The 2019 Schizophrenia International Research Society Conference, 10–14 April, Orlando, Florida

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Review article

The 2019 Schizophrenia International Research Society Conference, 10–14 April, Orlando, Florida: A summary of topics and trends

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ABSTRACT

The Schizophrenia International Research Society (SIRS) recently held its first North American congress, which took place in Orlando, Florida from 10-14 April 2019. The overall theme of this year's congress was United in Progress – with the aim of cultivating a collaborative effort towards advancing the field of schizophrenia research. Student travel awardees provided reports of the oral sessions and concurrent symposia that took place

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Rapporteur reports

during the congress. A collection of these reports is summarized and presented below and highlights the main themes and topics that emerged during the congress. In summary, the congress covered a broad range of topics relevant to the field of psychiatry today.

1. Introduction

The Schizophrenia International Research Society (SIRS) recently held its first North American congress, which took place in Orlando, Florida from 10-14 April 2019. The overall theme of this year's congress was *United in Progress* – with the aim of cultivating a collaborative effort towards advancing the field of schizophrenia research.

Judge Steven Leifman opened the congress with his keynote talk, in which he called for an end to the criminalization of mental illness. He highlighted the plight of individuals living with a serious mental illness as well as their families and caregivers who are often forced to turn to the criminal justice system for help, since the mental health system have failed them. There were five plenary sessions during the congress, which addressed the following topics: the effectiveness of cognitive behavioral therapy, the use of stem cells to study schizophrenia, the role played by gluten in the treatment of the illness, the importance of mobile phones in patient care, schizophrenia as a disorder of the self, and schizophrenia and substance use disorder.

Student travel awardees provided reports of the oral sessions and concurrent symposia that took place during the congress. A collection of these reports is summarized and presented below and highlights the main themes and topics that emerged during the congress.

2. Environmental risk factors

The timing of trauma exposure featured in a number of the talks. Michael Bloomfield (University College London, UK) discussed the findings of a systematic review on the effects of developmental stress and trauma on dopamine function. He proposed that divergent alterations in the dopaminergic system occur depending on the timing and nature of developmental exposure. He used positron emission tomography (PET) to investigate the dopamine synthesis capacity in healthy adults who have and who have not been exposed to psychosocial adversity. The study findings suggest that developmental trauma exposure may alter the dopaminergic function at several levels, which in turn may impair a range of neurocognitive processes to induce vulnerability to psychosis.

The importance of the timing of developmental trauma also featured in other talks. Luis Alameda (Institute of Psychiatry, Psychology, & Neuroscience at King's College London, UK) presented a study that explored the association between specific adversity types, the timing of exposure, and the main symptom dimensions in First Episode of Psychosis (FEP). In this study childhood adversities were categorized according to the timing of exposure: early <12 years, and late $12>18$ years. While sexual abuse and neglect were associated to the positive dimension, emotional abuse and bullying was associated to the depressive dimension. The timing of exposure of sexual abuse or neglect did not moderate its effect on the positive symptoms. However, only bullying occurring late, and not early, was associated with the depressive dimension. These results suggest specific associations between different adversities and symptom domains, and adolescence seems to be a specific critical period for the effects of bullying on depressive symptoms in FEP. Anthony Grace (University of Pittsburgh, USA) discussed the work he had done on the effect of environmental stress in animal models. He explained that stress is induces the loss of hippocampal parvalbumin (PV) interneurons and leads to an overactive dopamine system. In particular, the timing of exposure to environmental stress is deemed important. Rats exposed to stress later in life did not experience a schizophrenia-like state but instead show signs consistent with depression. He suggests that in adulthood, the perineural nets (PNN) protects PV interneurons and therefore stress experienced during adulthood is associated with a different type of impairment. In another animal study, Xiyu Zhu (University of Pittsburgh Department of Neuroscience, USA) presented data on a rodent model, wherein rats were exposed to either 10 sessions of foot-shock stress, 3 sessions of restraint stress, or combined stressors, delivered either in pre-puberty or in adulthood. Adolescence stress alone, in the absence of prenatal methylazoxymethanol acetate (MAM), produced long-term dopamine hyperactivity and schizophrenia-like behaviors. A distinct pattern of response was observed when the stress exposure occurred during adulthood, suggesting adolescence could be associated with greater stress-sensitivity.

Urs Braun (Central Institute of Mental Health, Germany) highlighted the importance of the social environment when studying schizophrenia. Adverse social environmental factors, such as an urban upbringing, ethnic minority background and low social status, affect the Anterior Cingulate Cortex (ACC) circuits. However, exposure to resources of resilience, such urban green space and physical activity, also affect the ACC circuits. This is consistent with the idea of potential neural resilience and risk effect converging on the same circuitry.

Sabina Berretta (McLean Hospital – Harvard Medical School), USA) discussed the role of the amygdala in stress response and anxiety symptoms in schizophrenia and bipolar disorder. When comparing postmortem tissue samples from the amygdala across healthy donors, donors with schizophrenia, and donors with bipolar disorder, somatostatin-expressing neurons were decreased in the lateral nucleus in both patient groups, with respect to healthy donors. This points to a disruption of molecular factors involved in stress- and anxiety- related symptoms in the amygdala of people with bipolar disorder and schizophrenia.

Daphne Holt (Massachusetts general Hospital, USA) discussed a study conducted in a student cohort. She proposed that there is a mechanistic pathway whereby early stress-induced abnormalities in the functioning of the medial temporal lobe lead to misperceptions and misinterpretations of sensory stimuli. This is based on a study, in non-help-seeking college students with subclinical delusional beliefs, that showed that emotional reactivity partially mediates the association between childhood adversity and psychotic experiences.

The impact of gene-environment interactions featured in the talk of Monica Aas (King's College, London, UK). She discussed the use of polygenic risk score (PRS) to investigate gene-environment interactions in patients with schizophrenia. She presented the findings of a study, which suggest a history of childhood trauma and PRS together explained a larger portion of the variance in case-control classification compared to either childhood trauma or PRS alone. This supports the contribution of both genetic factors and childhood adversity experiences in psychosis. She also presented findings from a study, which explored the associations of hair cortisol levels, childhood trauma exposure, and cognition in patients with schizophrenia ($n = 25$) and bipolar disorder ($n = 35$) relative to healthy controls ($n = 94$). Higher hair cortisol levels were observed in patients who reported childhood trauma compared to healthy controls. In a preliminary analysis, marginal associations were also found between hair cortisol levels, global assessment of functioning scores and cognition. This suggests that hypothalamic-pituitary-adrenal axis dysregulation could help characterize a subgroup of patients with schizophrenia and bipolar disorder who experienced childhood maltreatment. In another talk she presented results from an analysis of the relationship between telomere length and childhood trauma exposure in patients with severe mental illnesses. Compared to healthy controls, patients with schizophrenia or bipolar

disorder had shorter telomere lengths. Telomere length was not associated with brain volume or clinical features. However, a history of childhood abuse was associated with shorter telomere length in the patient sample.

Raquel Gur (University of Pennsylvania, USA) presented data from a longitudinal study of participants enrolled in the Philadelphia Neurodevelopment Cohort (n ~ 9500) who underwent clinical assessment, neurocognitive testing, and a subsample neuroimaging (MRI) and genomic assessments. Environmental factors assessed included neighborhood characteristics (e.g. crime, household income, marriage status) and a history of exposure to traumatic stressful events. In this study, children at high-risk for psychosis who lived in an unfavorable environment had poorer cognitive performance compared to those living in a favorable environment. Low brain volumes and activation to a threat task predicted vulnerability and symptom persistence. There was a significant interaction between genetic and environmental factors.

Golam Khandaker (University of Cambridge, UK) presented recent work investigating the relationship between childhood infections, intelligence, and the risk of non-affective psychosis in adulthood. The results suggest that early-childhood infection was associated with subsequent lower IQ and increased risk of psychosis. The association between infection and psychosis was mediated and moderated by IQ, and the associations were similar in the general population and in full-sibling pairs discordant for exposure. He concluded that lower premorbid intelligence in individuals may arise from unique environmental factors, such as early-childhood infection, and early-childhood infection may increase the risk of non-affective psychosis, partly by interfering with neurodevelopment and partly by exaggerating the effects of cognitive vulnerability to psychosis.

Mary Clarke (Royal College of Surgeons) reported on the recent findings in a Finish cohort suggesting that exposure to stress during pregnancy, especially during late pregnancy, increase the risk of a psychiatric disorder. Specific associations were observed with mood and personality disorders. Interestingly, the odds of a personality disorder increased with the severity of stress exposure, suggesting a dose-response association. Importantly, observed associations were not affected by depression during pregnancy.

3. Substance abuse and smoking

The high incidence of tobacco smoking in schizophrenia patient cohorts came under discussion. Faith Dickerson (Sheppard Pratt Health System, USA) presented findings illustrating an association between cigarette smoking and poorer overall cognitive functioning, a higher incidence of suicide, and premature mortality in schizophrenia. She argued that the evidence clearly contradicts the idea that smoking is merely a means of self-medication. Instead, she advocates that smoking cessation should be an important target when treating patients living with schizophrenia. Robin Murray (King's College London, UK) reviewed the findings of a meta-analysis, which suggests that the prevalence of tobacco use in first episode patients is higher compared to non-users and smoking is associated with an earlier age of illness onset. He suggests that tobacco smoking may be a causative risk factor for psychosis. The meta-analysis revealed that the effect of smoking is independent of cannabis use in first episode psychosis. He proposed that smoking might be related to persistent activation of the dopamine system.

Smoking cessation interventions came under the spotlight. Mary Brunette (Dartmouth Medical School, USA) highlighted the importance of web-based smoking cessation interventions for patients with schizophrenia. Her findings suggest that brief, web-based interventions can be as effective as in-person treatment interventions in terms of motivating patients to stop smoking. However, intensive interventions may be required in order to achieve long-term smoking cessation. Nevertheless, she explained that web-based interventions could be of particular value for patients who do not have access to conventional smoking cessation interventions. Gail Daumit (John Hopkins University School of Medicine, USA) and Eden Evins (Massachusetts General Hospital, USA) are co-directing a randomized clinical trial of a tobacco smoking cessation intervention for persons with serious mental illness that incorporates behavioral counseling and cessation pharmacotherapy tailored to participants' readiness to quit. The intervention also includes weight management counseling and physical activity. She explained that this type of approach is significant as it addresses multiple cardiovascular risk behaviors, in particular as weight gain is often associated with smoking cessation in patients with serious mental illnesses.

In addition to cigarette smoking, substance use was a topic that featured prominently during the congress. Deepak D'Souza (Yale University School of Medicine, USA) proposed that cannabinoid induced acute and persistent psychosis (CIAPP) is a distinct subtype of psychotic disorders. He based this on a prospective study, studying hospitalized CIAPP cases with three control groups, including psychosis unrelated to cannabis, cannabis use disorder, and healthy controls. He found a distinct behavioral, cognitive, and electrophysiological profile of CIAPP. Also, CIAPP patients had fewer residual symptoms with shorter duration of psychosis compared to the psychosis without cannabis use group. Oliver Howes (King's College London, UK) investigated the association between cannabinoid 1 receptor (CB1R) availability and memory in first episode psychosis. He presented findings showing a reduced CB1R availability in first episode psychosis, with hippocampus, striatum, anterior cingulate and thalamus being most significant. He found that in the FEP group there was a lower CB1R in the anterior cingulate cortex (ACC), but a higher activation in the ACC during memory encoding. He concluded that in untreated FEP there is reduced CB1R availability, which is associated with altered cortical function during memory encoding.

Melissa Weibell (Stavanger University Hospital, Norway) presented outcome data from the Scandinavian early Treatment and Intervention in Psychosis Study (TIPS). At 10-year follow-up, on motor speed and verbal learning indices, patients who stopped using substances within the first two years of follow-up, improved over time whereas non-users and users did not. Within the stop- and episodic use groups, patients with narrow schizophrenia diagnoses performed worse compared to patients with other diagnoses on verbal learning and on the overall composite neurocognitive index. Early cessation of substance use was associated with less cognitive impairment and some improvement over time on some cognitive measures, indicating a milder illness course and superior cognitive reserves to draw from in recovering from psychosis. However, the group with continued use had more severe positive and depression symptoms. Musa Sami (Department of Psychiatry, King's College London) presented work on the differences in psychotic experiences between patients with a first episode of psychosis and controls. The findings suggest that cases had more intoxication experiences than controls. The extent of cannabis used predicted both euphoric-like and psychotic-like experiences. However, euphoric or psychotic experiences did not depend on the potency of the cannabis used. Frederika Scheffler (Department of Psychiatry, Stellenbosch University, South Africa) presented data on the differences in hippocampal subfields volumes in first episode schizophrenia spectrum disorders. She found a significant interaction effect for group by cannabis use. She proposed that the volumetric difference between groups may be due to inflammation or the compensatory changes in schizophrenia, given that the subiculum is associated with the HPA axis and is involved in memory as well as dopamine regulation. Rashmi Patel (King's College London, UK) presented epidemiological data from the Electronic Health Record from the South London and Maudsley NHS Foundation Trust. Of the sample of 29,412 with a psychotic illness, 3657 patients had comorbid substance use, the majority being male. Unnatural deaths were three times more common in the comorbid substance use group. He stressed the need for addressing substance use in patients with psychotic disorders. Marco Colizzi (Institute of Psychiatry, Psychology and

Neuroscience, King's College London) presented a double blind randomized control trial aimed at investigating in healthy subjects whether altered striatal glutamate measures underlie the acute psychotomimetic effects of intravenous delta 9 tetrahydrocannabinol (d9-THC), which is the psychoactive compound of cannabis. Results showed that compared to placebo, d9-THC increased glutamate + glutamine metabolites (Glx). He proposed that lower baseline Glx in the striatum may be a marker for developing psychotic symptoms following exposure to cannabis.

Luccas Coutinho (Universidade Federal de Sao, Brazil) discussed age of illness onset and cannabis use. He conducted a study including 175 patients with a first episode of psychosis. He found that 41.2% of the sample reported cannabis use and approximately 50% had used cannabis before 16 years of age. The cannabis users had a lower mean age of onset of psychosis. Deidre Anglin (The City College of New York, USA) proposed that aberrant salience could partially explain the association between cannabis use and psychotic like experiences (PLE). She presented findings revealing that frequent cannabis users had higher PLEs and higher scores on the aberrant salience inventory (ASI). Regression models and mediation analysis indicated that recent cannabis use and PLEs were significantly explained by ASI scores.

4. Mental health in children and adolescents

A better understanding of the risk factors for psychosis in adolescents and children could lead to more effective early intervention programs. Maija Lindgren (National Institute for Health and Welfare, Finland) suggests that psychosis risk symptoms in adolescents are good predictors of persistent psychiatric service use. This is based on the findings of a study that included 715 non-psychotic adolescents (between the ages of 15-18 years). The findings revealed that psychosis risk symptoms (positive, negative, disorganized and general symptom domains) are predictors of continued service-use, even when baseline psychiatric diagnoses and the development of psychosis at follow-up were accounted for. This suggests that even though psychosis risk symptoms are not always indicative of psychopathology, they may be useful for predicting the need for persistent psychiatric care.

Lauren Moran (McLean Hospital/Harvard Medical School, USA) highlighted the potential risks associated with prescription amphetamine use in the treatment of adolescents and young adults with Attention Deficit Hyperactivity Disorder (ADHD). Her findings indicate that amphetamine, in comparison to methylphenidate, is associated with an increased risk of treatment-emergent psychosis in young people with ADHD.

Gregory Strauss (University of Georgia, USA) compared patients with schizophrenia with clinically high-risk youth to determine if reward processing impairments, known to be assoicated with avolition, are present in both groups. The findings point to impaired avolition in both groups. However, in the high risk group the hedonic response was most important, while value representation was most central in the chronic group. He proposed that different reward processing domains are more prominent during different phases of the illness.

Benjamin Perry (University of Cambridge, UK) presented findings suggesting that a genetic predisposition for Type 2 Diabetes Mellitus (T2DM) is longitudinally associated with a risk for psychosis. However, it was not found to be a risk factor for depression. His findings are based on a large epidemiological study including more than 4000 participants. He suggests that minor genetic variations, which predispose individuals to metabolic alterations during childhood, may over time increase the risk for diabetes and psychosis.

Paul Allen (University of Roehampton and King's College London, UK) presented a study that compared clinical high-risk (CHR) individuals to healthy controls, to determine if elevated glutamatergic levels are associated with hippocampal dysfunction. They found a positive relationship between glutamatergic metabolite levels (Glx: glutamate and glutamine) and task-related activation in the hippocampus and dorsal striatum in controls and a negative relationship in CHR individuals. It was emphasized that this finding supports existing animal models, suggesting that there is an association between increases in hippocampal glutamatergic metabolite levels and reduced hippocampal function during the development of psychosis.

Alison Yung (University of Melbourne, Australia) presented findings from a study comparing individuals at ultra high risk for psychosis with and without persistent negative symptoms. She found that at baseline those with persistent negative symptoms were more likely to have poor premorbid social adjustment, a history of childhood neglect, and impairment in certain cognitive domains. At follow-up, those with persistent negative symptoms were also more likely to have impaired psychosocial functioning and poorer speed of processing.

The importance of studying genetic liability for schizophrenia in adolescents and children came under discussion. Lotta-Katrin Pries (Maastricht University Medical Centre, Netherlands) proposed that a polygenic risk for schizophrenia moderate the relationship between childhood adversity and psychotic-like experiences. This is based on the findings of a general population twin cohort study including adolescents and young adults. The study showed that the interaction between polygenic risk for schizophrenia and childhood adversity were significant predictors of negative and positive affect, and subtle psychosis expression. In addition, two presenters referred to a family history of psychosis/schizophrenia in their respective talks, which is a proxy for genetic liability. Nicole Karcher (Washington University School of Medicine, USA) presented findings, from a population-based study conducted in school-age children between the ages of 9 and 11 years, highlighting predictors of psychotic-like experiences. She identified the following predictors of psychotic-like experiences, namely a family history of psychosis, impaired cognitive functioning as well as internalizing symptoms. Psychotic-like experiences were also related to impaired connectivity within certain neural networks, even when controlling for the abovementioned predictors. Ditte Ellersgaard (Mental Health Centre Copenhagen, Denmark) discussed the findings of a study assessing psychotic-like experiences in children as young as 7 years of age, with a family history of psychotic disorders. Children with a family history of schizophrenia had the highest incidence of psychotic-like experiences, followed by those with a family history of bipolar disorder.

Suicidal behavior in children and adolescents featured in two talks. Patricia Graham (The Institute of Living/Hartford Healthcare Behavioral Health Network) emphasized the importance of suicide risk amongst adolescents reporting psychotic symptoms. She found that approximately half of young people enrolled in day treatment program for psychosis reported suicide ideation and past suicide attempts. She proposed that in particular delusions, obsessive compulsive symptoms, cognitive inflexibility, and feeling accepted are important suicide risk factors to consider when treating adolescents. Martin K. Rimvall (Child and Adolescent Mental Health Center, Mental Health Services, Capital Region of Denmark, Denmark) suggests that persistent psychotic experiences in childhood are important risk factors for suicidal behaviour in adolescence. He based this on the findings of a large longitudinal study assessing psychotic experiences in children at age of 11 and again at 16 years.

5. Non-pharmacological interventions

Cognitive interventions prominently featured in a number of talks. Heather A. Adams (Maryland Psychiatric Research Center, University of Maryland School of Medicine, USA) presented findings from a study which examined the efficacy of cognitive behaviour therapy for psychosis (CBTp) in reducing distress secondary to symptoms, improving functioning, and reducing overall symptoms associated with the illness in a group of 53 inpatients who took part in weekly one-hour illness education sessions. Study participants attended 71% of the offered groups, and 84% showed moderate to high engagement. Distress and

symptoms were reduced, and global functioning increased, from baseline to post-treatment. Patients agreed that CBTp helped them to learn skills aimed at improving their daily lives and reported overall satisfaction with the intervention. She highlighted that future CBT interventions should prioritize reduction in distress secondary to symptoms and improvement in overall functioning. The application of cognitive behavioral interventions, particularly with a chronically ill, treatment resistant sample, was discussed. Eva Velthorst (Icahn School of Medicine, Mount Sinai, USA) presented the findings of a randomized control trial assessing the effectiveness of cognitive behavioral therapy (CBT) in the treatment of social withdrawal and negative symptoms in recent onset psychosis. Patients were randomized to either CBT with treatment, or treatment as usual. Initially, the CBT group had greater functional outcomes, however after six months there were no significant between group differences. She suggests that with a longer intervention period, in patients who are more stable, CBT could have a more pronounced effect on social withdrawal and negative symptoms. Jessica Wojtalik (University of Pittsburgh, USA) suggested that the early use of cognitive enhancement therapy (CET) should be considered when treating patients with recent onset schizophrenia. She discussed a randomized control trial conducted in a sample of 106 individuals with early course schizophrenia. Patients were randomized to either receive CET or a comparison treatment (Enriched Supportive Therapy [EST]). Those in the CET condition demonstrated greater gains in social cognition and functioning over 18 months of treatment.

Karuna Subramaniam (University of California San Francisco, USA) proposed that social cognitive training could be an effective treatment option for impaired reward anticipation and goal-directed behaviors to earn rewarding outcomes in patients with schizophrenia. She based this on the findings of a double-blind randomized control trial where patients receiving intensive computerized social cognitive training were compared with patients receiving cognitive training without the social component. The group that received the social cognitive training had significantly increased medial prefrontal activity post-intervention which predicted and potentiated patients' goal-directed rewarding outcomes (i.e., their motivation and ability to earn more rewarding outcomes). Related to the topic of social cognitive training, Deepa Purushothaman (National Institute of Mental Health and Neurosciences, India) presented results from a study, which examined the effects of intranasal vasopressin on altruistic behaviour in schizophrenia patients (n = 30) compared to healthy controls (n = 30). Both groups participated in a "dictator game" which involves choosing whether to keep (less altruistic) or share (more altruistic) money. Patients further received a single dose of either intranasal vasopressin or saline placebo in a double-blind counterbalanced design. Altruistic behaviour was increased in patients treated with vasopressin, and a lesser response was associated with higher childhood trauma exposure. These findings suggest that vasopressin, known to play a role in social cognition in schizophrenia, could also improve altruistic behaviour.

The association between cognitive behavioral intervention and memory improvement was discussed by Martin Lepage (McGill University, Canada). He presented a brief cognitive training, namely Strategy for Semantic Association Memory training (SESAME), which targets the self-initiation of semantic strategies in schizophrenia. SESAME training led to significant improvements in memory performance that were associated with increased activity in the left dorsal lateral prefrontal cortex. These findings suggest the feasibility of a brief cognitive intervention in patients with schizophrenia, which may benefit from improved memory performance, particularly in patients with a greater cortical "reserve".

In addition to more conventional cognitive behavioural interventions aimed at improving memory, Tobias Schwippel (University Hospital Tuebingen, Germany) explored the use of transcranial direct current stimulation (tDCS). He presented findings from a study, which investigated the effects of right dorsolateral prefrontal cortex tDCS on working memory performance in patients with schizophrenia (n = 32). In this study, 2 mA (but not 1 mA) tDCS improved working memory accuracy during high cognitive load, and decreased reaction time during mid- to high cognitive load, suggesting a shift towards increased accuracy at the expense of longer reaction times. These findings support the role of tDCS in improving cognitive functioning in schizophrenia. However, higher current intensities might be required in this population relative to healthy individuals. Other presentations on the use of tDCS included that of Priscilla Oomen (UMC Groningen, Netherlands). She described a randomized, double-blind, placebo-controlled trial that compared twice-daily 20-minute treatments of 2 mA tDCS for 5 days to placebo in 54 patients with medication-resistant auditory hallucinations. The trial showed no significant differences between active treatment and placebo. However, this may be due to a small sample size and the lack of clear data regarding the optimal electrode and wiring placement. Amy Pinkham (The University of Texas at Dallas, USA) proposed that an increase in neural activity in the right rostrolateral prefrontal cortex could be key to improve introspective accuracy in individuals living with schizophrenia. In an attempt to increase neural activity in this region she used tDCS as an intervention. However it did not lead to immediate significant behavioral improvement and instead showed a potential delayed effect on introspective accuracy. She emphasized that more work is needed to determine if a longer duration of stimulation will be more effective.

Susanna Konsztowicz (McGill University, Canada) discussed the effectiveness of a cognitive-behavioral-based intervention in treating illness engulfment. Illness engulfment is a process whereby an individual's concept of themselves becomes defined mainly by their illness. She conducted a trial whereby patients were either assigned to treatment as usual or to a brief cognitive behavioral-based intervention. The intervention reduced levels of illness engulfment and improved self-esteem. However, it did not have an effect on depression and quality of life.

Ian Ramsay (University of Minnesota, USA) discussed the neurobiological underpinnings of cognitive remediation. He presented findings suggesting that improvement in cognitive functioning, with targeted cognitive training, is associated with changes in cortical thickness. He based this on a study comparing the effect of targeted cognitive training in patients with recent onset schizophrenia (N = 21) and health controls (N = 22). Those with reduced cortical thickness at baseline were better able to make gains with the intervention. Changes appeared in several brain regions over the course of treatment, especially in regions important for cognitive control and auditory processing. Results support the idea that cognitive training can be highly effective, but will be most effective when personalized and targeted to functional and structural brain plasticity methods.

Keith Nuechterlein (University of California, Los Angeles, USA) presented findings from a randomized controlled trial that compared the effects of an individual placement and support plus workplace fundamentals (IPS-WFM) intervention versus conventional vocational rehabilitation plus social skills training on cognitive performance and occupational/educational reintegration in first-episode schizophrenia. In total, 69 patients took part in one of the two interventions and were assessed on cognition and school/work recovery at baseline, 6 months, and again at 18 months. IPS-WFM doubled the number of patients who returned to work/school within 6 months. In the following 12 months, 92% of IPS-WFM participants remained in work/school. While baseline cognitive deficits predicted work/school return at 6 months, neither intervention improved cognitive performance over time. Supported employment/education was identified as a powerful tool for helping first-episode patients return to work/school. However, cognitive interventions are still needed and may be particularly useful to further improve outcome.

Clinicians may find it difficult to decide on a specific type of remediation that best suit patients' individual needs. Studies assessing predictors of response to cognitive remediation may be helpful in this regard. Mike Best (Queen's University, Canada) proposed that specific

types of cognitive remediation are associated with better outcomes than others. He based this on the findings of a randomized controlled trial, which compared perceptual and executive training in schizophrenia-spectrum disorders. The study found that over time, executive training was associated with greater cognitive improvement as well as functional outcomes, in comparison to perceptual training. He noted that executive training is potentially an important predictor of treatment outcomes. Similarly, Matthew Kurtz (Wesleyan University, USA) studied predictors of response to cognitive remediation in a secondary data analysis of two RCTs. His findings suggest that baseline executive functioning errors and digit span performance are good predictors of cognitive outcomes in cognitive remediation for schizophrenia. Interestingly, baseline symptoms were not predictors of response. Inconsistent with his hypothesis, age at study entry did not predict the degree of improvement in working memory outcomes across these two RCTs. Lastly, signal detection analysis suggested that cognitive variables at study entry, rather than demographic, illness or symptom variables were most effective at accurately predicting cognitive improvers and non-improvers after CR treatment. Lana Kambeitz-Ilankovic (Ludwig-Maximilian University, Germany) suggests using techniques, such as machine learning, to individualize patient treatment. She presented findings from a study that showed that machine learning, using structural neuroimaging data, can accurately predict which patients with schizophrenia are more likely to show improved functional outcomes following intensive computer-based neurocognitive interventions.

In the future cognitive remediation interventions could take advantage of pupillometry. Jimmy Choi (Olin Neuropsychiatry Research Center, USA) highlighted the benefits of pupillometry-based cognitive training. Unlike conventional computerized cognitive training, pupillometry-based cognitive training adjusts for difficulty level by taking into account effort used and level of engagement on neurophysiologic barometers. This type of cognitive training may be more useful than other types of interventions.

6. Inflammation and immune system

The theme of inflammation and the blood-brain barrier featured in the talks presented below. Michael Benros (Mental Health Centre Copenhagen, Denmark) reviewed epidemiological findings, which provide evidence for infections, autoimmunity and neuroinflammation as risk factors for psychosis. He explained that individuals that have autoimmune diseases with potential presence of brain-reactive antibodies and that also acquire infections have a further increased risk of psychosis, potentially due to disruption of the blood-brain barrier. Moreover, meta-analysis of CSF studies have indicated that the integrity of the blood-brain barrier is affected in individuals with psychosis. Lastly, he highlighted results from a recent meta-analysis indicating beneficial effect of anti-inflammatory agents in the treatment of psychotic disorders; however, large-scale biomarker-based RCTs are still lacking and needed to identify individual with psychosis that are more likely to respond to anti-inflammatory treatment. Hannelore Ehrenreich (Max Planck Institute of Experimental Medicine, Germany) showed that functional autoantibodies against the N-methyl-D-aspartate-receptor subunit NR1 (NMDAR1-AB) belong to the normal autoimmune repertoire of mammals. She discussed prerequisites for symptomatic consequences and gave examples of inducers of NMDAR1-AB formation or boosting, ranging from infection to chronic life stress, e.g. as experienced upon migration. In situations of chronic life stress, these AB may even have an antidepressant (ketamine-like) action. Matthew Campbell (Trinity College Dublin, Ireland) emphasized the importance of claudin-5 protein levels in schizophrenia. Post-mortem studies in schizophrenia patients suggest a decrease in claudin-5 levels in the frontal cortex, which may be related to a blood-brain barrier disruption. He suggests that more attention should be paid to the role played by claudin-5 and how to repair the intergrity of the blood-brain barrier. Emily Severance (Conte Center for Schizophrenia Research at Johns Hopkins, USA) pointed out that Inflammatory Bowel Disease, Irritable Bowel Syndrome and Coeliac Disease are highly comorbid with psychiatric comorbidities. She proposed that an imbalance of the microbiome in the gut could increase the risk for schizophrenia. She explained that blood-brain barrier impairment as well as blood-gut barrier dysfunction is associated with increased levels of certain autoantibodies in animal and human samples. Katherine Burdick (Brigham & Women's Hospital, Harvard Medical School, USA) discussed research investigating cognition and inflammation. The study found that inflammation contributed significantly to adverse cognitive outcome in patients with both bipolar disorder and schizophrenia. The effect was also evident in remitted patients. Cognitive domains affected by inflammation include cognitive flexibility, reward processing, spatial processing and social cognition. She suggests that inflammation is an important predictor of cognitive impairment not only during active phases of psychosis, but very importantly also in remitted patients. Outi Mantere (McGill University, CAN) reported that insulin resistance was associated with an activation of the peripheral immune system in patients with first-episode psychosis by applying gene expression analysis. These findings may provide implications for add-on treatments to prevent physical complications in psychosis. Jarno Honkanen (University of Helsinki) discussed ongoing work examining the transcriptome of both effector and regulatory T cells in a sample of 32 patients and 48 healthy controls. Preliminary results show potential differences in variation between LPS treated and not treated levels of IL1B, in both cases and controls. These findings may indicate a linkage between peripheral immune system and psychosis. Jarmo Hietala (University of Turku, Finland) presented work using the latest generation of translocator protein (TSPO) ligands in a sample of 14 patients with first-episode non-affective and affective psychosis and 16 healthy controls. Glial TSPO binding was lower in first-episode psychosis and also related to serum cytokine levels. CCL-22 was considered to be of particular importance, as it seems to be elevated in psychosis. Similarly, Simon Cervenka (Karolinska Institutet, Sweden) presented an individual-participant data meta-analysis of TSPO positron emission tomography (PET) studies in schizophrenia. The data together with immune marker analysis support aberrations in both central and peripheral immune cell function in schizophrenia.

Tyler Lesh (University of California, Davis) talked about how animal models can complement human studies and offer additional mechanistic insights. They reported that in humans, maternal infections during gestation increase risk for schizophrenia and other psychiatric disorders. Based on the maternal immune activation (MIA) model, they sought to test the hypothesis that maternal immune response contributes to changes in the developing brain and behavior of non-human primate (NHP) offspring. Although no significant group by time interactions were identified, a significant main effect of group was identified in both white and gray cingulate cortex free water, with MIA-exposed offspring showing higher free water. These data suggest that extracellular free water values are increased in MIA-exposed offspring, particularly in the cingulate cortex. These findings parallel human studies identifying increased free water in patients with schizophrenia.

7. Disorder of the self

Lénie Torregrossa (Vanderbilt University, USA) discussed the idea of schizophrenia as a disorder of the self where splitting of different psychological functions, loss of unity of the self, dissociations, and anomalous sense of agency are prominent symptoms. Together with her colleagues, she studied the quality of two internal signals, the heart beat and emotional embodiment, in schizophrenia patients, hypothesizing that such signals would be noisier in patients compared to healthy controls. The study findings suggest that interoceptive accuracy was reduced in patients compared to controls, even after controlling for time perception, body mass index, resting heart rate, and heart rate

variability. They also found evidence for a decreased quality in reported bodily sensation of emotions. Together, these results suggest an increased level of internal noise in people with schizophrenia.

Anne Giersch (INSERM French Medical Research Institute, France) explored the possibility of an association between patients' often fragmented experience of time and bodily self-disturbance in psychosis. She found differences between patients and controls, when using sequential effects and electroencephalogram (EEG). An abnormal sensitivity to sub-threshold asynchronies were found in the patient group only. Despite distinguishing events in time unconsciously, patients showed an impairment in predicting sequences which could be related to problems in producing coherent information sequences at the millisecond level.

Neeltje Van Haren (Erasmus Medical Centre, Rotterdam, Netherlands) discussed a study that assessed the role of aberrant multisensory integration (body ownership) and sense of agency in the manifestation of self-disturbances. The study used the rubber hand illusion (RHI) paradigm. Patients with schizophrenia ($N = 54$) had a smaller increase in strength of the subjective illusion after synchronous relative to asynchronous stroking compared to healthy controls ($N = 56$). Also, in the patient group, the subjective RHI correlated with severity of delusions. Proprioceptive drift (estimation of the index finger position) was not affected, thus suggesting selective alterations in embodiment and prime-based agency inference processing in schizophrenia. Furthermore, results suggest that both prime-based agency processing and embodiment underly self-disturbances.

Steven Silverstein (Rutgers University Behavioural Health Care, USA) proposed, in light of evidence for perceptual and cognitive as well as body ownership disturbances in schizophrenia, the possibility of integrating the established notion of schizophrenia as a neurocognitive disorder with the emerging evidence for a disorder of self-experience. He suggested that some of the symptoms experienced by patients with schizophrenia, such as broadened representations of body parts and lengthening of time intervals, may reflect an attempt to compensate for the increased noise and reduced consistency of interoceptive signals. He concluded by suggesting that body-ownership issues in schizophrenia should be viewed from within the perspective of Information Theory.

8. Cognition and functionality

James Gold (University of Maryland, USA) examined the impact of working memory deficits in schizophrenia. He found that patients, compared to controls, had reaction times that were nearly three times longer when they had to hold a single item in their working memory. This suggests that patients focus too much attention on the single item they have to remember, which impacts on the time they take to respond to a second stimuli. He argues that this explains why some patients living with schizophrenia may have slower reaction times when engaging in complex, multi-tasking activities that require them to store information while performing another task. Relating to the topic of memory impairment, Anne Marie Teti (Institute of Living at Hartford Hospital, USA) presented research that compared time-based relative memory versus events-based prospective memory across the course of schizophrenia. Clinically high-risk ($n = 25$), first-episode ($n = 20$) and chronic ($n = 35$) patients showed time-based prospective memory impairment compared to controls ($n = 29$), while only chronic patients showed impairment in events-based prospective memory. Attention deficits also increased from high-risk to first-episode to chronic patients. The findings suggest that time-based prospective memory impairments are evident in high-risk and first-episode patients and may represent a promising target for compensatory interventions to improve long-term functioning.

MacKenzie Jones (University of Miami, USA) found in both healthy controls and in patients with schizophrenia that an overconfidence in your ability to perform on a social cognitive task is not related to actual task performance. Instead, a sense of confidence was related to higher levels of self-reported depression in the patient group. This suggests that patients' current mood may be an important contributor to poor social functioning.

Improving functional outcomes and community integration was an important theme that emerged during the congress. Els van der Ven (Columbia University, USA) discussed 1-year trajectories of social and occupational functioning among a large cohort ($n > 600$) of people with recent-onset psychosis receiving early intervention services in the US. Four distinct trajectory classes of social and occupational functioning were identified. The converging (59.2%) group had disparate trajectories (low occupational, higher social) which eventually converged. The other groups had high-stable (14.8%), moderate-stable (14.7%) and low-improving (11.4%) trajectories. She found that improvements in symptoms were most noticeable in the first six months of enrolment. In particular, a female gender, being employed or in school at enrolment and private insurance status were associated with the most favorable trajectory of social and occupational functioning. Jonathan Wynn (VA Greater Los Angeles Healthcare System UCLA, USA) discussed the role of motivation as a predictor of community integration at baseline and 12 months later in homeless veterans with psychosis. He emphasized the importance of interventions targeting motivational challenges to improve community integration of homeless individuals after they are housed. Philip Harvey (Leonard M Miller School of Medicine, University of Miami, USA) reported on performance-based functional capacity measures in patients with schizophrenia using the Virtual Reality Functional Capacity Assessment Task (VRFCAT). The results revealed that patients with higher scores on reduced emotional experience were able to engage in socially relevant virtual reality simulations, in that their performance was significantly poorer on social relevant compared to solitary activities. The results pointed to the differential validity of solitary compared to socially relevant virtual reality simulations and their impact on patients who manifest social anhedonia and amotivation.

9. Neurocognition

Alfredo Sklar (Western Psychiatric Hospital, USA) presented a study investigating deficits in selective attention early in the disease course, through neurophysiological evoked responses to identify the pattern of cortical activity associated with those impairments through cortical source localization of evoked responses. Results revealed a selective attention deficit in first episode schizophrenia. Source localization analyses revealed that different patterns of cortical activity were associated with the impairment, with healthy controls showing more activity in efficient, parallel search regions across tasks and first episode patients showing more activity in inefficient, serial search mechanisms in response to a minor attention related challenge. This suggests that even during the early course of the illness, cognitive control mechanisms are disrupted.

Jun Miyata (Kyoto University, Japan) proposed the jumping to conclusions (JTC) bias of patients with schizophrenia, which is related to delusion, is associated with abnormal transition between brain states. This is based on a study including resting state functional magnetic resonance imaging data using Energy Landscape Analysis (ELA) of networks of interest (NOIs). Results showed that low-energy, stable brain states were characterized by either consistently deactivated or consistently activated brain states of all NOIs, while high-energy, unstable brain states were characterized by activation and deactivation of salience-related NOIs. Healthy participants showed significant correlation between more conservative decision making and more frequent transition between these two brain states. This relationship was broken in schizophrenia patients, with near-trend level correlation between more hasty decision making (JTC) and more frequent transition.

Ilvana Dzafic (Queensland Brain Institute, Australia) presented a study examining regularity learning in the psychosis spectrum, extending into the healthy population, in both stable and changing conditions. The study included a total of 66 participants, 22 of whom had

schizophrenia, 22 of whom were healthy controls, and 22 of whom were non-psychotic patients (i.e., had a different psychiatric disorder). Both clinical groups were worse than controls in regularity learning, but regularity learning was also associated with a continuous measure of psychic experience administered across groups, suggesting psychic experience is the driving factor, rather than a categorical diagnosis. Regularity learning errors and predictor error attenuation were related, linking implicit and explicit regularity learning behavior. The findings also revealed greater connectivity in the left primary auditory cortex in schizophrenia, suggesting a compensatory role.

Kathryn Lewandowski (Harvard Medical School/McLean Hospital, USA) reported on the findings from a study investigating the cognitive profile, clinical symptom severity, community functioning and resting state brain connectivity in patients with psychosis and healthy controls. There was reduced network connectivity in frontoparietal and motor networks in both cognitively intact and impaired patients compared to controls. Furthermore, in the cognitively impaired group additional connectivity reductions were identified in particular sub-networks. Her work emphasizes the importance of studying the neurobiological correlates of impaired cognitive functioning in psychosis.

Cassandra Wannan (University of Melbourne, Australia) presented a study on the neural correlates of visuospatial associative memory performance. It was found that in comparison to healthy controls, chronic and first episode psychosis patients have impaired visuospatial associative memory. In patients these impairments were related to hippocampal subfield volumes in the CA4/dentate gyrus and the stratum. The same was not found in the controls. She proposed that specific hippocampal subfields, such as the hippocampal stratum layers and the dentate gyrus, may be particularly sensitive to the effects of chronic stress and inflammation.

Various other presenters implicated the important role played by the hippocampus in schizophrenia. Alison Preston (University of Texas at Austin, USA) discussed the neural mechanisms that mediate the effects of past experiences on future learning. Knowledge extraction occurs by representing commonalities and differences between past and present events to sustain flexibility and decision-making in new contexts. Such capabilities are enabled by memory integration, a process through which related events become interconnected in the brain. She used an associative memory inference task during functional magnetic resonance imaging to study processes underlying learning and inferential judgment. Patients with schizophrenia showed impaired performance at the inference task, as well as, aberrant anterior hippocampal-posterior mPFC signaling. This suggests that hippocampal novelty signaling may be critical for memory integration and may underlie memory deficits in schizophrenia. Daniel Ragland (University of California at Davis, USA) presented a model in which dorsolateral PFC (dlPFC) and hippocampal deficits may be at the heart of relational memory impairments in people with schizophrenia. He discussed a study that found that individuals with schizophrenia can encode item-specific information to support familiarity-based recognition, but are disproportionately impaired in relational encoding and recollection, which involve the functioning of medial temporal lobe and prefrontal cortex. Similar abnormalities are observed in first episode psychosis and individuals at high-risk for psychosis, suggesting that episodic memory impairment predates disease onset. Suzanne Avery (Vanderbilt University, USA) presented work on relational memory and hippocampal function in cohorts of early and chronic patients with schizophrenia. Participants underwent a relational memory task during functional magnetic resonance imaging. They were exposed to repeated face and object images to study novelty response and habituation. Both early and chronic schizophrenia patients showed impairments in relational memory ability compared to healthy individuals. Relational memory impairments were associated with hippocampal habituation deficits in both the early and chronic course of the illness. This strengthens evidence supporting the role of the hippocampus in relational memory impairment in schizophrenia.

10. Neurobiology

Karen Tangmose (Copenhagen University, Denmark) proposed that thalamic glutamate levels are involved in the neural coding of prediction errors (the difference between what we expect and what actually happens) in patients with schizophrenia. She based this on findings of a study examining glutamatergic levels in the thalamus and its relationship with striatal prediction error coding in a first episode treatment naïve cohort. The study results suggest that there is a trend toward higher glutamate levels in patients versus controls. Also, a negative correlation was found between thalamic glutamate and prediction error signal in patients only.

Abanti Tagore (University of Toronto, Canada) proposed that cortical hypodopaminergia underlies cognitive impairment in schizophrenia. She based this on a positron emission tomography (PET) study examining the release of cortical dopamine during a cognitive challenge in healthy controls (HC), people with first episode psychosis (FEP), and participants at clinical high-risk for psychosis (CHR). Results revealed that when comparing FEP and HC, the FEP group had significantly less dopamine release than healthy controls in the anterior cingulate cortex and a trend toward less dopamine release in the dorsolateral prefrontal cortex, but there were no differences between groups when comparing CHR and HC.

Daniel Lodge (UT Health San Antonio, USA) discussed the prospects of targeting hippocampal interneurons as an early intervention approach for schizophrenia treatment. The experiments by his group involved a developmental disruption model of schizophrenia with prenatal methylazoxymethanol acetate (MAM) rats that is known to recapitulate some of the histological, neurophysiological and behavioral alterations of the syndrome. He presented data that examined the hypothesis that restoring GABAergic signaling would result in the rescue of the phenotype in the MAM rat model. The findings revealed an overexpression of the α5 GABA receptor subunit and was associated with increased tonic GABA currents, decreased ventral hippocampal activity, normalization of aberrant dopaminergic neuronal population activity in the ventral tegmental area, and reversed the deficits in extracellular set shifting. This provided a proof of concept regarding the underlying circuit level pathology in the MAM model in hippocampal parvalbumin interneurons.

Zheng Li (National Institute of Mental Health, USA) presented on the regulation of dendritic spine development during adolescence by Dysbindin-1 gene. In a set of experiments she investigated dysbindin-1 null mutant mice and its influence on dendritic spine morphology, synaptic transmission and spatial working memory. She found that the mice had a decreased number of dendritic spines in adolescence but not in adulthood. This was shown to be overexpression of surface dopamine 2 receptor (D2R), leading to internalization of GluN2B and reduction of cAMP, which in turn inhibit spine maturation. The specificity of D2R activation and GluN2B inhibition as the underlying mechanisms was demonstrated with agonist Quinpirole and antagonist Ro25-6981 respectively, demonstrating the endocytosis of GluN2B with D2R activation. The specificity of these effects in adolescence was demonstrated by treating the mice with D2R antagonists in adolescence but not in adulthood. This suggests that there is a critical window of intervention in adolescence that could prevent cognitive dysfunction.

Min Tae Park (University of Western Ontario, Canada) reported on the use of the previously validated MAGeT Brain algorithm to study the hippocampal subfields in First-Episode Psychosis and whether anomalies correlate with glutamate receptor density. Authors leveraged high resolution 7T brain MR images, previously published atlases of the serotonin receptor system, and gene expression data from the Allen Human Brain Atlas to test for correlations between serotonin and glutamate receptor genes. Results show selective reduction of the hippocampal subfields in early psychosis in line with previous findings, with CA4-dentate gyrus demonstrating greatest reductions. Gene expression analysis indicated 5-HTR1A and 5-HTR4 receptor subtypes as

predictors of AMPA and NMDA expression. Volumetric differences in the subfields correlated most strongly with 5-HT1A and 5-HT4 receptor densities. Overall, results demonstrate glutamate-driven hippocampal remodeling in FEP.

Laurence Coutellier (The Ohio State University) discussed how the brain specific transcription factor Npas4 mostly expressed in excitatory cells is associated with cognitive impairments, i.e., deficiency in npas4 leads to cognitive deficits. Npas4 regulates the adolescent development of prefrontal PV system. Also, adolescent (but not adult) deletion of Npas4, as well as specific deletion of Npas4 in parvalbumin interneurons, lead to cognitive deficits. These data show that the brain specific transcription factor Npas4 may be an important molecular mediator of the effects of the developmental NMDA receptor hypofunction on PV-I dysfunction, thereby contributing to cognitive deficits.

11. Imaging studies

The findings of studies using the ultra-high field 7-Tesla MRI were presented in a number of talks. Lena Palaniyappan (University of Western Ontario, Canada) presented findings from a study, which aimed to explore the contribution of brain glutamate and glutathione concentrations to the prediction of early treatment response in first-episode schizophrenia patients ($n = 26$). Low glutamate levels were associated with poorer social and occupational functioning at baseline, while higher baseline glutathione were associated with a decreased time to respond to antipsychotic treatment. In particular, it took patients with high glutathione levels only four weeks to achieve a 50% reduction in symptom severity, compared to nine weeks in patients with low glutathione levels. These findings support the added value of measuring glutathione levels for improved early prognostication and tailoring of treatment in first-episode schizophrenia. Adrienne Lahti (University of Alabama, Birmingham, USA) presented results from a study, which sought to explore the relationship between cortical glutamate/GABA levels, blood-oxygen level dependent response during a cognitive task, and functional brain connectivity during resting state in first-episode psychosis patients ($n = 21$) compared to healthy controls ($n = 21$). In this study, glutamate levels were lower in patients versus controls, and showed opposing associations with the blood-oxygen level dependent response in the two groups. This suggests that the dynamics of major neural networks disrupts the relationship between cortical glutamate levels and the blood-oxygen level dependent response during the resting state. Hilleke Pol (University Medial Centre Utrecht Brain Centre, Netherlands) presented data on the relationship between brain GABA/Cr concentrations and cognitive performance in schizophrenia patients ($n = 17$) compared to healthy controls ($n = 23$). In this study, medical prefrontal GABA concentrations were lower in patients compared to controls, and associated with better cognitive functioning. These findings support the notion that changes in brain metabolism, including altered cortical GABA levels are associated with cognitive performance in schizophrenia. Sophia Frangou (Icahn School of Medicine at Mount Sinai, USA) presented data from a study, which explored the use of ultra-high field brain imaging to detect intra-cortical myelination abnormalities in recent-onset schizophrenia patients ($n = 17$) and healthy controls ($n = 22$). In this study, patients showed abnormal “flattening” of the myelin distribution curve, in frontal, visual, auditory and somatosensory areas The findings indicate that intracortical myelin imaging can be used to identify regions showing evidence of early neurodevelopmental abnormalities in cortical organization.

Achim Burrer (University Hospital of Psychiatry, University of Zurich, Switzerland) presented a study that investigated whether motivational deficit in healthy individuals with schizotypal personality traits (SPT) and patients with first episode psychosis (FEP) are associated with reduced striatal volume and reduced thickness of the orbitofrontal cortex (OFC). Results showed a negative association between apathy and lower volume of right nucleus accumbens and putamen bilaterally in individuals with SPT. In patients with FEP, apathy was negatively associated with reduced OFC thickness. No structural associations were identified with diminished expressivity. Thus, structural correlates of apathy could be observed in healthy individuals with high SPT, and in patients with first episode psychosis.

Gemma Modinos (Institute of Psychiatry, Psychology, & Neuroscience at King's College London, UK) presented a multi-site case-control meta-analysis of structural MRI scans in non-help seeking individuals with schizotypy, based on the notion of dimensional continuity on the psychosis-spectrum between the general population and patients with psychosis. Results showed a significant reduced volume of left putamen in high schizotypy compared to low schizotypy. The results support a profile of subcortical abnormalities involving the striatum in healthy individuals with subclinical psychotic-like experiences.

Philipp Homan (Feinstein Institute for Medical Research, USA) proposed that alterations of certain connectome measures could be implicated in cognitive deficits in individuals with schizophrenia. The graph theoretical approach of cortical network mapping was applied to diffusion weighted imaging and structural MRI data to derive measures of network organization and network efficiency and a regression analysis was used to predict individual variation of higher cognitive and social cognitive performance. The main findings revealed that impairments specifically in reasoning capacity were significantly associated with rich club organization in patients.

Vishnu Murty's (Temple University, USA) presented a study investigating the interaction between contextual information, episodic memory and large-scale memory networks in first episode psychosis. In this study patients showed a trend towards greater connectivity within the anterior medial networks compared to controls, while completing a resting-state scan. While there were no group differences with regard to the posterior medial networks, the integrity of posterior medial networks predicted individual differences in the organization of verbal learning. He concluded that interactions across large-scale memory networks might influence the types of contextual information that patients used during verbal learning.

Lindsay Oliver (University of Toronto, Canada) presented a study aimed at detecting functional connectivity in separate subnetworks underlying the same complex social cognitive task in individuals with schizophrenia spectrum disorders and healthy controls. The findings revealed that in low performers, greater functional connectivity across social cognitive subnetworks was associated with lower social cognitive performance when compared to high performers across both patients and controls. A combination of both upregulated and downregulated mirroring, empathy, and mentalizing networks were related to better social cognitive performance.

12. Big data

Bo Cao (University of Alberta, Canada) introduced the term ‘big data’ as a relative term that can be differently defined dependent on one's perspective (i.e. data volume, data variety or data velocity) or one's intention of analyzing the data. He discussed his study, which focused on identifying and predicting biomarkers in medication-naïve individuals with first-episode schizophrenia and predicting individual responses to antipsychotic treatment within the field of precision medicine with the use of machine learning. The main findings of the study were that the identification of patients (balanced accuracy: 78.6%) and the antipsychotic treatment response prediction were successful (balanced accuracy: 82.5%) with using functional connectivity data.

Jennifer Coughlin (John Hopkins Medicine, USA) discussed the utility of imaging in psychiatric research – and PET imaging in particular. PET imaging may optimize diagnostic precision through the development of novel radiotracers for targeting key proteins relevant to psychosis. One of such new developments is [^{18}F]FNDP, which binds

soluble expoxide hydrolase. Other new radiotracers relevant to study of neuroimmunity were also presented. She proposed incorporating PET imaging in clinical research protocols that focus on studying the neuroimmune response in psychosis, which can run parallel to study of biomarkers in blood or cerebrospinal fluid. She also emphasized a need for a consortium platform to share PET data to move the field forward. Another talk referring to the role played by consortia is that of Neda Jahanshad (Keck School of Medicine, USA). She emphasized the main goals of the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA) consortium, namely to overcome major shortcomings of structural neuroimaging studies in schizophrenia, including incorrect or lack of statistical correction and the lack of replication studies due to the use of different scanners and underpowered candidate neuroimaging genetic studies. She mentioned that the ENIGMA Genome-wide Association study (GWAS) of subcortical structures, with approximately 15,000 subjects, showed highly consistent and replicated data across sites. She also referred to the fact that the latest GWAS resulted in optimized replication data of structural cortical measures across the whole human brain, including measures of surface area and cortical thickness that allows one to study age effects across the lifespan.

However, challenges with the use of big data were also discussed. In particular, the long duration of collaborative projects across many different sites and the agreement on harmonized protocol steps. Ofer Pasternak (Harvard Medical School, USA) proposed the development of data harmonization to overcome some of these challenges. In particular, he discussed advanced diffusion MRI acquisition and analysis methods based on Free-Water Imaging to improve specificity in a harmonized schizophrenia diffusion tensor images (DTI) data set.

13. New paradigms of discovery

Roman Kotov (Stony Brook University, USA) discussed the value of using a dimensional approach to diagnosing patients with psychotic disorders. He discussed the usefulness of a hierarchical, multi-dimensional framework of symptoms and traits, called the Hierarchical Taxonomy of Psychopathology (HiTOP). HiTOP is a model that characterizes psychopathology dimensionally rather than binary absent/present states. According to this model schizophrenia can be categorized into two distinct spectra, namely psychoticism and detachment with various symptom dimensions falling under each spectra. He suggests that this framework has greater validity and reliability than conventional diagnostic manuals.

Brett Clementz (University of Georgia, USA) discussed the Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP) project, which used biotypes to diagnose patients with schizophrenia. He explained that there are different levels of intrinsic activity across the different biotypes, which is not evident when comparing patients across diagnostic and statistical manual of mental disorders (DSM) categories. His team furthermore found that by using the biotypes and deviations in level of intrinsic neural activity they were able to accurately predict which patients are more likely to respond to different treatment types. In future, clinicians might find the use intrinsic neural activity useful as a biomarker for differential treatment response. Similarly, Rebekah Trotti (University of Georgia, USA) presented findings from the bipolar-schizophrenia network on intermediate phenotypes (BSNIP) study in which the authors compared emotional scene processing between healthy controls (n = 197) and patients classified across three biotypes, i.e. those with 1) low cognitive control and low sensorimotor reactivity (n = 198), 2) low cognitive control and high sensorimotor reactivity (n = 176), and 3) high cognitive control and average sensorimotor reactivity (n = 243) using EEG. Principal component analysis identified two components of interest, namely an occipital component involved in early visual processing, and a later emotionally-driven central parietal component. Patients in the first group (n = 198) differed the most from the other study groups on both components. These findings suggested that the BSNIP biotypes may be a useful for distinguishing psychosis patients in terms of emotional scene processing and may represent an index of functional impairment.

Michael Kirschenbaum (Zucker Hillside Hospital, Psychiatry Research, USA) studied Google search entries in people with first-episode psychosis. He found that the majority Google searches were not related to mental health and of those that were related to mental health, the searches often targeted delusion related content, illicit drugs, or motivational deficits. He proposed that Google search content differs from clinical intake documentation and suggests that online search behavior can provide a unique source of patient information.

Emily Eisner (University of Manchester) presented results from a pilot study that explored the feasibility, acceptability and validity of a smartphone application (ExPRESS) used to assess early signs and basic symptoms as putative predictors of psychosis relapse. Patients diagnosed with psychosis (n = 18) used the application for six months, during which they were prompted by the application to indicate their mood, symptoms, and early signs of relapse. Over the course of the study, participants completed 65% of the application assessments and completion declined gradually over time. Greater depression and fear of relapse at baseline was associated with decreased likelihood of completing the application. The application showed high acceptability and good predictive validity in terms of predicting symptoms over a period of three weeks. These findings indicated that app-based monitoring is a feasible, acceptable and valid means of predicting and assessing relapse that will decrease the burden on both patients and caregivers.

Robert W. Buchanan (University of Maryland School of Medicine, USA) introduced the notion of identifying individuals with schizophrenia spectrum disorders based on the neural strategy used to perform the 'Imitate/Observe' fMRI task, rather than based on their clinical diagnosis. In this study, Ward's hierarchical clustering of fMRI data during the social cognitive task was applied to characterize participants into groups dependent on shared or similar neural patterns of neural network activation. They were able to identify three clusters with distinct patterns of neural circuit engagement during the performance of the Imitate/Observe task, which were not related to clinical diagnosis or clinical site. There were significant differences in social cognitive and neurocognitive test performance across the three clusters.

Aristotle Voineskos (Centre for Addiction and Mental Health, Canada) presented findings from a multi-center prospective study, which investigated the neural underpinnings of social processes in schizophrenia spectrum disorders. Study measures included neuroimaging, cognitive assessment, and several behavioral tasks. The study used a data-driven approach to identify functional MRI biomarkers of social function and cognitive performance. The study also identified three data-driven clusters of participants based on patterns of neural activity during the facial imitate/observe functional MRI task, and interestingly cluster membership was not related to schizophrenia diagnosis. Relating to the theme of neurobiological underpinnings of social processes as relevant markers, Erin Dickie (University of Toronto, Canada) discussed the advantages of using the personalized intrinsic network topography (PINT) approach when studying potentially relevant biological markers in individuals with schizophrenia. She applied this newly developed toolbox to resting-state data collected as part of the Social Processes Initiative in Neurobiology of the Schizophrenia(s) SPINS study and other datasets on an individual level. The main findings were that correlations between well-established cortical networks and the striatum as well as the cerebellum were increased in both patients and controls when using PINT compared to group templates. When patients and healthy controls were compared, statistically robust reduced and increased functional connectivity patterns of cortical-subcortical connections were found. The PINT approach may be more useful than previous group-based approaches.

14. Treatment outcomes and clinical trials

Findings from the amisulpride and olanzapine followed by open-

label treatment with clozapine in first-episode schizophrenia (OPTiMISE) study were presented. Mark Weiser (Sheba Medical Center, Israel) explained that individuals presenting with a first episode of psychosis often respond well to antipsychotics but frequently experience a relapse, particularly when antipsychotics are discontinued. His talk focused on the prediction of subsequent relapse among those who met remission criteria during the OPTiMISE study. In multivariate analyses, cannabis was the only statistically significant predictor of relapse. He noted that this corresponds with findings from previous studies showing that cannabis is an important relapse predictor given that cannabis affects dopamine release, which is related to symptom severity. However, he also raised the possibility that cannabis use may be simply a marker of a more severe type of illness. Armida Mucci (University of Campania L. Vanvitelli, Italy) focussed on the prevalence and impact of persistent negative symptoms (not confounded by depression or extrapyramidal symptoms) in the OPTiMISE sample. Negative symptoms were associated with poor psychosocial functioning. Persistent negative symptoms predicted the worse psychosocial functioning at the end of all treatment phases and were the most resistant to antipsychotic treatment including clozapine. Lone Baandrup (Psychiatric Center Glostrup, Denmark) examined the psychometric properties of the negative symptom sub-scale of the positive and negative syndrome scale (PANSS), using data from phase 1 of the OPTiMISE study. Rasch models were used to investigate whether the information kept in the seven negative symptom items was exhausted by the sum across items. Based on the findings of the rasch analysis she found that the negative symptom subscale did not possess the necessary properties to be a valid rating scale: items were inconsistent and did not allow calculation of sufficient individual scores containing complete negative symptom information for each participant. In contrast, an individual item approach better fulfilled the criteria of the Rasch model: the sum score for each negative symptom item across visits was a sufficient measure of the latent initial value.

A number of presenters focused in their talks on predictors of treatment outcome. Kate Merritt (Institute of Psychiatry, Psychology, & Neuroscience, King's College London, UK) discussed the relationship between symptomatic reduction and change in glutamate during initial antipsychotic treatment using proton magnetic resonance spectroscopy. The results revealed that the nature of the response to antipsychotic medication could be related to the pattern of changes in glutamatergic metabolite levels over the course of treatment, emphasizing the links between treatment response and alterations in central glutamate function. Jennifer Barnett (Cambridge Cognition, UK) suggested that latent inhibition, a learning phenomenon known to be disrupted in schizophrenia, may be a potential biomarker for stratification in schizophrenia drug development. Their study established a reliable measure of latent inhibition and showed it could be modified by both pharmacological and clinically-relevant manipulations in healthy volunteers by using double-blind crossover designs. Brian Miller (Augusta University, USA) identified significant correlations between cytokine levels and psychopathology scores in patients with schizophrenia using a meta-analysis approach, which may benefit understanding and treatment of schizophrenia. In particular, they suggest that these modest but significant correlations are indicative of a biological gradient across the disease course that should be further explored in relation to the underlying pathophysiology of schizophrenia. Cameron Carter (UC Davis Health System, Imaging Research Centre, USA) found that baseline frontoparietal task-related activity significantly predicted clinical improvement after one year of treatment in patients with early psychosis. He also indicated the potential utility of functional magnetic resonance imaging in personalized medicine, as treating patients presenting with low frontoparietal activation by specialized intervention may improve outcome. Daniel Martins-De-Souza (University of Campinas, Brazil) identified biomarkers predictive of response to medication in plasma from patients before and after treatment with antipsychotics. They sought to validate the main biological processes previously found associated with schizophrenia, such as tripartite synapses, spliceosomas, myelination and alterations associated with energetic pathways, as well as the role of the endocannabinoid system in glia.

The following talks highlighted the theme of recovery and relapse. Sidhant Chopra (Brain and Mental Health Hub, Monash University, Australia) discussed the protective effects of atypical antipsychotics on grey matter decline in psychosis. The relationship between greater volumetric increase in the pallidum and better symptomatic outcome suggests a key role of this structure in mediating symptom recovery. Jose Rubio (Northwell Health, USA) presented on the incidence rate and risk factors of relapse in patients diagnosed with a schizophrenia spectrum disorder on maintenance treatment with long acting injectable antipsychotics, for whom treatment adherence was confirmed. In a national cohort, the results revealed that over a follow-up period of up to 20 years, almost one third of patients relapsed despite ongoing antipsychotic treatment. Greater risk was observed for younger individuals and also for lower clinical stability achieved despite antipsychotic treatment.

Olivier Corbeil (Mental Health University Institute of Quebec, Québec, Canada) examined the association between aripiprazole exposure and problem gambling in patients treated for first-episode psychosis. The results revealed that the use of aripiprazole was associated with more than a 10-fold increased risk of problem gambling. These findings highlight the need to systematically evaluate gambling history in all first-episode patients at entrance in first-episode psychosis programs.

Ina Weiner (Tel-Aviv University) presented data on maturation-dependent efficacy of an ultra-low dose (0.045 mg/kg) of risperidone in preventing structural brain and behavioral abnormalities in adult female and male rats prenatally exposed to polyinosinic-polycytidilic acid (poly-I:C). Based on previously published trajectories of structural and behavioral deficits in poly-I:C offspring of both sexes, RIS was given in four different time-windows (TWs) between young adolescence and young adulthood. Adult poly-I:C offspring of both sexes had smaller hippocampus, striatum, and prefrontal cortex volumes and larger lateral ventricles volumes, disrupted latent inhibition LI and excessive response to amphetamine. In both sexes, RIS prevented both structural and behavioral abnormalities when given at TWs prior to but not after the emergence of behavioral abnormalities. Because behavioral abnormalities emerged later in females than males, RIS was effective longer in females. These results demonstrated that prevention of behavioral abnormalities required reversal of structural deficits and that efficacy of prevention is lost with maturation.

Amanda Lyall (Brigham & Women's Hospital, Harvard Medical School) reported results from a clinical trial wherein participants were scanned at treatment onset and then randomly assigned to 16 weeks of treatment with either risperidone and omega-3 or risperidone and placebo. Participants were also scanned at the end of the clinical trial. Their results suggest that omega-3 supplementation may partially attenuate risperidone treatment-related white matter alterations in patients with recent-onset psychosis.

Clinical trials on the efficacy of antipsychotic drugs in the treatment of cognitive impairment associated with schizophrenia (CIAS) came under discussion. Stephen Brannan (Karuna Pharmaceuticals, USA) reported on lessons learned from Forum's two global, placebo-controlled, Phase III trials in stable patients with Cognitive Impairment Associated with Schizophrenia (CIAS). All treatment groups showed improvement, including the Placebo group. The post hoc analyses revealed the following. Firstly, learning effects can be sustained, it is not easy to get to the “plateau” where learning ceases to increase between testing (i.e. the frequency of testing may be a factor, regional differences add to the variance of a global program, differences in experience in rating the outcome measures can be critical - raters should thus be experienced, low enrolling sites add to the variance and harm potential drug-placebo differences). Subjects who are substantially noncompliant add to the variance. Increasing enrollment speed can have deleterious

effects (i.e. subjects "stable" on two antipsychotics had much larger placebo responses than those stable on one antipsychotic, subjects enrolled at the end of the study had substantially different responses than those enrolled at the beginning of the study). Lastly, the impact of which antipsychotic subjects were stable on played a role (i.e. the greater the sedative properties, the less the cognitive benefit, anticholinergic properties-the greater the effect, the less the cognitive benefit). Kiri Granger (Cambridge Cognition, UK) investigated individual-level trajectories of cognitive performance among patients with schizophrenia enrolled in a multi-national Phase II clinical trial. They conducted a re-analysis of an existing trial on 463 patients with schizophrenia. Participants completed two different neurocognitive test batteries, the Cambridge Neuropsychological Test Automated Battery (CANTAB) and the MATRICS Consensus Cognitive Battery (MCCB) at four time points: screening, baseline, week 6 and 12. Individual level trajectories of cognitive performance revealed that patients who performed below the normative mean at screening, showed a consistent improvement in their performance across the rest of the study, while patients who perform in the healthy individual range did not improve. John Hutchison (Autifony Therapeutics, UK) presented on AUT00206, a novel drug that modulates Kv3.1 and Kv3.2 channels. In animal models, it showed an increase of the activity of parvalbumin interneurons and a rescue of cognitive function. The potential of AUT00206 has been evaluated first in healthy volunteers (Phase 1a) and subsequently in patients (Phase 1b). Potential effect of the drug on cognitive performance was evaluated with the Cambridge Neuropsychological Test Automated battery (CANTAB); potential effect on neural circuitry was assessed from measurement of auditory-evoked potentials, including the mismatch negativity (MNN) response. Phase 1a support the safety and potential efficacy of AUT00206. The phase 1b is currently underway to establish whether AUT00206 can positively impact cognitive outcomes. Interestingly, Jack Cotter (Cambridge Cognition, UK) presented the findings of a systematic review of clinical trials published between 2000 and 2019. The findings revealed that only 11.5% of pro-cognitive pharmacotherapy trials conducted in patients with schizophrenia required the presence of an objectively assessed cognitive deficit as part of their patient eligibility criteria. This is important as recent evidence has suggested that up to a quarter of patients exhibit 'normal' cognitive performance (relative to matched healthy controls), and that these individuals are significantly less likely to exhibit changes in cognition when participating in intervention trials. He suggested that the exclusion of these patients, or at least the stratification of patients based on cognitive performance at baseline, could provide additional statistical power to observe pro-cognitive treatment effects in clinical trials.

Gjessing Jensen Karsten (Mental Health Centre, Capital Region of Denmark) discussed the Tolerability and Efficacy of Antipsychotics (TEA) trial, which investigated the cardiometabolic effects of extended release quetiapine versus aripiprazole in youth with first episode psychosis in Denmark. The study found greater weight gain in the youth randomized to quetiapine compared to the youth randomized to aripiprazole after 12 weeks of treatment. Aripiprazole also had a more favorable profile in terms of several other cardiometabolic indicators, including waist circumference, blood pressure, cholesterol, insulin increase, and insulin resistance. Bjϕrn H. Ebdrup (University of Copenhagen, Denmark) reviewed the treatment of antipsychotic-associated obesity with the glucagon-like peptide-1 (GLP-1) receptor agonist exenatide, an antidiabetic drug. The study randomized patients with schizophrenia and obesity to exenatide or placebo. It was found that exenatide was not associated with weight loss after 3 months but was associated with subtle improvements in bone markers. In contrast, a meta-analysis suggests that GLP-1 agonists are effective for antipsychotic-induced weight gain, especially in patients treated with clozapine and olanzapine.

Marc-André Roy (Université Laval, Canada) presented a retrospective cohort analysis of 22 patients who experienced neutropenia and were either re-challenged ($n = 16$) or maintained ($n = 6$) on clozapine and followed for a mean of 7.2 years. At the end of the observation period, only one patient stopped clozapine due to neutropenia after the patient experienced 11 neutropenias. The results suggest that maintaining a patient on clozapine or re-challenging the patient with clozapine after a few months could be a useful treatment option following a neutropenia episode after discussing risks/benefits with the patient and his/her family.

Alan Breier (Indiana University School of Medicine, USA) presented findings from an eight-week randomized "add-on" study investigating fingolimod, an anti-inflammatory agent approved for relapsing multiple sclerosis, versus placebo in schizophrenia. The study randomized 40 subjects and found that there was no significant difference between fingolimod and placebo in terms of cognition and symptoms. However, there was a relationship between fingolimod-induced percent lymphocyte decreases and diffusion tensor imaging fractional anisotropy (DTI-FA) increases.

Kenneth Koblan (Sunovion Pharmaceuticals, Inc., USA) discussed a study that investigated SEP-363,856, a novel psychotropic agent with a non-D2 mechanism of action, for the treatment of schizophrenia. SEP-363,856 is a full agonist at TAAR1 and 5-HT1A. SEP-363,856 reduced striatal activation in a reward processing task. Furthermore, in a 4-week randomized, placebo-controlled trial, SEP-363,856 reduced total psychotic symptoms and negative symptoms. The drug was well-tolerated in the 4-week randomized controlled trial and in the subsequent 6-month open label period.

Thomas Guillot (Neurocrine Biosciences, Inc, USA) discussed a study investigating the long-term effects of valbenazine on tardive dyskinesia in patients with schizophrenia /schizoaffective disorder. Valbenazine is a highly selective vesicular monoamine transporter 2. After either 42 or 48 weeks of treatment with valbenazine, participants were recruited to be followed for an additional 72 weeks, and in this longer follow-up period, valbenazine continued to be generally well-tolerated with high rates of patient satisfaction and improvements in tardive dyskinesia symptoms.

Matthijs Bossong (University Medical Center Utrecht, Netherlands) presented a study that found cannabidiol reduced resting state perfusion in a brain network comprised of the parahippocampus, hippocampus, and striatum in a 3-week randomized controlled trial comparing placebo ($n = 17$) with purified cannabidiol ($n = 16$) in individuals at clinical high risk for psychosis. While total symptom scores decreased more with cannabidiol than placebo, the differences were not statistically significant.

15. Genetic studies

Lynn DeLisi (VA Boston, USA) presented a historical perspective on the genetic heritability of schizophrenia. Schizophrenia is considered a complex non-mendelian trait, and involves multiple genetic factors, as well as gene-environment and epistatic interactions. Initial family and twin studies support a high heritability for the disorder (~80%). Early linkage studies also led to the identification of initially promising risk genes of interest, such as dysbindin and neuregulin. Genome-Wide Association Studies (GWAS) conducted over the last decade have identified hundreds of other significant sites with promising leads that do not include the earlier findings. However, some of the heritability for schizophrenia cannot be explained only by these variants, suggesting the involvement of rare mutations with a large effect size within some families. Genetic testing may hold value in the near future for prediction of treatment response as a promising avenue for further research, but it is unlikely to be useful for predicting who will develop schizophrenia.

The relationship between genetic factors and cognitive functioning came under discussion. Cecilie Lemvigh (University of Copenhagen, Denmark) conducted a twin study ($N = 214$) to investigate the association between specific cognitive domains, using the Cambridge

Neuropsychological Test Automated Battery, and genetic liability for schizophrenia. The study findings indicate that the spatial span task, which is a measure of working memory, is associated with genetic liability for schizophrenia, which is independent of IQ. Giada Tripoli (King's College London, UK) also investigated the association between cognition and genetic factors. She examined whether the genetic risk that someone has for schizophrenia (defined by a polygenic risk score) is associated with facial emotion recognition, a measure of social cognition. Her study included 412 individuals with a first episode of psychosis and 805 healthy controls. The study findings indicate that a higher polygenic risk score for schizophrenia is a predictor of poorer facial emotion recognition, especially for negative emotions.

Jaana Suvisaari (National Institute for Health and Welfare, Finland) presented ongoing work examining CCL22 and 37 other important cyto- and chemokines in a longitudinal study. The cohort consisted of a clinically high risk (CHR) participants (n = 35), patients with a first episode of psychosis (FEP) (n = 129) and healthy controls (n = 130). The study supports elevated levels of CCL22 in FEP, additionally showing elevated levels in CHR. Elevated CCL22 level was correlated with symptom severity at both baseline and one-year follow-up. Increased levels of CCL22 also correlated with almost half of the other immune markers studied.

Johannes Vogt (Phillips-University Marburg, Germany) discussed the role of synaptic lipid signaling (lysophosphatidic acid signaling/LPA signaling) in neuropsychiatric disorders specifically in the context of schizophrenia. He and his team utilized electron microscopy, cell culture experiments, mass spectrometry and electrophysiological experiments to probe the scope and extent of synaptic LPA signaling in the mouse model. They noted that autotaxin (ATX) is synthesized in the astrocytic compartment, and selectively modulates excitatory but not inhibitory synapses on glutamatergic neurons. Further, both pharmacological and cell-type specific genetic inhibition of ATX resulted in rescue of hyperexcitability, and this was further demonstrated in the ketamine model of schizophrenia where cortical hyperexcitability, hyperlocomotion and a reduced PPI were reversed to wild type levels. The results point towards a novel mechanism to target with future drug therapies that can restore excitatory inhibitory imbalance by targeting synaptic ATX.

Inna Gaisler-Salomon (University of Haifa, Israel) presented data on the regulation of glutamate homeostasis by neuron-astrocyte interaction and its relevance to cognitive function in schizophrenia. She investigated the molecular, functional and behavioral implications of disrupting glutamate dehydrogenase activity in the brain using mouse models with CNS-Glud1 homozygous and heterozygous mutations. She tested the interaction of this mutation with an environmental manipulation by a stress exposure paradigm with social isolation. Homozygous CNS-Glud1 mutant mice displayed schizophrenia relevant phenotypes such as amphetamine induced hyperlocomotion, spatial acquisition and reversal deficits in the water T-maze and social preference deficits. This was accompanied by astrocytic glutamate metabolism deficits. These abnormalities were absent in heterozygous mice but upon exposure to stress by adolescent social isolation, the cognitive deficits could be recapitulated even in these mice.

Sinead O'Donovan (University of Toledo, USA) reported on cell type specific alterations in adenosine generating pathways in schizophrenia. She investigated the adenosine hypothesis in enriched populations of pyramidal neurons and enriched populations of astrocytes from the dorsolateral prefrontal cortex of schizophrenia subjects and corresponding controls (n = 16/group). The effects of chronic antipsychotic exposure in the postmortem sample were controlled for by examining gene expression patterns in haloperidol-decanoate treated rats. No change was found in adenosine kinase gene or protein expression, considered a key regulator of extracellular adenosine levels. However, genes involved in extracellular adenosine-generation were significantly altered in a cell-specific manner (ENTPD1 and 2 in astrocytes, ENT1 and adenosine receptor A1 in pyramidal neurons). A1 receptor expression changes may be driven by antipsychotic exposure. The results provided new insights into the role of adenosine hypofunction in schizophrenia.

Philip Haydon (Tufts University, USA) presented in vitro and in vivo work suggesting that NMDA receptor hypofunction in schizophrenia may be related to diminished activity of the α7-nAChR that is expressed on astrocytes in the hippocampus. His work explored the role of astrocyte in synapse modulation mainly during sleep. This modulation seems to be NMDAR/D-serine-dependent according to time of the day and darkness. NMDAR co-agonist site saturates during the dark phase (active phase) – endogenous d-serine decreases. Nicotinic receptors are particularly important in astrocytes: optogenetic stimulation of cholinergic fibers causes an alfa-7 dependent increase in occupancy of co-agonist site of NMDAR, but neuronal alfa7 are not required for cholinergic control of NMDAR co-agonist. He found that deletion of astrocytic alfa7 nicotinic receptor leads to reduced hippocampal d-serine in male mice, but not in female. The findings may guide strategies for using medications that stimulate the α7-nAChR to normalize NMDA receptor function in schizophrenia. Similarly, Anthony Grace (University of Pittsburgh, USA) presented data from animal studies of a developmental disruption model of schizophrenia that support aberrant activity of the α7-nAChR, as well as the ability of novel classes of α7-nAChR-modulating drugs acting in the hippocampus to reverse the hyperdopaminergic tone. His presentation focused on the MAM developmental model of schizophrenia that is based on the dopamine hyperresponsivity hypothesis of schizophrenia. Compared to control rats, MAM rats had significantly increased number of active DA neurons in the ventral tegmental area driven by an overactive hippocampus. Both full and partial agonists reduced the hyperdopaminergic state in MAM rodents compared to controls This is a novel finding suggesting the potential of alpha 7 receptors as a therapeutic target for schizophrenia.

Then, Jennifer Coughlin (Johns Hopkins University, USA) presented in vivo imaging findings using [^{18}F]ASEM PET in patients with recent onset of psychosis. In this study, [^{18}F]ASEM with positron emission tomography (PET) was used to test for low in vivo availability of the hippocampal α7-nAChR in individuals with recent onset psychosis compared to healthy controls (HC). Results showed that, among patients with recent onset psychosis, hippocampal [^{18}F]ASEM binding (total distribution volume) was lower in comparison to controls. Among patients, higher hippocampal [^{18}F]ASEM binding was associated with better verbal memory and processing speed.

Sharon Hunter (University of Colorado, USA) presented data from a recent clinical study probing preventative pharmacologic strategies targeting cholinergic signaling in psychosis. In a double blind randomized control design, 100 pregnant women were given 900 mg of choline or corn oil daily and for 3 months, the infants received 100 mg of choline. At 4 weeks of age, supplemented infants had better cerebral inhibition with P50, which was true even for infants with increased genetic risk. It was also noted that the males responded better than the females to choline supplementation. She emphasized the importance of increasing the choline levels in maternal diet, treating maternal mental health conditions like anxiety and depression, and abstinence from nicotine and cannabis, to help preserve normal development.

Kiran Girdhar (Mt Sinai, USA) presented research on differential histone medication in schizophrenia patients (n = 250) compared to controls (n = 330). Differential binding of enhancer regions were evident between the two groups. Pathway analysis further showed enrichment in enhancer regions for potassium and calcium channels. There was also significant enrichment for genome-wide association study loci for differentially modified enhancer regions.

Victoria Rodriguez (King's College London, UK) presented findings from a study, which explored whether a polygenic risk score for schizophrenia, bipolar disorder and depression can distinguish between diagnostic categories for affective psychosis. Both the polygenic risk score for schizophrenia and bipolar disorder effectively distinguished between non-affective psychosis and bipolar disorder compared to

controls, whereas only the bipolar polygenic score was able to distinguish psychotic depression versus controls. The schizophrenia polygenic risk score could further distinguish between affective and non-affective psychosis and, within the former, between bipolar psychosis and psychotic depression.

Guillo Pergoa (University of Bari Aldo Moro, Italy) presented results from a study, which compared the neurophysiological correlates of polygenic risk and co-expression (miR-137 network translation). Co-expressed genes were associated with miR-137, which was involved with working memory and emotional face processing. A polygenic co-expression index was developed to predict treatment response to olanzapine in patients.

16. Negative symptoms

Dawn Velligan (University of Texas Health Science Centre at San Antonio, School of Medicine, USA) reviewed the literature on the Motivation and Engagement (MOVE) program, which consists of different therapeutic components to improve negative symptom domains and functioning. She highlighted that psychosocial interventions, such as MOVE are associated with improvement in only certain domains, but not all domains.

Jason Holden (University of California, San Diego, USA) presented a novel intervention for negative symptoms in schizophrenia, called the Mobile-assisted Cognitive Behavioural Therapy for Negative Symptoms (mCBTn), which combines Cognitive-Behavioral Social Skills Training and a smartphone intervention ("CBT2go" application). He conducted a study to determine whether weekly group CBT sessions paired with the CBT2go application could reduce defeatist attitudes. Results show significant reductions in both defeatist beliefs and motivational negative symptoms over time (up to 24 weeks) in comparison to baseline, with medium to large effect sizes.

Melanie Bennett (University of Maryland School of Medicine, USA) presented on the topic of enhancing community functioning in veterans with schizophrenia. Results were presented from an ongoing randomized clinical trial of a behavioral intervention to increase community engagement across three centers, called Engaging in Community Roles and Experiences (EnCoRE). To date, 108 veterans with schizophrenia spectrum disorders and negative symptoms have enrolled. Taken together, participants were positive about the program and in particular about the benefits of action planning and social skills training. Those who attended more often reported more frequent use of EnCoRE skills and strategies to increase participation in community activities. Participants reported doing more activities that they found enjoyable, and there was some suggestion that people continued this after the program ended.

Felice Reddy (VA Greater Los Angeles, USA) presented a study that used an intervention consisting of Motivational Interviewing (MI) and cognitive behavioural therapy (CBT) interventions for the treatment of negative symptoms. She randomized veterans with schizophrenia and negative symptoms to 12 weeks of either group-based MI + CBT for negative symptoms (treatment arm) or a mindfulness skills training group (control arm). Participants in the treatment arm showed improved motivational negative symptom scores. However, no changes have been observed on the defeatist beliefs or community functioning measures, though this may be due to the behavioral focus of the intervention, or its length.

Thomas Pollak (Institute of Psychiatry, Psychology & Neuroscience, King's College London) examined plasma samples from individuals at clinical high risk (CHR) for psychosis and healthy controls and found toxoplasma exposure was related to severity of negative symptoms and poor functional outcomes in CHR individuals. Moreover, he suggested Epstein-Barr virus (EBV) exposure could be a protective factor for developing psychosis.

Anthony Ahmed (Weill Cornell Medical College New York Presbyterian Hospital, USA) critiqued the two dimensional model of negative symptoms. According this model symptoms are categorized into either diminished expressions or anticipated experience of emotions. Instead he proposed that a five factor model is more appropriate. Together with his colleagues he conducted a serious of studies, which included a factor analysis examining the latent structure of negative symptoms from the Scale for the Assessment for Negative Symptoms (SANS), Brief Negative Symptom Scale (BNSS), and Clinical Assessment Inventory for Negative Symptoms (CAINS), as well as a network analysis, which was applied to examine the latent structure of negative symptoms in American and Italian outpatients rated on the BNSS. The findings provide support for a five-factor structure model, including emotional blunting, anhedonia, asociality, avolition and alogia.

17. Psychosis among migrants and minorities

Brian O'Donoghue (Orygen, the National Centre of Excellence in Youth Mental Health, Australia) investigated whether migrants have an increased risk of developing a first episode of psychosis (FEP) and transitioning to a full psychotic disorder. Data included records from individuals aged 15–24 years with a FEP who presented to an early psychosis centre in Melbourne between 2011–2013 ($N > 700$), and records from a cohort of young people identified as ultra-high risk ($N > 400$). Overall, there was no significant difference in risk of psychosis for migrants as a total group. However, migrants from North and Middle East Africa and Sub-Saharan Africa showed increased risk of developing a FEP compared to individuals born in Australia. In contrast, migrants from Asia showed decreased risk of developing a FEP compared to natives. First-generation migrants were under-represented in the ultra-high risk cohort, suggesting that they are less likely to attend ultra-high risk clinics. With regard to transitioning, data was pooled from other groups ($N > 2000$), revealing no difference in the rate of transition for migrants versus those born in Australia. Thus, particular migrant groups in Australia have increased risk of developing a FEP but are under-represented in ultra-high risk clinics.

Els van der Ven (Columbia University, USA) presented data investigating the risk of psychotic disorder in first- and second-generation immigrants across urban and rural areas in different host countries. Incidence rates were analyzed from individuals with a first episode of nonorganic psychosis from the European Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI) study, including 19 centres across Europe ($N > 1500$). Overall, there was a higher incidence of psychotic disorders among non-Western migrant groups in Europe. Regions with greater overall incidence also had a higher incidence rate among migrants, including London, Amsterdam, Paris, and Creteil. The relative risk between sites was quite variable, with almost a seven-fold increase in variation in migrants. These results indicate that among migrants and their descendants there is large variation in the incidence of psychosis across regions, suggesting that not only region of origin, but also region of destination, confers psychosis risk.

Kelly Anderson (Western University, Canada) presented work investigating whether there are differences across ethnic minority groups in hospitalization and involuntary admission after psychosis onset, and whether there are symptom and behavior differences between groups. Migrant groups had increased rates of hospitalization and involuntary admission in comparison to a general population reference group, aside from migrants from Latin America. Further, the rates of involuntary admission were slightly higher in refugee groups. Elevated risk of involuntary admission was also seen in African and Caribbean immigrants, and Caribbean refugees in particular, in comparison to immigrants from Europe. Lastly, migrants were more likely to be perceived as being more aggressive and posing a risk of harm to others than the general population. Thus, migrant status confers greater risk of involuntary admission, and migrant groups show different clinical presentation, or are at least perceived to. However, adjusting for differences in clinical presentation did not negate the relationship between

migrant status and involuntary admission, suggesting that this is not driven by clinical presentation alone.

Oladunni Oluwoye (Washington State University, Spokane, USA) presented work on racial and ethnic differences in psychiatric symptoms and service utilization in participants enrolled in the multi-center Recovery After An Initial Schizophrenia Episode – Early Treatment Program (RAISE-ETP) for first-episode psychosis. Seventeen sites were randomized into usual community care ($N = 181$) and 17 to NAVIGATE ($N = 223$), a coordinated specialty care model for first episode psychosis. In the community care group, non-Hispanic Black participants were less likely to receive individual therapy than non-Hispanic white participants, and Hispanic families were less likely to receive family psychoeducation than non-Hispanic white families. Within NAVIGATE, non-Hispanic Black participants were less likely to receive family psychoeducation than non-Hispanic white participants. Among non-Hispanic Black participants, those with family involvement at baseline had better quality of life across the 24-month treatment period, though this was not the case in non-Hispanic white participants. These results suggest that non-Hispanic Black individuals are less likely to receive some services in community care in comparison to non-Hispanic white individuals. Further, non-Hispanic black families are less likely to receive family psychoeducation, and this lack of family engagement negatively impacts quality of life outcomes. Thus, identifying cultural barriers to treatment engagement for those experiencing their first episode of psychosis needs further investigation.

18. The early identification and prevention of psychosis

Lotta-Katrin Pries (Maastricht University, Netherlands) reported on the low 6-year incidence (0.3% − 0.9%) and transition (0.1% − 1.2%) rates in low-, moderate- and high-risk general population subgroups in the Netherlands Mental Health Survey and Incidence Study (NEMESIS) sample ($n = 6071$). Although 49% of all cases in the high-risk group could have been prevented if the risk had been eliminated, the lower incidence (0.5%) and transition (1.2%) rates in this group still suggest that only small benefits can be expected from preventive approaches. A striking observation was the high prevalence of affective symptoms across all risk groups (75% − 97%), once again underlining the multidimensional nature of psychopathology in individuals at risk of psychosis.

Philip McGuire (King's College London, UK) addressed whether the North American Prodrome Longitudinal Study (NAPLS) risk calculator can be applied to the European Network of National Schizophrenia Networks Studying Gene Environment Interactions (EU-GEI) data. Unlike NAPLS, however, EU-GEI verbal learning and social function measures were not significantly associated with psychosis risk, although the direction of the associations was similar to those in the NAPLS cohort. He concluded that the NAPLS RISK calculator can not be applied directly to EU-GEI data yet, due to differences in outcome measures between the two studies. However, harmonized initiatives such could aid the development of a risk calculator that can be used in both Europe and North America.

Treatment for at risk individuals was a much-contested topic at the congress. Alison Yung (Orygen Youth Health Research Centre, Australia) presented a historical review and analysis of the literature to examine ethical and practical issues in early intervention for psychosis. She explained that there are difficulties with ultra-high risk (UHR) identification, as the UHR threshold is an arbitrary line. Therefore, the treatment of UHR individuals including detection, service issues, communication, intervention, and whether UHR criteria are valid remains in question. Mark Weiser (Sheba Medical Center At Tel Hashomer, Israel) presented on the risk-benefit ratio of antipsychotic treatment in the prodromal phase. In recent years second generation antipsychotics have proven to have many more side effects than was previously appreciated. However, the initial estimate of a 40% conversion rate in high risk groups have fallen to around 10%. The stigma of being labeled as having a high risk of developing schizophrenia added to the increasing concern of the ethical implications of early diagnosis and pharmacological intervention in high risk groups further complicates matters. Cognitive behavioral therapy (CBT) as well as Omega-3-fatty acid supplementation, was raised as a suitable alternative for early intervention in psychiatry. It was argued that CBT could help bolster resilience in those at high risk for significant mental illness. Even though conversion to schizophrenia is quite rare, 90% of high-risk patients are likely to develop some form of mental illness worth following up. Diana Perkins (University of North Carolina At Chapel Hill, USA) conducted a review of the literature as well as government registries for the current status of early pharmacological and psychotherapeutic intervention. The results of the meta-analyses conclude that there is insufficient evidence to support any particular intervention at present. Several clinical trials are underway to examine the effects of specific pharmacological treatments, psychotherapies, and a stepped-approach to care. The psychosis clinical high-risk syndrome is not yet fully recognized by standard diagnostic systems used by clinicians to document medical services. Currently there exist little agreed-upon diagnostic categories for attenuated psychosis, as well as evidence-based treatment guidelines. This makes the communication of diagnostic and treatment uncertainties in high-risk patients very difficult and ethically challenging. Robert Freedman (University of Colorado Health Sciences Center, USA) presented work on docosahexaenoic acid (DHA) and choline as prenatal nutrients to prevent mental illnesses. A key ethical issue with large-scale supplementation is balancing the effectiveness of the nutrient with cost as well as potential side-effects for the population at large. Studies are challenging because results will not be known for decades. Nevertheless, for prenatal choline, positive effects on cognition have been recorded as long as 7 years after birth. The AMA now recommends evidence-based amounts of choline along with folic acid and Vitamins A and D for all pregnant women. Accordingly, new placebo-controlled randomized trials of these micronutrients would deprive women of standard prenatal care. Panel members were in agreement that an ethical trial design would offer all women supplements and record maternal levels during pregnancy as the key intervention variable, rather than treating some women with placebo. Fetal developmental problems may not inevitably presage mental illness, but neither can later interventions reverse these early defects. Therefore, improving prenatal prevention has its own ethical imperative. The discussant, William Carpenter (University of Maryland School of Medicine, USA) concluded that the use of antipsychotics in clinical high risk patients remain unresolved. Psychotic like experiences are ubiquitous in clinical high risk, but symptoms of full psychosis emerge in a minority of cases. Concerns have been expressed that CHR includes false positive cases for psychosis and may lead to excessive AP drug treatment. But the CHR construct identifies persons who merit clinical care [no false positives] only some of whom progress to full psychosis. Patients are treated according to their presenting problems, not their diagnosis. CHR is associate with potential progression to full psychosis. Risk calculators contribute to estimate of risk at the outset and clinicians are further informed if psychotic-like symptoms progress over time. He suggests that we move away from trying to predict the development of a specific diagnosis, and rather focus on more general presentations along a spectrum of potential psychopathology. Diagnostic class will be clarified over time and CHR as defined by the Attenuated Psychosis Syndrome in Section 3 of DSM-5 serves as a placeholder diagnostic category.

19. Language impairments

Alban Voppel (UMC Groningen, Netherlands) presented findings on speech measures in a schizophrenia cohort, both as a central symptom and as a side-effect of antipsychotics. Patients with schizophrenia were divided in high versus low DA2 receptor efficacy groups, controlling for dosage. A relatively short semi-structured interview was used with the

purpose of speech elicitation. Transcription and editing were performed and the results obtained confirm that pathological speech is also influenced by medication: D2R occupancy of medication has a significant effect on speech measures. Semantic incoherence of speech was computed using word2vec comparing healthy controls with the schizophrenia cohort; measures of coherence showed significant differences, usable for classification, conforming the utility of automatic linguistic analysis to measure pathological speech, a main feature of schizophrenia.

Elkin Gutierrez (IBM Research, USA) presented on an algorithm that was used to identify metaphoricity of individual words within a sentence. This was then applied to speech produced by patients based on open-ended interviews. The results showed that metaphoricity for free speech was higher in clinical high-risk (CHR) individuals and patients with schizophrenia than healthy controls. Metaphoricity was not explained by bizarreness or sentiment coherence. These findings confirm increased production of metaphoricity in free speech. Additionally, they suggest the putative role of metaphoricity in the identification of an individual as CHR.

Natália Mota (Brain Institute at Federal University of Rio Grande do Norte, Brazil) presented on the use of graph theory to measure thought disorganisation through graph analysis of dream reports. The results evidenced fragmented speech in patients with schizophrenia, as well as fewer words and smaller connected components when talking about a dream or affective images compared to other subjects, but not when talking about daily life events. Furthermore, speech connectedness correlated with negative symptoms and with brain dysconnectivity.

Terje Holmlund (University of Tromsø, Norway) discussed the relevance of using technological advances in the form of smart devices as an effective and affordable way to monitor clinical events. A mobile tool was developed to enable participants to remotely self-administer daily interactions through a smart device. The analysis of speech samples revealed that it was possible to detect abnormalities in the structure of language in schizophrenia. The results also show that new technologies provide unprecedented opportunities for remotely monitoring behavior.

Eric Tan (Swinburne University, Australia) points out that abnormal speech patterns are prevalent in individuals with schizophrenia and in combination with machine learning could potentially be used as an objective diagnostic marker for the disorder. It was found that in comparison to healthy controls, schizophrenia patients surprisingly had more utterances per minute. He used machine learning to successfully differentiate patients from controls based on the number of word revisions, words used per minute, and the number of utterances with omissions.

20. Sensory processing

Various presenters focused on visual processing impairments in their talks. Brian Keane (Rutgers University, USA) proposed that visual shape completion could potentially serve as a useful biomarker in schizophrenia. He based this on a study assessing shape completion in schizophrenia patients. The study found equivalently impaired visual shape completion in first episode and chronic patients, suggesting that this abnormality could potentially be a fixed trait at the time of the diagnosis. Patients also had impaired shape completion compared to bipolar disorder patients, indicating that the effect is relatively illness specific. The deficit is additionally linked to cognitive disorganization and poor premorbid functioning. All patient groups showed normal responses to alterations in illusory contour salience, suggesting that patients can form illusory contours, but not utilize them to discriminate shapes. In summary, visual shape completion is worse in schizophrenia, present at illness onset, with large effect sizes (>0.8), not explained by attention, motivation, and broad orientation tuning, which implicates later processing stages: i.e. individuals diagnosed with schizophrenia form illusory lines, but do not properly use them perhaps because of impairments to higher-order cognition. Scott Sponheim (University of Minnesota, USA) presented data from two experiments. One, a combined magnetoencephalography MEG/ functional imaging study in schizophrenia, examining brain responses while participants detected contours made up of visual elements, surrounded by a dense field of similar elements. The findings indicate that during contour perception there was diminished MEG response. A second study examined these disturbances in a combined group of schizophrenia patients, first degree relatives of schizophrenia patients, as well as healthy controls. The study investigated object perception and neural timing and found anomalies in N400, which is associated with identifying objects. The study suggests that the initial registration of visual stimuli could be the core feature of visual disturbances in schizophrenia. Diminished effects of perceptual context during contour detection may reflect genetic liability for schizophrenia and is apparent in biological relatives of individuals with this disorder. Ivy Tso (University of Michigan Medical School, USA) presented data on the role of altered gaze perception processing in schizophrenia. The study involved a group of 47 schizophrenia and 55 bipolar patients, with 55 healthy controls. Participants were shown faces with varying gaze directions and asked whether they were making eye contact with the participant. The slope and absolute threshold of the perception curve were used as indices. The study revealed reduced perceptual sensitivity as well as an increased self-referential bias for both patient groups. Although schizophrenia tended to have more severe abnormalities on average than bipolar disorder, differences were not statistically different. Effective connectivity analysis suggests a primary dysfunction of the visual cortex, with aberrant top-down processes compensatory in nature. Antigona Martinez (Nathan S. Kline Institute of Psychiatry, USA) used a motion detection task to study visual processing in patients with schizophrenia and autism. Both patient groups showed impaired motion sensitivity and face emotion recognition. Visual processing deficits were associated with distinct neural responses in each group: while schizophrenia patients demonstrated deficient neural response, autism patients demonstrated elevated neural response during motion processing. Steven Silverstein (Rutgers University, USA) used electroretinography (in which flashes of light of various intensities, colors, and frequencies are presented to the center of the eye) to examine retinal processing abnormalities in schizophrenia patients. Compared to a group of age- and sex-matched psychiatrically healthy control subjects, people with schizophrenia showed deficient retinal processing at higher light intensities, but not at lower intensities, suggesting that they may have difficulty accurately representing stimulus changes as intensities increase. In contrast, deficits were not detected in a comparison group of patients with major depressive disorder.

Caitlyn Kruiper (University Medical Center Utrecht, Netherlands) studied the relationship between sensory gating and cognitive fragmentation in an antipsychotic naïve, first-episode schizophrenia cohort. Sensory gating is the pre-attentive automatic process whereby irrelevant sensory information is filtered out, saving processing resources for more salient inputs. She did not find strong evidence supporting a relationship between sensory gating and poor cognition. However, sensory gating was associated with general symptomatology.

Jason Johannesen (Yale University School of Medicine, USA) presented three separate studies examining the psychometric, functional and neurophysiological correlates of social attribution task-multiple choice (SAT-MC) performance in schizophrenia. The first study examined the psychometric properties of the SAT-MC compared to standard video based cognitive tests in a group of schizophrenia patients as well as patients with a substance use disorder. The second study examined functional relationships of the SAT-MC and affect recognition (BLERT) performance across neurocognitive, metacognitive, theory of mind (ToM), and symptom domains in 72 adults with schizophrenia. Lastly, in an ongoing study, an adapted version of the SAT-MC was used to study neurophysiological correlates using EEG in a group of chronic SZ patients, clinically high-risk patients as well as matched healthy

volunteers. It was found across studies that the SAT-MC has good construct validity and diagnostic specificity for schizophrenia, and correlates with processes outside that of the visual modality, such as memory encoding and emotional intelligence. Preliminary psychophysiological findings implicate occipital gamma-band desynchronization as a candidate mechanism of animacy perception. It was concluded that the SAT-MC, and associated visual science construct of animacy perception, capture a core aspect of social cognitive difficulties in schizophrenia characterized by failure to integrate primary perceptual processes with top-down interpretative abilities.

Studies relating to the theme of auditory processing deficits were presented. Alice Medalia (Columbia University, USA) tested whether the presence of early auditory processing (EAP) deficits can be used to personalize cognitive remediation (CR) of schizophrenia patients. Patients with baseline EAP deficits made significantly more cognitive gains when CR included EAP training, while patients without EAP deficits showed no benefit from EAP training. These findings suggest that EAP treatment is only indicated in people with identified EAP deficits and that EAP should be assessed at baseline to personalize CR. Amanda Mccleery (University of California, Los Angeles, USA) used a mismatch negativity (MMN) task to study predictive coding in schizophrenia patients. Patients with auditory hallucinations, but not non-hallucinators, showed impaired MMN. These findings suggest hallucinations may be associated with deficits in prediction signaling related to noisy or aberrant sensory processing. Julien Laloyaux (University of Bergen, Norway) reported on work that explored the role played by noise frequencies and expectations on the elicitation of false perceptions using white noise in people with auditory hallucinations (AH). They selected hallucination-prone and non-prone subjects, among undergraduate students to perform a semantic signal detection task varying the level of expectation associated with the perception of a word and as well as the frequencies of the noise presented during the task. In conclusion, the study found that false perceptions in the white noise paradigm in people with AH are driven by both: (i) specific frequencies contained in the white noise and (ii) a high level of expectation. These results support the latest cognitive models of AH that claim that AH arise from an interaction between top-down and bottom-up cognitive mechanisms. Ann Shinn (McLean Hospital, USA) explored auditory hallucinations across the psychosis spectrum: evidence of cerebellar dysconnectivity. She aimed to investigate whole-brain resting state functional connectivity abnormalities associated with lifetime auditory hallucinations in patients across the psychosis spectrum. The results suggest that aberrant cerebellar connectivity may be a feature of auditory hallucinations (1) across the spectrum of psychosis, (2) in schizophrenia, and (3) in bipolar disorder with psychotic features. The findings also suggest that auditory hallucinations in schizophrenia and bipolar disorder can be distinguished by differences in the direction of cerebello-temporal connectivity. Katharina Stegmayer's (University of Bern, Switzerland) discussed a study on auditory verbal hallucinations with emotional content in schizophrenia. The study included 88 participants with auditory verbal hallucinations AVH (n = 33), non-AVH (n = 15), and controls (n = 40). It was found that patients with AVH had increased perfusion within the left superior temporal gyrus compared to non-AVH patients and healthy controls. The results suggest that AVH is linked to a dysfunction of basic language areas. Marek Kubicki (Harvard Medical School, USA) investigated the association between microstructural white matter abnormalities and auditory verbal hallucinations. In this study, 23 chronic schizophrenia subjects (mean duration of illness 16.5 years) and 23 matched healthy controls were included. The study used FreeSurfer parcellations for tractography seeding. Stochastic tractography method was used for generating tracts. Fractional anisotropy was calculated and averaged over the tracts separately for dorsal and ventral connections. The results suggested that schizophrenia is associated with white matter pathology. Their results also pointed out that myelin abnormalities likely account for the findings. Moreover, it showed that white matter myelin pathology could lead to decreased connectivity.

21. Physical health, aging and mortality

Several talks focused on physical health and lifestyle interventions aimed at individuals living with a serious mental illness. Leopoldo J. Cabassa (Washington University in St. Louis, USA) presented results from a qualitative study assessing client's experiences of a peer-led healthy lifestyle program. A subset of participants who completed the lifestyle program reported that the program enhanced their insight into a healthy lifestyle and self-reported behavioral changes in terms of diet and exercise. Additionally, clinically significant improvements in weight-loss (23.8%), cardiorespiratory fitness 32.8%) and CVD risk reduction (45.8%) were reported in this group of participants. Benjamin Druss (Emory University, USA) presented two mobile health (mHealth) studies assessing the use of mobile devices to promote physical health in people with SMI. The first study was a randomized trial of a mobile personal health record for individuals with SMI and medical comorbidity, and the second was a trial of differing forms of financial incentives coupled with wearable devices to increase physical activity among inactive individuals with SMI. The study findings suggested that mHealth can be used to support improvements in quality of care and health behaviors in SMI. Kelly Aschbrenner (Department Of Psychiatry, Geisel School of Medicine at Dartmouth College, USA) presented an overview of a study protocol and baseline data for a randomized controlled trial evaluating the effectiveness of a peer group lifestyle intervention enhanced with mobile health technology to address cardiometabolic risk in young adults with serious mental illness. Her presentation included a review of studies on evidence-based lifestyle interventions for individuals with a serious mental illness (SMI). Findings suggest that modifications may need to be made to existing interventions to meet the needs of young mental health service users, including peer support and use of popular technologies to support health behavior change to improve health in this group. Nuray Çakici (Academic Medical Center, Amsterdam) conducted a meta-analysis on blood compounds in drug-naïve first-episode schizophrenia and depression, and identified similar changes in growth, immune and glucose factors in both disorders. These findings might indicate shared preventive strategies and treatment for immune and metabolic dysfunctions present in the early illness course in both the disorder types. Martin Strassnig (University of Miami, USA) presented ecological momentary assessment data on sedentary behavior in people with schizophrenia (n = 100) and healthy controls (n = 71). A consistent picture emerged in people with schizophrenia, namely they completed more surveys at home, were less likely to be in the company of others, and spent the majority of time on sedentary activities (for example, watching television, resting and/or smoking). The results highlight the lack of daily activity patterns in people with schizophrenia, and underline the need for exercise-focused interventions.

The topic of accelerated aging in schizophrenia emerged during the congress. Brian Kirkpatrick (University of Nevada School of Medicine, USA) discussed the history and current knowledge on accelerated aging associated with schizophrenia. He focused in his talk on how developments in molecular technologies and neuroimaging can support further research aimed at exploring the roles of oxidative stress, impaired glucose tolerance, and inflammation on brain age in schizophrenia patients. He emphasized that genomic testing in particular has consistently identified a strong correlation between DNA epigenetic methylation and biological age in schizophrenia populations. He also noted the importance of considering previous confounds including antipsychotic exposure, dietary habits and body mass index when exploring accelerated aging in schizophrenia. Leticia S. Czepielewski (Universidade Federal do Rio Grande do Sul, Brazil) presented a study investigating the role of telomere length as a proposed marker for accelerated aging in schizophrenia. In addition, the study considered the effects of CCL-11 levels as a marker of inflammation on telomere length,

global gray matter volume, and verbal episodic memory performance. In this study, schizophrenia patients had decreased telomere length compared to unaffected individuals, which was associated with higher inflammation, poorer verbal episodic memory, and reduced gray matter volumes in the brain. Shorter telomere length also mediated the deleterious effects of longer illness duration on verbal memory, which was also correlated with higher inflammation. Igor Nenadic (Philipps-Universität Marburg, Germany) presented work done on the influence of schizophrenia subtype on the association between actual age and estimated brain age assessed from a T1 brain scan using a machine learning tool. The findings suggest brain age differences between controls and two patient groups, namely first-episode schizophrenia patients, and those at ultra-high risk for psychosis. Importantly, the same was not found in a cohort of bipolar disorder patients. Julia Sheffield (Vanderbilt University Medical Center, USA) proposed that accelerating aging and associated changes in connectivity of the cingulo-opercular and fronto-parietal networks are characteristic of psychotic disorders. She identified reduced global efficiency of these networks, known to be implicated in higher-order cognitive functioning, in patients with chronic psychotic disorders, but not first-episode patients. The findings suggest that the connectivity of these networks is preserved in first-episode psychosis, but markedly reduced in patients with chronic illness. Tamsyn Van Rheenen (University of Melbourne, Australia) presented a study investigating age-related changes in fluid reasoning, working memory, frontal brain volume and its relationship with cognitive reserve in patients with schizophrenia. Patients, when compared to controls and considered as a whole group, had increased age-related reductions in brain volume, but there were no significant between group differences in age-related change of fluid cognition. Age-related decline in fluid cognition was evident in patients with low cognitive reserve, but there was no difference in age-related brain volume change between patients with high or low cognitive reserve. This suggests that higher cognitive reserve in a subgroup of schizophrenia patients buffers against ageing effects on fluid cognition by protecting against pathologically exaggerated brain volume deterioration.

Elias Mouchlianitis (Institute of Psychiatry, Psychology, & Neuroscience at King's College London, UK) presented a study investigating the association between glutamate and neurostructural integrity in patients with treatment-resistant schizophrenia. The findings suggest that there is a significant positive correlation between anterior cingulate cortex Glu/Cre and brain-PAD only for the treatment-resistant patients ($P = 0.014$). There was no significant correlation for the treatment-responsive group or the healthy participants. The study indicates glutamate levels to be associated with accelerated brain ageing in treatment-resistant patients.

22. Computational approaches

Albert Powers (Yale University School of Medicine, USA) presented findings from a study that used a conditioning paradigm to explore to what extent prior beliefs about the external world dominates over sensory information in the production of auditory hallucinations. Participants were presented with repeated pairings of a visual stimulus and a faintly-presented auditory stimulus during an fMRI experiment. Participants were asked to report whether the auditory stimulus was present when the visual stimulus was presented. Patients with psychosis with and without hallucinations were compared with healthy voice-hearers and healthy controls. Irrespective of psychosis status, conditioned hallucinations occurred more frequently, and were reported with stronger conviction, in participants who hallucinate. Computational modeling also showed an increased reliance on prior beliefs in those with hallucinations irrespective of psychosis status. This suggests that both patients and controls who experience auditory hallucinations exhibit greater reliance on prior beliefs compared to incoming sensory information. High-level model parameters encoding volatility beliefs about the stimulus relationships discriminated between participants with and without psychosis. Activity in anterior insula and superior temporal sulcus encoded low-level perceptual beliefs and differentiated hallucinating from non-hallucinating groups, while activity in parahippocampal gyrus and cerebellum encoded volatility beliefs and differentiated psychotic from non-psychotic participants.

John Torous (Harvard Medical School, USA) discussed the value of exploring smartphone data to support cognitive assessment in schizophrenia patients based on the characterization of “digital fingerprints”. He argued that digital phenotyping and collection of passive device data could hold promise in the prediction of possible relapse in patients.

Kathryn Hess (École Polytechnique Fédérale de Lausanne, Switzerland) presented data on the use of topological analysis to predict functional and social outcomes in early psychosis patients ($n = 101$) with similar clinical and/or metabolic profiles followed up over three years. The application of topological analysis based on baseline psychopathology identified three patient groups with distinct patterns of social and occupational outcomes. The group characterized by low levels of negative and depressive symptoms at baseline had better social and occupational functioning at follow-up and a distinct biological profile. In contrast, the patient group with high levels of positive symptoms at baseline showed the worst social and functional outcomes at three years. She emphasized the value of emerging computational techniques to predict functional outcomes in early psychosis based on clinical and metabolic assessments at baseline.

Dominic Dwyer (Ludwig-Maximilian-University, Germany) presented a study that used a combination of clinical, imaging-based, and combined data to predict social and role functioning in a group of clinically high-risk ($n = 116$) and recent-onset depression ($n = 120$). As part of the study, a predictive model for functional outcome with a high sensitivity and specificity was developed. The presenter emphasized that, while external validation of this model was necessary, it provides a good example of how combining multi-modal data can support the development of improved prediction models for functional outcomes in high-risk patient groups.

23. Interdisciplinary interventions

Jimmy Choi (Olin Neuropsychiatry Research Center, USA) presented data from a study, which sought to engage schizophrenia patients with low motivation in physical exercise as part of a rehabilitation program. Towards this goal, a clinical trial was conducted to explore the efficacy of an “exergame” intervention, which combines elements of physical activity with neurocognitive rehabilitation exercises, sometimes within a virtual reality environment. The intervention resulted in an improvement in negative symptoms and working memory in patients irrespective of their motivation. However, a significant improvement in processing speed and positive symptoms was only evident in the high-motivation group. Results from this study supported the value of “exergaming” to engage schizophrenia patients with low motivation in physical activity.

Mike Best (Queen's University, Canada) presented findings from an open-label pilot study, which sought to explore the value of a novel intervention for internalized stigma in first-episode psychosis patients ($n = 15$). The eight-session BOOST (Be Outspoken Overcoming Stigmatizing Thoughts) group intervention took the form of brief group treatment sessions, and combined elements of cognitive restructuring with assertive communication skills and peer support. In this study, BOOST was shown to improve internalized stigma, self-esteem and global life satisfaction.

Kee-Hang Choi (Korea University, South Korea) presented findings from a randomized controlled trial that explored the efficacy and tolerability of a structured psychotherapeutic approach as an adjunct to treatment as usual in schizophrenia spectrum disorder patients. Behavioral activation therapy consisted of a once weekly hour-long face-to-face session conducted over ten weeks. In this study, behavioral activation was associated with a reduction in negative symptoms post-

treatment. However, this effect was not maintained at six-month follow-up. Behavioral activation may offer a suitable approach to decreasing negative symptom severity in schizophrenia patients, although a longer intervention period (>10 weeks) or follow-up sessions may be necessary to maintain the beneficial effects of the intervention.

Piper Meyer-Kalos (University of Minnesota, USA) presented results from a pilot study which explored the feasibility of Individual Coping Awareness Therapy (I-CAT) as a means of combating stress in patients with early schizophrenia ($n = 6$). In this study, I-CAT improved stress management, resilience and symptom severity, and was shown to be both feasible and tolerable. These findings provided the basis for a randomized controlled trial using the I-CAT in early schizophrenia, which is currently in progress.

Jie Lisa Ji (Yale University, USA) discussed how integrating neuroimaging and transcriptomic data could be leveraged to inform therapeutics as a part of the Gene Expression Mapping Integrated with Neuro-Imaging for Discovery of Therapeutics (GEMINI-DOT) initiative. As part of this initiative a study was conducted, which included 24 healthy participants. The participants were randomized to receive placebo, lysergic acid diethylamide (LSD), or ketanserin (a 5-HT2A receptor antagonist) and LSD. The study integrated resting-state functional connectivity and gene expression data and found that whole-brain spatial patterns of LSD effects corresponded to 5-HT2A receptor cortical gene expression in humans, which suggests that the 5-HT2A receptor is likely involved in LSD's neuro-pharmacology.

Jerrilyn Kent (University of Minnesota, USA) presented findings from a study, which explored temperoparietal junction activation in patients with psychosis ($n = 50$) and at-risk first-degree relatives ($n = 21$) compared to controls ($n = 29$) in response to an implicit theory of mind task. In this study, temperoparietal junction activation was lower in patients and their relatives compared to controls, suggesting an association with shared genetic liability.

24. Patient adherence and engagement

Dawn Velligan (University of Texas Health Science Center at San Antonio, School of Medicine, USA) discussed the value of engagement focused care in schizophrenia to facilitate long-acting injectable antipsychotic use and medication follow through. She presented findings suggesting that the engagement focused program promotes the appropriate use of long-acting injectables by targeting three stakeholder groups; administrators, prescribers and the end users. She highlighted the importance of focusing on engagement and recovery goals in promoting medication follow through and acceptance of long-acting injectable medication.

Joy Noel Baumgartner (Duke Global Health Institute, USA) presented results from a study that sought to develop a culturally appropriate version of the Family Psycho-education intervention for adults living with psychotic disorders in lower- to middle-income countries. In this study, thematic analysis was performed on qualitative data obtained from interviews conducted with patients, providers, caregivers, religious leaders, healthcare managers and government officials living in Tanzania ($n = 80$). The study highlighted the role and value of family, religion, faith, and hope as important themes to consider in the development of psycho-education interventions. An adapted intervention was developed which included an orientation session and education workshop with family members, as well as ongoing patient-relative group sessions. This intervention differed from conventional family psychoeducation insofar as it incorporated tailored topics and exercises that were culturally appropriate and engaging.

Isaac Lema (Muhimbili University of Health and Allied Sciences, Tanzania) presented findings from a mixed method study where the research team sought to develop and test a customized adherence enhancement program for treatment with long-acting injectable antipsychotics in Tanzanian patients with a chronic psychotic disorder. The study found that poor medication adherence was associated with negative patient attitudes and more severe symptomatology. Findings from this research support the potential for use of long-acting injectables in chronic schizophrenia in lower- to middle-income health settings.

Martha Sajatovic (Case Western Reserve University, USA) presented results from a web-based survey on long-acting injectable antipsychotic use with the goal of assessing current practice and developing appropriate treatment guidelines for the management of psychotic disorders. A total of 34 research practitioners were asked about their experiences and recommendations for selecting and treating patients with long-acting injectables during the initiation and maintenance phases of therapy. Respondents indicated that approximately 30% of their patients were treated with long-acting injectable antipsychotics, which were recommended for patients with poor insight, unstable housing, a history of violence, and social isolation. There was agreement that long-acting injectable antipsychotics should to be used to screen for non-adherent versus treatment-resistant patients prior to moving on to clozapine treatment.

25. Conclusion

In summary, a broad range of topics was covered during the first North American SIRS congress. Interesting new work was presented investigating schizophrenia as a disorder of the self, with presenters emphasizing that individuals living with the illness experience an aberrant sense of agency and body ownership. Several sessions addressed potential environmental risk factors. In particular, the influence of childhood adversity as well as the role played by neighbourhood factors, such as violence and poverty were considered. The importance of timing of adversity featured, with presenters emphasizing that earlier versus later trauma exposure was associated with distinct deficits and symptoms. Other topics included the effects of smoking and substances. It was emphasized that tobacco smoking is not merely a means of self-medication. Instead, the data suggest that it is associated with suicidal behaviour and an earlier age of illness onset. The link between cannabis use and psychosis featured prominently and it was proposed that cannabis use is an important predictor of relapse. Inflammation and the disruption of the blood-brain barrier as well as the blood-gut barrier as potential risk factors for psychosis came under the spotlight. It was proposed that higher levels of inflammation are associated with shorter telomere length, which is in turn associated with accelerated aging, in schizophrenia cohorts. In terms of cognition and functioning, memory deficits and their association with the hippocampus were highlighted. It was suggested that treatments should target hippocampal parvalbumin interneurons by restoring GABAergic signaling. Relating to the topic of functionality, the use of virtual reality to assess functional capacity was addressed. Then the role played by genetics came under discussion. Genetic testing could play an invaluable role in the future when it comes to the prediction of treatment response. In terms of pharmacological treatments, the development of novel antipsychotic drugs targeting cognitive impairment and negative symptoms, as well as the use of long-acting injectables were addressed. Presenters discussed the reasons why some patients relapse despite receiving assured treatment, i.e. long-acting injectables. The efficacy of non-pharmacological interventions was covered and in particular the efficacy of CBTp and tDCS.

In terms of moving the field forward, novel ways of early identification of individuals living with schizophrenia spectrum disorders were addressed. Presenters provided evidence supporting the efficacy of using a multi-dimensional approach to identify symptoms, with some suggesting that patterns of similar neural network activation could be useful in identifying patients. Others also proposed that more emphasis should be placed on biotypes, and here impaired visual processing and language impairments could be important biomarkers. Another topic that has gained great momentum over the past few years and that featured prominently during the congress is that of computational approaches. A number of presenters illustrated the usefulness of

techniques, such as machine learning and topological analysis, to identify patients and predict functional outcomes as well as antipsychotic treatment response. The advantages of big data and consortiums, such as ENIGMA and GWAS came under discussion.

Other equally important topics that were covered during the congress include the identification and treatment of at-risk for psychosis populations. Presenters highlighted that the diagnosis of, and identification of effective treatment, for individuals at-risk for psychosis remain problematic. It was suggested that less emphasize should be placed on diagnosis and whether individuals with attenuated psychosis go on to develop a psychotic disorder. Instead the focus should be more on the presenting problems of the treating at-risk individuals. Psychosis risk in vulnerable groups, such as migrants and refugees was discussed. However, the evidence is inconclusive as to whether or not these populations are at greater risk for psychosis. Nevertheless, the evidence clearly suggests that immigrants and migrants are less likely to have access to mental health services, which in itself is highly problematic.

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Supplementary materials

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