia patients.
Antipsychotic medications have been used to control impulsivity and aggressiveness. They have a double function, to treat the disorder and the behavior dyscontrol.

The objective of this study was to evaluate the prescription of antipsychotics in schizophrenia and study their effectiveness in the treatment of impulsivity.

Methods: This is a cross-sectional study, descriptive and analytical, conducted among a population of 74 patients (30 women and 44 men).
The diagnosis of schizophrenia was selected in those patients as TR DSM IV criteria.

We used a questionnaire to collect clinical data and we also used the BIS scale (Barratt Impulsivity Scale).

Results: The average age was equal to 42.8.
More than half patients were prescribed conventional antipsychotics (66.2%) including whom 59.5% received long-acting neuroleptics.

33.8% of patients were prescribed atypical antipsychotics. An association of two antipsychotics was observed in 18.9%of cases.

There was a significant correlation between the association of two antipsychotics, the prescription of long-acting neuroleptics and impulsivity.

Motor and cognitive impulsivity scores were higher in patients receiving two antipsychotics.

There was no significant difference between scores of impulsivity in patients who received classic neuroleptics compared to those who received atypical antipsychotics.

Discussion: Antipsychotics are used in the treatment of impulsivity in schizophrenia.
Several studies have shown that clozapine was more efficient than conventional antipsychotics.

Another study published in 2006 showed a superiority of clozapine:

clozapine > olanzapine

clozapine > haloperidol

The treatment of impulsivity in schizophrenia decreases suicidal attempts.

It appears from our study that the association of two antipsychotics has no effect in the treatment of impulsivity in schizophrenia.

The comparison between conventional and atypical antipsychotics has shown no difference in the treatment of impulsivity.

V118. DISCONNECTED SENSORIMOTOR AND COGNITIVE CEREBELLAR ZONES CONTRIBUTE TO AUDITORY VERBAL HALLUCINATIONS

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Background: Positive symptoms of psychosis may be the result of faulty coordination and automatization of motor and higher-order cognitive functions, partly due to cerebellar dysfunction. Specifically, auditory verbal hallucinations (AVH) have been related to altered processing of sensory feedback to one's own action. Such alterations highlight the role of dysfunctional cerebellar circuitry in psychosis. However, how exactly the cerebellum contributes to AVH remains unclear.
Methods: A systematic search of electronic databases identified a broad range of cerebellar neuroimaging studies in psychotic patients, reporting volume, structural connectivity, or resting-state functional connectivity data. Twenty-two studies were selected for review: 11 focused on the specific effects of AVH and 11 probed the effects of aggregated positive symptom scores. Meta-analysis was used to probe the consistency of cerebellar differences and their relationship with sociodemographic and clinical measures. An exploratory Activation Likelihood Estimate analysis (ALE) tested the regional specificity of cerebellar differences in patients with such symptoms.
Results: Cerebellar differences were more consistently associated with AVH than with aggregated positive symptom measures, particularly when considering resting-state functional connectivity data. These differences were not moderated by age, sex, medication, or symptom severity. The ALE meta-analysis revealed a spatial convergence of these differences in Lobules V-VI and Crus I.
Discussion: Cerebellar dysconnectivity might indicate a specific liability for AVH, particularly in sensorimotor (Lobules V-VI) and cognitive (Crus I) cerebellar zones. These abnormalities may contribute to altered sensory feedback processing and, consequently, affect higher-level cognitive functions (e.g., cognitive control) in AVH.

V119. INDIVIDUAL PLACEMENT AND SUPPORT FOCUSING ON EMPLOYMENT AND EDUCATION FOR YOUNG PEOPLE AT CLINICAL HIGH RISK OF PSYCHOSIS: A FEASIBILITY STUDY

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Background: This study aimed to assess the feasibility of implementing Individual Placement and Support (IPS) with a focus on educational and employment goals, within a clinical service for the early detection of individuals at clinical high risk of psychosis (CHR).
Methods: Between June 2019 and April 2021, participants were recruited and received up to 6 (+/-2) months support. Primary outcome: enrolled participants, attended sessions and disengagement rates were analysed to assess feasibility. Secondary Outcomes: enrolment in mainstream education or/and employment, hours spent working or studying, salary, level of functioning and self-efficacy at baseline and follow-up were compared.
Results: Thirty-one participants were recruited, 13 of whom were remotely recruited after the first COVID-19 lockdown. Dropout rates were relatively low (16.1%), and 26 participants (83.9%) completed the programme. Secondary outcomes: At follow-up, 73.1% participants were employed, were working on average more hours per week [t(25)=-2.725; p=0.012], and were earning significantly more money [t(25)=-3.702; p=0.001]. compared to baseline. Gains in educational outcomes were less clear and a reduction in hours of study per week was observed. Global Assessment of Functioning [T=248.50; p=0.001] and Social Occupational Functioning [t=-3.273; p=0.003] were significantly higher at 6-month follow-up compared to baseline. No differences were found in participants' self-efficacy
Discussion: Findings indicate that research procedures are appropriate and that IPS implementation within a CHR clinical team is feasible. Secondary outcomes also suggest that IPS may be a beneficial intervention for young people at CHR. A longer follow-up might be needed to assess its impact on educational outcomes.

V120. DEVELOPMENT OF A DIGITAL PROGRAM FOR TRAINING COMMUNITY HEALTH WORKERS IN THE DETECTION AND REFERRAL OF SCHIZOPHRENIA IN PRIMARY CARE SETTINGS IN RURAL INDIA

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Background: Digital technology is an important approach for training community health workers (CHWs) to deliver mental health care in primary care settings in rural India. Few studies have considered whether similar digital training programs could build capacity of the frontline workforce towards improving treatment outcomes for persons living with schizophrenia in low-resource settings. This study aimed to develop and contextualize the content for a digital program for training CHWs in the detection, referral, and follow-up with patients with schizophrenia in community settings, and to assess the acceptability and feasibility of this program.

Methods: An iterative design process was employed. First, to develop the training curriculum, evidence-based content from existing community programs for schizophrenia care was incorporated into the course, and reviewed by experts to ensure clinical utility and fidelity of the adapted content. Second, to contextualize the content for local settings in rural India, CHWs were enrolled to provide qualitative feedback on the appropriateness of language, content, an initial prototype of the digital training program including digital platform through one-to-one discussions. Focus group discussions were then used to understand the acceptability and feasibility of the digital training prototype - to inform modifications and improvements to the design and layout. Qualitative data was analyzed using a framework analysis approach based on predetermined themes related to acceptability and feasibility of digital training content and platform.
Results: Development of the initial prototype involved review of the content by 12 'experts' with clinical expertise in delivering mental health care and specifically care for persons with schizophrenia. This included 7 psychiatrists, 3 Psychologists, 1 Counsellor and 1 Service User. A total of 23 CHWs participated in this study, of which 11provided feedback for contextualization of the training content and 12 for acceptability and feasibility of the digital training prototype in a focus group discussion. During contextualization of training content key, feedback pertained to simplifying the language and presentation of the content by removing technical terms and including interactive content and images to enhance interest and engagement for digital training. During digital training prototype testing, few CHWs recalled seeing people in the community with similar symptoms but were unaware of this illness and available treatments. They shared that training can help them identify symptoms of schizophrenia and connect patients with specialists. They were also able to understand misconceptions around and discrimination towards people with schizophrenia, how to address these challenges by supporting others and spreading awareness about schizophrenia in their communities. Despite limited familiarity with using digital technology for learning, they liked the digital training, as this saves their time and can be done with their routine work.
Discussion: This study contributes to mounting evidence on the use of digital technology for training CHWs in low-resource settings, and represents an important preliminary step towards building community capacity to reduce delays in the early detection and treatment of schizophrenia and referrals. While this study focused on the development of a digital training program, acceptability and feasibility, continued efforts are necessary to determine if such approaches can specifically develop their skills for identification and referral of schizophrenia. We anticipate CHWs beliefs and knowledge on schizophrenia can be changed and they can help in mitigating barriers to accessing treatment for Schizophrenia.

V121. THE STABILITY OF EMERGENCY DIAGNOSIS OF PSYCHOSIS AT HOSPITAL ADMISSION

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Background: The validity of the selection criteria for register-based studies has been little studied. Previous studies, which have compared register-based diagnoses to case records, have shown that psychosis diagnoses in the registers have been quite valid. However, the characteristics of the emergency setting may decrease the validity of the diagnoses. Our aim is to compare psychosis diagnoses given in emergency department at hospital admission to hospital discharge diagnosis.
Methods: We used data from the Finnish Quality Register for Psychosis Care. All people with non-affective psychosis diagnosis (International Classification of Diseases [ICD]-10 codes

F20-F29) between years 2010-2018 were identified from the care register for health care (n = 50 058). The register contains hospital care, specialized outpatient care and primary health care (from 1.1.2011) in Finland. We identified people whose first psychosis diagnosis was given on the day of psychiatric hospitalization or a day before.
Results: Altogether, 11 122 people received their first psychosis diagnosis in emergency department. Most of them had other or unspecified nonorganic psychotic disorder diagnosis (75%) or acute and transient psychotic disorder diagnosis (17%). Of people with first psychosis disorder diagnosis at emergency department, 62% received psychosis diagnosis as a discharge diagnosis. If the person did not receive psychosis diagnosis, the most common discharge diagnoses were substance use disorder diagnoses as well as mood and anxiety disorder diagnoses.
Discussion: Over half of people with psychosis diagnosis in emergence department received psychosis diagnosis also at discharge. However, when compared to discharge diagnosis emergency diagnosis does not appear to be reliable. Therefore, hospital discharge diagnosis should be used when selecting people for a psychosis cohort from registers.

V122. PSYSCAN CLINICAL HIGH-RISK AND HEALTHY CONTROL COHORTS: RECRUITMENT METHODS AND BASELINE CHARACTERISTICS

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Background: Predicting adverse outcomes in individuals at clinical high-risk for psychosis (CHR) is not possible solely on the basis of a clinical assessment. The PSYSCAN Consortium aims to combine neuroimaging, clinical, cognitive and genetic and omics data to facilitate the prediction of psychosis onset, course and outcome within the CHR population. The ultimate goal is to use these data to improve individualised patient care.
Methods: The study adopted an international, multi-centre, naturalistic, longitudinal design. Individuals at CHR were assessed at baseline, 3-, 6- 12- 18- and 24- months, we additionally recruited a group of demographically-similar healthy controls (HC) who completed assessments at baseline, 6- and 12- months. Psychopathology, including attenuated psychotic

symptoms, was assessed using semi-structured interviews and self-report questionnaires. Brain structure and function were measured using structural MRI, resting-state functional MRI, and Diffusion Tensor Imaging. Cognition was assessed using a computerised battery (iPad device) of four neuropsychological tests derived from the CANTAB battery and a paper and pencil short version of the Wechsler Adult Intelligence Scale III. Blood samples were collected to obtain whole blood, serum, and plasma in order to assess genetic, proteomic, metabolomics, and immune markers. A hair sample was collected at baseline for keratinocyte biomarker analysis.

Results: A total of 234 CHR participants and 139 HC, aged 16-40 years were recruited between July 2016 and December 2019 from sites located in Europe (London, Edinburgh, Amsterdam, Maastricht, Utrecht, Madrid, Naples), Australia (Melbourne), Asia (Seoul, Hong Kong) and the Americas (Toronto, Sao Paulo). Final follow-up assessments are still to be completed across a small number of sites. This presentation will describe the baseline sociodemographic and clinical features of the CHR and HC cohorts.

Discussion: International, multi-centre consortiums can facilitate the recruitment of large samples of individuals at CHR for psychosis. Our extensive assessment schedule has provided a rich and comprehensive dataset that will support the development of prediction models to determine risk of psychosis onset and other clinically-relevant outcomes in this high-risk population.

V123. REGIONAL COMPARISON OF PAIRED RATINGS IN A STUDY OF NEGATIVE SYMPTOM SCHIZOPHRENIA

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Background: Site-independent review of recorded site-based interviews is a useful surveillance method to assure ratings reliability in clinical trials. Previous reports about paired ratings in schizophrenia examined subjects experiencing an acute exacerbation of psychosis. In the present analysis, we conducted a regional comparison of paired ratings of the Positive and Negative Syndrome Scale (PANSS) and Brief Negative Symptom Scale (BNSS) in subjects diagnosed with negative symptom schizophrenia at trial sites in Europe and the United States (USA).

Methods: The data came from a Phase 2, 12-week, randomized, double-blind study to evaluate the efficacy and safety of 3 Dose Levels of TAK-831 in the adjunctive treatment of adult subjects with negative symptoms of schizophrenia (TAK-831-2002: ClinicalTrials.gov Identifier: NCT03382639). TAK-831 is a highly selective and potent inhibitor of D-amino acid oxidase (DAO), a peroxisomal enzyme active toward neutral D-amino acids that is being investigated for the treatment of schizophrenia.

We obtained video-recorded site-based PANSS and BNSS interviews during the trial. At baseline, eligible subjects had BNSS total scores (12-item, excluding item 4) ≥28 and no more than 2 moderate-severe ratings (≤5) on the PANSS positive symptom items (P1, P3, P4, P5, P6) or unusual thought content (G9) with a maximum of 2 items rated "5", and no more than a moderate rating on conceptual disorganization (P2). We used intraclass correlation (ICC) and Bland-Altman analyses to compare paired ratings of all 30 PANSS items and 13 BNSS items.

Results: The ICC was r= 0.839 for paired PANSS ratings (n=1006) and r= 0.871 for paired BNSS ratings (n=892). Bland-Altman scatterplots revealed that 4.8% of paired PANSS scores and 4.7% of paired BNSS scores were outside the confidence intervals.

For all pairs, the site-based mean total BNSS and PANSS scores were significantly lower than the paired site-independent scores ($p<0.0001$ and $p= 0.006$ respectively).

In the regional analysis, the mean site-based BNSS scores were significantly higher in Europe than the site-based USA scores ($p= 0.025$) but total PANSS scores were lower in Europe than the USA ($p= 0.07$).

The mean site-based PANSS positive symptom subscale score was significantly lower in Europe compared to USA scores ($p<0.0001$) whereas the mean site-based PANSS negative symptom subscale and Marder negative symptom factor scores were significantly higher in Europe than in the USA ($p<0.0001$ and $p=0.0007$ respectively).

The magnitude of symptom severity influenced the extent of paired scoring deviations on both rating instruments in both regions. For instance, total site-based PANSS scores □80 generated significantly greater site-based paired scoring deviations than site-independent scores whereas site-based PANSS scores <70 generated significantly lower site-based scoring deviations.

Discussion: We observed high paired scoring correlations on both the PANSS and BNSS but significant regional scoring differences on positive and negative symptoms between European and USA ratings. These differences may reflect different patient populations or regional differences in ratings. We also observed a bi-directional pattern of scoring deviations such that site-based ratings were significantly higher than site-independent ratings when the symptom severity was high but lower when symptom severity was low. We noted a similar bi-directional pattern in studies of major depressive disorder and acute exacerbation of psychosis in schizophrenia. The significant regional differences noted on the PANSS and BNSS scores in this study suggests that merging multi-national data may increase scoring variability and mute signal detection.

V124. ENDOGENOUS MEASUREMENTS OF GLUTATHIONE, GLUTAMATE, AND GAMMA-AMINO BUTYRIC ACID USING PROTON MAGNETIC SPECTROSCOPY

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Background: Schizophrenia is a complex psychiatric illness where abnormal concentrations of neurotransmitters within the synaptic cleft lead to abnormal neurotransmission. Abnormal neurotransmission could be affecting the balance and role of a network of neurotransmitters such as gamma-aminobutyric acid (GABA) and glutathione (GSH), and glutamate (GLU) [1]. Magnetic Resonance Imaging (MRI), a non-invasive in-vivo imaging modality, can quantify the chemical composition of voxel in a human brain to study the abnormal neurotransmission in schizophrenia. Many MRI pulse sequences have been successful at detecting GLU, GABA, and GSH independently but none have been successful at providing high-quality measurements of all three simultaneously. This is due to their extremely low in-vivo concentrations, strongly coupled spins in their spectral signature, and interference of neighboring signals [2]. Therefore, there is an unmet need to implement an effective technique to quantify all three neurotransmitters accurately and simultaneously to understand the pathophysiology of schizophrenia. One promising technique involves the use of an advanced MRI pulse sequence that uses a narrow-band radiofrequency pulse to selectively isolate the signal of a molecule of interest in the human brain spectrum [3]. In addition to this highly selective pulse sequence,

the use of a higher field strength scanner will increase the sensitivity of all three neurotransmitters [2]. Using this narrow-band and highly selective pulse sequence at 7 Tesla could be used to quantify endogenous levels of GLU, GABA, and GSH in brain regions relevant to schizophrenia. The objective is to develop, test and validate this narrow-band and highly selective pulse sequence at 7 Tesla to target GLU, GABA and GSH in a human brain.
Methods: An advanced MRS pulse sequence known as Delays Alternating Nutation Tailored Excitation Point RESolved Spectroscopy (DANTE-PRESS) uses a narrow-band radiofrequency pulse to selectively isolate the signal of a metabolite of interest in the human brain spectrum [3]. To complete this, DANTE-PRESS will be programmed within the software environment of the 7 Tesla MRI scanner at Robarts Research Institute at Western University. Phantom studies will be conducted to obtain data on water solutions of GABA, GSH and GLU at in-vivo and double in-vivo concentrations. This is to validate the technique and its ability to measure concentrations. Next, the pulse sequence will be tested in the anterior cingulate cortex and the temporal lobe in ten healthy volunteers to demonstrate feasibility and estimate test-retest reliability. The method will then be included in an ongoing longitudinal study of schizophrenia to explore its usefulness in early identification of patients that experience poor treatment outcome.
Results: DANTE-PRESS can isolate metabolites of interest while suppressing unwanted signals that would have contributed to chemical shift displacement errors, such as isolating glutamine from glutamate. Furthermore, the suppression from DANTE-PRESS can effectively suppress signal from water such that water suppression is not required. DANTE-PRESS can produce high quality and simple spectral signatures of multiple metabolites simultaneously. In vivo, many pulse sequences have attempted to quantify GABA, GLU and GSH in the anterior cingulate cortex independently with coefficient of variances of 3%, 3% and 24% respectively [4][5]. It is anticipated that DANTE-PRESS will be able to quantify high-quality measurements of GABA, GSH, and GLU at 7 Tesla with coefficient of variance below these values.
Discussion: Due to variations in neuronal activations, patients with schizophrenia experience variability in their response to standard treatments [1]. It is crucial to develop a method that can obtain high-reliability measurements of GABA. This will provide in vivo human evidence to test GABA's role in models of schizophrenia involving the simultaneous action of excitation or inhibition imbalance. Understanding GABA's role would enable psychiatrists and pharmaceutical companies to develop medication tailored towards patients who are predicted to not respond to standard treatment. This could reduce the distress associated with multiple unsuccessful treatment trials.

V125. ATTACHMENT, EMOTIONS, AND PARANOID IDEATION IN CLINICAL AND NON-CLINICAL SAMPLE: EXPERIENCE SAMPLING STUDY

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Background: Proper functioning within interpersonal relationships is a significant indicator of mental health and overall well-being. Insecure attachment can lead to adverse experiences of self and others which can cause many disruptions in everyday life. It can be associated with low self-esteem, self-doubt, increased suspiciousness, distrust, or excessive dependency on others which, together with emotional lability, could take an active part in the aetiology and/or maintenance of paranoid ideation in insecure people. The goal of this study is to examine the

associations of adult attachment dimensions to daily experience of paranoid ideation and how they affect the relationships of daily emotions and paranoid ideation.
Methods: The sample consisted of 60 participants (26 healthy participants (HC) and 34 individuals (P) diagnosed with schizophrenia, affective disorder, or anxiety disorder). Age ranged between 19-55 years (HC: M=31.31 and SD 11.03; P: M=33.85 and SD=11.22). The research consisted of two parts, 1) cross-sectional administration of tests and scales followed by 2) Experience Sampling in daily life. For this study, we administered the Experiences in Close Relationships – Revised and an Experience Sampling Method protocol (ESM) where we asked about daily experience of emotions, paranoid ideation, social context, and beliefs about others 10 times per day for 6 consecutive days. Both samples (HC and P) had sufficient compliance for ESM research with 73% of completed notifications in HC and 70% in P sample.
Results: We found statistically significant higher levels of attachment-related anxiety and avoidance and a higher level of daily paranoid ideation [β=.604, SE=.200, p=.002, 95% CI (.213 to .996)] in patients with diagnosed mental disorder compared to healthy control subjects. Associations between both attachment-related anxiety and avoidance and daily experience of paranoid ideation were observed across the whole sample. We found association to attachment-related anxiety [β=.334, SE=.097, p=.001, 95% CI (.144 to .523)], and attachment-related avoidance [β=.277, SE=.113, p=.015, 95% CI (.055 to .499)]. Negative emotions were associated with daily paranoid ideation [β=.166, SE=.035, p<.001, 95% CI (.096 to .235)]. We did not find an association of daily positive emotions with decrease of paranoid ideation. The attachment-related anxiety moderated the association between daily negative emotions and paranoid ideation [β=.093, SE=.035, p=.008, 95% CI (.024 to .162)], while attachment avoidance did not. With increased attachment-related anxiety, the association between negative emotions and paranoid ideation amplifies.
Discussion: Based on our results, both attachment-related anxiety and avoidance could be associated with an increase of daily paranoid ideation across the paranoid continuum from healthy to pathological. Our findings support that attachment-related anxiety could be a stronger pathway to experiencing daily paranoid ideation compared to avoidance. When the need of closeness to others is not saturated enough, it could lead to emotional lability, increased negative emotions, suspiciousness, and distrust which often creates a vicious cycle of negative experience and often intensifies paranoid ideation. Results need to be further replicated and extended to broader clinical and non-clinical samples.

V126. LUMATEPERONE 42 MG IN AN OPEN-LABEL SWITCH STUDY IN PATIENTS WITH STABLE SCHIZOPHRENIA: SAFETY BY PREVIOUS ANTIPSYCHOTIC

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Background: Lumateperone (LUMA) is a mechanistically novel antipsychotic that is FDA approved for the treatment of schizophrenia. An open-label study (Study 303) evaluated the safety and tolerability of LUMA in outpatients with stable schizophrenia who switched from previous antipsychotic (PA) treatment. This post hoc analysis of Study 303 investigated the safety and tolerability of LUMA stratified by PA in patients who switched to LUMA treatment for 6 weeks.

Methods: Adult outpatients (≥18 years) with stable schizophrenia were switched from PA to LUMA 42 mg once daily for 6 weeks followed by switching to another approved antipsychotic for a 2-week follow up. Post hoc analyses were stratified by most common PA: either risperidone or paliperidone (RIS/PAL); quetiapine (QET); aripiprazole or brexpiprazole (ARI/BRE); olanzapine (OLA). Safety analyses were evaluated by visit and included adverse events (AE), vital signs, and laboratory tests.
Results: The safety population comprised 301 patients, of which 235 (78.1%) were previously treated with RIS/PAL (n=95), QET (n=60), ARI/BRE (n=43), or OLA (n=37). Rates of treatment-emergent AEs (TEAEs) while on LUMA were similar between PA groups (44.2%-55.8%). TEAEs with incidences of ≥5% in any PA group were dry mouth (5.4%-8.3%), somnolence (4.2%-13.5%), sedation (1.1%-5.4%), headache (2.3%-8.1%), diarrhea (2.1%-8.3%), cough (1.1%-7.0%), and insomnia (0-5.0%). Most TEAEs were mild or moderate in severity for all groups. Rates of serious TEAEs were low and similar between groups (0%-7.0%). Extrapyramidal symptom (EPS)-related TEAEs were observed in those switched from RIS/PAL and OLA with 1 case of akathisia and 1 case of tardive dyskinesia in each group (1.1% and 2.7%, respectively).
Statistically significant (P<.05) decreases from baseline were observed in the OLA group that switched to LUMA in total cholesterol (by Day 8) and low-density lipoprotein cholesterol (by Day 15) with significant decreases at every visit thereafter on LUMA treatment.

Statistically significant decreases in prolactin levels were observed by Day 8 in both the RIS/PAL (P<.0001) and OLA (P<.05) groups that switched to LUMA, with continued statistically significant decreases for every visit thereafter on LUMA treatment, except for OLA at Day 25. Patients who switched from RIS/PAL to LUMA showed significant (P<.05) decreases by Day 25 of the treatment period for body mass index, waist circumference, and weight. At follow-up, 2 weeks after patients switched back from LUMA to another antipsychotic, none of these decreases in laboratory parameters or body morphology observed while on LUMA maintained significance.

Discussion: In outpatients with stable schizophrenia, LUMA 42-mg treatment was well tolerated in patients switching from a variety of PAs. Patients switching from RIS/PAL or OLA to LUMA had significant improvements in cardiometabolic and prolactin parameters. These data further support the favorable safety profile of LUMA in patients with schizophrenia.

V127. A STRUCTURED BENEFIT-RISK ASSESSMENT TO EVALUATE A COMBINATION OF OLANZAPINE AND SAMIDORPHAN FOR THE TREATMENT OF SCHIZOPHRENIA AND BIPOLAR I DISORDER

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Background: A combination of olanzapine and samidorphan (OLZ/SAM) that provides the efficacy of olanzapine while mitigating weight gain was recently approved by the FDA for the treatment of schizophrenia and bipolar I disorder. To improve communication of the OLZ/SAM benefit-risk profile, a structured framework was utilized.
Methods: The Benefit-Risk Action Team framework was used to evaluate OLZ/SAM with analyses completed for each pivotal study. ENLIGHTEN-1 evaluated antipsychotic efficacy and safety vs placebo. ENLIGHTEN-2 evaluated the weight profile of OLZ/SAM vs olanzapine. Benefit-risk outcomes were selected based on study outcome parameters, known

risks of olanzapine and samidorphan, and public health importance. A subset of opioid antagonist risks was not assessed due to clinical trial exclusions; however, they were factored into the overall evaluation. Risk differences and confidence intervals were analyzed.
Results: In ENLIGHTEN-1, OLZ/SAM had lower risks of psychiatric discontinuation and treatment nonresponse compared with placebo; higher risks of hyperprolactinemia, weight gain (≥7%), sedation, and worsening of fasting triglycerides and glucose, and no difference for fasting total and LDL cholesterol, neutropenia, orthostatic hypotension, and movement disorders. In ENLIGHTEN-2, OLZ/SAM had reduced risks of weight gain and waist circumference increases compared with olanzapine, along with similar risks of relapse and psychiatric discontinuation and no difference in metabolic worsening, neutropenia, hyperprolactinemia, orthostatic hypotension, sedation, and movement disorders.
Discussion: Based on this assessment, OLZ/SAM has comparable efficacy and a safety profile consistent with olanzapine, with reduced weight gain. A structured approach to assessing the benefit-risk profile of a product facilitates transparent evaluation and communication.

V128. PATIENT VERSUS CAREGIVER AND CLINICIAN REPORTS OF COGNITIVE DIFFICULTIES IN PATIENTS WITH SCHIZOPHRENIA SWITCHING TO LONG-ACTING INJECTABLE ANTIPSYCHOTIC ARIPIPRAZOLE LAUROXIL: A POST HOC ANALYSIS

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Background: Discrepancies between patient- and clinician-perceived cognitive functioning in people with schizophrenia have been associated with functional impairment, which can be further confounded by side effects of treatment. Perceived cognitive impairment and level of agreement between patient, clinician, and caregiver responses on the New York Assessment of Adverse Cognitive Effects of Neuropsychiatric Treatment (NY-AACENT) were assessed for patients with schizophrenia switching to the long-acting injectable antipsychotic aripiprazole lauroxil (AL).
Methods: Clinically stable adults with schizophrenia with inadequate response or intolerability to paliperidone palmitate or risperidone LAI were switched to 6-month, open-label treatment with AL (441, 662, or 882 mg monthly or 882 mg q6wk). NY-AACENT patient, caregiver, and clinician forms were completed at baseline and month 6 or early termination. Level of agreement between groups in ratings of cognitive difficulty (not present, mild, moderate, severe, extreme) in NY-AACENT domains (Working Memory, Attention/Vigilance, Verbal Learning/Memory, Visual Learning/Memory, Reasoning and Problem Solving, Speed of Processing, Social Cognition) was evaluated at baseline and last assessment using weighted kappa coefficients.
Results: Fifty-one patients (mean age, 40.6 years) were enrolled; 35 completed the study. At baseline (n=50), cognitive difficulties were most commonly rated 'not present' or 'mild' in all NY-AACENT domains by patients (58%–86% across domains), clinicians (62%–94%), and caregivers (50%–92%). Percentages reporting cognitive difficulties 'not present' or 'mild' increased at last assessment for all reporters. Weighted kappa coefficients indicated fair to substantial agreement between patients and clinicians across domains at last assessment (0.32–0.64; baseline: 0.14–0.55); patient-caregiver agreement ranged from 0.07 to 0.50 at last assessment.

Discussion: In this analysis, clinician, caregiver, and patient reports indicate reduced cognitive impairment, on average, in all NY-AACENT domains after 6 months of AL treatment. Patient-clinician agreement on magnitude of improvement was higher than patient–caregiver agreement and increased from baseline to last assessment.

V129. IMPAIRED LOAD-DEPENDENT FUNCTIONAL CONNECTIVITY DURING VISUAL WORKING MEMORY IN FIRST-EPISODE PSYCHOSIS

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Background: Aberrant network connectivity is increasingly viewed as a core dysfunction in psychosis and may underlie many of its associated cognitive and functional deficits. Working memory, the ability to retain sensory information in a readily accessible form, relies upon coordinated activity across distributed brain regions and has consistently exhibited impairments in schizophrenia. Recent studies in first-episode schizophrenia spectrum (FE) populations suggests a preservation of working memory network function during low-load conditions with disruptions becoming apparent as task complexity increases. The present study assessed visual network connectivity and its contribution to load-dependent working memory impairments in FE.

Methods: Magnetoencephalography was recorded from 35 FE and 27 matched healthy controls (HC) during a lateralized change detection visual working memory task. Structural MRI was acquired separately to facilitate localization of cortical activity. Impaired alpha-band desynchronization was previously identified among FE within bilateral dorsal occipital (Occ) regions. Here, whole-brain alpha-band functional connectivity with bilateral OCC was assessed using phase-locking value (PLV). Connections exhibiting significant modulation of PLV by memory load identified across all participants were identified using paired t-tests (FDR-corrected). PLV modulation within these networks was compared between groups. Correlations between functional connectivity, performance, and symptomatology were performed (FDR-corrected across comparisons).

Results: The effect of task condition on performance differed by group ($p=.004$) with greater impairment in memory capacity among FE during high ($p=.002$) compared to low ($p=.02$) load conditions. Across groups, Occ exhibited significant load modulated connectivity with five regions (ROIs). While HC exhibited PLV enhancement with load in all connections, FE failed to show PLV modulation between right Occ and left inferior frontal gyrus (IFG), lateral occipito-temporal sulcus, and anterior intermediate parietal sulcus (AIPS). Smaller PLVs between right Occ and both left IFG ($r=-.54$) and AIPS ($r=-.55$) during high-load condition were associated with increased SAPS Reality Distortion scores in patients.

Discussion: As previously observed, FE exhibited impaired working memory capacity during high, but not low load conditions compared to HC. Examination of functional connectivity across the visual working memory network revealed a similar load dependent deficit in FE who were unable to enhance communication between perceptual and executive networks in response to increasing cognitive demands. Furthermore, the degree of impairment in the connectivity between occipital and fronto-parietal regions was associated with increased positive symptoms in these patients. These findings highlight the contribution of network connectivity to cognitive control deficits and symptoms in early psychosis and provide potential targets for future interventions. Future studies examining effective connectivity would also enhance our knowledge of information flow through this executive network by describing the directional nature of communication between regions.

V130. EMBODIED TEMPORALITY AND MOVEMENT: A MENTAL HEALTH PROPOSAL

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Background: Main goal is to contribute to Embodied Psychopathology and Psychotherapy through neuroscientific informed framework and phenomenological methodology e.g. How can understanding of mental disturbance (and development) be pursue without a proper understanding of the structuring processes of individual experience? How can therapeutic work be done without directly addressing the individual's lived body?
Research on Mental Health require study of the constituting processes of embodied experience e.g. Embodied cognition and subjectivity is a temporally-structured process (Husserl, E 46 2002) i.e. is three-part: ever-flowing present, remains of what just passed (memory) and advance of what is yet to come (anticipation).

Temporal experience is constituted from the Flow of consciousness (Husserl E 93 2002).

Embodied temporal and movement experience are basal record of psychopathological manifestations (Fuchs T and Pallagrosi M 297 2018).

Psychopathological study of embodied temporal experience must be continued (Strauss E 1952; Minkowski E 1970).

Temporal experience is associated to the functioning of the Default Mode Network (DMN) (Aryutova K and Stoyanov D, 6 2021).

Connectivity malfunction of the Triple Network i.e. Salience, Central Executive and DMN, is hypothetically associated with schizophrenia (Bolton et al. 2020).

Research question: How is the flow of consciousness related to the kinaesthetic flow?

Hypothesis: A mutual synchrony is instantiated between both of them.

Methods: A sample of 44 patients (n=44, schizophrenia Undifferentiated (F20.3 ICD-11, 295.9 DSM-V)), 1-year diagnosis (Max. Not in pharmacological treatment) and 44 healthy controls, paired by age and sex. The qualitative part includes a descriptive protocol for gesture-posture-movement and a narrative element, the quantitative part includes 2 brain-imaging scans taken before and after all of the trials, and breath and heart rate monitoring along the trials. The first trial is applied, based on the information gathered, a set of 3 embodied (movement and temporal focused) therapeutic sessions (1 week long) are designed and applied for the remaining trials (1-week trial-1 week therapeutic session). Each trial is followed by a structured interview focused on exploring the patient's kinaesthetic and consciousness flow, their response is video recorded. To assess the patient's narrative a conceptual scale is proposed.
Results: Looking forward to presenting this research funded by PUMS and NAWA, through the program NAWASTER 2021-2022. The research protocol designed is presented with two articles in process of publication, based on the latter, looking forward to receiving feedback from experts and colleagues.
Discussion: Looking forward to presenting this research funded by PUMS and NAWA, through the program NAWASTER 2021-2022. The research protocol designed is presented with two articles in process of publication, based on the latter, looking forward to receiving feedback from experts and colleagues.

V131. OPIOID PRESCRIPTION DISPENSING PATTERNS IN PATIENTS WITH SCHIZOPHRENIA: REAL-WORLD EVIDENCE FROM THE IBM® MARKETSCAN® RESEARCH DATABASES

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Background: Prescription opioid dispensing patterns over time were assessed for individuals with schizophrenia compared with matched controls.
Methods: Health insurance claims data from the IBM® MarketScan® Commercial Database and the Multi-State Medicaid Database were analyzed. Individuals aged 18-64 with ≥1 inpatient or ≥2 outpatient claims for schizophrenia during the year preceding the analysis year (2015-2019) were included, with age- and sex-matched controls. Baseline demographic and clinical characteristics were evaluated. Opioid dispensing during each analysis year was defined as either chronic (coverage for ≥70 days in any 90-day period, or ≥6 prescriptions dispensed during analysis year) or nonchronic (≥1 prescription dispensed, not meeting chronic definition).
Results: Schizophrenia patients had a higher prevalence of medical and psychiatric comorbidities, including pain diagnoses, versus controls. Among patients with schizophrenia in the Commercial database, chronic opioid dispensing decreased from 6% (controls: 3%) in 2015 to 2% (controls: 1%) in 2019, and in the Medicaid database, from 15% (controls: 15%) to 7% (controls: 6%). Among patients with schizophrenia in the Commercial database, nonchronic dispensing decreased from 15% (controls: 16%) in 2015 to 11% (controls: 11%) in 2019, and from 23% (controls: 24%) to 15% (controls:13%) in the Medicaid database.
Discussion: From 2015 to 2019, opioid dispensing rates were generally similar between schizophrenia patients and controls, with a significant decrease in chronic and nonchronic dispensing over this time period in both groups, across databases.

V132. ESTABLISHING SERVICES FOR YOUTH AT CLINICAL HIGH RISK OF PSYCHOSIS IN A SOUTHWESTERN FRONTIER STATE: THE UNIVERSITY OF NEW MEXICO CONNECT PROGRAM

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Background: The University of New Mexico Health Sciences Center (UNM HSC) CONNECT (COllaborative INterdisciplinary Evaluation and Community Treatment) program for youth at clinical high risk of psychosis (CHR) was initiated in 2019, funded through the new SAMHSA initiative which provided four years of funding to establish new CHR-P programs throughout the US. UNM was a study site for both the RAISE-ETP treatment trial for first episode psychosis (FEP) and the EDIPPP study of CHR youth. While the Early FEP program continued through state set-aside funds, there was a hiatus in CHR services between the end of the EDIPPP study in 2010 and the beginning of the current program.
UNM is located in Albuquerque, the sole large urban center in what is a largely frontier and rural state on the southwestern US border. New Mexico has a unique ethnic-racial profile, with the largest proportions of both Hispanic (49%) and Native American (11%) individuals of any US state. NM has notably high levels of socioeconomic stressors potentially affecting child mental health: from 2012-2021 NM was consistently ranked as 49th or 50th in the US on a

combined measure of overall child well-being (2021 Kids Count); and the 2016 National Survey of Children's Health reported 18% of children in NM as having 3 or more adverse child experiences (ACEs), tying Arizona for highest rate in the US.

Methods: The CONNECT program is an outpatient coordinated specialty care (CSC) program using a stepped care model providing services up to two years. The Early FEP and CONNECT teams are the only specialized CSC services in the state. Due to differences in funding sources, administrative structure, and geographic catchment areas, the two teams function independently. While the Early FEP team is funded by the state to act statewide, the CONNECT team is funded through the local government to provide services for individuals residing within Bernalillo County. Both teams include transition age youth, and there have been administrative challenges in relation to physical site of service provision, reimbursement, and scope of practice to support transition age services. The FEP program is situated with adult MH services, while CONNECT is based within the child MH service.

Results: An IRB-approved data repository was created to house both required evaluation data and supplementary clinical information from consenting participants, with data available to clinicians through a "dashboard" that includes both group and individual data over time. Over the first 27 months of the project, there were 245 referrals, of which 111 were assessed with the Structured Interview for Psychosis Risk Syndromes (SIPS), and 61 enrolled into the service. 47 of these consented to data being included in the repository, including 24 males, 19 female, and 4 transgender youth; 40% were 15 or younger and 60% between 16-25. 68% were white; Native American, Black, and Asian were each 6.3%. 38% were Hispanic and 62% non-Hispanic. In 2020 UNM (PI Crisanti) received NIH grant funding to pilot interventions to increase early intervention for early psychosis in the UNM general student population, primarily through instituting universal screening, which significantly increased the number of young adults enrolled.

Discussion: Despite a number of challenges, including adjusting to the COVID-19 pandemic, the CONNECT CHR team is now in its third year of providing services. One question is how to optimize CHR outreach and service to match the needs of the racial-ethnic communities of New Mexico. Another is the role of ACEs in CHR, especially given the high rates of multiple ACE in NM, and how to provide appropriate treatment for youth with CHR from highly stressed backgrounds.

V133. INITIAL ENGAGEMENT IN EARLY PSYCHOSIS INTERVENTION SERVICES: FINDINGS FROM ELECTRONIC MEDICAL RECORD DATA

Alexia Polillo*[1], George Foussias[2], Albert Wong[2], Wei Wang[1], Jacqueline Veras[3], Aristotle Voineskos[2], Nicole Kozloff[2]

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Background: Pathways to early psychosis intervention (EPI) care, a process involving symptom identification, help-seeking, contact with mental health services, and EPI referral, have been well-studied with the goal of reducing treatment delays and the duration of untreated psychosis. Despite the clear mandate for 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. Many studies have explored ongoing engagement in EPI services, identifying a lack of family involvement and problem substance use as robust predictors of EPI disengagement. However, few studies have examined initial engagement, even though the first contact with EPI services is a critical step in ongoing service engagement. Understanding

factors associated with initial engagement in EPI services is essential for reducing treatment delays. The objective of this study was to elucidate factors associated with initial EPI engagement as measured by attendance at the first consultation appointment, with a focus on pathways to care and health equity factors.
Methods: We examined the electronic medical record (EMR) data for all patients aged 16-29 who were referred to a large EPI program over a 2-year period from January 2018 to December 2019. The primary outcome was rate of attendance at the EPI consultation appointment. Baseline demographic variables, including age, gender, self-reported racial/ethnic group, country of birth, and sexual orientation, were extracted from a standardized health equity form that is routinely completed by patients around the time of their first appointment. Additional variables included referral source and the number of days from referral to consult appointment. We used descriptive statistics to calculate baseline characteristics of patients referred to EPI services based on referral source. Logistic regression was used to model the odds of attendance at the consultation appointment, while controlling for other baseline factors.
Results: A total of 1,002 patients were referred to EPI services over the 2-year period, with more than half being referred through outpatient psychiatrists or primary care providers (52.7%). In the unadjusted models, patients who were older (OR=.926, 95% CI .887-.967), belonged to racial/ethnic minority groups other than White, Black or Asian (OR=.686, 95% CI .442-1.07), identified as LGBTQ2S+ (OR=.784, 95% CI .535-1.15), had increased days to consult (OR=.981, 95% CI .971-.990), and were referred from the ED (OR=.561, 95% CI .395-.796) had a decreased odds of attending their consultation appointment. Patients who were female (OR=1.35, 95% CI .974-1.88) and referred from an inpatient unit (OR=1.39, 95% CI .941-2.04) had an increased odds of attending their consultation appointment. In the final adjusted models, being referred from the emergency department (OR=.341, 95% CI .202-.577) or an inpatient unit (OR=.540, 95% CI .324-.901) and having increased days to consult (OR=.977, 95% CI .966-.988) were associated with a decreased odds of attendance at the consultation appointment.
Discussion: We found that referral from the emergency department and inpatient unit, as well as service delays are associated with decreased odds of attendance at the consultation appointment, a critical point in EPI service engagement. These results suggest that interventions to improve the transition from acute referral sources to outpatient services and reducing wait times may help facilitate a key step on the path to recovery among young people with psychosis.

V134. MOTOR ABNORMALITIES IN ANTIPSYCHOTIC-NAIVE INDIVIDUALS WITH SCHIZOPHRENIA AND HIGH-RISK POPULATIONS: A META-ANALYSIS OF INSTRUMENTAL ASSESSMENTS

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Background: Growing evidence suggests that motor dysfunction is a strong candidate endophenotype for schizophrenia. Much of the evidence is based on rating scales, but instrumental measures of motor function have a number of advantages, including sensitivity to subclinical differences, precise quantification, and relative objectivity when diagnosis is discernible. Because antipsychotic medication affects motor performance, studies of motor function as a neural expression of risk must exclude participants with antipsychotic exposure. Here, we provide the first meta-analysis of motor performance in antipsychotic-naive schizophrenia patients and high risk groups as assessed solely with instrumental measures of skeletomotor function.

Methods: PubMed, EMBASE, and PsycInfo databases were searched to identify studies assessing motor function in antipsychotic-naive individuals with schizophrenia and high-risk populations. Inclusion criteria were: 1) use of at least one instrumental measure to capture ongoing skeletomotor control; 2) comparison of the index group to healthy controls; 3) reporting of means and standard deviations. Motor tasks that had a significant executive component or yielded only a reaction time were not included. Effect sizes were Cohen's d, and meta-analyses were performed in Comprehensive Meta-Analysis (CMA v. 3) using the random-effects model. Publication bias was assessed using a funnel plot.
Results: Our search strategy yielded 434 unique references. Full-text screenings resulted in the exclusion of studies primarily for being off-topic (n=235), having no ongoing skeletomotor instrumental measure (n=74), including currently/formerly medicated participants (n=45) or only non-human subjects (n=31), etc. 24 studies met all inclusion criteria. Motor performance significantly differed between the index and control groups across studies ($d = .591$; $p < .001$). To investigate effect size by population, we divided the studies into those of antipsychotic-naive individuals with schizophrenia (n=8), clinically high-risk participants (schizotypal personality and UHR) (n=11) and non-clinical high-risk populations (psychometric schizotypy and first-degree relatives) (n=9). (4 studies included more than one population.) Each population had significant motor impairments, with the largest effects in antipsychotic-naive individuals with schizophrenia ($d = .843$; $p < .001$) then clinically ill at-risk individuals ($d = .550$; $p < .001$) and clinically healthy high-risk individuals ($d = .454$; $p < .001$). All motor domains assessed yielded significant deficits: fine motor control ($d = .700$, $p < .001$), diadochokinesia ($d = .412$, $p < .001$), force instability ($d = .386$, $p < .001$), and Parkinsonian symptoms (defined as bradykinesia and tremor) ($d = .313$, $p < .001$). There was no evidence of publication bias.
Discussion: Consistent with previous reviews that have included data from medicated participants and/or data from rating scales, the current review of solely instrumental measures in participants never exposed to antipsychotics finds significant motor deficits both in individuals with schizophrenia and in high-risk populations. Thus, even the most conservative approach suggests that motor deficits are a behavioural expression of neural risk for schizophrenia rather than a clinical expression of the illness itself or of exposure to medication. Development of a battery of instrumental measures of motor function would strengthen translational work in this area, and would allow stronger conclusions to be made about profiles of motor strengths and weaknesses, by facilitating the accumulation of data directly comparing functions within the same individuals.

V135. EVALUATING A CHILD AND ADOLESCENT BEHAVIORAL HEALTH DEPARTMENT'S COMFORT, KNOWLEDGE, AND PRACTICE HABITS RELATED TO CARE OF PATIENTS WITH PSYCHOSIS SYMPTOMS

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Background: As knowledge about pre-morbid risk factors and subthreshold symptom expressions expand, it is incumbent upon child and adolescent mental health departments to take an active role in screening, assessing, and treating patients with psychosis symptoms. This study assesses a multidisciplinary cohort of clinicians in a child and adolescent behavioral health department at a major academic children's hospital on comfort, knowledge base, and practice habits related to the care of patients with psychosis symptoms.

Methods: A self report survey was created and distrusted among all clinical providers in a child adolescent behavioral health department and completed by 86 clinicians (MD, LCSW, NP, PhD, PsyD). The survey assessed three main components: knowledge assessed by awareness of standardized screening scales, referral options, and of Coordinated Specialty Care as the gold standard for first episode psychosis care. Practice habits assessed by reported frequency of screening patients at clinically high risk for psychosis, use of standardize scales, and willingness to incorporate standardize scales into practice. Comfort assessed by reported comfort treating, diagnosing, and referring patients with psychosis symptoms to specialty clinics.
Results: Responses followed a trend demonstrating greater comfort, knowledge, consistent screening practice habits in prescribing clinicians when compared to non-prescribing clinicians. 89% of clinicians reported they would agree to use standardized scales in patients with risk factors with psychosis (targeted screening). Notably, a majority of clinicians (52%) were unaware or unsure that the gold standard treatment for first episode psychosis is coordinated specialty care.
Discussion: Our study showed a range in comfort among child and adolescent mental health providers in screening, referring, and treating patients with psychosis-spectrum symptoms. The trend demonstrated by responses was greater comfort with screening, referring, and treating patients with psychosis symptoms in the prescribing clinician cohort versus non-prescribing practitioners. This is notable given that psychologists and licensed clinical social workers have a broader range of practice within the pediatric setting, are often integrated into other specialty practices, and can be first line providers for non-acute cases.

V136. ASSOCIATION BETWEEN ABERRANT GYRIFICATION, SYMPTOM SEVERITY AND SOCIAL AND VOCATIONAL FUNCTIONING IN DRUG-NAIVE FIRST EPISODE PSYCHOSIS

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Background: Schizophrenia is a disorder of cerebral connectivity associated with disturbances of cortical development. In patients with established illness, widespread defects in gyrification alongside cortical thinning are seen, yet the status of gyrification among first episode samples and the prognostic value of gyrification on later functioning has been largely unknown. As antipsychotics are associated with cortical thinning, which has secondary effects on cortical folding, we investigate the anatomical distribution of gyrification in antipsychotic naïve first episode patients, and report their association with later functioning.
Methods: We performed automated surface-based morphometric assessment of gyrification on 3-dimensionally reconstructed cortical surfaces across multiple vertices that cover the entire cortex. We recruited a sample of 65 antipsychotic naïve first episode psychosis patients and 33 healthy controls group matched for age, sex, and parental sociao-economic status. After comparing patients to controls in a cortex wide analysis, we assessed associations between patient gyrification patterns and baseline clinical characteristics from the Positive and Negative Syndrome Scale (8-Item version). Finally, we assessed associations between gyrification at baseline with functional outcomes assessed 6-12 months after the initial scan. Assessment of functional outcomes included The Social and Occupational Functioning Assessment Scale

(SOFAS) as well as assessment of vocational activity defined using "Not engaged in employment education or training (NEET)" criteria.
Results: After adjustments for intracranial volume and gender, patients showed increased gyrification in the right precentral gyrus (Cluster inclusion at p = 0.005). Among patients, more severe positive and negative symptoms were associated with increased bilateral fronto-temporal gyrification (Cluster inclusion at p = 0.005). Only negative symptoms were associated with changes in cortical thickness, with more severe negative symptoms being associated with increased cortical thickness in the left temporal pole and middle temporal gyrus. Finally, higher gyrification in parietal regions of the right hemisphere at baseline was associated with vocational inactivity following 6-12 months of treatment. After adjusting for individual differences in baseline functioning, higher gyrification trended toward association with lower follow-up SOFAS scores superior parietal regions in the right hemisphere, however, this association only survived with cluster inclusion set at p = 0.05.
Discussion: Our findings add to an emerging body of evidence suggesting increased gyrification may be a feature of early psychotic illness. Further, for the first time to our knowledge, we show associations between increased gyrification with later functional deficits. These findings warrant further longitudinal investigations to establish their prognostic value in psychosis.

V137. CLOZAPINE AND LONG-ACTING INJECTABLE ANTIPSYCHOTIC COMBINATION: A RETROSPECTIVE CHART REVIEW

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Background: Nearly 50% of clozapine users are noncompliant to clozapine, and only 40% show significant improvement. Clozapine combination with long-acting injectable antipsychotics (LAI) may be an effective and tolerable way to prevent patients from adverse effects of noncompliance and insufficient response. In this study, we aimed to investigate the clinical characteristics of patients receiving clozapine and LAI combination from Ankara Etimesgut Community Mental Health Center (CMHC) and Hacettepe University Hospital (HUH).
Methods: We detected patients on the combined treatment for the last one year with ICD-10 diagnosis of schizophrenia (F20.x) or schizoaffective disorder (F25.x). Demographic and clinical characteristics, Clinical Global Impression scores (CGI), Global Assessment of Functioning scores (GAF), and reported side-effects were collected retrospectively from the medical charts and electronic records. This study was approved by the Ethics Committee of Hacettepe University (Project no: GO21/356).
Results: We determined 23 patients using clozapine and LAI combination (CMHC n=7, HUH n=16). Two patients were excluded from the analysis, because they received the combined treatment while switching from a LAI to clozapine. The remaining 21 patients' (female/male: 13/8) median age was 42 years (min-max: 21-60), and median duration of illness was 20 years (min-max: 3-37).
In 45% of the sample, clozapine was combined with a LAI because of insufficient response (n=6) and insufficient response along with non-compliance (n=3). In the remaining 12 patients, clozapine was started under an ongoing LAI treatment because of treatment resistance and non-compliance. The median duration of the combination and the previous medication were 14

months (min-max: 5-183) and 18 months (min-max: 1-204), respectively (Z=-0.019, p=0.985). The median clozapine dose under the combination was 350 mg/day (min-max: 200-800).

The most common side effects of the combination were hypersalivation (33%) and sedation (25%). In four patients (19%), extrapyramidal side effects and hyperprolactinemia were occurred. Two patients developed seizure, and one patient experienced transient cardiac marker elevation. No serious adverse events or hematologic side effects were observed. Clozapine serum levels were available in 8 patients on the combination. The median clozapine level was 820,5 ng/ml (min-max: 449-1100).

The hospitalization rate was 14% (n=3) after the combined treatment. When compared to the initiation of the combination, the median CGI score significantly reduced from 5 (min-max 4-7) to 4 (min-max: 2-6) (Z=-3.372, p=0.001), and the median GAF score significantly improved from 40 (min-max: 20-60) to 50 (min-max: 25-75) (Z=-3.383, p=0.001) during the combined treatment. On the CGI-Improvement scale, 67% of the sample had a score of 3 (minimally improved) or 2 (much improved). The number of hospitalizations per year significantly decreased after the combined treatment (0.31±0.45 vs 0.09±0.37, Z=-3.099, p=0.002).

Discussion: Clozapine and LAI combination may reduce the illness severity and hospitalization risk with an acceptable tolerability. Since the most common reasons for clozapine discontinuation are the side effects of the drug, noncompliance and lack of efficacy, combining clozapine with LAIs may be a worthwhile strategy for clozapine resistant patients. This combination may also improve functioning by reducing illness burden. However, our results are preliminary and based on retrospective data with a small sample size. Objective measures of side effects are absent although medical and electronic records were detailed. These findings should be re-examined in a prospective controlled study design.

V138. CELL TYPE-SPECIFIC MANIFESTATIONS OF CORTICAL THICKNESS HETEROGENEITY IN SCHIZOPHRENIA

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Background: Brain morphology differs markedly between individuals with schizophrenia, but the biological basis of this heterogeneity is poorly understood. Here, we sought to determine whether cortical thickness (CTh) heterogeneity in schizophrenia relates to interregional variation in distinct neural cell types, as inferred from spatially-resolved gene expression data (provided by the Allen Brain Institute) and person-specific genomic variation.
Methods: This study comprised 1849 participants in total, including a discovery (140 individuals with a schizophrenia-spectrum disorder and 1267 controls) and a validation cohort (335 individuals with a schizophrenia-spectrum disorder and 185 controls). To characterize CTh heterogeneity, normative ranges (i.e., centiles) were defined on healthy controls for 34 cortical regions and then deviations from these ranges were measured for each individual with schizophrenia. CTh deviations were systematically combined with regional gene expression profiles of seven neural cell types. To investigate implicit biological links between individuals, patients were classified into broad subtypes based on associations between individual CTh deviations and gene expression profiles. Subtypes were then validated against genomic data drawn from the same individuals.
Results: In both discovery and validation cohorts, CTh deviations were explained by gene expression profiles of five out of seven neural cell types: 1) astrocytes; 2) endothelial cells; 3) oligodendrocyte progenitors (OPC); 4) excitatory; and 5) inhibitory neurons. Clustering individuals with schizophrenia according to cell-patterned cortical deviations distinguished distinct patient subtypes, which were consistent across both cohorts examined. In a neuronal/endothelial subtype, CTh deviations covaried with polygenic risk for schizophrenia (sczPRS) calculated specifically from genes marking neuronal and endothelial cells ($r=-.40$, $p=0.010$). Whereas, in a glia/OPC subtype, CTh deviations covaried with sczPRS calculated from glia and OPC-linked genes ($r=-.30$, $p=0.028$).
Discussion: Our multi-scale analysis of genomic, transcriptomic, and brain phenotypic data indicates that CTh heterogeneity in schizophrenia relates to inter-individual variation in cell-type-specific functions. Decomposing heterogeneity in relation to cortical cell types enables prioritization of schizophrenia subsets for future disease modeling efforts.

V139. CULTURALLY TAILORED FAMILY PSYCHOEDUCATION FOR ADULTS WITH SCHIZOPHRENIA IN TANZANIA: RESULTS OF THE KUPAA PILOT CLINICAL TRIAL

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Background: Family psychoeducation (FPE) is an evidence-based practice from high-income countries to help individuals with psychotic disorders and their relatives cope more effectively with illness. FPE has never been tested in a low-resource setting such as Tanzania where family involvement for illness management is fundamental. This study pilot tested a culturally tailored family psychoeducation model ("KUPAA") for adults with psychotic disorders and their relatives that was appropriate for settings where participants might have both traditional and biomedical ideas about mental illness and that used relatives as co-facilitators. Pilot clinical trial objectives were to test impact on relapse, functioning and quality of life among an outpatient treatment-engaged population with schizophrenia.

Methods: This study is an individually-randomized group treatment trial in two hospital facilities in Dar es Salaam and Mbeya, Tanzania. Participants were enrolled as pairs (n=66 pairs): individuals living with schizophrenia plus their relative/caregiver (e.g. recovery partner). Inclusion criteria for individuals with schizophrenia included attending outpatient psychiatric services at a government hospital, ages 18-50 years, and relapse within past year. Matched caregivers were ages 18 years or older. Interview data were collected at baseline, immediate post-intervention, and ~4 months post-intervention. For patient-participants, primary outcomes included relapse, defined as hospitalization or non-hospitalized relapse between end of intervention (Feb 2020) and participants' final interview date (Aug-Oct 2020), functioning/disability (WHODAS 2.0), and quality of life (WHOQOL-BREF). The intervention arm received KUPAA, which had 3 components: an individual joining session between facilitator and participant-pair; a 1-day educational workshop; and 12 multi-family psychoeducation group sessions (~6 pairs per group; 6 groups total) held weekly. Sessions focused on problem-solving and group exercises that promoted identifying personal strengths, dreaming for the future, and friendship. Controls received standard of care that was largely medication management.

Results: Among 66 patient-participants (22 women and 44 men), 33 were in the intervention arm and 33 were in the control arm. Their average age was 33 years; 67% were single, 62% had secondary education or higher, 57% worked recently, and mean length of illness was 9 years. The caregivers (n=66) were largely parents (49%), siblings (18%), partners (11%) or other relatives. Their mean age was 50 years old. Nine of 33 treatment arm participants had a relapse, and 14 of 31 (n=2 missing) control arm participants had a relapse. Characteristics, including WHODAS and WHOQOL scores, were similar across study arms at baseline. At 4-month post-intervention, the mean WHODAS score for intervention participants was 14.89 (SD 14.66) and for control participants it was 26.67 (SD 21.58). The WHOQOL score among intervention participants was 94.88 (SD 20.98) and among control participants 77.39 (SD 16.95). Results from linear mixed models comparing baseline and endline indicate that changes in WHODAS and WHOQOL scores were significant and meaningfully different across study arm.

Discussion: Individuals living with psychotic disorders and their families have a right to recovery-oriented mental health services tailored to their cultural context. Pending a fully powered effectiveness trial, this pilot RCT indicated that the KUPAA model of family psychoeducation was acceptable, feasible and promising for reducing risk of relapse, and improving both functioning and quality of life for individuals living with schizophrenia in Tanzania.

V140. THE RELATIONSHIP BETWEEN THE NEGATIVE SYMPTOM ASSESSMENT (NSA-16) FACTOR SCORES AND THE PERSONAL AND SOCIAL PERFORMANCE SCALE (PSP)

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Background: The sixteen item version of the Negative Symptom Assessment (NSA-16) (Axelrod et al, 1993) is commonly utilized in clinical trials as a primary or a secondary outcome to assess negative symptoms. In clinical trials assessing negative symptoms the Personal and Social Performance Scale (PSP)(Morosini, 2000) is commonly used with a measure of negative symptoms such as the NSA-16 to further delineate functional impact of the disorder. We have previously reported strong correlations between the PSP and the NSA-16 total score (Daniel, 2020). In the current analysis we explored the relationship between the individual NSA-16 factors and the PSP total score and its domain scores.

Methods: PSP and NSA data were pooled from 2,490 subjects participating in 5 clinical trials in negative symptom schizophrenia. We calculated the scores and change from baseline for 5 previously identified NSA factors (Axelrod, 1993). Pearson and polyserial correlations were calculated between the individual NSA factors and PSP and its individual domains and between change from baseline in the NSA factors and PSP and its domains as appropriate.

Results: The strongest correlations observed were between the Motivation NSA factor and the PSP total score (rho = -0.69), PSP domains: A (Socially useful activities) (rho = 0.69), B (Personal and social relationships) (rho = 0.65), and C (Self care) (rho = 0.58). The weakest correlations were observed between the PSP domain D (Disturbing and aggressive behavior) and all 5 NSA factors (rho = 0.25 or lower).

For change from baseline the strongest correlations were observed for the Motivation factor and the PSP total score change (rho = -0.56), followed by PSP domains B (rho = 0.52) and A (rho = 0.52). Surprisingly, the correlation between change in Motivation and PSP domain C was relatively weak (rho = 0.36). The weakest correlations were observed for the PSP domain D with all 5 NSA factors (all rho below 0.2). All findings were statistically significant.

Discussion: Our analyses identified moderate to strong correlations between all 5 NSA factor scores and the PSP total score and PSP domains A to C. This was not unexpected given the overlap in symptom and functional domains of the two scales. Not surprisingly, the PSP domain D examining disruptive and aggressive behaviors had the weakest correlations with all of the NSA-16 factors. Of the 5 NSA-16 factors, Motivation had the strongest correlations with all the PSP domain scores. NSA Social involvement and Emotion/affect factors showed only moderate correlation levels with PSP domains A and B. Surprisingly, NSA Communication and Retardation factors showed relatively weakest correlations with the PSP domains A and B, where one might expect these factors to play a stronger role. With the exception of the NSA Motivation factor, the correlation was below 0.5 for the remaining 4 factors with the PSP domain C. The relationships in the change from baseline between the 5 NSA factors and the PSP total score and its domains were generally weaker. The strongest correlation was observed between change in Motivation and the PSP total score, reaching only a moderate level and 11 out of the 25 explored relationships showed only weak to very weak relationship. The main reason for this decrease in strength may be driven by measurement error which could be summed across baseline and the subsequent visit in the case of change data. We currently have no clear explanation for the weak correlation between change in Motivation and change in Self care. To conclude, based on the analyzed data, motivation is the single most relevant factor

related to the overall level of functioning and motivation should thus be one of the key targets for future treatments of negative symptoms in schizophrenia.

V141. A SCALABLE PLATFORM FOR INTEGRATED MULTI-MODAL NEUROIMAGING PROCESSING AND ANALYSIS ACROSS PSYCHOSIS SPECTRUM DISORDER STUDIES

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Background: A key opportunity for informing the mechanisms underlying psychosis spectrum disorders (PSD) is by combining multiple clinical neuroimaging datasets to map variation in neural circuits to clinical and behavioral features. Multiple recent efforts in the psychiatric research community have collected and shared well-powered neuroimaging datasets across the psychosis spectrum; these datasets have huge potential for informing neuro-behavioral variation in PSD, through multi-modal neuroimaging, rich phenotypic data, and substantial clinical heterogeneity. However, one limitation to unifying analyses across these studies is the variety of scanners, study designs, and acquisition parameters used. There are currently no field-wide standards for preprocessing and analytic techniques, leading to methodology-specific pipelines, inconsistent choices across researchers, and irreproducible results. In order to take advantage of the full potential of these datasets and map stable, robust, and reproducible neuro-behavioral relationships in PSD, data from different studies and parameters must be processed and analyzed in a standardized manner. This motivates the need for a comprehensive framework that allows for flexible, scalable end-to-end workflows with support for different neuroimaging software and datasets.

Methods: Here, we present the Quantitative Neuroimaging Environment and Toolbox (QuNex), a flexible software platform designed to unify psychiatric neuroimaging workflows by supporting multiple commonly-used pipelines across neuroimaging modalities. QuNex provides an integrated, versatile, and flexible neuroimaging environment that supports input data from multiple species and onboarded from a variety of popular neuroimaging, as well as behavioral data from task performance or symptom assessments. The QuNex suite is available as a container that and contains all necessary dependencies needed for running processing and analytic functions for ease of distribution, portability, and execution. To maximize efficiency and scalability for large combined datasets, QuNex natively supports high-throughput, parallel processing in high-performance compute environments or via cloud deployment. Importantly, QuNex also provides a comprehensive set of tools for community contribution, engagement, and support. Here we demonstrate QuNex by combining data from 16 neuroimaging studies relevant to PSD, totaling 10984 structural and functional scans from 51 scanners. We preprocess these data by leveraging QuNex's native support for the Human Connectome Project's Minimal Preprocessing Pipelines. We then use the in-built subject-level and group-level general linear modelling engine to show how QuNex can be used to generate multi-variate statistical results from combined multi-modal neural data across resting-state functional connectivity, task-based activation maps, and diffusion-weighted probabilistic tractography.

Results: We show that QuNex has a 98% preprocessing success rate across all PSD datasets, including those collected on scanners from three major manufacturers (GE, Philips, and Siemens) and both with and without simultaneous multi-slice acquisition. QuNex's quality control system also enables thorough and convenient inspection to identify (and subsequently

amend or exclude) poor-quality scans. We show that diverse clinical datasets can be consistently processed to produce standardized outputs and generate comparable features from multiple modalities. Next we highlight a cross-modal use case by extracting features relevant to language processing from myelin, diffusion tractography, resting-state, and task activation functional data. We furthermore show how statistical neural output maps from QuNex can be easily used with other independent clinically relevant sources of information, including molecularly-informed gene expression maps and data-driven dimensions of symptom variation.

Discussion: Robust, consistent, and reliable processing of neuroimaging data is a key step towards mapping stable and reproducible neuro-behavioral variation that meaningfully parse clinical heterogeneity in PSD. QuNex provides a much-needed flexible and unified platform for processing and analysis of diverse clinical datasets, providing the foundation for increasing statistical power, capturing clinical heterogeneity, elucidating neuro-behavioral relationships, and informing potential treatment targets in the psychosis spectrum.

V142. PSYCHOMETRIC PROPERTIES OF THE RUSSIAN VERSION OF "HINTING TASK" TEST

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Background: Numerous studies reveal a pronounced deficit of social cognition in patients with schizophrenia and schizophrenia spectrum disorders, which is a predictor of a decrease in the functional outcome. The aim of the study was to evaluate psychometric properties of the Russian-language version of the "Hinting task" (HT) in 3 schizophrenia spectrum conditions.

Methods: The study involved 136 patients with ICD-10 schizophrenia spectrum disorders that were enrolled into the study upon written informed consent. 85 of them were diagnosed with schizophrenia (group 1); 22 – with schizotypal disorder (group 2); 29 – with schizoaffective disorder (group 3). The study participants were between 18 and 64 y.o. (avg. 32.3±9.2 y.o), 68 of them were male, duration of the disease was 9.2±7.4 years. To assess internal consistency we used Cronbach's alpha, construct validity was investigated with Spearman`s rho correlations with Relationship across domains (RAD-15), Brief assessment of cognition in schizophrenia (BACS), Ekman faces, Personal and Social Performance scale (PSP) and Positive and Negative Syndroms Scale (PANSS). Inclusion criteria were PANSS<80, CDSS<6, not disrupted behavior, ability to give informed consent, no alcohol or drug abuse in the past six months.

Results: Cronbach's α for the whole schizophrenia spectrum sample was 0.74. The average correlation between the HT items was r=0.23 ($p<0.05$). Each item statistically significantly correlated with the overall score. Mean score (SD) for group 1 was 15.4 (3,6), in group 2 - 16.6 (2.9), in group 3 - 17.2 (2.6), with $p<0,01$ between group 1 and 3. In all groups but 1, we registered profound "ceiling effect". The min and max values of the total score on the HT in group 1 were 3 and 20, in group 2 - 7 and 20, in group 3 - 8 and 20 with the most maximum score density in group 3. Correlations with RAD-15, Ekman test and BACS and were found to be significant only in the schizophrenia group (r=0.32, r=0.37, r=0.39, respectively, $p<0.05$). In the group 1, there was only a weak negative correlation with the N subscale of thy PANSS (r=-0.32). In group 3, moderate negative correlations with N subscale (r=-0.4) and G (r=-0.5)

and moderate positive correlation with PSP (r=0.65), in group 2 no significant correlation with clinical scales were revealed.
Discussion: The Russian-language version of the HT has similar results with the original and other translated/adapted versions. The Cronbach's α indicates sufficient internal consistency which was confirmed in other studies. Schizoaffective group showed overall better results with higher density of max scores than schizophrenia group. The correlation between the sum of HT and PANSS N scores can be explained by the connection of social cognitions with negative symptoms. It can be assumed that there are correlations between expression disorders and social cognitions, which requires further research. A weak positive correlation between the ToM domain and basic cognitive functions can be traced in other studies. The absence of HT correlations with other cognitive scales in groups 2 and 3 is probably associated with a relatively small sample in these groups.
Conclusion. Russian version of the HT tool is a valid measure for the theory of mind in patients with schizophrenia spectrum disorders. We are still working on controls sample, but current study shows heterogeneity of ToM impairments in different schizophrenia spectrum disorders.

V143. A LONGITUDINAL ASSESSMENT OF ANTERIOR CINGULATE CORTEX GABA IN ANTIPSYCHOTIC MEDICATION-NAïVE FIRST EPISODE PSYCHOSIS PATIENTS

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Background: Gamma-aminobutyric acid (GABA) functions as the main inhibitory neurotransmitter in the mature central nervous system. Data from animal and postmortem studies suggest brain GABAergic dysfunction in psychosis spectrum disorders, but little is known about GABA pathology in the early illness stages and effects of antipsychotic medications.
Methods: In this study, we used magnetic resonance spectroscopy (MRS) with a MEGA-PRESS sequence [TR/TE = 1500/68ms; 256 averages; voxel size: 30x 40x 20mm] to quantify GABA in the anterior cingulate cortex (ACC) in antipsychotic medication-naïve first-episode psychosis (FEP) patients and to assess putative modulatory effects of antipsychotic medication on GABA levels after six and sixteen weeks of treatment with risperidone. Subjects were followed longitudinally and we included spectra from 73 FEP (baseline n = 57; week 6 n = 47; week 16 n = 45) and 69 healthy controls (baseline n = 67; week 6 n = 51; week 16 n = 52) and used GANNET to quantify GABA with respect to internal water.
Results: Using a mixed model repeated measures analysis, we found a significant reduction in GABA in FEP compared to healthy controls, when the entire sample was taken into consideration ($F = 9.07$, $p = .0030$), but we did not observe a significant main effect of time or an interaction of group and time. We then used paired sample t-tests to assess changes in GABA between baseline and after sixteen weeks of antipsychotic treatment but did not find a significant change over time ($t= -0.25$; $p= 0.80$).
Discussion: To our knowledge, this is the first longitudinal MRS study assessing GABA dysfunction in the dorsal anterior cingulate cortex (ACC) in vivo in antipsychotic medication naïve FEP. We observed that GABA levels in this region were significantly reduced in patients, suggesting that GABA dysfunction in this pivotal brain region may be an important feature of the core pathophysiology. Interestingly, this dysfunction does not appear to be attenuated by conventional antipsychotic treatment. It will be important to develop alternative

pharmacological interventions that specifically target GABAergic dysfunction in first episode psychosis patients.

V144. LONG-ACTING INJECTABLE ANTIPSYCHOTIC (LAI) PRESCRIBING TRENDS DURING COVID-19 RESTRICTIONS IN CANADA: A RETROSPECTIVE OBSERVATIONAL STUDY

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Background: The COVID-19 pandemic has had significant impacts on how mental health services are delivered to patients throughout Canada. In particular, the reduction of in-person healthcare services have created unique challenges for individuals with psychotic disorders that require regular clinic visits to administer and monitor long-acting injectable antipsychotic medications. In response to pandemic related restrictions the Canadian Psychiatric Association and the American Psychiatric Association issued guidelines recommending LAI treatment should be considered a medically necessary procedure.

Methods: To better understand how LAI usage was impacted, national and provincial patient-level longitudinal prescribing data from Canadian retail pharmacies were used to examine LAI prescribing practices during the pandemic. The dataset captured approximately 72% of all pharmacy prescriptions nationally. Prescribing data on new starts of medication, discontinuations of medications, switches between one- and three-month LAI formulations, antipsychotic name, concomitant medications, payer plan, gender and age were collected from January 2019 to December 2020 for individuals >18-years of age, and examined by month, as well as by distinct pandemic related epochs characterized by varying degrees of public awareness, incidence of COVID-19 infections and public health restrictions.

Results: At both the national and provincial level the proportion of medication new starts and discontinuations remained stable throughout the pandemic and were not statistically different from the pre-pandemic comparator period (March – May 2019). Second-generation LAIs accounted for 96.3% of all LAI new starts with paliperidone palmitate found to be the most prescribed (46.9%), followed by aripiprazole (42%). Anti-epileptics were the most frequent concomitant medication class prescribed, with 20.5% of LAI new starts also having an anti-epileptic drug dispensed. All study epochs had significantly more switches from the one-month paliperidone palmitate LAI formulation to the three-month formulation, compared with switches from the three-month to one-month formulation. Chi-square analysis showed that the proportion of average monthly switches to the three-month LAI formation were significantly greater during the primary COVID escalation period (March – May 2020) compared with both the COVID maintenance period (June – August 2020; $p<0.01$), and the second Covid escalation period (September – November; $p<0.01$). No significant differences were found when comparing the average number of monthly switches from three-month to one-month formulations between epochs.

Discussion: Equal numbers of LAI new starts and discontinuations prior to and during the pandemic suggests prescribing of LAI antipsychotics, for those already in care, continued unchanged throughout the pandemic. The observed consistency of LAI prescribing contrasts with other areas of healthcare, such as cardiovascular and diabetes care, which experienced decreases in medication prescribing during the COVID-19 pandemic. Most LAI prescription new starts (80.4%) were filled and paid by publicly funded insurance plans, suggesting that the majority of individuals on LAIs were in a lower socioeconomic bracket, and that their access to medication by this route continued during the pandemic. Concomitant medication information showing significant use of valproate and lamotrigine in conjunction with LAIs

suggests more common use of LAIs for several psychiatric conditions including bipolar disorder and possibly borderline personality disorder than were expected.

V145. EXECUTIVE AUDITORY ATTENTION CIRCUITOPATHY IN FIRST-EPISODE PSYCHOSIS

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Background: Selective attention is a core deficit of schizophrenia that is present at the first episode of psychosis (FEP). We previously demonstrated FEP are impaired in modulating the scalp-level, EEG-measured N100 and source-resolved M100 MEG activity in auditory cortex with selective attention. Attention enhancement is related to both local oscillatory changes (e.g., coupling between low frequency phase and high frequency power (PAC)) and long-range oscillatory connectivity within a general executive attention network involving frontal, parietal, precuneus, and auditory regions. Here, we investigated differences in phase-amplitude coupling with attention in auditory regions and identified an executive modulation network with functional connectivity changes with attention and deficits in FEP.

Methods: MEG was recorded from 27 FEP and 31 matched healthy controls (HC) while individuals either ignored tones while watching a silent movie or attended tones by pressing a button to oddball tones. Phase amplitude coupling (PAC) between low frequency (4-13Hz) phase and high frequency (30-100Hz) amplitude was calculated in 3 bilateral auditory regions defined by the HCP parcellation (A1, lateral belt, and parabelt). PAC differences with attention were calculated and FDR corrected for multiple comparisons. Functional subregions of the precuneus, a hub for executive control of attention, were used as seed regions for identifying functional connectivity increases with attention measured with phase locking value in the theta band with all other HCP brain regions. Group differences in connectivity changes with attention between regions were investigated.

Results: In all participants, there was a significant increase in PAC between the theta phase (5-7 Hz) and gamma amplitude (35-40 Hz) in left A1 with attention (FDR<0.05). There were no significant differences between groups. In HC, there was a significant increase in functional connectivity between the left precuneus and left frontal pole, temporo-parieto-occipital junction, and auditory medial belt with attention. The right precuneus had significantly greater connectivity with right prefrontal cortex and lateral occipital cortex with attention. FEP had significant reductions in their ability to enhance connectivity between these regions in both the left and right hemispheres with attention (p's<0.05).

Discussion: These results demonstrate increased PAC with attention in auditory cortex, a function which appears to remain intact in FEP. Theta frequency is the likely carrier frequency from executive areas that enhance local neuronal activity with attention in auditory cortex. The overall network involved in the attention modulation includes areas in frontal, precuneus, temporo-parieto-occipital junction, and auditory cortex, and FEP are impaired in enhancing connectivity within this network with attention. Thus, these novel findings indicate a distributed attention modulation circuit with functional deficits in very early psychosis. This circuitopathy provides a systems-level target for novel interventions, such as non-invasive brain stimulation. Improvement of attention modulation deficits in FEP, should improve real-world functioning, and might improve functional outcome if targeted early in the disorder.

V146. TOPOLOGICAL PERTURBATIONS IN THE FUNCTIONAL CONNECTOME SUPPORT THE DEFICIT/ NON-DEFICIT DISTINCTION IN ANTIPSYCHOTIC MEDICATION-NAïVE FIRST EPISODE PSYCHOSIS PATIENTS

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Background: The deficit syndrome is a clinical subtype of schizophrenia characterized by enduring negative symptoms. Converging lines of evidence suggest that deficit syndrome and non-deficit syndrome patients differ substantially in their neurobiology, but differences in functional connectome alterations remain poorly understood. Here, we use graph theory analytics in a group of antipsychotic medication-naïve first episode psychosis patients (FEP), who do or do not display clinical features of the deficit syndrome, to characterize functional connectome properties in these two groups.

Methods: We acquired resting state fMRI on a Siemens Prisma scanner equipped with a 20 channel head coil [anterior> posterior and posterior> anterior; TR= 1550ms; TE= 37.80ms; flip angle= 71°, MB factor= 4; voxel size= 2mm3; 225 volumes] in a group of 65 antipsychotic medication-naïve FEP and 72 matched controls. 22 patients displayed clinical features of the deficit syndrome (FEP-DS) and 43 did not (FEP- NDS), as assessed with the Schedule for the Deficit Syndrome. Data was preprocessed with the conn toolbox (version 18a); no global signal regression was performed. We used the GRETNA (version 2.0) toolbox in Matlab to estimate weighted absolute network matrices and calculate network measures with a sparsity threshold. To assess topological connectome differences between groups we used MANCOVAs with age, sex and mean framewise displacement as covariates. To correct for multiple comparisons we used Bonferroni correction.

Results: We enrolled 72 healthy controls (23.8 +/- 5.4 years, 45 male), 43 FEP-NDS (age: 24 +/- 6.6 years, 24 male), and 22 FEP-DS (age: 23.5 +- 5.4 years, 21 males). Global ($F= 4.60$, $p=.01$) and local ($F= 4.18$, $p= .01$) network efficiency were significantly different between the three groups, where we observed reduced global ($t= 3.90$, $p< .01$) and local network efficiency ($t= 3.31$, $p< .01$) in the FEP-DS group. In addition, network synchronization differed between groups, where reductions were observed in the FEP-NDS group ($t= 2.33$, $p= .02$). Small-worldness and cluster coefficient did not significantly differ between groups. Clustering coefficient was marginally increased in FEP-NDS, when compared to FEP-DS ($p = .069$).

Discussion: Here, we demonstrated that topological perturbations differ between clinical subgroups, suggesting that functional brain networks are differentially affected in first episode psychosis patients who display clinical features of the deficit syndrome compared to those who do not. Taken together, our data add to the growing body of neuroimaging studies that support the idea that the deficit syndrome has a unique underlying pathophysiology. Future studies could potentially benefit from stratifying patients accordingly when investigating target engagement and efficacy of novel treatments.

V147. SYNTACTIC COMPLEXITY IN CANNABIS USERS: AN ACTIVE INFERENCE HYPOTHESIS ABOUT LINGUISTIC MARKERS OF REALITY DYSCONNECTION

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Background: Background and hypothesis: Cannabis use, often seen in patients with psychosis, can affect speech production and increase social disability. Clinicians rely on speech to infer mental states. In this study, we apply the notion of active inference, a neurobiological theory of brain function and disorders, to speech production in cannabis users. On this basis, generating syntactic complexity (the act of grouping words, phrases and clauses in a recursive, hierarchical fashion during speech) depends on the goodness of fit of the speaker's beliefs about the referent object in the speech's content. We hypothesized that a dysconnection with reality (e.g., while using cannabis) would decrease this goodness of fit, indexed by a decrease in the syntactic complexity of the produced speech.
Methods: Method: We acquired language data from 63 cannabis users and 48 nonusers (irrespective of psychosis status). All participants performed a 4-minute speech-elicitation task describing four pictures from the Thematic Appreciation Test. Multiple fine-grained measures of syntactic complexity were extracted using open source TAASSC, and a Bayesian-network model (comprising 26 clause complexity indices and group membership) was fit to the data.
Results: Results: The Bayesian network revealed that among the 26 syntactic complexity indices the index "existential 'there' per clause" (there as an empty word that denotates the existence of a referent usually followed by a locative —e.g., "there is a woman on the bridge") had the highest probability of a causal association with group membership. Nonusers (Mean = 0.132, Sd = 0.074, 95% HDI = [0.111, 0.154] produced more clauses comprising existential there than cannabis users [M = 0.096, Sd = 0.06, 95% HDI = [0.082, 0.11]. A Bayesian independent-samples t test robustly confirmed this difference (BF10 = 9.934).
Discussion: Discussion: Existential sentences are non-canonical constructions that indicate reality acknowledgment (i.e., the notion of presence and that of existence —"there is a world out there"). Furthermore, there' constructions realize the pragmatic function of introducing a new referent into the discourse. (e.g., "there is also a man on the bridge"). In active inference, using the existential 'there' would increase the complexity of the speaker's beliefs model with the ensuing increase in its goodness of fit —i.e., it indicates that the subject not only is changing the canonical constructions in information packaging S-V-O but also their beliefs to better reflects what exists in a scene picture. Low use of existential 'there' in cannabis users suggests a diminished ability to change their beliefs to acknowledge the external reality —a sort of dysconnection that is also observed in psychosis. A formal (mathematical) demonstration of this goodness-of-fit reduction is congruent with the linguistic findings. We call for further applications of computational linguistics to dissect the effect of cannabis use and psychosis.

V148. LOCALIZED TO GENERALIZED DEFICIT CHANGES IN HIPPOCAMPAL SUBFIELD VOLUMES IN MEDICATION NAïVE FIRST EPISODE PSYCHOSIS PATIENTS AFTER 16 WEEKS OF ANTIPSYCHOTIC TREATMENT

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Background: Volume deficits of the hippocampus and its subfields are widely reported across multiple illness stages in psychosis spectrum disorders. Hippocampal atrophy is associated with increased psychosis symptomology. Studies also show that hippocampal volume declines at a greater rate as the illness progresses when compared to healthy controls. Some evidence suggests that hippocampal subfields may show greater sensitivity to morphological abnormalities than the hippocampus as a whole. Previous research indicates that this volume loss may initiate in the CA1, spreading to additional subfields as the illness progresses. The goal of this project was twofold: First, determine patterns of abnormal hippocampal and subfield volumes in antipsychotic drug (APD) naïve first episode psychosis (FEP) patients

prior to medication; And second, investigate the progression of volume decline over a 16 week trial of APD treatment.
Methods: We recruited 93 FEP (age=23.35, 66%M) and 80 matched HC (age=24.21, 59%M). FEP were enrolled in a 16-week risperidone trial. Structural data was collected from participants at baseline (prior to antipsychotic medication for FEP), and after 6 and 16 weeks of antipsychotic medication. Hippocamapal and hippocampal subfield volumes were assessed using FreeSurfer 7.1.1. To determine if FEP and HC groups differed in hippocampal and subfield volumes over time we utilized a series of general linear mixed models (random factor = subjects; fixed effects = group | time). Age and intracranial volume were entered as covariates of no interest. Post-hoc univariate ANCOVAs for regions with significant group x time interactions during the initial analysis were utilized to further investigate group differences at each scan time (false discovery rate [FDR] was used to correct for multiple comparisons). Follow-up pairwise comparisons from the linear mixed models were then used to determine if any significant differences in volume occurred across scan times. Significance was determined based on Bonferroni corrected 95% confidence interval.
Results: FEP showed deficits in baseline CA1 and presubiculum volumes. Furthermore, subfield volume deficits continued to spread after baseline, including not only the CA1 and presubiculum across all time points, but also the granule cell layer of dentate gyrus volume at week 6 and further increasing to the CA4 by week 16.
Discussion: This study presents evidence of localized hippocampal subfield volume deficits among FEP prior to APD. Furthermore, we show that this initial deficit pattern spreads to more subfields over 16 weeks of APD treatment becoming more regionally generalized. These results are in line with previous literature that suggests initial hippocampal dysregulation and volume deficits likely begins in the CA1 before generalizing to the rest of the hippocampus as the illness progresses. Previous research also implies that this may be due to localized glutamatergic imbalance early in the disease that becomes more widespread as the illness progresses via efferent glutamatergic projections.

V149. CUMULATIVE EFFECTS OF TRAUMA HISTORY AND PERCEIVED CURRENT NEIGHBORHOOD VIOLENCE ON PARANOID IDEATION

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Background: Neighborhood crime has been shown to be associated with increased paranoid ideation (e.g., Wilson Smith et al.., 2016; Vargas, Rouhakhtar, et al., 2020). Additionally, experiences of trauma such as childhood abuse or victimization have been found to related to psychotic experiences including paranoid ideation (e.g., Bentall, Wickham et al., 2012; Morgan, Gayer-Anderson et al., 2020; Varese, Smeets, et al., 2012). Often neighborhood context and personal trauma history have been examined separately but research indicates that these can have cumulative impacts on risk for psychotic experiences (Newbury, Arseneault, et al., 2017).
The current study sought to examine the association between paranoid ideation and combined effects of personal trauma history and perceived neighborhood crime levels in a transdiagnostic sample of individuals with psychotic disorders. We sought to examine the following hypotheses: 1) personal history of trauma would be associated with self-reports of current neighborhood violence, 2) greater trauma and self-reports of neighborhood violence would be related to more severe paranoid ideation, and 3) perceptions of neighborhood violence would

add incremental prediction to paranoid ideation above and beyond variance accounted for by trauma history.

Methods: To ensure a range of paranoid ideation, data were collected from a transdiagnostic sample of adults (Total N = 120) including individuals with psychotic disorders (N=98; 82%) and healthy controls (N=22; 18%). The Neighborhood Environment Scale (NES; Mujahid et al., 2007) was used to assess perceptions of the occurrence of violence in an individual's neighborhood. The experience of trauma was assessed with the Trauma History Questionnaire (THQ; Hooper et al., 2011). The THQ provided assessments of an individual's experience of crime victimization, general disaster trauma (e.g., weather related), and physical and sexual trauma. Paranoid ideation was assessed with the revised Green Paranoid Thoughts Scale (GPTS; Freeman et al., 2019).

Results: Correlational analyses indicated that perceptions of neighborhood violence were not associated with THQ scales including crime victimization ($r = -.09$, ns), general disaster trauma ($r = -.10$, ns), or physical and sexual trauma ($r = .13$, ns). As predicted, greater paranoid ideation was related to perceptions of greater neighborhood crime ($r = .29$, $p < .005$). Paranoid ideation was also related to trauma history: crime victimization ($r = .19$, $p < .05$), general disaster trauma ($r = .26$, $p < .005$), and physical and sexual trauma ($r = .24$, $p < .005$). Regression analyses indicated that the block of THQ trauma scores accounted for a significant amount of variance in paranoid ideation, $R2 = .097$, $F = 4.01$, $p < .01$. Neighborhood violence subsequently entered into the regression model led to a significant increment in explained variance in paranoid ideation, $R2 = .185$, $R2\text{-change} = .088$, $F\text{-change} = 11.99$, $p < .005$.

Discussion: Results indicated that trauma history and perceptions of neighborhood violence were actually unrelated. This unexpected result indicates that prior traumas and current neighborhood perceptions of violence are largely independent and counter concerns that trauma may simply lead to biased perceptions of current neighborhood violence. Replicating prior research, correlational analyses indicated that all forms of prior trauma were related to greater paranoid ideation. Further, current perceptions of neighborhood violence were also related to increased paranoid ideation. Finally, regression analyses indicated that trauma history and perceptions of neighborhood violence had unique and additive impacts on paranoid ideation. The results reinforce prior findings from adolescents with psychotic experiences (Newbury et al., 2017) indicating the cumulative effects of neighborhood factors and personal trauma and extend these findings to an adult outpatient sample of individuals with a range of psychotic disorders. Interventions targeting paranoia may need to consider both prior trauma history as well as current environmental factors.

V150. HIGHER LEVEL EMOTION PROCESSING IN RECENT-ONSET SCHIZOPHRENIA AND RELATED DISORDERS: WHAT ARE THE COGNITIVE AND CLINICAL CORRELATES?

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Background: Social cognition refers to the mental processes underlying social interactions including perceiving, interpreting, and generating responses to the intentions, dispositions, and behaviors of others. The Social Cognition Psychometric Evaluation Study has highlighted four core domains of social cognition relevant for people with schizophrenia, including emotion processing. Emotion processing includes both lower-level (emotion perception/recognition) and higher-level (understanding and managing emotions) processes. While several prior studies have assessed lower levels of emotion processing, there are still very few information regarding the variables that could contribute to higher-level emotion processing. Higher-level emotion processes are complex functions that encompass a set of brain networks. For example, recent models of brain networks support that both mentalizing and emotion regulation rely on prefrontal and cingulate systems for attention, response selection, and mental state attribution. As a result, the brain networks involve in emotion regulation could also be involved in other cognitive functions, such as attention, memory, executive functions, speed of processing or theory of mind. Clinical variables such as anxiety or depressive symptoms have also demonstrated their impact on emotion regulation. The aim of this study is to explore the cognitive and clinical correlates of higher-level emotion processing in schizophrenia and related psychotic disorders.
Methods: Twenty-seven participants with recent-onset schizophrenia and related psychotic disorders were recruited. They were aged between 18 and 39 years old, with less than five years of treatment for their psychotic disorder and were clinically stable. Higher-level emotion processing was assessed using the Mayer Salovey Caruso Emotional Intelligence Test (MSCEIT). Cognitive variables included the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) to assess speed of processing, attention/vigilance, working memory, verbal and visual learning and problem solving as well as a theory of mind task (Combined stories test). Clinical variables were assessed using the three dimensions scoring of the Positive and Negative Syndrome Scale (PANSS) (i.e., positive, negative, general psychopathology). Correlations were conducted between the MSCEIT and the cognitive (neurocognition, theory of mind) and clinical (three dimensions of the PANSS) variables.
Results: Regarding the correlations between higher-level emotion processing and cognitive variables, significant correlations were observed between the MSCEIT and theory of mind, ($r(27) = 0.599$. $p < 0.001$) as well as verbal learning ($r(27) = 0.403$. $p = 0.037$) and visual learning ($r(27) = 0.424$. $p = 0.028$). No significant correlation was found between the MSCEIT, and the three dimensions of clinical symptoms.
Discussion: These results are in line with previous studies that revealed associations between social cognition, episodic memory and affect regulation, due to commune brain networks underpinning these variables. For example, emotion regulation and episodic memory both rely on hippocampal networks. The absence of associations between emotion regulation and the clinical symptoms may be partly explained by the three dimensions of the PANSS used in this study. Using a five-dimension rating, we might expect associations between emotion regulation and the depression/anxiety and excitability/hostility dimensions. Future studies using larger samples and refined clinical variables would be helpful to disentangle the direction and nature of the associations with higher-level emotion processes.

V151. DISCRIMINATION IN INDIVIDUALS AT CLINICAL HIGH RISK FOR PSYCHOSIS

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Background: The social defeat theory of psychosis suggests that experiences of social defeat, defined as social rejection or exclusion, increase risk for psychotic disorders (Selten et al., 2013). One branch of social defeat are experiences of discrimination. The relationship between discrimination and psychotic symptoms has been examined in individuals with psychotic disorders and healthy non-clinical samples, but is less well studied in individuals at clinical high risk for psychosis (CHR). This study had two primary objectives. First, to identify group differences between CHR and healthy controls (HC) on perceived discrimination and social defeat. Moreover, we sought to determine whether rates of perceived discrimination and social defeat were associated with positive psychotic-like symptoms.
Methods: Both CHR and HC individuals were recruited through the community. Due to the pandemic this study was completed entirely online and participants live throughout the country. Participants provided basic demographic information, completed clinical interviews including the Structured Interview for Prodromal Syndromes (SIPS) and the Structured Clinical Interview for the DSM-5 (SCID) and completed self-report questionnaires including the Everyday Discrimination Scale and the Defeat Scale used in these analyses.
Results: The results of this study show higher rates of perceived discrimination in CHR relative to HC individuals ($p < .001$). Additionally, CHR individuals report higher levels of social defeat relative to HC ($p = .031$). In contrast to previous literature, within the CHR group, higher rates of perceived discrimination and social defeat were not associated with more severe positive psychotic symptoms ($p > .053$). When we look across the entire group (CHR and HC) we see that both discrimination and social defeat experiences are correlated with greater positive psychotic symptoms ($p < .05$).
Discussion: The results of this study are consistent with the social defeat theory of psychosis. Our CHR group reports higher rates of social defeat and discrimination, a type of social defeat, relative to our HC group. This finding is consistent with previous epidemiological literature that suggests that specific types of social factors are associated with a greater risk for psychosis. Additionally, previous research suggests that higher rates of discrimination are associated with greater conversion rates in CHR, thus assessing these experiences is particularly clinically relevant (Stowkowy et al., 2016).

V152. SYNERGISTIC EFFECTS OF MULTIPLE TYPES OF PERSONAL AND POPULATION-LEVEL STRESSORS ON EXPERIENCES OF IDEAS OF REFERENCES AMID ONGOING SOCIAL UNREST AND COVID-19 IN HONG KONG

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Background: Ideas of reference (IOR) mark some of the most common symptoms of psychosis that are also implicated across a wide spectrum of psychopathological conditions. Studies have shown that IOR can predict future psychosis onset and may suggest poorer prognosis. While IOR, as a form of psychotic symptoms, are generally considered to be endogenous (i.e., greater weights given to intrinsic factors in their pathogenesis), how such experiences can be directly influenced by ruminative thoughts about external events (i.e., event-based rumination) and repeated experiences of different types of personal and population-level stressors as they evolve remain to be elucidated.
In more stable societal contexts, the study of extrinsic influences on IOR can be challenging due to the highly varied environmental contexts across individuals. Furthermore, previous

studies that emphasised the consequences of personal life stressors can also prevent a more detailed study of the specific contributions of extrinsic and intrinsic factors in the development of psychopathological symptoms, since the degree to which such personal stressors impact an individual is also contingent upon one's mental state. The co-occurrence of large-scale population-level stressors, i.e., those that are imposed on the entire population (relatively less varied across individuals), such as social unrest and the global COVID-19 pandemic, afforded an opportunity to examine the roles played by extrinsic factors on IOR experiences in greater depth.

Methods: Data were collected from 9,873 participants of a large-scale online mental health survey tool during a period of ongoing social unrest and COVID-19 in early 2020 in Hong Kong. Experiences of IOR were determined by the degree to which the participant considers the self-referential experience to be exclusively directed to oneself. The additive and interaction effects among social unrest-related traumatic events (TEs), COVID-19 pandemic-related events (PEs), and personal stressful life events (SLEs), on IOR severity were explored.

Results: Hierarchical regression analyses revealed that, accounting for age, gender, and past psychiatric history, event-based rumination ($\beta = 0.28$), the number of TEs ($\beta = 0.24$), PEs ($\beta = 0.04$), and SLEs ($\beta = 0.10$), and also past adverse experiences ($\beta = 0.07$) were significantly associated with IOR severity, all $p < 0.001$. Altogether, the variables explained 28.7% of the variance in IOR severity.

In addition, the series of two-way analysis of variance revealed significant dose-effect and synergistic effects of the different types of stressors on IOR severity. Specifically, significant main effects of recent-TEs (i.e., experienced within the past month), $F(2, 9861) = 94.7$, $p < 0.001$, and prior-TEs (i.e., experienced over one month but within the past year), $F(2, 9861) = 84.6$, $p < 0.001$, were observed. A significant recent-TEs X prior-TEs interaction effect was also observed, $F(4, 9861) = 3.5$, $p = 0.007$. Significant additive effects of prior-TEs, $F(2, 9861) = 110.4$, $p < 0.001$, and COVID-19 PEs, $F(2, 9861) = 21.3$, were also revealed. In addition, apart from the main effects of recent-TEs, $F(2, 9861) = 130.6$, $p < 0.001$, and personal SLEs, $F(2, 9861) = 86.1$, $p < 0.001$, a significant recent-TEs X personal SLEs interaction effect was also observed, $F(2, 9861) = 3.4$, $p = 0.009$.

Discussion: While intrinsic factors contribute to the development and maintenance of psychopathological states, such as IOR, accounting for the effects of multiple types of external factors is crucial for designing appropriate intervention strategies, particularly in the current world of ongoing large-scale crises.

V153. EEG BIOMARKER OF WORKING MEMORY IMPAIRMENT IN PEOPLE WITH PSYCHOSIS: DOMAIN-SPECIFIC OR GENERALIZED IMPAIRMENT?

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Background: People with psychotic disorders such as schizophrenia or schizoaffective disorder (PSY) exhibit robust and reliable deficits in working memory capacity compared to healthy control subjects (HCS), although the neural mechanisms that give rise to these impairments remain unknown. We and others have reported evidence that event-related desynchronization within the alpha frequency band of the electroencephalogram (9-13 Hz; alpha-ERD) represents a critical mechanism by which visual memories are consolidated and retrieved in healthy individuals (Erickson et al., 2019; Fukuda et al. 2017). Furthermore, we

have observed that alpha-ERD is robustly impaired in PSY, with a Cohen's d effect size of >1.0 (Erickson et al., 2017). Taken together, these observations implicate alpha-ERD impairment in PSY as a primary mechanism by which working memory capacity is constrained. Though alpha-ERD represents a plausible candidate mechanism of working memory impairment, it is not yet known at what stage this process is impaired. There are several sub-processes that are engaged in a typical working memory task, including (but not limited to) perception/encoding, selection, consolidation, maintenance, response selection, and updating. Thus, it is not yet known whether alpha-ERD impairments in PSY reflect a failure at the consolidation stage of memory formation or at an earlier stage such as encoding. Additionally, it has yet to be clarified whether alpha-ERD reduction is associated with having a psychotic illness, per se, or having a serious mental illness more generally.

Methods: The present study is being conducted to determine whether alpha-ERD impairment in PSY (a) represents a working memory-specific disruption or a more generalized visual processing impairment; and (b) is unique to individuals with psychotic illness. Nine PSY, 6 individuals with primary mood disorders with psychotic features (Mood+), 9 individuals with primary mood disorders without psychotic features (Mood-), and 13 HCS have completed all study procedures. All participants completed a three-variant change detection task sequence while EEG was recorded: one in which participants were asked to maintain the colors of the squares in memory (memory condition); one in which participants were asked to attend to the colors of the squares in search of a target color (attention condition); and one in which participants passively viewed the colored squares (passive condition). alpha-ERD was measured in response to the onset of the sample array in all three conditions with set sizes 1, 2, 3, 4, and 5 items. It was expected that PSY would exhibit normal alpha-ERD in the passive and attention conditions, with significant alpha-ERD impairment in the memory condition. This would indicate that they have a unique impairment in the consolidation stage of working memory. It was further expected that PSY would exhibit the greatest level of impairment, with Mood- participants exhibiting the least impairment and Mood+ individuals exhibiting intermediate levels of impairment. Such a finding would indicate a specificity of the alpha-ERD impairment to the presence of a psychotic illness.

Results: A group x condition x set size (4 x 3 x 5) ANOVA revealed several significant effects. There was a significant effect of condition ($F(2,66)=48.16$; $p<0.001$), with follow-up t-tests revealing that alpha-ERD in the memory condition was significantly larger than alpha-ERD in the passive ($t's>5.02$; $p's<0.001$) and attention ($t's>5.54$; $p's<0.001$) conditions across all set sizes. There was also a significant effect of set size ($F(4,132)=13.11$; $p<0.001$), with alpha-ERD being significantly smaller at lower set sizes. Finally, there was a trend-level effect of group ($F(3,33)=2.68$; $p=0.063$). To further interrogate the group effect, alpha-ERD was averaged across set sizes for the passive, attention, and memory conditions, separately. Contrary to our predictions, we found that PSY exhibited reduced alpha-ERD in all three conditions ($t's>2.12$; $p's<0.05$). That is, even in conditions without a memory demand, PSY exhibited impaired alpha-ERD compared to HCS. Mood+ and Mood- participants did not differ significantly from HCS in alpha-ERD for either of the three conditions ($t's<1.67$; $p's>0.11$), although Mood- participants were qualitatively the most similar to HCS and Mood+ participants were intermediate between PSY and Mood-. Finally, alpha-ERD was significantly associated with cognitive capacity as measured by the Wechsler Abbreviated Scale of Intelligence (WASI; $r=-0.38$; $p<0.05$) and MATRICS Consensus Cognitive Battery (MCCB; $r=-0.54$; $p<0.01$).

Discussion: The present results indicate that a key biomarker of working memory impairment may reflect a more generalized visual impairment in PSY that is not specific to working memory per se. Furthermore, this biomarker appears to show some specificity to the presence of a psychotic disorder, as PSY exhibit the largest impairment with Mood- showing the least

impairment and Mood+ showing an intermediate level of impairment. Such findings are consistent with a model of cognitive impairment in PSY that emphasizes the impact of degraded sensory representation on downstream cognitive processes.

V154. EVALUATING APATHY DYNAMICS IN PATIENTS WITH SCHIZOPHRENIA DURING METACOGNITIVE TRAINING

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Background: Apathy plays an important role in schizophrenia symptomatology, influencing outcomes, social function, independent housing, employment and interpersonal interactions which result in a decline in quality of life. Apathy is understood as an amotivational syndrome which manifests early even during the prodromal phase of the disorder. Follows decline in motivation, everyday activity, academic and professional involvement and also treatment. Modern principles of psychosocial therapy include motivational enhancement therapies, however it was noticed that group therapy itself may increase motivation in those patients. Metacognitive training (MCT) is a best practice method of group psychological treatment for people with schizophrenia, aimed to improve social cognitive impairments which finally result in positive symptoms improvement too. Hence it was interesting to investigate MCT possible effects on apathy patterns during MCT.

Methods: 40 day care patients with ICD-10 schizophrenia spectrum disorders were enrolled into the study upon written informed consent. There were 11 men and 29 women among them. Inclusion criteria were PANSS<80, CDSS<6, not disrupted behavior. Patients were not in an acute psychotic phase and not depression (PANSS – 68.4±9.6; CDSS – 4.8±2.9). Apathy was measured with a Russian version of Apathy Evaluation Scale (AES) which included clinician version (AES-C) and a self-report version (AES-S). Mean age for men was 32,5±8,8 years, for women – 35,3±8,8 years, 28 patients (70%) had higher education (bachelor or master degree), only 8 patients (20%) had own families, 22 patients (55%) were single, 10 patients (25%) – divorced. 14 patients (35%) were on a disability pension. All patients received standard pharmacotherapy in stable doses. Assessments were performed twice: before MCT and after the final module (8 sessions). Statistical analysis performed in Statistica for Windows 10.0, nonparametric Wilcoxon criteria used.

Results: Enrolled patients were clinically stable with no prominent depressive symptoms. At the inclusion and after MCT the following mean scores were detected: PANSS N subscale decreased from 18.5±4.5 to 13.5±3.7; ($p<0.001$), on the AES-C scale, during repeated examination, the sum of points decreased from 40.5±7.6 to 33.5±7.1 ($p=0.001$). The AES-S did not differ significantly (32.5±7.4 vs. 31.5±7.2 ($p=0.68$). To assess discrepancy and clinical and self-report apathy perception we used coefficient (AES-C/AES) which at the inclusion was 1,2±0,21 vs. 1.07±0.27 ($p=0.009$).

Discussion: Given the discrepancy in the assessment of apathy on the part of the clinician and the patient, it can be assumed that patients' insight of the symptoms of apathy is insufficient. The data obtained on the decrease in the severity of manifestations of PANSS, negative symptoms and apathy are registered only by clinicians, while patients do not notice changes in their condition. Conclusion: it can be assumed that group therapy has a positive effect on behavioral activation and, following this, on apathy, which is reflected by changes in the N subscale of PANSS and the overall AES-C score. However, judging by the AES-C/ AES-S

ratio, patients do not notice these changes. On the one hand, this can be regarded as a lack of insight into negative symptoms. On the other hand, it requires additional psychosocial efforts in order to draw the attention of patients to the apathy symptoms experienced. Limitation of the study is the absence of TAU control group which is now being recruited.

V155. THE RELATIONSHIP BETWEEN SOCIAL ANXIETY RELATED SELF-BELIEFS, PARANOID IDEATION AND AFFILIATIVE RESPONDING IN PSYCHOSIS

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Background: Negative symptoms and social impairment are key characteristics of psychosis (Kring and Moran, 2008), and negative symptoms have been associated with less positive appraisals of an interaction partner (Blanchard et al., 2015). Paranoid ideation and social anxiety are also common in psychosis, and feelings of vulnerability and negative self-beliefs contribute to paranoid symptoms (Meisel et al., 2018). Similarly, models of social anxiety emphasize the role of negative or maladaptive self-beliefs, including high standard beliefs (e.g., "I need to be liked by everyone."), conditional beliefs (e.g., "If I don't say something interesting, people won't like me."), and unconditional beliefs (e.g., "People think I am inferior.") (Wong et al., 2014). These negative self-beliefs are associated with poorer functioning, and can prevent engagement in social interactions (Campellone et al., 2016). Individuals with psychosis also anticipate more negative emotions related to social situations, driven by negative beliefs (Engel et al., 2016). No study has examined the association between negative self-beliefs, paranoid ideation, and anticipatory affiliative deficits in individuals with psychosis.

The present study sought to examine the following hypotheses 1) paranoid ideation and social anxiety are related to negative self-beliefs, 2) negative self-beliefs are associated with decreased affiliative responding to a social interaction partner before the affiliative bonding task, reflected by less positive appraisals of the partner and less willingness to interact further and 3) negative self-beliefs will be associated with decreased affiliative responding after the bonding task.

Methods: Data were collected from a transdiagnostic sample of adults with psychotic disorders and non-clinical participants. Negative self-beliefs were measured using the Self Beliefs Related to Social Anxiety scale (SBSA; Wong et al., 2014), which assessed high standard, conditional and unconditional beliefs. Social anxiety was assessed with the Social Interaction Anxiety Scale (SIAS; Brown et al., 1997). Paranoid ideation was measured using the Revised Green Paranoid Thought Scale (R-GPTS; Freeman et al., 2016). Participants completed a novel social interaction task with a highly affiliative partner (see McCarthy et al., 2017 for full description). and appraised their interaction partner, and their desire to interact with the partner in the future, before and after the dyadic interaction.

Results: Analyses (N = 107) found high standard, conditional and unconditional beliefs were significantly related to social anxiety (rs. = .29-.65, ps < .005) and to paranoid ideation (rs. = .27-.55, ps < .005). Only unconditional beliefs were significantly associated with lower appraisals of partner before the bonding task ($r = -.25$, $p = .01$). Following the task, only conditional beliefs were significantly associated with lower appraisals of partner ($r = -.23$, $p = .02$) and less willingness to interact with the partner in the future ($r = .20$, $p = .03$).

Discussion: These results indicate that negative self-beliefs are associated with both social anxiety and paranoid ideation in psychosis. Further, negative self-beliefs were related to less positive appraisals of the interaction partner, and less willingness to interact with said partner in the future. These findings highlight the role of negative, maladaptive self-beliefs in social anxiety and paranoid ideation, as well as the detrimental impact these beliefs can have on the formation of affiliative relationships in those with psychosis. Results and implications will be discussed further at the time of presentation.

V156. SOCIAL COGNITION, SOCIAL FUNCTIONING, AND DAILY SOCIAL EXPERIENCES IN PERSONS WITH SCHIZOPHRENIA

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Background: Social cognitive impairments are common in schizophrenia. Deficits in facial affect recognition—one type of social cognitive impairment—can lead people with schizophrenia to have difficulty interpreting others' thoughts/intentions and respond with appropriate behavior (Pinkham et al., 2011; Ruocco et al., 2014). While prior work shows relationships between social cognition and psychosis symptoms (Ruocco et al., 2014) and lower social functioning and skills (Fett et al., 2010; Halverson et al., 2019), few studies have examined the extent to which deficits in affect recognition impact social outcomes in daily life.
Methods: Thirty-one participants with schizophrenia completed an eight-week mobile phone-based intervention aimed at improving social skills and motivation. At baseline, participants completed the Penn Emotion Recognition Test (ER-40), which assesses accuracy and response time in facial affect recognition; they also completed assessments of psychosis symptoms (using the Brief Psychiatric Rating Scale (BPRS)) and social functioning (using the Social Functioning Scale (SFS)). During the intervention, participants responded to twice-daily surveys assessing the presence of recent social interactions and appraisals of these interactions (e.g., perceptions of social competence) using ecological momentary assessment (EMA). We examined associations between facial affect recognition at baseline and 1) symptoms of psychosis and social functioning, at baseline and between baseline and post-intervention, and 2) EMA-reported social interactions and appraisals throughout the intervention.
Results: Greater ER-40 total accuracy was associated with significantly lower baseline BPRS score ($r = -0.45$, $p = .01$), but was unrelated to change in BPRS, SFS scores at baseline, or changes in SFS across the intervention. There were generally negligible associations between ER-40 total accuracy and EMA-reported social interactions and appraisals in daily life. Greater total accuracy showed a moderate, non-significant association with lower anxiety following recent social interactions ($r = -0.28$, $p = .13$). ER-40 response time was unrelated to psychosis symptoms, social functioning, or daily social behavior.
Discussion: These results support previous findings of associations between affect recognition and psychosis symptoms in schizophrenia (Ruocco et al., 2014). Small, non-significant associations between ER-40 total scores and EMA-reported social interactions and appraisals suggest affect recognition may not be strongly associated with social experiences and functioning in daily life. Future research should explore the potential associations between other measures of social cognition and daily social experiences, as well as potential associations with other aspects of social interactions, such as objective indicators of social competence.

V157. AMYGDALA SYMMETRY PREDICTS DISTRESSFUL AUDITORY VERBAL HALLUCINATIONS IN SCHIZOPHRENIA PATIENTS

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Background: Hearing voices is a common symptom in psychiatric conditions including schizophrenia. These 'auditory verbal hallucinations' (AVH) become highly distressful for reasons that remain largely unknown. We hypothesized that AVH are associated with increased symmetry of the amygdala, which is a brain region involved in both language and emotion processing. Functional evidence for increased symmetry of neural activity in schizophrenia is abundant, with amygdala driving the decoding of emotional voices in sensory cortices. Moreover, amygdala nuclei have distinct functional correlates and structure, which makes it essential evaluating the impact of symmetry for each pair of amygdala nuclei on AVH to predict disease severity. We used a recently-developed measure for calculating structure symmetry/asymmetry, called the "distance index" (DI), for comparing left-right volume coherence for each amygdala nucleus, starting from the assumption that higher DI corresponds to lower coherence and that, in contrast, lower DI corresponds to higher coherence between amygdala nuclei.

Methods: We collected structural MRI scans from 71 schizophrenia patients and 71 healthy controls. AVH severity was measured with the Positive and Negative Syndrome Scale (PANNS), and perceived distressful emotional content was measured with the Beliefs about Voices Questionnaire (BAVQ). We used the most recent anatomical parcellation of the amygdala in nine nuclei implemented in FreeSurfer based on high-resolution 7T MRI maps of postmortem brain samples. We entered the nuclei DIs across patients and controls in regression analyses with clinical measures as predictors, in order to identify those nuclei exhibiting significant differences in symmetry. Furthermore, we correlated nuclei DI across patients with their scores on the BAVQ-R to determine if the same nuclei with high symmetry compared to controls also correlated with beliefs about AVH.

Results: The output of the regression equations using DI values and scores over the seven BAVQ subscales across patients as predictors was significant for the 'omnipotence' and especially for the 'behavioral resistance' BAVQ subscales, with p-values of 0.019 and < 0.001 respectively. Regression analyses revealed a key role of the accessory-basal nucleus in identifying distressful AVH. Regression analyses between DI scores and the P3 item, which indexes AVH severity, highlighted three amygdala nuclei, the corticoamygdaloid, the paralaminar and, above all, the accessory-basal nucleus, with p-values of 0.047, 0.032, and 0.005 respectively. We subsequently grouped all patients into low-AVH and high-AVH groups based on their P3 score to compare the symmetry of each amygdala nuclei pair in one-sample t-tests for each group against controls. For the low-AVH group, results were not significant; for the high-AVH group, symmetry of the accessory-basal nucleus was significantly higher in patients compared to controls, $t(39) = 2.35$, $p = 0.02$, as was the coherence of the corticoamygdaloid nucleus, $t(39) = 2.78$, $p = 0.008$.

Discussion: These findings demonstrate that structural symmetry of amygdala nuclei underlies severity and content of AVH in schizophrenia patients, which further underscores the relevance of the amygdala to emotional language processing.

V158. EXAMINING CHANGES TO FRONTAL LOBE SUPERFICIAL WHITE MATTER IN FIRST EPISODE SCHIZOPHRENIA

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Background: Magnetic resonance imaging (MRI) is commonly used to non-invasively study changes of the brain. In particular, diffusion MRI (dMRI) enables the reconstruction of structural connectivity, which when combined with diffusion tensor modelling allows for quantitative assessment of changes along the trajectory that is sensitive to the microstructural environment. Recently, studies have employed dMRI to investigate the superficial white matter (SWM), residing just below the cortical surface with a "U"-shaped trajectory and having an important role in cognitive function. These tracts are some of the last to reach full maturation, often developing late into adulthood in healthy subjects. Consequently, the SWM may be vulnerable to developmental aberrations underlying schizophrenia. In this study, we investigated the SWM of the frontal lobe in patients diagnosed with first episode schizophrenia (FES), examining changes along its trajectory and relating the changes to their clinical presentations. We hypothesized that patients diagnosed with FES would demonstrate abnormal SWM presentations, and these changes will relate to symptom severity.

Methods: Data was collected from patients with untreated FES (n=53; 44M/9F, ages 16-39) and healthy controls (n=31; 19M/12F, ages 16-29) with a 7-Tesla MRI system located at Robarts Research Institute in London, Canada. Diffusion data was acquired twice with opposite phase encoding directions with the following parameters: repetition time/echo time (TR/TE) = 5100/50.2 ms; 2mm isotropic resolution; b-value = 1000 s/mm^2 (64 directions) with 2 b-value = 0 s/mm^2. Anatomical data was acquired with a MP2RAGE sequence: TR/TE: 6000 / 2.83 ms; 0.75mm isotropic resolution.

Distortion correction was performed for anatomical data, while common pre-preprocessing steps were applied to the dMRI. This included distortion correction, denoising and minimization of Gibbs ringing effects. dMRI data was also rigidly aligned with the subject's anatomical data. Quantitative maps of fractional anisotropy (FA), radial diffusivity (RD), and axial diffusivity (AD), were derived from modelled diffusion tensors and mapped to the structural connectivity. Further, whole-brain probabilistic tractography was performed and SWM was identified using established parameters for determining "U"-shaped trajectory. Individual tracts were identified by comparison with a labelled SWM template. The Desikan-Killiany atlas was used to extract the SWM located in the frontal lobe. Quantitative changes were correlated with collected PANSS scores.

Results: Multiple SWM tracts exhibited quantitative changes along its trajectory, occurring adjacent to the sulcus. In 8 out of the 11 identified tracts exhibiting a change, both a reduction in FA and increase in RD was found in patients diagnosed with FES. These tracts were found to be distributed throughout the frontal lobe. Following correction for multiple comparisons, the quantitative changes were found to occur irrespective of the symptom severity.

Discussion: Quantitative changes to the SWM suggest the occurrence of demyelination, disrupting normal brain connectivity at the time of first presentation in schizophrenia. The lack of symptom correlations may relate to insufficient power or frontal SWM demyelination being an invariant feature irrespective of symptom severity in schizophrenia. Given that the patients in this sample had <3 days of antipsychotic exposure on average, aberrant SWM integrity is unlikely to be a consequence of medication use.

V159. USING ECOLOGICAL MOMENTARY ASSESSMENT TO EVALUATE THE SELF-ASSESSMENT IN PARTICIPANTS WITH SCHIZOPHRENIA

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Background: Previous literature suggests that Individuals with Schizophrenia tend to overestimate their functioning in several domains. They often generate self-reports of their abilities that are not congruent with available objective information. It has been suggested that these individuals do not base their self-reports on their aggregated experience but instead rely on momentary moods, self-generated ideas, or other experiences. There are many advantages of using EMA paging to examine the momentary correlates of self-reported and observer-reported global functioning in daily activities and work, but we are focusing on the collection of objective data.

Methods: There were 101 individuals with schizophrenia surveyed in this study. Ecological Momentary Assessment (EMA) was used to sample participant daily activities. Participants received surveys 3 times per day for a period of 30 days. Each survey asked the participant where they were, who they were with, and what they were doing. Additionally, they were also asked what mood and psychotic symptoms they were experiencing. After the EMA Period, participants and their observers completed the specific Levels of functioning (SLOF) measure to rate the participant functioning in everyday activities. Lastly, we examined whether if momentary responses were associated with self and observer evaluated work skills and everyday activities.

Results: There were a total of 6,814 survey responses from people with schizophrenia that had analyzable data, with adherence to surveys at 75%. Being home more commonly during surveys was associated with self- reported better functioning in everyday activities and work skills than participants who were more commonly away while being alone more commonly was associated with self-reported better functioning in everyday activities. Those that reported hearing voices, feeling paranoid and experiencing other psychotic symptoms on their EMA surveys, tended to report better functioning in work and everyday activities domains. Participants who overestimate their functioning in comparison to observer reports, had lower sadness, more psychotic symptoms, and were also more likely to be home than those who did not overestimate their functioning.

Discussion: Over half of the participants with schizophrenia overestimated their competence compared to observer ratings. They was a noticeable disconnect between their momentary activities and their global self-assessments, in that participants who were home the majority of the time reported being particularly good at activities that can only be performed away from. Patients with these reports also endorsed psychotic symptoms, suggesting a possible link between implausible assessments of everyday experiences and classical psychotic symptoms.

V160. THE COMPLEX RELATIONSHIP BETWEEN BEING BLACK AND MINORITY ETHNIC, AND VIOLENT INCIDENTS IN A PSYCHIATRIC INTENSIVE CARE UNIT

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Background: Black and Minority Ethnic (BME) groups are at a higher risk of developing psychotic disorders, being compulsory admitted, and experiencing more positive symptoms compared with their white counterpart. Moreover, BME individuals are found to be overrepresented in UK violent criminal offences; however, little specific research exists on violence and aggression behaviour in hospital. Psychiatric intensive care units (PICU) provide care for higher risk patients in the context of higher security access and staffing levels. PICUs have special facilities such as seclusion rooms for supervised confinement to manage disturbed more aggressive patients, and limit the use of restraint. The aim of this study was to find out patients' ethnicities admitted to a PICU setting in Lewisham, South London, and whether there was an association between being BME and violent incidents.

Methods: We collected data from patients consecutively admitted to Johnson PICU, South London and Maudsley NHS Foundation Trust from January 2020 to October 2021. These included sociodemographic characteristics, misuse of illicit substances prior to admission, duration of admission and measures of violence and aggression in Hospital, such as Dynamic Appraisal of Situational Aggression (DASA) score on admission, whether seclusion was needed (and its duration), as well as any electronic Datix incident reports for violence.

We used univariate logistic regression to estimate the probability of being secluded based on being BME. We subsequently estimated a multivariate logistic regression model adding age, police involvement and daily cannabis use before admission as covariates.

Results: 176 patients had a unique admission at Johnson PICU in the considered time frame. Thirty-four (19.32%) of patients were White British. The remaining 142 (80.68%) patients were in BME groups, with a subcategory of a majority of 101 (57.39%) being Black (African and Caribbean). A further 15 (8.52%) were of mixed race; 14 (7.94%) were White Eastern European migrants; 6 (3.41%) were Asian; and 6 (3.41%) were of other ethnic minority groups. BMEs showed more police involvement on their admission, compared to White British patients (chi2= 3.8907, p=0.049). There were no differences in DASA score between White British group and all other BMEs (M=4.2 v M=4.4, t=0.4, p=0.66), nor differences in the number of Datix incidents (M=1.4 v M=2, t=-0.97, p=0.33).

BMEs were more likely to be placed in seclusion (chi2= 5.78, p=0.016), however there were no differences in the length of seclusion between the two groups M=3.1 v M=2.7, t=0.3, p=0.3).

Being BME was associated with a higher risk of being in seclusion (OR 1.16 [95% C.I. 1 – 1.34], p=0.044. However, multivariate logistic regression showed that the effect of being BME and being placed in seclusion was absorbed by daily use of cannabis (OR 1.76 [95% C.I. 0.61 – 5.08], p=0.02).

Discussion: This study shows a double representation of BMEs at PICU than the expected population living in Lewisham. However, it may be difficult to generalise these findings outside of multicultural London.

BMEs may have more police involvement due to systemic bias that has been highlighted in many studies and recently politically. Notably, we showed that the risk of being placed in seclusion was associated with daily rather being of a BME background, suggesting that there are more intersectional complexities to understanding violence than ethnicity alone.

Understanding more about BME how ethnicity may be linked to violence can help inform staff and policies more about racial disparities in mental health. The Race equality foundation has recommended that we acknowledge BME patients' lived experience and how their wider social identities impact them.

V161. THE EFFECTS OF TRANS-CRANIAL DIRECT CURRENT STIMULATION ON COGNITION IN SCHIZOPHRENIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Cognitive deficits in schizophrenia and psychotic disorders remain an unsolved problem in psychiatric care. Interventions ranging from pharmacological to cognitive remediation therapies have been trialed with no conclusive effectiveness. New approaches have emerged for the amelioration of cognitive deficits in the form of non-invasive brain stimulation such transcranial direct current stimulation (tDCS) (Brunoni and Vanderhasselt, 2014). TDCS delivers weak electrical currents to the brain through electrodes placed on the scalp (Nitsche and Paulus, 2001). The application of tDCS in schizophrenia has been mainly focused on its effects on auditory-verbal hallucinations with only recent studies examining its effects on cognition (Li et al, 2016; Pondé et al, 2017). Studies examining the effects of tDCS in cognition in healthy controls (Fregni et al, 2005) and psychiatric populations (Dedoncker et al, 2016) have showed promising results. Here we conducted a systematic literature review of studies adopting double-blind, randomized, sham-controlled trials examining the efficacy of tDSC in cognition in schizophrenia by specifically focusing on studies stimulating the dorsolateral prefrontal cortex (DLPFC) as this brain area has been proven to have an important role in cognitive function, particularly executive function, working memory, maintaining and updating goal representation (Barch et al, 2003).

Methods: We performed a systematic literature search in three different databases – Medline, Embase and PsychINFO – as outlined by the PRISMA and Cochrane Collaboration guidelines. Predefining search terms and their derivatives were "tDSC", "schizophrenia", "cognition" and "DLPFC". Screening of search result abstracts and the full-text of eligible studies, as well as publication bias using the Cochrane tool, was done by two independent reviewers. Extraction of qualitative and quantitative data was done by one reviewer. Meta-analysis will be performed using a random-effects model. Size and significance of effect will be calculated by the standard mean difference between tDCS and sham stimulation for five cognitive domains: learning and memory, executive functions, attention, perceptual motor function, social cognition. Publication bias will be assessed using Egger's test, whereas heterogeneity will be examined using the I^2 statistic.

Results: Our search resulted in 148 records after removing duplicates. Screening of abstracts yielded 24 articles for full-text assessment, with 16 studies meeting our eligibility criteria. Across trials, the most frequently used neurocognitive battery was the MCCB, and the most frequently measured cognitive domain was working memory assessed by the n-back task. Preliminary qualitative results show that application of tDSC over the DLPFC of patients with schizophrenia improves working memory performance compared to sham stimulation with 9 studies reporting statistically significant differences. Further quantitative analyses will elucidate the significance of such results as well as the finer details of the effects of stimulation duration, intensity and trial design.

Discussion: Transcranial direct current stimulation could be a viable tool both in clinical and commercial settings as a single or adjunctive therapeutic method in the amelioration of the detrimental cognitive deficits experienced by patients with schizophrenia. Systematic literature reviews and meta-analysis of currently published studies should elucidate the next steps in establishing protocols of application.

V162. INTERACTION BETWEEN CORTISOL LEVELS, NERVE GROWTH FACTOR CONCENTRATION AND COGNITIVE FUNCTIONS IN PATIENTS WITH FIRST EPISODE SCHIZOPHRENIA – PRELIMINARY FINDINGS

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Background: One of the basic features of schizophrenia is considered to be cognitive impairment. Numerous studies have shown that patients with schizophrenia achieve significantly lower results than control groups in most neurocognition tests in all cognitive domains. Cognitive deficits as well as the onset and course of the disease are considered to be greatly affected by the susceptibility to stress. The system involved in physiological stress response is an HPA axis, which is known to be altered in patients with schizophrenia. Furthermore, recent research suggests HPA axis hyperreactivity in schizophrenia patients with higher basal cortisol levels compared to the healthy controls. Abnormal afternoon cortisol levels were connected to impaired memory functions. Brain derived neurotrophic factor (BDNF) plays an important role in brain neuroplasticity and has been connected to cognition in schizophrenia. Exposure to stress and increased glucocorticoid levels have shown to reduce BDNF expression. The association between cortisol and BDNF still remains unclear. The aim of this study is to investigate the influence of cortisol levels and BDNF concentration on cognitive functions in patients with first episode schizophrenia (FES).

Methods: This cross-sectional ongoing study involves 34 drug naive FES patients and 32 healthy control participants. The study was approved by the Ethical Comitee of University Hospital Sestre milosrdnice and all participants gave their informed consent to participate in the study. Cognitive functions (declarative memory, attention, working memory, processing speed and executive functions) were measured by 5 KOG screening instrument for cognition assessment in psychiatric disorders, while salivary cortisol levels were measured from multiple samples. BDNF concentrations were determined by ELISA.

Results: This ongoing study with data still being processed shows that a group of patients with FES compared to the healthy controls scored lower results according to cognitive domains measured by 5 KOG test. The preliminary results also show association to higher diurnal cortisol levels and decreased concentrations of BDNF when compared to the control group. Until now we found an association between cortisol levels and deficits in memory and executive functions, but there is no statistically significant association between BDNF concentration and deficits in measured cognitive domains.

Discussion: The present results suggest the influence of abnormal cortisol levels and BDNF concentration on specific cognitive deficits in patients with first episode schizophrenia. To the best of our knowledge this is the first study which combines the above parameters and examines their relationship with cognitive functions in FES patients. In accordance to the previous research, there may be an association between cortisol levels and BDNF concentration with cognitive functions, although in chronic schizophrenia. Abnormal cortisol levels and BDNF concentration may be involved in changes of specific cognitive domains what could have an impact on early diagnosis and therapeutic interventions of cognitive disfunction.

V163. PREVALENCE OF LONG-ACTING INJECTABLE (LAI) ANTIPSYCHOTIC USE IN CANADIAN EARLY INTERVENTION SERVICES FOR PSYCHOSIS

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Background: The prescribing of LAIs for psychotic disorders in Canada has been historically low (~6%) compared with regions in Europe, Australia, and China. LAI medications are particularly efficacious when used early in the course of treatment for psychosis as the timing of the medication allows for prolonged periods of remission to facilitate recovery. Consequently, treatment recommendations were developed in 2013 by members of the Canadian Consortium for Early Intervention in Psychosis (CCEIP) - a national body of early intervention services clinicians - advising clinicians to offer LAIs as a treatment choice to patients in all phases of illness. To assess the role of LAIs in early intervention programs (EIP) for psychosis and the potential impact of these guidelines, surveys were completed in 2016 and 2020 at a total of 22 Canadian EIS for psychosis sites.

Methods: Data were collected from two national surveys of early intervention services (EIS) for early phase psychosis (EPP). A cohort of EPP programs were collected in 2016 (N=18; (11 hospital based, 7 community-based) and another in 2020 (n=12; 10 hospital based, 2 community-based). This included a group of programs (N=8) that responded to both surveys where direct comparisons were made between the two epochs. LAI use was measured for overall frequency, for frequency of use in different years of program enrollment, as well as the impact of sociodemographic factors such as ethnicity, age and gender and clinical delivery variables such as injection models and community treatment orders on rates of use.

Results: Cross-sectional analysis identified a significant increase ($p<0.05$) in overall LAI usage between time-points. In 2016, the overall reported percentage of patients across eighteen EIS sites (n=2,373 patients) on an LAI was 25.5%; 67% of which were men. In 2020, the overall reported percentage of patients across twelve EIS sites (n=2,284 patients) on an LAI was 35.1%; 69.8% of which were men. Across all sites, the most prescribed LAI medications were long-acting paliperidone palmitate (49% of all patients using an LAI in 2016; 47.4% in 2020), and long-acting aripiprazole (41.2% of patients using an LAI in 2016; 49.7% in 2020). Longitudinal analysis of eight EIS sites (n=2,2453 patients) also identified a significant increase ($p=0.007$) in the overall number of patients on LAIs, increasing from 28.9% in 2016 to 34.1% in 2020. In particular, LAI usage for patients in the second program year saw the greatest increase between time-points, significantly increasing ($p=0.0114$) from 25.6% in 2016 to 36.1% in 2020. LAI usage in program year one (37.2% in 2016; 33.6% in 2020) and program year three (29.4% in 2016; 27.6% in 2020) remained stable between time-points. Encouragingly, longitudinal data also revealed a significant increase ($p=0.026$) in LAI usage among patients under extended leave/ community treatment orders (CTO) across the study period; increase from 16.2% (56/345 patients across eight sites) in 2016, to 25.2% (108/429 patients) in 2020. Generally, LAI accessibility within EIS programs was rated positive for both survey years; however commonly identified barriers to LAI use included cost of medication (e.g., insurance coverage), patient's lack of desire for treatment with LAIs, and issues with LAI delivery (e.g., inconvenience of traveling to the clinic).

Discussion: These results support an increase in LAI use, accessibility, awareness, and increased level of prescribing comfort among Canadian clinicians in regards to LAI antipsychotic use for early stages of psychotic disorders. LAI use in EIS for psychosis in

Canada have increased from 2016 to 2020 and the prevalence of LAI use is now in line with other regions of the world.

V164. NATURAL LANGUAGE PROCESSING ANALYSIS ON SELF-DIALOGUE TO COMPUTE THOUGHT DISORDER OF CLINICAL HIGH RISK AND SCHIZOPHRENIA SUBJECTS

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Background: Thought Disorder (TD) in Schizophrenia (SCZ) is mainly a disorder of language and communication in which the speaker violates the syntactical and semantic conventions governing the language usage. These disturbances comprise of Positive TDs such as loss of semantic coherence, derailment, looseness of association, tangentially, and Negative TDs such as reduced syntactic complexity, shorter sentences, fewer dependent clauses, and poverty of content. One way to measure these thought disorders in a conversation is to model the responses of the subject as a Self-Dialogue and look at how coherent one sentence is with the following sentence. Manual analysis to measure coherence in such long open-ended interviews is time-consuming and requires a lot of training. Therefore, in this study, we propose a method to measure Thought Disorder by calculating the Mutual Information of the Kernalized Hashcodes of consecutive sentences in subject responses of an Open-Ended Interview.

Methods: Transcripts of speech samples were obtained from a total of 363 subjects from New York, Melbourne and Toronto. Out of 363 subjects, 126 were Healthy Controls, 172 were patients at Clinical High Risk (CHR) and 65 were patients with SCZ. Structured Interview for Prodromal Syndromes (SIPS) was used to determine the CHR status and the Structured Clinical Interview for the DSM-IV-TR (SCID) was used to diagnose the patients with SCZ. The responses of the Open-Ended Interviews were separated for every subject and modeled as a Self-Dialogue. We obtained Kernalized Hashcodes (Garg et al, 2019) which are binary vectors, and essentially capture all the relevant information from a given sentence by using the iterative clustering algorithm in the background. We calculate the Mutual Information between the consecutive hashcodes of the sentences for all the subjects. Mutual Information is used to measure the dependence of one variable onto the other and in this context, it is used to measure the similarity of thoughts and coherence in the subject's responses.

Results: On an average Healthy Controls had the maximum Mutual Information (Mean = 3.5) followed by CHRs (Mean = 2.9) and the lowest was observed for patients with SCZ (Mean = 2.3). Significant differences were found between the Healthy Controls and CHRs ($s = 0.21$, $p < 0.001$) and Healthy Controls and SCZ ($s = 0.34$, $p < 0.001$).

Discussion: These findings suggest that modeling the responses of the subject as a Self-Dialogue and measuring Mutual Information between the Kernalized hashcodes of consecutive sentences can give us a concrete measure of Thought Disorder.

V165. ACTIVE AND PASSIVE SMARTPHONE ASSESSMENT OF GREENSPACE EXPOSURE AND DAILY SOCIAL INTERACTIONS IN PEOPLE WITH SCHIZOPHRENIA

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Background: Although exposure to the level of vegetation in a given area (i.e., "greenspace") is associated with positive outcomes, the mechanisms linking greenspace and mental health remain unclear. One mechanism could be the degree to which areas of greenspace support and enhance social interactions and relationships. Identifying such mechanisms in people with schizophrenia (SZ) are of particular interest, given characteristic challenges with social skills and limited access to greenspace (e.g., higher likelihood of living in urban areas).
Methods: In the current study, we examined associations between greenspace exposure and social behavior in daily life among 31 people with SZ over a 60-day period. Participants reflected on their social interactions, including number of interactions and affect associated with these interactions, twice daily using smartphone-based Ecological Momentary Assessment (EMA); continuous geo-location was collected passively from the phone's GPS.
Results: Greenspace exposure on a given day was unrelated to EMA-reported number of interactions (b = -0.95, 95% CI: -4.42, 2.51) or motivation to interact on that day (b = 3.82, 95% CI: -5.28, 12.91). More greenspace exposure on a given day was associated with significantly greater EMA-reported calmness (b = 2.94, 95% CI: 0.88, 5.0) and lower anger (b = -2.45, 95% CI: -4.30, -0.58) about recent interactions. Greenspace exposure was not significantly associated with EMA-reported happiness (b = -0.01, 95% CI: -3.79, 3.75), excitement (b = -1.91, 95% CI: -4.06, 0.24), or anxiety (b = -3.32, 95% CI: -7.51, 0.87) about recent interactions.
Discussion: Findings suggest that greenspace exposure may set the stage for interactions associated with more pleasant affect. Future work can help elucidate the mechanisms through which greenspace exposure contributes to beneficial social interactions in people with SZ.

V166. RECOMMENDATIONS TO IMPROVE QUALITY OF DATA COLLECTION IN E-RESEARCH: LESSONS LEARNT IN EARLY PSYCHOSIS RESEARCH

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Background: Universally, the COVID-19 pandemic outbreak has compelled a rapid shift to virtual practices. In many cases, researchers have had to adapt from conventional in-person practices to cyberscience-based methodologies, including online study recruitment and data collection. Some benefits of internet-based methods include lower costs compared to in-lab recruitment, timely data collection, and facilitated access to hard-to-reach populations. However, some drawbacks have been noted, including the potential for inaccurate responses, duplicate survey completion, and the use of automatic survey-takers or bots, which can significantly reduce the quality of data. Arguably, concerns around privacy and confidentiality may be especially salient in research with service users with psychosis.
Methods: We aim to orient and familiarize academic researchers conducting online research with special populations like early psychosis service users about best practices to improve data quality in internet-based research. A rapid review by a general internet search of the literature was conducted on strategies to mitigate problems with data collection in online research during summer 2021. These strategies were then implemented in an ongoing e-study targeting patients, families, and clinicians with experience in early psychosis services across Canada.
Results: A 12-step data quality checklist was adapted and implemented from existing literature. The strategies include not sharing the full survey link publicly, collecting and checking paradata, attention check questions, etc. The items are categorized from most to least effective in terms of implementability and potential for securing quality data. Drawing from

our experiences, we discuss the implications and integrity of conducting online research in the context of early psychosis, including a need for monitoring speed of survey completion, screening email addresses and open-ended responses, informed consent through phone call, etc.
Discussion: Given their unique strengths, the challenges of internet-based research and data collection should not deter researchers from utilizing such measures. The onus for conducting ethical and high-quality research is on researchers. Furthermore, our study provides concrete practices and insights for advancing research using e-methods, particularly in early psychosis.

V167. THE ASSOCIATION BETWEEN COGNITIVE BIASES AND SCHIZOTYPAL PERSONALITY TRAITS

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Background: Schizotypy represents a subclinical manifestation of the schizophrenia-spectrum. Cognitive models of schizophrenia highlight the role of cognitive biases in the onset and maintenance of symptoms. Schizotypy provides an opportunity to examine factors associated with the schizophrenia-spectrum without the confounds of other illness-related factors. To date, there is some evidence to suggest that cognitive biases are present in schizotypy, but it is still unclear which biases are specific to schizotypy and not a function of comorbid depression or anxiety, and whether sex and culture moderate this association. The current study examined relationships between cognitive biases and schizotypy to determine which biases are most specifically associated with schizotypy. The current study also examined sex and cultural differences in the association between cognitive biases and schizotypal personality traits.
Methods: 462 participants completed measures of depression, anxiety, cognitive biases, cognitive schemas, and schizotypy. Independent samples t-tests were conducted to examine differences between individuals who scored high and low on the Schizotypal Personality Questionnaire (SPQ). A Bonferroni correction was applied to control for multiple comparisons and was set at $p = .003$. Hierarchical regression analyses were conducted to examine the associations between cognitive biases and schizotypy after controlling for depression and anxiety. Moderated regression analyses were conducted to investigate the moderating role of biological sex and culture in the association between cognitive biases and schizotypy.
Results: 317 participants were categorized as "low SPQ" and 76 participants were categorized as "high SPQ" based on their scores on the SPQ. Self-referential processing ($t(391) = -11.28$, $p < .001$), the belief inflexibility bias ($t(391) = -4.36$, $p < .001$), the attention for threat bias ($t(391) = -6.32$, $p < .001$), and the external attribution bias ($t(391) = -5.77$, $p < .001$) were associated with schizotypy categorically. Self-referential processing ($\beta = .340$, $t(378) = 7.49$, $p < .001$), the belief inflexibility bias ($\beta = -.113$, $t(378) = -2.47$, $p = .014$), and the attention for threat bias ($\beta = .102$, $t(378) = 2.24$, $p = .026$) were also associated with schizotypy continuously. The jumping to conclusions bias was not associated with schizotypy categorically ($t(391) = -2.02$, $p = .044$), nor continuously ($\beta = -.061$, $t(378) = -1.49$, $p = .136$). The belief inflexibility bias and social cognitive problems were associated with schizotypy and not associated with depression or anxiety. These associations were not moderated by biological sex or culture.
Discussion: Cognitive biases are likely to be an important factor to consider in the etiology and maintenance of schizotypy. In other words, it is possible that cognitive biases may be one factor that increases the likelihood of transitioning to psychosis. The belief inflexibility bias in particular may be an important risk factor for the schizophrenia-spectrum and further research

will be important to determine whether this bias is also associated with the likelihood of transitioning to psychosis. Treatments that directly target such cognitive biases, such as cognitive behavioural therapy and metacognitive training may be helpful for individuals with schizotypy.

V168. REVISING THE DSM-5 ALTERNATIVE MODEL FOR PERSONALITY DISORDERS DIAGNOSTIC CRITERIA FOR SCHIZOTYPAL PERSONALITY DISORDER

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Background: Schizotypal personality disorder (SPD) is one of the most researched and diagnosed personality disorders (PDs) in Section II (i.e., the main text) of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). In Section III of the DSM-5 – the Alternative Model for Personality Disorders (AMPD) outlines a modified approach and set of diagnostic criteria to diagnose PDs, including SPD. These modifications were meant to address the problems with the Section II PD diagnostic system. The Section III approach, although offering improvements, still perpetuates many of the same weaknesses that plagued Section II. Based on empirical research not available at the time of the development of the AMPD, we offer a set of modifications for the diagnosis for SPD that addresses the shortcomings of both Section II and Section III that, in turn, increases the "diagnostic signal" for this important disorder.
Methods: We used data from a recent meta-analysis (N = 7,017 – 9,895) that provided the average weighted correlation between the pathological personality traits that form the AMPD and the diagnostic criteria for each PD (see Watters, Bagby, and Sellbom, 2019). We then identified traits that were mostly unique (vis a vis the other PDs) and had at least a medium effect association with the diagnostic criteria for SPD; traits with a large effect size (≥.50) were marked as particularly important with respect to diagnostic relevance.
Results: Based on our empirically grounded method designed to maximize SPD diagnostic homogeneity and minimize co-morbidity, we propose the presence at least five traits for a diagnosis for SPD (cognitive/perceptual dysregulation, unusual beliefs/experiences, suspiciousness, withdrawal, and eccentricity) and that two of these traits (cognitive/perceptual dysregulation and that one of these traits (unusual beliefs/experiences) which had a large effect size must be present to confer a diagnosis of SPD.
Discussion: In Section II of the DSM-5 the diagnostic criteria for SPD produce a bewildering array of 126 different combinations that meet this diagnostic criterion for this disorder, minimizing its unique diagnostic signal. In the Section III AMPD, the diagnostic criteria reduced the different distinct combinations of traits to 15, a rate still much too large to produce a strong and unique diagnostic signal. Using the published empirical data on SPD, the diagnostic model proposed here reduces the possible combination to four combinations, substantially reducing the within-SPD heterogeneity and improving its diagnostic signal.

V169. HALLUCINATION-PRONENESS IS ASSOCIATED WITH FAILURE TO DOWN-WEIGHT EXTREME EVIDENCE IN A PERCEPTUAL AVERAGING TASK

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Background: Hallucinations are characterized by disturbances of perceptual processes involved in decision-making about environmental stimuli. A rich literature has elucidated the processes involved in healthy human perceptual decision-making, yet little of this work has been applied to improving our understanding of the mechanisms of hallucinations. Some basic work has employed "perceptual averaging" paradigms, finding that observers tend to demonstrate particular patterns in weighting as they extract "statistical summary" information from perceptual evidence. Some theories of psychosis posit specific aberrations in "statistical reasoning", thus making such paradigms a useful experimental tool for probing psychotic mechanisms.

Methods: In the present study, we examine the relationship of dimensions of hallucination- and delusion-proneness and performance on a multielement perceptual averaging task in a non-clinical sample. Observers made dichotomous judgments about the "average color" of an array of stimuli that varied in how clearly they fell into one of two color categories (red or blue). We used logistic regression to quantify the relative weight observers gave to array elements as a function of how extreme (far from the array mean and decision boundary) the element is. We further employed computational models to shed light on precise algorithmic alterations associated with hallucination-proneness.

Results: We found that individuals more prone to hallucinations (but not delusions) exhibited a pattern of giving increased weight to perceptual evidence that was more extreme and less weight to evidence that was less extreme. This strategy was in contrast to the so-called "robust averaging" method employed by observers in the task generally (and by those low in hallucination-proneness) whereby the evidence value of extreme information is suppressed (group*strategy interaction: $F(1,124)=6.70$, $p=.011$). The effect remained when controlling for delusion-proneness, which contrastingly did not predict weighting strategy ($p>.16$). High- and low-hallucination-prone groups could further be distinguished by computational models characterizing different algorithmic strategies on the task ($d=.40$, $p=.038$). Lastly, hallucination-proneness was associated with a diminished responsivity to evidence variability, such that control observers increased robust averaging with increased variance ($F(2,89)=5.72$, $p=.005$), but high hallucination-prone observers did not ($F(2,33)<1$).

Discussion: We found that hallucination-proneness is associated with a failure to engage in adaptive downweighting of potentially unreliable (extreme) evidence during perceptual averaging, as well an insensitivity to evidence variance. Computational model-fitting suggested that high hallucination-prone individuals more likely employ a simple averaging algorithm, relying solely on evidence strength, while other observers integrate more evidence characteristics and compute a "robust" probability ratio between competing choice options. These findings provide support for frameworks such as the aberrant salience theory of psychosis and generate important future directions for understanding the perceptual mechanisms underlying hallucinations.

V170. EQUITY IN MENTAL HEALTH SERVICES FOR YOUTH AT CLINICAL HIGH RISK FOR PSYCHOSIS: CONSIDERING MARGINALIZED IDENTITIES AND STRESSORS

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Background: Prevention and early intervention programs have been initiated worldwide to serve youth at Clinical High Risk for Psychosis (CHR-P), who are adolescents and young adults experiencing subclinical psychosis and functional impairment. The primary goals of these efforts are to prevent or mitigate the onset of clinical psychosis, while also treating comorbid issues. It is important to consider issues of diversity, equity, and inclusion in CHR-P work, especially as these programs continue to proliferate around the world. Further, there is a long history in psychiatry of misdiagnosing and mistreating psychosis in individuals from racial and ethnic minority groups. Although there have been significant developments in early intervention psychosis work, there is evidence that marginalized groups (broadly defined) are underserved by current CHR-P screening and intervention efforts. These issues are compounded by the contexts of continued social marginalization and significant mental health disparities in general child/adolescent services.

Methods: Within this narrative review and call to action, we use an intersectional and minority stress lens to review and discuss current issues related to equity in CHR-P services, offer evidence-based recommendations, and propose next steps. Our search terms included CHR-P and related terms, terms related to various social identities (e.g., Crenshaw, 1990; Hays, 1996), and terms including and related to diversity, equity, and inclusion. Snowballing techniques were used by searching the reference lists of relevant articles. All searches were conducted in February and March 2021. In particular, our intersectional and minority stress lenses incorporate perspectives for a range of marginalized and underserved identities related to race, ethnicity, and culture; faith; immigration status; geography/residence; gender identity; sexual orientation; socioeconomic status/class; and ability status.

Results: Individuals at CHR-P who possess minoritized identities face tremendous, potentially cumulative, stigma-related stressors and traumas, which confer risk for psychopathology. In addition to heightened stress sensitivity among youth at CHR-P in general, minoritized youth at CHR-P may contend with multiple stigmatized identities (e.g., related to race, ethnicity, and culture; faith; immigration status; geography/residence; gender identity; sexual orientation; socioeconomic status/class; and ability status). Minoritized youth at CHR-P and their families also often face significant barriers to accessing care and receiving culturally responsive assessment and treatment.

Discussion: We offer wide-ranging recommendations covering clinical care, research, training, outreach, and policy/systemic factors. Our recommendations are based on the narrative review conducted and include evidence-based suggestions based on empirical research and future directions guided by identified gaps in CHR-P work. We separated some of these recommendations by identity status to draw attention to specific concerns within categories, while also providing overarching recommendations to improve equity that apply across identity status. Though not an exhaustive list, we believe that these recommendations can increase awareness of equity issues in CHR-P work and, most importantly, contribute to the development of a more equitable early-stage psychosis system of care. To our knowledge, this was one of the first attempts to comprehensively discuss considerations for historically marginalized and oppressed groups to help promote equity in CHR-P research and services. Although we discussed issues relevant for many aspects of identity, additional research is needed to have a more nuanced understanding how to improve services for youth in which these identities intersect to create unique challenges (e.g., LGBTQ+, racial/ethnic minority youth).

V171. IMPAIRED GRID-LIKE REPRESENTATIONS AT THETA FREQUENCY IN SCHIZOPHRENIA

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Background: Schizophrenia is a chronic brain disorder characterised by distortion of thoughts and perception. Several studies have shown a key role of the hippocampal formation in the pathophysiology of schizophrenia. Patients show impaired theta coherence between medial temporal lobe (MTL) and medial prefrontal cortex (mPFC), and impairment of knowledge structuring and inferential processes. Both the hippocampal formation and mPFC contain hexadirectional modulation of activity, indicative of grid cell populations. Grid cells play an important role in mapping the environment and are believed to represent the vector relationships or transition structure between task states. With other cell populations in the hippocampal formation, they play a fundamental role in inference, episodic memory, and spatial navigation. According to this framework, grid cells use relational knowledge to support generalisation and inference. Here, we investigate whether schizophrenia is associated with disrupted grid firing patterns.

Methods: To test this hypothesis, we asked 18 participants with diagnoses of schizophrenia and 26 controls (matched for age, sex and IQ) to perform a spatial memory task in magnetoencephalography (MEG), while navigating a virtual reality environment. We first analysed theta (4-10 Hz) power during movement onset compared to stationary periods. We then looked for the hexadirectional modulation of theta band oscillatory activity by heading direction during movement onset, and source-localised the signal. We also controlled for other symmetries in theta frequencies (four, five, and eight fold) and hexadirectional modulation in other frequencies. The same participants performed an inference task outside MEG, which we used for correlation analysis.

Results: The peak of theta power during movement onset was stronger in controls compared to patients ($p < 0.05$). In the control group, we found hexadirectional modulation of theta power by movement direction in the right entorhinal cortex ($p<0.005$). This effect was absent in patients with a significant difference between groups ($p<0.05$), suggesting that their entorhinal grid firing patterns may be disrupted. No other symmetry modulated theta power significantly in controls or patients, and hexadirectional modulation during movement onset was found only in theta frequencies in controls. Performance in the inference task was significantly impaired in schizophrenic patients, and spatial memory performance in both controls and patients was positively correlated with their performance in the inference task.

Discussion: These results are consistent with the hypothesis that impairments in knowledge structuring and inference associated with schizophrenia may arise from disrupted grid firing patterns in entorhinal cortex. Although further work is needed to better understand the role of grid cells in health and disease, this work provides new insights into dysfunction of the hippocampal formation in schizophrenia.

V172. THE RELATIONSHIP BETWEEN SCHIZOTYPY, THEORY OF MIND, CYBER VICTIMIZATION AND CYBERBULLYING BEHAVIORS IN ADOLESCENTS AND YOUNG ADULTS

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Background: Prior literature has established the relationship between schizotypy and theory of mind (ToM) deficits. However, how is schizotypy related to cyberbullying behaviors and cyber victimization which are closely related to ToM ability are yet to be investigated. The present study aims to evaluate: (1) whether ToM deficits are related to schizotypy; and (2) whether schizotypy is related to cyberbullying behaviors and cyber victimization in adolescents and young adults.
Methods: 100 adolescents and young adults with the mean age of 20.5 years (30 males and 70 females) were examined. Emotional and disruptive behavior problems including schizotypy, cyberbullying experiences and cyber victimization of all participants were assessed by the same set of psychological measures. A computer task was also administered to assess participants' theory of mind (The Reading the Mind in the Eyes Test (RMET)).
Results: Correlational and t-test analyses were performed. With the entire sample (n= 100), schizotypy was significantly and positively related to cyberbullying behaviors ($r= 0.24$, $p< 0.05$). Such relationship was mediated by cyber victimization. Furthermore, in the high schizotypy group (n=50), reaction time responding to emotional stimuli in RMET was slower than the control group (n= 50).
Discussion: Findings suggest that theory of mind deficits, cyber victimization and cyberbullying problems are found in schizotypy. Since schizotypy poses a high risk for the development of schizophrenia, these findings provide insight for the implementation of prevention and intervention of psychosocial behaviors at different stages of schizophrenia which might potentially reduce schizophrenia symptomatology in the community.

V173. SLEEP QUALITY MODERATES THE RELATIONSHIP BETWEEN SCHIZOTYPY AND PERSPECTIVE-TAKING

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Background: Social cognition is impaired in people diagnosed with schizophrenia and other psychotic disorders. Social cognitive difficulties are not isolated to individuals with long-term schizophrenia, though, and have been reported in first-episode, ultra-high risk, and prodromal psychosis. Additionally, subclinical paranoia and schizotypy, a personality factor that may, at high levels, confer risk for the development of psychotic disorders, have been shown to be related to worse social cognitive performance. While schizotypy and paranoia are associated with social cognition, less work has examined the associations between sleep quality, schizotypy and paranoia, and social cognition. Sleep quality has been examined in relation to both schizotypy and paranoia as well as social cognition, but the influence of sleep quality on the relationships between these variables has yet to be examined. Indeed, high sleep quality may serve as a protective factor that reduces the negative relationship between schizotypy or paranoia and social cognition. This study aimed to explore this possibility in a nonclinical sample. We hypothesized that, consistent with past research, elevated paranoia and schizotypy would be related to worse social cognition. Further, we hypothesized that sleep quality would moderate this relationship, such that the relationship between schizotypy/paranoia and social cognition would be weaker or absent for those with better sleep quality.
Methods: This study recruited undergraduates through SONA Systems at the University of Southern Mississippi (n = 458) and additional nonclinical participants through Amazon's Mechanical Turk (n = 211). Participants completed measures of schizotypy, paranoia, sleep quality, and two measures of social cognition: the Reading the Mind in the Eyes Test (RMET),

a measure of theory of mind, and the Interpersonal Reactivity Index (IRI), a measure of self-reported empathy.
Results: Preliminary results suggest that higher scores in schizotypy and paranoia are related to worse scores on the RMET ($r = -.27$, $p < .001$ and $r = -.25$, $p < .001$, respectively), and the Empathic Concern ($r = -.11$, $p < .001$ and $r = -.15$, $p < .001$, respectively) and Perspective-Taking ($r = -.16$, $p < .001$ and $r = -.14$, $p < .001$, respectively) subscales of the IRI. These relationships are such that individuals with worse schizotypy or paranoia have worse social cognition scores. Sleep quality, measured continuously, did not moderate the relationships between schizotypy or paranoia and the RMET or the Empathic Concern subscale of the IRI. Sleep quality did significantly moderate the relationship between schizotypy and the Perspective-Taking subscale of the IRI ($R2 = .05$, $F(3, 603) = 10.97$, $p = .007$). Contrary to our hypothesis, individuals with better sleep quality, elevated schizotypy is related to worse perspective taking, but for individuals with poorer sleep quality this relationship is nonsignificant ($t = -.39$, $p = .70$).
Discussion: Our findings indicate that for individuals with poor sleep quality, schizotypy is not significantly associated with social cognition. This suggests that other factors that were not measured in this study, such as global cognition or state affect, may be influencing social cognition more strongly than schizotypy when individuals are getting poor sleep. Additional research should assess other factors (e.g., global cognition, state affect) that may influence social cognitive abilities in individuals with low quality sleep. Further research should be conducted that includes both clinical and nonclinical samples to assess if this relationship differs in individuals with psychotic disorder diagnoses, and to test the presence of this relationship for other social cognitive domains and tasks.

V174. PREVALENCE OF SLEEP DISORDERS IN VETERANS WITH SEVERE MENTAL ILLNESS: EXAMINATION IN VA VISN 4 HEALTH RECORD DATA FROM 2011-2019

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Background: People with severe mental illnesses (SMI) experience high rates of sleep disturbance, which is linked to worse symptomatology and quality of life as well as increased risk for suicide attempt. Indeed, SMI symptomatology and sleep disturbance are hypothesized to bidirectionally aggravate symptom presentation and negatively impact psychiatric and sleep treatment outcomes for this group. Clinical research indicates higher prevalence estimates than medical record-based studies, suggesting that sleep disorders in SMI may be underrecognized and undertreated in clinical practice. As the largest integrated healthcare system in the U.S., the Veterans Administration (VA) medical centers maintain electronic medical record data that provides a unique opportunity to better understand sleep disorder diagnoses in Veterans with SMI. In light of increased attention paid to diagnosis and treatment of sleep disorders in VA over the past decade (e.g., VA-wide rollout of cognitive behavioral therapy for insomnia, increased used of home sleep apnea testing), this represents an important and timely area of investigation.

Methods: Given the impact of sleep disturbance for Veterans with SMI and the lack of updated sleep diagnosis prevalence rates for this group, this study estimated the 12-month prevalence of diagnosed sleep disorders among Veterans with and without SMI in VA VISN 4 health record data in 2019. We further examined lifetime prevalence of sleep diagnoses in all Veterans and examined changes in prevalence of sleep disorders over 9 years (2011-2019; N=573,974). Relevant demographic characteristics and comorbidities were also examined.
Results: In 2019, 21.8% of Veterans with SMI were diagnosed with at least one sleep disorder, up from 10.9% in 2011—and exceeding prevalence in Veterans without SMI (15.1%) in 2019 (x^2 [2, N=259,675] = 341.6, $p < .001$). Breathing-related sleep disorders were most common in Veterans with SMI (14.4%), followed by insomnia (10.9%); a similar pattern emerged in Veterans without SMI. When comparing diagnostic groups within Veterans with SMI, Veterans with major depressive disorder with psychosis were diagnosed with sleep disorders at the highest rate (34.5%), followed by Veterans with bipolar disorders (25.2%); the lowest rate was found in Veterans with schizophrenia-spectrum disorders (16.2%); x^2 [2, N=10,956] = 173.5, $p < .001$). Across the nine-year study period, 14.5% of Veterans met criteria for a sleep disorder.
Discussion: Overall, findings suggest that sleep disorder diagnoses in Veterans with SMI have doubled over the past decade, possibly reflecting enhanced detection in this group, likely related to VA-wide rollouts of enhanced diagnostic and treatment procedures for sleep disorders. Still, prevalence estimates from clinical research (indicating 50% or more of people with SMI may meet criteria for a sleep disorder) are notably higher than those identified here, underscoring the need to further optimize efforts to detect sleep disorders in people with SMI. More work is needed to understand how prevalence of sleep disorders differs between Veterans with schizophrenia-spectrum disorders, bipolar disorders, and major depressive disorder with psychosis – and whether concerns brought up in treatment are perceived similarly by providers across groups or whether other factors might influence how sleep concerns are diagnosed and treated.

V175. SOCIAL ANXIETY IN SCHIZOPHRENIA: EFFECT OF A COGNITIVE BIAS MODIFICATION TRAINING

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Background: Schizophrenia is associated with multiple comorbid disorders, namely anxiety disorders, and more specifically social anxiety. Several studies have demonstrated that not only does social anxiety worsen the prognosis of schizophrenia, but it also impedes with the overall social recovery of the person. Recent studies and models suggest that cognitive biases, especially attentional and interpretive biases, may be causally related to social anxiety and can be modified using Cognitive Bias Modification Training (CBMT). This type of treatment has demonstrated a moderate to strong effect size in reducing social anxiety in individuals with social anxiety disorder. However, it remains to be determined if CBMT could be useful in reducing social anxiety in individuals with comorbid social anxiety and schizophrenia. The objectives of this presentation are to present the CBMT we have developed, using online avatars, and to present preliminary results of the pilot study that is being carried out.
Methods: Although the study is still underway, a total of 38 participants have been recruited to date. The study has two groups of participants: 1) people with schizophrenia and comorbid

social anxiety, and 2) subjects with social anxiety only. Inclusion criteria are: aged 14 to 30 (from 18 for group 1), to have a stabilized psychotic disorder (for group 1), and presenting a diagnosis of social anxiety (for both groups). Participants are evaluated before and after the treatment, using measures of social anxiety (LSAS, SAQ. SPIN), overall anxiety (GAD-7), depression (BDI-II), quality of life (WHOQOL-Bref), and cognitive biases (CBQ). The Cognitive Bias Modification Training (CBMT) we developed consists of 24 sessions (3 times par week), of 20 minutes on average. During the sessions, participants receive an assisted computerized training (participation in the study is completely online) whereby dynamic faces of avatars are presented and the participant needs to recognize the emotion portrayed. A filter adding 'noise' increases the level of difficulty and forces the participant to focus on certain parts of the face, as the participant becomes better at recognizing the emotions. This training can help participants recognize neutral and positive emotions more effectively, and react in a more balanced way to negative emotions (modification of cognitive bias).

Results: The preliminary results suggest the training is feasible and acceptable for the participants. Following treatment, a significant reduction in social anxiety was observed in both groups. However, some other variables evaluated were not significant, but this may be due to the small number of participants recruited to date. We anticipate having a larger sample to present by the conference. The results will be presented in more details and compared with the literature.

Discussion: These preliminary results show that the Cognitive Bias Modification Training (CBMT) is an intervention that seems promising for the treatment of social anxiety. However, further research is needed to confirm these results and to study the effect and relevance of the CBMT in people with schizophrenia and social anxiety. It is important to note that an advantage of this training is that it can be followed completely online from home, which can be an interesting option for people who are too socially anxious to attend treatment, who have transportation issues, or do not have access to other treatment options.

V176. FIVE-YEAR STABILITY AND PREDICTIVE UTILITY OF MISMATCH NEGATIVITY IN PSYCHOTIC DISORDERS

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Background: Reduction in mismatch negativity (MMN) amplitude is one of the most robust findings amongst psychophysiological measures in schizophrenia and other psychotic disorders. It has been associated with deficits in functioning, cognitive deficits, and reality-distortion symptoms. Because of the robust and replicable nature of these effects, several studies have named MMN as a potential "break-through biomarker" in schizophrenia. However, the predictive utility of this component in such samples is not yet clear, as few studies exist in which the relationships between MMN and such symptoms have been evaluated over long periods of follow-up, particularly in chronic illness.

Methods: In the present study, we examined the stability of MMN amplitude over five years in individuals with psychotic disorders (cases; N=132) and never-psychotic subjects (NP; N=170), as well as longitudinal associations with outcome variables, including clinical symptoms, level of impairment in functioning, and cognitive deficits (as measured by IQ). First, bivariate Pearson correlations were used to examine stability in MMN amplitude between timepoints one (T1) and two (T2). Next, hierarchical regression models were employed in order to examine the extent to which T1 MMN predicted T2 outcomes over and above subjects' scores on these measures at T1.

Results: MMN exhibited good temporal stability in the overall sample, with significant correlations between amplitude at T1 and at T2 (r=.538). This was also the case when examined in cases alone (r=.534) and NP subjects (r=.515). In the full sample, hierarchical regression models revealed T1 MMN to be a significant predictor of auditory hallucinations (p=.019) and functional impairment (p=.01) at T2, over and above scores on these measures at T1 and controlling for group (cases vs NP). These effects also remained significant in cases alone: MMN at T1 was significant in predicting auditory hallucinations (p=.023) and functional impairment (p=.04) at T2 over and above subjects' scores on these measures at T1. In no model was MMN at T1 a significant predictor of IQ at T2 over and above IQ at T1 (full sample: p=.44; cases only: p=.31).
Discussion: Thus far, few studies have reported on longitudinal associations between MMN amplitude and symptoms in chronic psychotic disorders samples. We found that MMN amplitude is a stable electrophysiological marker over up to five years, indicating that it measures a stable neural deficit with reasonable reliability and is a promising biomarker. Furthermore, we found that MMN amplitude is a significant predictor of level of impairment as well as auditory hallucinations up to five years after its recording, over and above subjects' T1 scores on these measures. Conversely, MMN did not predict subsequent IQ over and above current IQ, implying less utility of MMN with regard to prediction of future cognitive decline. This pattern may help to inform models of illness course, suggesting that patients with more severe reduction of MMN amplitude are more likely to experience a subsequent reduction in functioning and increase in psychotic symptoms, and may benefit from additional monitoring and services.

V177. UNDERESTIMATION OF SOCIAL FUNCTIONING IS MORE STRONGLY ASSOCIATED WITH INCREASED DEPRESSION IN PEOPLE AT CLINICAL HIGH-RISK VERSUS DEPRESSIVE DISORDERS

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Background: Poor insight is broadly observed in people who experience psychosis and is associated with poor social functioning, negative symptoms, and, paradoxically, greater depression. An increasingly utilized insight framework in psychosis research uses introspective accuracy and bias derived from standardized objective ratings adjusted for self-assessment. In addition to depression and negative symptoms, people at clinical high risk for psychosis (CHR) show impairments in social functioning, suggesting insight could play a role. Scoping reviews suggest better insight could increase shared decision-making and engagement in the CHR period. Therefore, understanding the relationship between insight, social functioning, negative symptoms, and depression in CHR can inform future treatment approaches.
The first aim of this study was to compare introspective accuracy and bias for social functioning in CHR without depressive disorders, depressive disorders not at CHR (DD), and community controls (CC). We included DD because of the paradoxical relationship between better insight and greater depression in individuals with psychosis. We hypothesized that CHR and DD would have lower accuracy for social functioning than CC, with CHR overestimating, DD underestimating, and CC in between. If accuracy and bias differed between CHR and DD, the second aim was to examine their associations with social functioning, negative symptoms, and depression among both groups. We hypothesized that, compared to DD, those at CHR would

have stronger associations between worse accuracy or bias and worse social functioning and negative symptoms, and less depression.

Methods: Participants were adolescents and young adults from the Multisite Assessment of Psychosis Risk study: CHR (n = 30), DD (n = 69), and CC (n = 34). To compute accuracy and bias we subtracted Z scores for the Social Functioning Scale – Psychosis Risk from the Global Functioning: Social Scale, with accuracy as the absolute value and bias unbound. We also used the Center for Epidemiological Studies Depression Scale and the Negative Symptoms Inventory – Psychosis Risk in. Group differences in accuracy and bias were tested with Welch's ANOVA and Games-Howell post-hoc tests, adjusted for false discovery rate, followed by Fisher's R to Z tests for their associations with social functioning, negative symptoms, and depression.

Results: Omnibus tests showed significant differences for accuracy ($p < .01$) and bias ($p < .01$). Post-hoc tests showed CC were the least accurate when compared to DD ($p = < .01$), with no differences between CHR and DD ($p = .66$) or CC ($p = .12$). Regarding bias, post-hoc tests showed CHR ($p < .01$) and DD ($p = .01$) differed from CC but not each other ($p = .20$), with the clinical groups showing limited bias in either direction. CHR and DD had no significant differences in their respective associations between bias and negative symptoms ($p = .13$) self-rated social functioning ($p = .32$), or other-rated social functioning ($p = .25$), However, CHR showed a stronger association between greater depression and underestimating social functioning ($p = .02$).

Discussion: There were no significant differences in accuracy for CHR, but DD had better accuracy than CC. Regarding bias, CHR and DD differed from CC, but not significantly from each other. Our findings suggest that CC had worse accuracy than CHR and DD, driven by underestimating their social functioning. Accurate estimation and reduced bias in CHR and DD could come from the psychological pain of social adversity and stigma nonspecifically related to mental health. However, the groups differed in one area. CHR had a stronger association between depression and underestimation of social functioning, which merits therapeutic attention as improvements are desirable.

V178. LONGITUDINAL EFFECTS OF ARIPIPRAZOLE ON HIPPOCAMPAL VOLUME, MEMORY, NEGATIVE SYMPTOMS, AND FUNCTIONING IN FIRST-EPISODE PSYCHOSIS

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Background: Cognitive and negative symptoms are prime targets for treatment in schizophrenia as they are closely linked and significantly impact outcome. Indeed, negative symptoms mediate the relationship between verbal memory and functioning in first-episode psychosis (FEP), an effect driven by the hippocampus. Though few antipsychotic medications improve negative or cognitive symptoms, aripiprazole, a dual-affinity D2 and 5-HT1A agonist, has been linked to memory improvement and increased hippocampal volume in both animal and human studies. However, the temporal characteristics of these changes and potential benefits on negative symptoms and functional outcome have yet to be determined.

Methods: 87 FEP patients and 56 healthy controls took part in an ongoing non-randomized concurrent controlled trial over 18 months following admission to an early psychosis intervention service. Three groups were examined at 4 timepoints (baseline [~3 months post-

admission], 6 months, 12 months, and 18 months): controls (T1=56, T2=50, T3=47, T4=40), FEP patients prescribed aripiprazole (T1=31, T2=28, T3=12, T4=11), and FEP non-aripiprazole (T1=56, T2=36, T3=28, T4=24). Choice of antipsychotic medication was determined by the treating psychiatrist. Participants underwent comprehensive clinical, cognitive, and high-resolution (0.64mm isotropic) T2-weighted 3T MRI at each timepoint. Generalized estimating equations (GEEs; first order autoregressive [AR(1)] correlation matrix; normal distribution; identity link function) were computed on symptoms (SAPS, SANS), functioning (SOFAS), verbal memory (CogState), and hippocampal subfield volumes derived from MAGeT-Brain. Groups differed on sex, education, and IQ, which were entered as covariates. Total brain volume was also covaried for analyses involving hippocampal volume.
Results: Positive symptoms decreased over 18 months in both patient groups, $\chi2 = 26.67$, df = 3, $p = 0.005$, particularly between baseline and 6 months. A significant interaction was observed for negative symptoms, $\chi2 = 13.67$, df = 3, $p = 0.003$, with pairwise comparisons revealing greater improvement in FEP aripiprazole versus non-aripiprazole, particularly at 18 months. A similar pattern was observed for functioning, $\chi2 = 7.84$, df = 3, $p = 0.05$, with greater improvement over 18 months in FEP aripiprazole. For verbal memory, a significant interaction, $\chi2 = 21.61$, df = 6, $p = 0.001$, showed stable verbal memory scores in controls and FEP aripiprazole, with FEP non-aripiprazole increasing over 12 months and decreasing back to baseline performance at 18 months. Both FEP groups were impaired on verbal memory relative to controls at all timepoints, though FEP aripiprazole outperformed FEP non-aripiprazole at baseline and 18 months. For hippocampal volume, a significant interaction was observed in left fimbria, $\chi2 = 23.03$, df = 6, $p = 0.0008$, driven by increasing volumes in FEP aripiprazole from baseline to 12 months, decreasing volumes in FEP non-aripiprazole from baseline to 6 months, and stable volumes in controls.
Discussion: In this naturalistic longitudinal FEP study, we observed ameliorating effects of aripiprazole relative to other antipsychotic medications on negative symptoms, verbal memory, functioning, and hippocampal volume over 18 months. The temporal progression of these changes is consistent with hypotheses of early changes in brain structure contributing to downstream improvements in symptoms and functioning. Moreover, the left fimbria, an important input-output region of the hippocampal circuit, emerged as a key region for these changes, suggesting a role for hippocampal-cortical connectivity. Thus, aripiprazole may target multiple symptoms of psychosis by decreasing positive symptoms through its dopamine modulator action and improving memory through increased hippocampal volume, with downstream beneficial effects on verbal memory, negative symptoms, and functional outcome.

V179. A SERVICE USER LED COMPARISON OF ACCEPTABILITY BETWEEN METHODS OF IMPLEMENTATION OF COGNITIVE REMEDIATION

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Background: Background: Improving the lives of people with mental health problems is not just about treating symptoms but how interventions allow people to achieve personal goals in recovery focussed services. Cognitive Remediation (CR) is a psychological intervention designed to improve the cognitive difficulties associated with schizophrenia. CR has durable effects on global cognition and functioning, as well as increasing confidence and motivation. To evaluate this intervention, it is crucial to measure its acceptability to service users. Users often have different perspectives from professionals and can provide additional and valuable insight into the acceptability of services and treatments that will affect their implementation.

We believe there is a need for a bespoke satisfaction measure, developed with the involvement of service users, for use in trials of computerised CR. Our aim was to create a service user led measure of the acceptability of computerised cognitive remediation therapy.
Methods: Method: Service users attending early intervention services, aged 18-35, within the first three years of their illness were recruited. Two focus groups met twice, facilitated by service user researchers and using a topic guide to generate discussion around the content and format of a measure. Following the initial focus groups, the service user researchers conducted a thematic analysis, and the data were used to generate a draft measure, which was taken to the second focus groups for respondent validation. The data were thematically analysed a second time and the measure amended accordingly. This measure was completed at the end of therapy in a large trial of three CR implementation methods with a smaller sample completing the survey twice within a brief period of time. Using this sample, the measure was explored psychometrically.
Results: Results: Eight services users took part in the development of the measure. The self-report measure contained 31 items overall, most in the form of brief statements with a six-point Likert response scale (18 items). Optional free-text space was also provided, as well as categorical items. The measure was grouped into four domains: effects of therapy, using the computer, therapy sessions, and the therapist. There was consensus that the measure was comprehensive and of an appropriate length and wording. A total higher score indicated a higher level of satisfaction. 150 participants took part in subsequent psychometric testing, and 60 in test retest analyses. The 18-item sum-scale gave a polyserial correlation with the "Overall satisfaction" item of .30 (p=.001) and with number of sessions of CRT completed .20 (p=.016; log-sessions r=.16, p=.052). Discriminant validity was suggested by the absence of association with baseline CAINS negative symptoms (p=.612) [p=.964] nor the cognitive composite (p=.902)[p=.978]. The 18 items provided an item sum score with Cronbach alpha of 0.814 and test-retest intraclass correlation of 0.772. An exploratory analyses indicated that the strength of association of Number-of-sessions (0.203) is estimated as stronger than that of Satisfaction (0.106), with only Number-of-sessions being significant (p=.002).
Discussion: Discussion: With the involvement of service users, we have developed a satisfaction measure for cognitive remediation therapy which captures the key satisfaction outcomes valued by service users. We have shown we can construct a measure of satisfaction that is acceptable, reliable and valid. We are currently carrying out the final analysis.

V180. DEFEATIST PERFORMANCE BELIEFS AND THE COGNITIVE PATHWAYS TO MOTIVATION DEFICITS IN SCHIZOPHRENIA

Late-Breaking Poster

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Background: According to the cognitive model, the development and maintenance of negative symptoms in schizophrenia are thought to be related to dysfunctional cognitions (i.e., beliefs and attitudes) that are fostered by recurrent failures and setbacks. To this end, defeatist performance beliefs, or overgeneralized negative beliefs about goal-directed activity, have been shown to link the relationship between neurocognitive impairments and negative symptoms, particularly amotivation. However, the extent to which these findings extend to more discrete facets of the motivation system, such as reward valuation, has yet to be explored.

Thus, in order to advance our understanding of the cognitive model of negative symptoms, the current study aims to examine the theorized psychological pathway to negative symptoms using an objective behavioural paradigm of motivation.

Methods: The sample consisted of 21 outpatients with schizophrenia. Participants were administered the SANS for negative symptoms, the BACS for neurocognition, the defeatist performance beliefs subscale of the Dysfunctional Attitudes Scale, as well as the computerized Evoked and Representational Responding Task (ERRT). The ERRT provides a framework for objectively indexing the degree to which individuals' internal representations of pleasure (i.e., liking) correspond with their behaviour (i.e., effort) by first presenting positive and negative valence images to be rated on the basis of subjective pleasantness and then offering the opportunity to either increase or decrease the likelihood of future exposure using a button pressing task. Two hypothesized models were tested with path analysis. The first model tested the paths from the BACS to defeatist performance beliefs to SANS amotivation to ERRT click rate for positive stimuli (i.e., approach motivation), and the second model tested the same paths but with the ERRT click rate for negative stimuli (i.e., avoidant motivation) instead.

Results: The first path model fit the data well, $\chi2 = 0.96$, $p = 0.81$, RMSEA = 0.00, 90% CI [0, 0.23], TLI = 1, AIC = 363.5, BIC = 369.1. According to this model, the path from BACS cognition to defeatist performance beliefs was significant, $\beta = -9.2$, $Z = -3.6$, $p < 0.001$, the path from defeatist beliefs and SANS amotivation was not significant, $\beta = 0.14$, $Z = 1.6$, $p = 0.1$, and the path from SANS amotivation to ERRT positive was significant, $\beta = -0.12$, $Z = -2.6$, $p = 0.009$. The second path model similarly fit the data well, $\chi2 = 2.8$, $p = 0.42$, RMSEA = 0.00, 90% CI [0, 0.38], TLI = 1, AIC = 370.9, BIC = 376.9. All paths in this model were significant, with the BACS predicting defeatist beliefs, $\beta = -7.2$, $Z = -2.6$, $p < 0.01$, defeatist beliefs predicting SANS amotivation, $\beta = 0.17$, $Z = 2.1$, $p = 0.04$, and SANS amotivation predicting ERRT negative, $\beta = -0.07$, $Z = -2.7$, $p = 0.008$.

Discussion: The current study supports existing conceptualizations of the cognitive model of negative symptoms and extends the findings by incorporating an objective behavioural measure of motivation. Dysfunctional cognitions such as defeatist performance beliefs have been repeatedly shown to represent an important link in the relationship between neurocognition and interview-based measures of negative symptoms; however, the preliminary findings of the current study may suggest greater nuance to the role played by these belief systems. That is, the results of our path models reveal that defeatist beliefs significantly predict amotivation in the context of negative avoidant behaviours, but not necessarily positive approach behaviours. Given the centrality of maladaptive beliefs in cognitive behavioural therapy for negative symptoms, these findings may offer an opportunity for enhanced treatment specificity.