npj | Schizophrenia

www.nature.com/npjschz

ABSTRACTS OPEN

Abstracts from the 5th Biennial SIRS Conference - Oral Presentations

npj Schizophrenia (2016) **2**, Article number: 16010; doi:10.1038/npjschz.2016.10

Firenze Fiera Congress Center, Florence, Italy, 2–6 April, 2016

Sponsorship: Publication of this supplement was funded by the Schizophrenia International Research Society

Tuesday 5 April, 2016

15:15	Oral Presentations (O)
O1.	NEURODEVELOPMENT: CHILDHOOD, ADOLESCENCE AND ADULTHOOD
O2.	GENETICS: MULTIFACETED APPROACH
O3.	EPIDEMIOLOGY: ROLES FOR ENVIRONMENTAL RISK FACTORS
O4.	PHENOMENOLOGY AND DIMENSIONAL DISCUSSION
O5.	BRAIN IMAGING-I: MOLECULES, STRUCTURES, AND FUNCTIONS
O6.	COGNITION: MULTIFACETED APPROACH
17:30	Oral Presentations (O)
O7.	NEUROBIOLOGY
O8.	CLINICAL TRIALS
O9.	PSYCHOSOCIAL FUNCTIONING
O10.	TREATMENT AND CLINICAL SERVICES
O11.	BRAIN IMAGING-II: MOLECULES, STRUCTURES, AND FUNCTIONS
O12.	BIOMARKERS

O1. Neurodevelopment: childhood, adolescence and adulthood

O1.1 Adult neurogenesis in the striatum: effect of psychiatric treatment

Dragos Inta[*1], *Peter Gass*[1]

[1]*Central Institute of Mental Health, Mannheim, Germany*

Background: For long time, the hippocampal dentate gyrus (DG) was the only brain region in which adult neurogenesis had been demonstrated in humans. This situation recently changed due to radiocarbon-14 dating that provided evidence for robust neurogenesis of specific, mainly calretinin (CR)-positive GABAergic interneurons in the adult human striatum. Similar adult-generated interneurons were described as well in the striatum of other species; however, the main focus of research continues to be on adult neurogenesis in the olfactory bulb, which is most likely absent or occurring at very low level in the human brain. The extent and the significance of this process for neuropsychiatric disorders is still unknown.
Methods: Fate-mapping studies in wildtype mice and rats and transgenic 5-HT3-EGFP and D3-EGFP mice that allow the *in vivo* labeling of newborn neurons migrating from the subventricular zone (SVZ) into the striatum under physiological conditions and following electroconvulsive seizure (ECS)
Results: At early postnatal stages many SVZ neuroblasts migrate from the SVZ into subcortical areas, nucleus accumbens, and ventral striatum. Postnatally-generated neurons belong to two classes of small-size GABAergic interneurons: CR-positive interneurons and CR-negative granule cells forming the Islands of Calleja (ICj). The ICj receive dense dopaminergic projections from the ventral tegmental area and substantia nigra, expressing high levels of dopamine D3 receptors. Moreover, they are activated by antipsychotic treatment with clozapine. ECS massively stimulates neurogenesis in the SVZ and striatum resulting in similar newborn CR-positive interneurons. Most ECS-triggered newborn interneurons were found in the medial striatum, which is part of the limbic circuitry, with afferents from the medial prefrontal and cingulate cortices.
Discussion: The striatum represents, like the DG, a main, yet poorly investigated area of postnatal neurogenesis in the mammalian brain. Rodents appear to represent a valid model for investigating postnatal/adult striatal neurogenesis, showing similar neuronal subtypes. ECS as animal model for electroconvulsive therapy (ECT) strongly stimulates neurogenesis in the adult striatum. The implications for striatal neuroplasticity and the dopamine system, as well as for schizophrenia are discussed.

O1.2 Maternal symptoms and neonatal behaviour in postpartum psychosis

Katie Hazelgrove[*1], *Alessandra Biaggi*[1], *Susan Conroy*[1], *Susan Pawlby*[1], *Montserrat Fuste Boadella*[1], *Carmine Pariante1*, *Paola Dazzan*[1]

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

Background: Individuals at risk of psychosis unrelated to gestation are reported to be more sensitive to daily life stressors, which in turn results in increased negative emotions and psychotic experiences (Myin-Germeys *et al.*, 2001, 2003). Furthermore, antenatal stress and anxiety have been associated with increased risk for postnatal psychopathology (Heron *et al.*, 2003), as well as less optimal neonatal behavioral outcomes (Browers *et al.*, 2001, Rieger *et al.*, 2004). However, the effects of antenatal stress and anxiety on maternal postnatal symptoms and neonatal behavior have never been examined in women at risk of postpartum psychosis (PP). The aim of this study was to investigate the effects of antenatal stress and anxiety on postnatal symptoms and infant behavior in a sample of women at risk of PP.
Methods: 75 Women were assessed at 25 weeks gestation: 34 were at risk of PP because of a diagnosis of bipolar disorder ($n=30$), schizoaffective disorder ($n=3$) or a previous PP ($n=1$), and 41 were healthy women. Maternal antenatal anxiety and stress were assessed using the State-Trait Anxiety Inventory (STAI: Spielberger, 1970) and the Perceived Stress Scale (PSS: Cohen, 1983). Maternal postnatal symptoms were assessed at 6 days postpartum using the Beck Depression Inventory (BDI: Beck, 1961), the Highs Scale (Glover, 1994) and the STAI. Finally, we assessed infant behavior at 6 days postpartum using the Neonatal Behavioral Assessment Scale (NBAS: Brazelton, 1973).
Results: Compared to healthy women, women at risk of PP had significantly higher antenatal anxiety (Mean = 28.5, SD = 7.5 versus Mean = 37.8, SD = 12.9, $U=282.5$, $Z=-2.9$, $P<0.01$) and perceived stress ($M=9.3$, SD = 5.6 versus $M=16.8$, SD = 7.8, $t(63)=4.5$, $P<0.001$). Furthermore, higher antenatal anxiety and perceived stress levels were significantly correlated with symptoms of depression ($r=0.45$, $P<0.001$; $r=0.47$, $P<0.001$, respectively) and anxiety ($r=0.61$, $P<0.001$; $r=0.59$, $P<0.001$, respectively) at 6 days postpartum, but not with manic symptoms.
Antenatal perceived stress was negatively correlated with infant's social interactive scores at 6 days postpartum ($r=-34$, $P<0.001$). Compared with the infants of healthy women, infants of women at risk of PP had lower social interactive ($M=7.4$, SD = 1.2 versus $M=6.5$, SD = 1.8, $U=409$, $Z=-2.4$, $P=0.016$), regulation of state ($M=6.3$, SD = 1.2 versus $M=5.7$, SD = 1.4, $t(69)=2.0$, $P=0.05$) and autonomic stability scores ($M=5.9$, SD = 1.2 versus $M=5.0$, SD = 1.4, $U=373.5$, $Z=-2.8$, $P<0.01$).
Discussion: The findings suggest that compared to healthy women, women at risk of PP experience more stress and anxiety during pregnancy and that these symptoms are associated with more postnatal depressive and anxious symptoms. The results also show that antenatal stress was associated with lower social interactive scores on the NBAS at 6 days. Finally, infants of women at risk of PP had less optimal social interactive, regulation of states and autonomic stability scores on the NBAS, suggesting they were less alert and less

able to attend to auditory and visual stimuli, less able to regulate their states in the face of increasing stimulation as well as being less physiologically stable. Taken together the findings suggest that exposure to antenatal stress and anxiety might have similar negative effects on both maternal and infant outcomes for women at risk of PP as those seen in other perinatal psychopathology.

O1.3 Accumulation of risk endophenotypes in children and adolescents at genetic risk of major psychoses: longitudinal findings from the eastern quebec densely affected families

Thomas Paccalet[*1], *Elsa Gilbert*[2], *Nancie Rouleau*[3], *Valérie Jomphe*[4], *Daphné Lussier*[4], *Nathalie Gingras*[5], *Marc Hébert*[5], *Chantal Merette*[5], *Michel Maziade*[5]

[1]*Université de Québec à Trois-Rivières et Centre de recherche CIUSSS-CN, Québec, Canada,* [2]*Université Laval et Centre de recherche CIUSSS-CN,* [3]*Université Laval,* [4]*Centre de Recherche CIUSSS-CN,* [5]*Université Laval et Centre de recherche CIUSSS-CN*

Background: Risk endophenotypes (cognitive[1] or electrophysiological[2]) observed in adult patients are found in children born to a parent affected by major psychoses (MP: affective and non-affective psychoses.)[3–5] Most studies exploring such endophenotypes investigated them separately or emphasized a search for single pathways in the trajectory toward the disease. Little is known about a potential accumulation of endophenotypes in a child and its relevance in the disease heterogeneity. Our objectives were: i) to investigate the accumulation of cognitive deficits and electroretinographic (ERG) anomalies in young offspring at genetic risk of adult MP; ii) to study the clustering of both cognitive and electrophysiological endophenotypes in these at-risk youths and adult patients.
Methods: In a stepwise selection strategy from a 25-year follow-up of 48 kindreds densely affected by MP starting with 1500 adults (405 were affected by MP), we longitudinally collected extensive measures of cognitive domains and ERG in high-risk offspring (HR, aged 6–26 years, $n = 85$), compared to 189 controls matched for age and gender. Participants were administered a neuropsychological, ERG, and clinical assessments.
Results: The presence of single deficits in different cognitive domains (verbal and visual episodic memory, working memory, processing speed, or executive functions) or single ERG anomalies in an individual was found more frequent in HR than in controls (odds ratio OR ~ 2.8 for cognition and ~ 3.0 for ERG). The relative difference in rates of a combination or a clustering of endophenotypes among HR versus controls was found greater with an OR of 3.6 for cognition and 4.9 for ERG. Data suggest that cognitive and ERG endophenotypes would be little correlated, allowing for a possible stratification of subgroups of children at risk. With a 9-year mean follow-up of the HR sample, we could preliminarily analyze the endophenotypes profiles of HR according to their clinical outcome and observed that HR who transitioned to MP tended to have more accumulation of risk endophenotypes than those who remained healthy.
Discussion: Even though a single risk endophenotype would be more frequent in HR than in the normal population, the presence of a combination of risk endophenotypes would be more specific of children and adolescent at risk. These findings are compatible with the multi-trait polygenic theory of psychosis. Cognitive and ERG endophenotypes could accumulate in a child independently of each other. However, both could characterize the HR who would later transition to a MP. Investigating the combinations of risk endophenotypes and their relationships might help for modeling the preclinical staging of children and adolescents at risk and for unraveling MP heterogeneity by labeling more homogeneous subgroups of individuals.
Uncited reference
1Child
References:
1. Maziade, M., *et al.*, Schizophrenia Bulletin, 2011.
2. Hebert, M., *et al.*, Schizophrenia Research, 2015.
3. Maziade, M. and Paccalet, T., Schizophr Res, 2013.
4. Hebert, M., *et al.*, Biological Psychiatry, 2010.
5. Niemi, L.T., *et al.*, Schizophr Res, 2003.

O1.4 Offspring with familial risk for severe mental illness and incidences for having a child and adolescent psychiatric diagnosis at age 0–17 years – a Danish register study

Anne Thorup[*1], *Thomas Munk Laursen*[2], *Trine Munk-Olsen*[2], *Preben Bo Mortensen*[2], *Kerstin J. Plessen*[3], *Merete Nordentoft*[4]

[1]*Child and Adolescentental Health Center; The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH),* [2]*Psychiatric Central Research Register, BSS, University of Aarhus and The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH),* [3]*Child and Adolescent Mental Health Center, Copenhagen, Denmark,* [4]*Mental Health Center; The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), Aarhus, Denamark*

Background: Offspring of parents with severe mental illness like schizophrenia, bipolar disorder, or major depressive disorder are at an increased risk of developing mental illness in adulthood themselves. In childhood they are known to show a wide range of neurodevelopmental abnormalities and cognitive deficits and to experience social adversities, trauma, or insufficient parenting. However, less is known about their risk for being diagnosed with a mental illness in childhood or adolescence.
Aim: We aim to investigate if individuals with familial high risk for SMI have an increased risk for being diagnosed with a mental illness during childhood and adolescence
Methods: Danish nationwide registers were linked to establish a cohort consisting of all persons born to parents diagnosed with schizophrenia, bipolar disorder, or major depressive disorder in the Danish Psychiatric Register between 1968 and 2013. The cohort was followed from birth until age 18 or until Dec 31, 2013. Incidence rate ratios (IRRs) and cumulative incidences for offspring diagnosed with a mental illness by parental mental disorder status were calculated using a regression model.
Results: IRR for all child and adolescent psychiatric diagnoses were increased for individuals born with a familial high-risk for schizophrenia, bipolar disorder, or major depressive disorder. We found that IRR for having any child psychiatric disorder and having a mother diagnosed with schizophrenia is 2.60, 2.06 if the father has schizophrenia, and 4.57, if both parents have schizophrenia. For individuals having a mother with bipolar disorder the IRR is 2.28 and for having father 1.77, while it is 3.10 if both parents suffer from bipolar.
Discussion: This is the first register study to demonstrate that familial high risk individuals during childhood are more likely to suffer from child psychiatric disorders. This also tells us that the children are in contact with mental health services although they are not offered any specific treatment in spite of their increased vulnerability.

O1.5 Mood disorders and schizophrenia in the offspring of antenatally depressed mothers in the Northern Finland 1966 birth cohort: relationship to parental history of severe mental disorder

Pirjo Mäki[*1], *Tiina Taka-Eilola*[1], *Sarianna Mykkälä*[1], *Merja Kyllönen*[1], *Juha Veijola*[1]

[1]*University of Oulu, Oulu, Finland*

Background: Maternal depression during pregnancy is common. Even so, there is lack of follow-up studies of the association between antenatal depression in mothers and severe mental disorders in the offspring later on in middle age. Among severe mental disorders at least schizophrenia is considered to be a neurodevelopmental disorder acting already *in utero* with high genetic vulnerability.
Our aim was to determine whether maternal antenatal depression specifically increases the risk for mood disorders in the offspring compared to schizophrenia when taking account parental severe mental disorder. Methods: The Northern Finland 1966 Birth Cohort includes 12,058 children, whose mothers were asked at mid-gestation if they felt depressed. The offspring were followed for over 40 years, and mood disorders and schizophrenia were detected using the Finnish Hospital Discharge Register, which was also used for identifying severe mental disorders in the parents till 1984, when the offspring were of age.
Results: Of the mothers, 14% had rated themselves as depressed during pregnancy. Of the parents, 10% had suffered from a severe,

hospital-treated mental disorder. Maternal depression during pregnancy increased slightly the risk for mood disorders in the offspring (OR 1.6; 95% CI 1.2–2.2) but not for schizophrenia, when compared with the children of mothers without depression.
The risks for both depression (crude OR 3.6; 95% CI 2.0–6.4) and bipolar disorder (7.8; 2.6–23.1) and also schizophrenia (4.3; 2.3–8.2) were higher in the offspring with both maternal antenatal depression and parental severe mental disorder than in those with a depressed mother but without parental mental disorder (for depression 1.4; 0.9–2.1; for bipolar disorder 1.7; 0.6–4.5, and for schizophrenia 0.9; 0.5–1.6) or those without maternal depression and with mental disorder in the parent (for depression 1.5; 0.9–2.3; for bipolar disorder 5.1; 2.4–11.0, and for schizophrenia 1.2; 0.7–2.3). The reference group was birth cohort members without maternal antenatal depression and without parental severe mental disorder. The statistically significant associations remained significant even after adjustment for maternal smoking during pregnancy, perinatal risk, father's social class, and family type at birth. Only for schizophrenia the risk was highest in the offspring of antenatally depressed mother and father with severe mental disorder (7.5; 2.2–26.2).
Discussion: Maternal depression during pregnancy increased the risk for mood disorders in the offspring slightly but not for schizophrenia when compared with the children of mothers without antenatal depression. Maternal antenatal depression did not specifically increase the risk for mood disorders in the offspring compared to schizophrenia when taking account parental severe mental disorder. The risks for both depression and bipolar disorder and also schizophrenia were higher in the offspring with both maternal depression during pregnancy and parental severe mental disorder than in those with a depressed mother but without parental mental disorder or those without maternal depression and with mental disorder in the parent. The reference group was birth cohort members without maternal antenatal depression and without parental mental disorder. The risk for schizophrenia was highest in the offspring of antenatally depressed mother and father with severe mental disorder. Maternal antenatal depression may have a stronger affect on subjects at risk of severe mental disorder due to familial history. Maternal depression may act as an adverse environmental factor in those with genetic vulnerability or with early environmental risk due to severe parental mental disorder maybe via epigenetic mechanism.

O1.6 Cognitive developmental trajectories in the extended psychosis phenotype

Josephine Mollon[*1], Anthony David[1], Glyn Lewis[2], Stanley Zammit[3], Abraham Reichenberg[4]*

[1]King's College London, London, UK, [2]University College London, London, UK, [3]Cardiff University & University of Bristol, [4]Icahn School of Medicine at Mount Sinai, New York, USA

Background: Schizophrenia patients show large cognitive deficits, which emerge years before illness onset. Subclinical psychotic experiences are prevalent across the lifespan and have also been associated with neuropsychological impairments. The course of neuropsychological impairment associated with psychotic experiences and psychotic disorder remains unclear.
Methods: The Avon (UK) Longitudinal Study of Parents and Children is a well-characterized, epidemiologically ascertained birth cohort, which began in 1991. Cognition was measured at age 18 months using the Griffiths Mental Development Scales, at age 4 years using the Wechsler Preschool and Primary Scale of Intelligence, at age 15 using the Wechsler Abbreviated Scale of Intelligence and at ages 8 and 20 using the Wechsler Intelligence Scale for Children. At age 18, psychotic experiences and psychotic disorder were established using the Psychosis-Like Symptom interview and depression using the Clinical Interview Schedule. We compared the following groups: 1) psychotic experiences, 2) depression 3) non-affective psychosis (psychotic disorder), 4) affective psychosis (comorbid for depression and psychotic disorder) to 5) controls. Standardized IQ at ages 18 months, 4, 8, 15, and 20 years, was used to explore cognition through infancy to early adulthood. Raw IQ, digit symbol coding, digit span, vocabulary, block design, and sky search scores at ages 8 and 20 were used to directly examine developmental change in the domains of general cognition, processing speed, working memory, language ability, visuospatial ability, and attention, respectively.
Results: There was a significant group by age interaction on standardized IQ for the non-affective psychosis group ($P = 0.022$, $d\Delta = -1.30$). At 18 months IQ was within normal range, but had dropped below controls by age 4 and continued to lag further and further behind through ages 8, 15, and 20. A significant main effect on standardized IQ for the psychotic experiences group ($P = 0.036$, $d = -0.27$) suggested a small, stable deficit. Significant main effects were seen for the non-affective psychosis group on raw IQ ($P = 0.004$, $d = -1.17$), vocabulary ($P = 0.005$, $d = -0.87$), and block design ($P = 0.001$, $d = -0.90$) scores, suggesting static, developmental deficits. Significant group by age interactions were seen for the non-affective psychosis group on raw IQ ($P = 0.005$, $d\Delta = -0.54$), digit symbol coding ($P = 0.001$, $d\Delta = -0.68$), digit span ($P = 0.004$, $d\Delta = -0.59$), and sky search ($P = 0.001$, $d\Delta = -0.44$) scores, suggesting developmental lags (i.e. improvement over time, but at a slower rate than controls).
Discussion: The developmental process of decline may be a specific marker of transition to non-affective psychotic disorder since it was not observed in depression, psychotic experiences, or affective psychosis.

O1.7 The impact of cannabis use on emerging psychotic experiences explained by the presence of affective symptoms

Josiane Bourque[*1], Maeve O'Leary-Barrett[2], Patricia Conrod[1]*

[1]University of Montreal, Montreal, Québec, Canada, [2]University McGill, Montreal, Québec, Canada

Background: The mechanisms by which cannabis use increases the risk for psychosis are still unclear. However, emerging evidence shows that the magnitude of risk appears to be dose-dependent, influenced by age of cannabis use initiation, as well as premorbid psychosis vulnerability. Thus, there is a crucial need to investigate the longitudinal development of these two phenomena in early adolescence, when they begin to manifest. We further examined whether the longitudinal relationship between cannabis use and psychotic-like experiences (PLEs) is mediated by changes in neurodevelopment and/or onset of anxiety/depression.
Methods: Substance use, clinical (e.g. PLEs) and cognitive data for 2237 adolescents (mean age 12.8 years old, 52.7% boys), was collected through a web-based survey at three different time points, with 12 months separating each assessment. General growth mixture modeling was used to confirm the distinct trajectories of PLEs in youths: a low decreasing (81.3%), a high decreasing (9.7%), and a moderate increasing (9.0%) trajectory. We then modeled substance use, clinical and cognitive data with unconditional latent growth models to allow for the representation of individual change in these developmental phenomena. The latent variables of the individual models, intercepts and slopes, were entered as risk factors of the PLEs trajectories. Finally, we examined the effects of potential mediators (cognitive and anxiety/depression factors) on the relationship between cannabis use frequency and PLEs group membership. All analyses were controlled for age, sex, and baseline socioeconomic status.
Results: A steeper increase in cannabis use frequency from 12 to 14 years predicted membership in the moderate increasing trajectory, relative to the low and high decreasing trajectories (OR = 1.43, $P < 0.001$ and OR = 1.26, $P < 0.05$). Adolescents with a less positive growth on IQ measure were more likely to be classified in the moderate increasing group relative to the high decreasing group (OR = 1.30, $P < 0.05$). Additionally, steeper increases in depressive and anxiety measures were associated with a greater likelihood to follow the moderate increasing trajectory relative to the low decreasing (ORs = 1.45, $P < 0.001$) or the high decreasing trajectory (ORs = 1.44, $P < 0.001$). The link between increasing cannabis use and the moderate increasing trajectory of PLEs was mediated by a steep growth in both depression and anxiety symptoms, not through changes in cognitive functioning.
Discussion: The main advantage of the present study was that we modeled, for the first time, adolescent substance use in a developmentally realistic way, instead of using baseline or cumulative substance use data to predict subsequent psychotic symptoms. We showed that an increasing cannabis use differentiated youths for

whom PLEs are transitory (high decreasing group) from those with increasingly persistent PLEs (moderate increasing group), who might be at risk for developing clinically significant psychotic symptoms. Interestingly, we observed a close temporal relationship between cannabis use, depression/anxiety and the increasing presence of PLEs such that the relationship between growth in cannabis use an increasing PLE trajectory was explained by increases in anxiety and depression. This was not the case for changes on cognitive measures. These results provide insight into the mechanisms that might mediate the impact of cannabis use on psychosis risk.

O1.8 Childhood and adolescence physical activity patterns – effects on psychosis risk

Elina Sormunen[*1], Maiju Saarinen[2], Raimo Salokangas[1], Risto Telama[3], Nina Hutri-Kähönen[4], Jorma Viikari[5], Olli Raitakari[2], Jarmo Hietala[6]*

[1]Department of Psychiatry, University of Turku, Turku, Finland, [2]Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku and Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital,Turku, Finland, [3]Department of Pediatrics, University of Tampere and Tampere University Hospital,Tampere, Finland, [4]LIKES Research Center for Sport and Health Sciences, Jyväskylä, Finland, [5]Department of Medicine, University of Turku and Turku University Hospital,Turku, Finland, [6]Department of Psychiatry, University of Turku, General Hospital Psychiatry Unit, Turku University Central Hospital, Turku Psychiatry, Turku, Finland

Background: Schizophrenia spectrum disorders are associated with high morbidity and mortality in cardiovascular and pulmonary diseases. The background of this excess morbidity and mortality is multifactorial, including smoking, obesity, dietary factors, and low physical activity, in particular after the onset of psychosis. However, the literature regarding physical activity among subjects at risk for psychosis is insufficient, and there is no developmental data on childhood physical activity and psychosis risk. Our aim was to examine whether specific physical activity and exercise patterns in childhood and adolescence predict later development of non-affective psychosis. This may have etiologic and early intervention relevance in schizophrenia-spectrum disorders.
Methods: The participants were derived from an on-going, population-based, epidemiologic longitudinal study Cardiovascular Risk of Young Finns. This cohort was initiated in 1980 and consists of 3596 children and adolescents from six age groups (3, 6, 9, 12, 15, and 18 years). Cardiovascular health parameters were measured every third year including physical activity. All psychiatric diagnoses of the participants were acquired, up to the year 2012, from the Finnish Hospital Discharge Register. Five DSM-IV-based diagnostic groups were formed and linked to sequential measures of physical activity: non-affective psychosis ($n = 68$), schizophrenia ($n = 41$) included, affective and anxiety disorders ($n = 111$), personality disorders ($n = 43$), addictive disorders ($n = 49$), and controls ($n = 3325$) with no life-time psychiatric diagnoses. Physical activity index and different physical exercise patterns, such as leisure time activity and exercise frequency, were measured by a self-report questionnaire before first hospitalization ($\leq$18 years). Sex, age, BMI, low birth weight, and parental mental disorders were also recorded and used as potential confounders in the analysis.
Results: Lower physical activity of children and adolescents (9–18 years) emerged as an independent risk factor for a later non-affective psychosis but not affective and anxiety disorders, personality disorders, or addictive disorders. Physical activity index (Relative Risk [RR] 1.2 [1.1–1.4]), lower leisure time activity (RR 1.8 [1.2–2.6]), lower exercise frequency (RR 1.2 [1.0–1.4]), and non-participation in sports club competitions (RR 2.7 [1.3–5.5]) were associated with later non-affective psychosis. This pattern was particularly clear in subjects with future schizophrenia. Psychiatric disorder of either parent and low birth weight, but not BMI, also predicted later non-affective psychosis. The associations between childhood and adolescence physical activity indexes and diagnosis of non-affective psychosis were not affected by adjustment with covariates.
Discussion: Low physical activity in childhood and adolescence is an independent risk factor for later non-affective psychosis, especially schizophrenia. Deviant motor and cognitive development may translate to altered patterns of physical exercise and activity in at-risk children and adolescents before the onset of psychosis. Further research is needed to assess the possibility of using exercise and physical activity interventions as a part of psychosis prevention programs.

O2. Genetics: multifaceted approach

O2.1 Association of schizophrenia gwas risk variants with cognitive deficits in the genus consortium schizophrenia sample collection

Gabriëlla Blokland[*1], Tracey Petryshen[2], GENUS Consortium[2]*

[1]Massachusetts General Hospital, Harvard Medical School, [2]Massachusetts General Hospital, Boston, USA

Background: Recent GWAS mega-analyses have identified many genetic variants with genome-wide significant evidence for association with schizophrenia (SCZ) risk. However, the case-control samples used in these analyses have limited phenotypic data to elucidate the role of these variants in brain dysfunction that characterizes the disorder. The Genetics of Endophenotypes of Neurofunction to Understand Schizophrenia (GENUS) Consortium aims to clarify the neurobiological role of known SCZ risk variants by testing their association with cognitive and neuroanatomical endophenotypes. Fifteen research groups have contributed a total of 4,896 SCZ cases, 804 genetic high-risk (GHR) subjects, and 3,331 healthy controls (HC) with genome-wide SNP data, cognitive data, and (in a subset) structural MRI data.
Methods: To select robust endophenotypes for genetic analyses, literature review and meta-analysis were performed to identify cognitive traits with high heritability, reliability, and case-control differences. Cognitive data were harmonized across samples by pooling controls for each test version and fitting a linear regression model (correcting for age, age^2, sex, and interactions), followed by calculating standardized residuals relative to controls. ANOVA with Tukey's HSD *post hoc* comparisons was applied to each phenotype to identify case-control differences. Genome-wide SNP data from each site were subjected to quality control procedures in Plink and imputed to the 1000 Genomes Phase III reference panel using a standardized pipeline. Genetic association analyses between the 108 independent SNPs and the polygenic risk scores from the Psychiatric Genomics Consortium SCZ analyses and the cognitive phenotypes were carried out in Plink and R with age, age^2, sex, and interactions, and 10 principal components for ancestry as covariates. Inverse variance weighted meta-analysis was used to combine summary statistics from individual samples.
Results: We selected 3 tiers of cognitive phenotypes (individual neuropsychological tests, cognitive domains, and general cognitive ability "g") with relatively high heritability according to meta-analysis ($h^2 = 28$–62%; average 43%). Cognitive phenotypes were confirmed to differ between SCZ and HC in our sample collection. SCZ performed significantly worse than HC for all individual cognitive tests, domain scores, and "g", with effect sizes (standardized mean difference) between -0.52 and -1.12, averaging -0.90 ($P < 0.001$). GHR individuals performed between SCZ and HC for Trails A, Category Fluency, and Word List Learning (effect size range relative to controls: -0.34; -0.35; -0.88; $P < 0.05$), similar to SCZ for Letter-Number Span and Continuous Performance Test, and similar to HC for Symbol Coding, BVMT, and Block Design ($P > 0.05$). We identified nominally significant associations between several of the 108 SNPs and multiple cognitive phenotypes. The polygenic risk scores were significantly associated with the verbal learning and memory domain score and "g" ($P < 0.01$), explaining 2–3% of the variance in these phenotypes.
Discussion: Careful harmonization of robust cognitive endophenotypes across sites is essential to minimizing noise in the data and thereby increasing power to detect genetic associations. Ongoing analyses in this large sample collection are expected to contribute towards elucidating the function of genetic variation in neural processes underlying SCZ pathophysiology. Multivariate analyses within and across phenotypic domains may identify phenotypic profiles associated with risk variants that may point to common neural mechanisms.

O2.2 Gene expression analysis in peripheral blood mononuclear cells of first episode psychosis patients from the genetic and psychotic disorders (gap) study

Daniel Leirer[*1], Valeria Mondelli[1], Marta Di Forti[1], Conrad Iyegbe[1], Charles Curtis[1], Hamel Patel[1], Elena Carra[1], Sara Fraietta[1], Marco Colizzi[2], Hugh R Williams[3], John Lally[1], Diego Quattrone[1], Olesya Ajnakina[1], Sang Hyuck Lee[1], Carmine Pariante[1], Gerome Breen[1], Paola Dazzan[1], Robin Murray[1], Richard Dobson[1], Stephen Newhouse[1]*

[1]King's College London,London, UK, [2]University Degli Studi Di Bari, Bari, Italy, [3]South London and Maudsley NHS Foundation Trust, Beckenham, UK

Background: Psychosis is associated with a number of psychiatric disorders, most notably schizophrenia and bipolar disorder. Due to the complex nature of the phenotype, which manifests as hallucinations and delusions, recent studies have attempted to identify transcriptional changes, which are subject to both genetics and the environment, by using gene expression microarrays in peripheral blood mononuclear cells (PBMCs). In this study a total of 150 controls and 163 first episode psychosis cases were recruited and had their gene expression profiles derived.
Methods: Using the Illumina HT 12 v4 gene expression microarray platform, we analyzed the PBMC samples from our cohort. We processed the data and identified differentially expressed genes using a LIMMA model incorporating age, sex, and ethnicity.
We proceeded to perform gene enrichment analysis as well as network analysis on the dataset.
Results: We notably report differential expression of genes associated to the Glutamate
system, post synaptic density, and the Mitochondria. In addition we validated a number of core genes identified in this study, and previous studies. Among these is Neurogranin (NRGN) which is directly associated to the Glutamate system and Septin 5 (SEPT5), a binding partner of Parkin (PARK2) and one of the genes deleted in DiGeorge syndrome.
Discussion: We report, to our knowledge, the largest PBMC based transcriptomic study conducted for first episode psychosis. Among the most interesting findings are our results indicating enrichment for Post Synaptic density probes and the Glutamate system. However this signal is largely confined to probes with very subtle differential expression, indicating that perhaps
We also report a number of probes associated to antiviral activity that are highly differentially expressed. These probes correspond largely to genes that are members of the Defensins family, and they have been shown to be differentially expressed in both Bipolar disorder and Schizophrenia. We hypothesize that at least part of this differential expression is due to Medication.

O2.3 Exploiting epidemiological links between rheumatoid arthritis and schizophrenia refines gwas in the hla region

Tulsi Malavia[*1], Joel Wood[2], Kodavali Chowdari[2], Lora McClain[1], Konasale Prasad[1], Vishwajit Nimgaonkar[1]*

[1]University of Pittsburgh, Pittsburgh, USA, [2]University of Pittsburgh, School of Medicine, Pittsburgh, USA

Background: Genome wide association studies (GWAS) have identified numerous risk alleles for schizophrenia, but it has been difficult to pinpoint susceptibility gene/s, particularly in the human leukocyte antigen (HLA) region. We exploited epidemiological clues to identify genes that might deserve further investigation. Many epidemiological studies have observed reduced risk for Rheumatoid Arthritis (RA) among patients with schizophrenia. We utilized this inverse relationship in risks (negative association) to narrow the list of potential genes, assuming that some gene/s might confer risk for both diseases, with risk being conferred by different variants (alleles) at the same locus.
Methods: *In silico* approaches were implemented to parse meta-analytic GWAS for both disorders. We obtained a list of single nucleotide polymorphisms (SNPs) with genome-wide significant associations ($P < 1E-8$) for both disorders and then used LD based pruning to generate independent disease-associated genome-wide lists with maximal significance. Pairwise LD between SNPs in each list were examined in order to find pairs of SNP, either identical or in tight LD ($r^2 \geqslant 0.8$), which were highly associated with both RA and SZ.
Results: This analysis resulted in 290 SNPs pairs, all located solely in the HLA region on chromosome 6p21. Four SNPs located in both the RA and SZ SNP list, but with different allelic associations, are localized to TNXB, NOTCH4, HLA-C, and C6orf10. Of these, HLA-C has the most plausible pathogenic roles in SZ and RA, by regulating natural killer cell (NKC) activity differently in RA and SZ.
Discussion: Our analysis indicates 4 genes in the HLA region that could underlie the genetic associations with SZ in the HLA region.

O2.4 Genetic variation in schizophrenia liability explained through intellectual ability and brain structure

Marc Bohlken[*1], Rachel Brouwer[2], Rene Mandl[1], René Kahn[2], Hilleke Hulshoff Pol[1]*

[1]University Medical Center Utrecht, Utrecht, The Netherlands, [2]Rudolf Magnus Institute of Neurosciences; University Medical Center Utrecht, Utrecht, The Netherlands

Background: Alterations in intellectual ability and brain structure are important intermediate phenotypes for studying genetic vulnerability for schizophrenia and underlying disease mechanisms. How variation in such phenotypes interacts with variance in schizophrenia liability due to genetic or environmental factors is an area of active investigation.[1–3] Using a multivariate twin modeling approach, we show novel leads for (genetic) pathways of schizophrenia development.
Methods: In a sample of 70 twins discordant for schizophrenia and 130 healthy control twins[3], structural equation modeling (openMx) was applied on 3 T T1-weighted structural and diffusion imaging data and behavioral data. Using a multivariate Cholesky decomposition, contributions of genetic (Rg = correlation due to genetic factors) and environmental (Re = correlation due to environmental factors) factors between human brain structure (cortical thickness, cortical surface and global white matter fractional anisotropy (FA)), intellectual ability (IQ) and schizophrenia liability were quantified.
Results: In total, 28.1% of the genetic variance (22.8% of total variance) in schizophrenia liability could be accounted for by sources shared with IQ, global-FA, cortical thickness, and cortical surface. The strongest contributor was IQ, explaining 16.4% of the genetic variance in schizophrenia liability (Rg = − 0.34 (95%CI: − 0.48– − 0.20)), followed by cortical thickness (Rg = − 0.22 (95%CI: − 0.35– − 0.06); explaining 6.3%), global-FA (rg = − 0.18 (95%CI: − 0.33– − 0.02); explaining 4.7%), and cortical surface (Rg = − 0.07 (95%CI: − 0.22–0.08); explaining 0.5%). Furthermore, 57.4% of the variation due to environmental factors (4.6% of total variance) in schizophrenia could be explained. Significant contributors to this environmental factor were IQ (Re = − 0.07 (95%CI: − 0.12– − 0.02); explaining 34.2%) and cortical surface (Re = − 0.07 (95%CI: − 0.12– − 0.02); explaining 13.4%).
Discussion: Intellectual ability, fractional anisotropy and cortical thickness share a significant proportion of genetic variance with schizophrenia liability, due to independent pathways. Importantly, our findings indicate that measuring brain-imaging phenotypes helps elucidate shared genetic variance of schizophrenia liability that is not captured by variation in IQ alone. As schizophrenia is a genetically complex disorder,[4] these phenotypes may constitute independent genetic markers for schizophrenia development.

References:

1. Hulshoff Pol HE, van Baal GCM, Schnack HG, Brans RGH, van der Schot AC, Brouwer RM *et al.* Overlapping and segregating structural brain abnormalities in twins with schizophrenia or bipolar disorder. Arch Gen Psychiatry **69,** 349–59 (2012).
2. Toulopoulou T, van Haren N, Zhang X, Sham PC, Cherny SS, Campbell DD*et al.* Reciprocal causation models of cognitive vs volumetric cerebral intermediate phenotypes for schizophrenia in a pan-European twin cohort. Mol Psychiatry:1–11 (2014).
3. Bohlken MM, Brouwer RM, Mandl RW, Van den Heuvel MP, Hedman AM, De Hert M*et al.* Structural Brain Connectivity as a Genetic Marker for Schizophrenia. JAMA Psychiatry. Published online. doi:10.1001/jamapsychiatry.2015.1925 (2015).

4. Cannon TD. Deciphering the Genetic Complexity of Schizophrenia. JAMA Psychiatry. Published online. doi:10.1001/jamapsychiatry.2015.2111 (2015).

O2.5 Genetic overlap between schizophrenia and the big five personality traits

Olav Smeland[1], Aree Witoelar[1], Min-Tzu Lo[2], Martin Tesli[1], Yunpeng Wang[3], David Hinds[4], Youna Hu[4], Joyce Tung[4], Srdjan Djurovic[1], Chi-Hua Chen[2], Anders Dale[2], Ole Andreassen[3]*

[1]NORMENT, KG Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo and Oslo University Hospital, Oslo, Norway, [2]University of California, San Diego, California, USA, [3]NORMENT, KG Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo and Oslo University Hospital, Oslo, Norway; University of California San Diego, California, USA, [4]23andMe, Inc., Mountain View, California, USA

Background: Despite the clinical relationship between personality and schizophrenia (SCZ), little is known about potential shared etiology. Here we explored genetic overlap across common variants between SCZ and the Big Five personality traits neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness.
Methods: Using summary statistics from genome-wide association studies (GWAS) we evaluated overlap in single nucleotide polymorphisms (SNPs). Applying conditional false discovery rate (FDR) methods, we compared GWAS of personality traits in the 23andMe cohort ($n = 59{,}176$) with GWAS of SCZ in the Psychiatric Genomics Consortium cohort ($n = 82{,}315$).
Results: We found polygenic overlap between SCZ and all personality traits except conscientiousness. Using conjunction FDR, we leveraged these genetic associations to identify two independent susceptibility loci shared by neuroticism and SCZ, and five independent susceptibility loci shared by openness to experience and SCZ. One susceptibility locus shared by neuroticism and SCZ showed the same direction of effect in the phenotypes, whereas the other showed opposite effect directionality. All susceptibility loci shared by SCZ and openness to experience displayed opposite directionality in the phenotypes. To validate our approach we show that pleiotropic-enriched SNP categories replicate at a higher rate using independent SCZ sub-studies.
Discussion: Our findings demonstrate that common SNPs associated with SCZ are also associated with normal personality traits, suggesting that part of the interrelation between personality traits and SCZ arises from a shared genetic basis.

O2.6 Unique dual cortico-striatal action of dopamine d2 receptor functionally selective ligands modulate schizophrenia-like phenotypes

Marc Caron[1], Nikhil Urs[1], Steven Gee[2], Thomas Pack[1], John McCorvey[3], Tama Evron[1], Joshua Snyder[1], Xiaobao Yang[4], Ramona Rodriguiz[1], William Wetsel[1], Jian Jin[4], Bryan Roth[3], Emiliana Borrelli[5], Patricio O'Donnell[2]*

[1]Duke University Medical Center, Durham, North Carolina, USA, [2]Pfizer, Inc., New York, USA, [3]University of North Carolina, Chapel Hill, North Carolina, USA, [4]Icahn School of Medicine at Mount Sinai, New York, USA, [5]University of California, Irvine, USA

Background: D2 dopamine receptors (D2R) are targets of most clinical antipsychotic drugs and activate downstream signaling pathways not only through canonical G protein pathways but also through β-arrestins, previously thought to mediate desensitization of GPCRs. We have shown previously that brain D2Rs, can signal through the ability of β-arrestin 2 (βarr2) to engage the Akt/GSK3 signaling pathway. Genetic deletion of components of this pathway recapitulates some of the effects of antipsychotics on mouse behaviors. The dopamine hypothesis of schizophrenia postulates hypodopaminergia in the prefrontal cortex (PFC) and hyperdopaminergia in the striatum, but current antipsychotics effectively reverse only excess striatal activity but do not fully reverse cortical deficits. To address this problem and the physiological relevance of the βarr2-dependent D2R signaling, we hypothesize that leveraging βarr2 functional selectivity at D2Rs simultaneously in the PFC and striatum may provide a more desirable antipsychotic profile
Methods: We have engineered a new mouse line for conditional deletion of the β-arrestin2 gene (βarr2flx) to inactivate βarr2 in various D2R+ neuronal populations and examined the profile of clinically used antipsychotics and two previously described functionally selective βarr2/D2R ligands (UNC9975A (75 A) & UNC9994A (94 A)) (Allen *et al.*, PNAS 2011). These were compared for their ability to modulate the behavioral responses to the psychostimulants amphetamine (AMPH) and phencyclidine (PCP), two pharmacological manipulations commonly used to assess striatal and cortical mediated antipsychotic-like behaviors in animals. In addition, these βarr2/D2R ligands were also examined by PFC infusions and by striatal and PFC electrophysiological recordings.
Results: In mice lacking βarr2 in either D2R+ medium spiny neurons (MSN) or all D2R+ neurons, all tested antipsychotics inhibited the AMPH response except 94 A, consistent with its selective βarr2 biased D2R profile. However, when assessed for inhibiting the psychomotor effects of PCP, 94 A lost its inhibitory effect only in mice lacking βarr2 in all D2R+ neurons or D2R+ cortico-striatal neurons but not D2R+ MSNs suggesting a role for cortical βarr2. In *in vitro* cellular reporter assays of D2R signaling 94 A, unlike 75 A, antagonizes only βarr2/D2R interactions but not G protein signaling. Interestingly, in such assays 94 A shows markedly increased agonist function upon over-expression of GPCR kinase 2 (GRK2) for βarr2/D2R interactions. In both mice and humans, expression of GRK2 and βarr2 is 3–5 fold higher in the cortex than in the striatum, recapitulating the cellular overexpression of GRK2 and βarr2, which enhances the ability of 94 A to show βarr2-dependent agonist properties in cellular assays. As expected, direct PFC infusions of 94 A or the D2R agonist quinpirole in wild type mice inhibited the response to PCP.
Electrophysiological recordings of D2R+ prefrontal-cortical fast spiking interneurons (FSI) revealed that 94 A displayed agonist properties and more effective D2R-mediated increases in action potentials of FSI than aripiprazole or quinpirole, an effect blocked by a D2R antagonist and absent in mice lacking βarr2. Conversely, unlike quinpirole, 94 A behaves as an antagonist in D2R+ MSNs.
Discussion: Our findings provide evidence that GRKs and β-arrestins are critical determinants for the physiological manifestation of functional selective signaling of D2Rs. Unlike current antipsychotics, the dual action of a drug like 94 A might be ideal to simultaneously reverse cortical hypodopaminergia and striatal hyperdopaminergia in schizophrenia and result in better clinical efficacy towards cortical-related symptoms such as cognitive impairment.

O2.7 Association of the polygenic risk score for schizophrenia with mortality and suicidal behavior. - A Danish population-based study

Thomas Laursen[1], Betina Trabjerg[2], Manuel Mathiesen[1], Sandra Melanie Meier[2], Ole Mors[3], Anders Børglum[1], David Hougaard[4], Preben Mortensen[2], Trine Munk-Olsen[2], Esben Agerbo[2]*

[1]Aarhus University, [2]National Center of Register-Based Research, Aarhus University, Aarhus, Denmark, [3]Aarhus University Hospital, Aarhus, Denmark, [4]SSI, Copenhagen, Denmark

Background: People with schizophrenia have a 2 to 3 fold higher mortality rates compared to the general population resulting in 15–20 years shorter life expectancy.
Schizophrenia runs in families and data from the Psychiatric Genomics Consortium shows that schizophrenia is a polygenic disorder, suggesting a genetic component in the development of schizophrenia.
We set out to examine the impact of this genetic predisposing, measured by polygenetic risk score (PRS) for schizophrenia, in two different settings:
1. The excess mortality in schizophrenia
2. The excess number of suicide attempts in schizophrenia
Methods: People with schizophrenia were defined among all singleton births in Denmark since 1981 and an ICD-10 F20 code for schizophrenia between January 1, 1994, and December 31, 2008. We selected controls born in Denmark, with the same gender and the same birthday, not previously diagnosed with schizophrenia. Day of death was found in the nationwide cause of death register. Suicide

attempts were identified by hospital records. All odds-ratios (ORs) with 95% confidence intervals not crossing 1.00 was considered significant. The PRS for schizophrenia was calculated using the SNP information from the Psychiatric Genomics Consortium, (discovery sample of 34,600 cases and 45,968 control individuals, excluding the Danish data).
Family history of psychiatric disorders was defined as having a mother/father with a contact to a psychiatric hospital in Danish registers.
The sample comprised 1,780 cases with schizophrenia and 1,768 age and gender matched controls.
Results: Outcome = Mortality
In total $N = 44$ persons with schizophrenia died ($N = 4$ controls). We found a basic adjusted OR, i.e. adjusted only for age, year at the matching time, sex, and the first 10 genomic principal components, equaling 8.76 (95% CI: 3.46;22.18) for death in people with schizophrenia compared to the control group. Further adjusting for PRS (OR = 1.00 (0.71;1.40)) and family history of psychiatric disorder (OR = 1.83 (1.02;3.27)) only reduced the OR for excess mortality in people with schizophrenia to OR = 7.76 (3.02;19.91). When we examined only people with schizophrenia, we found a OR for excess mortality equaling 1.08 (0.75;1.55) for the PRS and 2.03 (1.12;3.71) for a family history of psychiatric contact. Outcome = Suicide attempts In total $N = 399$ persons with schizophrenia tried to commit suicide two or more times (20 controls). $N = 257$ (42 controls) tried one time. Two or more suicide attempts was associated with a basic adjusted OR = 33.49 (21.16;53.00) while one suicide attempt was associated with a basic adjusted OR = 9.86 (7.03;13.82). The PRS did not affect this OR for suicide attempts (either in the case-control or case only setup), while family history of psychiatric disorders did.
Discussion: Genetic predisposition, measured by the poly genic risk score, does not influence the excess mortality and or the risk of suicide attempts. In contrast there is a strong significant effect of family history of psychiatric disorders.
This could suggest that family history of psychiatric disorders is also an indicator of the environment associated with growing up in a family with psychiatric disorders rather than merely a genetic component.
Most important the results suggests that the unacceptable high excess mortality among people with schizophrenia is not entirely based on a genetic predisposition, but to a large degree also a result of amendable factors such as stressful life events.

O2.8 Age-at-migration and risk of first episode psychosis in England: epidemiological evidence from the sepea study

James Kirkbride[*1], *Yasir Hameed*[2], *Gayatri Ankireddipalli*[3], *Nikolett Kabacs*[4], *Carolyn Crane*[4], *Oliver Jenkins*[2], *Danica Ralevic*[2], *Ben Walden*[2], *Suneetha Siddabattuni*[2], *Mukhtar Nasir*[2], *Konstantinos Ioannidis*[4], *Antonio Metastasio*[2], *Jesus Perez*[5], *Peter Jones*[5]

[1]*UCL,London, UK,* [2]*Norfolk & Suffolk Foundation Trust, Norwich, Norfolk,* [3]*North Essex Partnership NHS Foundation Trust, Essex,* [4]*Cambridgeshire & Peterborough Foundation Trust, Cambridge, UK,* [5]*University of Cambridge, Cambridge, UK*

Background: Although migrant populations experience elevated first episode psychosis [FEP] risk compared with the white British population, it is unclear whether age-at-migration to the UK modifies this risk. We therefore sought to test whether age-at-migration was associated with FEP risk in a large epidemiological cohort collected in the East of England.
Methods: Incidence data on all people, aged 16–35 years, presenting with ICD-10 FEP (F10-33) as part of the 3.5-year SEPEA study were obtained. Participants were classified according to age-at-migration ("UK-born, white British", "UK-born, ethnic minority", 0–4[infancy], 5–12[childhood], 13–19[adolescence] or 20+ years) and broad ethnic group (non-British white ethnicities; black Caribbean, African & other black ethnicities; Pakistani & Bangladeshi; other Asian ethnicities; other ethnic groups). Poisson regression was used to model FEP incidence by age-at-migration, after adjustment for age and sex, using the 2011 census to estimate person-years at-risk.
Results: We identified 670 participants with FEP over 2.02 m person-years. Relative to the UK-born white British group, excess risk in first generation migrant groups ($n = 105$) peaked in childhood (incidence rate ratio [IRR]: 2.1; 95%CI: 1.2–3.8) after adjustment for age, sex, and ethnicity. This pattern was independently observed in non-British white (IRR: 2.6; 95%CI: 1.2–5.3), black Caribbean & African (IRR: 6.3; 95%CI: 2.8–14.0), and Pakistani & Bangladeshi groups (IRR: 3.5; 95%CI: 0.9–14.1; $P = 0.077$). Other Asian immigrants, moving to the UK in adulthood, had lower FEP rates (IRR: 0.2; 95%CI: 0.1–0.9). Only migrants from Caribbean & African countries showed elevated risk in other migration periods (infancy: IRR: 5.5, 95%CI: 1.4–22.1; adolescence: IRR: 4.4, 95%CI: 2.3–8.5). Rates were also elevated amongst UK-born ethnic minorities (IRR: 2.7; 95%CI: 2.1–3.5). Similar patterns were observed when the analysis was restricted to non-affective psychoses.
Discussion: Our data suggested that moving to the UK during childhood was most strongly associated with increased FEP risk; while migration in adulthood did not confer increased risk, UK-born ethnic minority populations experienced elevated rates. Our data support the possibility that childhood and adolescence may be particularly vulnerable windows when migration increases the risk of psychosis.

O3. Epidemiology: roles for environmental risk factors

O3.1 Artistic creativity, iq and risk for schizophrenia and bipolar disorder: a Swedish population-based case-control study and sib pair analysis in 4.5 million individuals

James MacCabe[*1], *Amir Sariaslan*[2], *Catarina Almqvist Malmros*[3], *Paul Lichtenstein*[3], *Henrik Larsson*[3], *Simon Kyaga*[3]

[1]*Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK,* [2]*University of Oxford, Oxford, UK,* [3]*Karolinska Institutet, Stockholm, Sweden*

Background: Most attempts to study the association between creativity and psychosis have been of poor quality, but recently evidence has begun to emerge suggesting a genetic overlap. To study this association objectively, large unbiased population samples are required. In this study we used data from national registries on higher education to test for an association between studying a creative subject and subsequent hospital admission for schizophrenia or bipolar disorder.
Methods: Using linked population based registries, we conducted a case control design, $N = 4{,}454{,}763$. Cases were defined as individuals admitted with a primary diagnosis of schizophrenia ($N = 20{,}333$) and bipolar disorder ($N = 28{,}293$) under ICD 9 or 10 criteria. The exposure was tertiary education in an artistic field (visual arts, dance, music, drama, media production, and design). In sensitivity analyses, we examined an alternative exposure that was not judged creative (Law and jurisprudence) and an alternative outcome (diabetes). We adjusted for educational level and conducted a sib pair analysis comparing sib pairs discordant for the exposure, to adjust for unmeasured familial confounders.
Results: Compared to the general population, individuals with an artistic education had approximately double the odds of developing schizophrenia (OR = 1.90, 95% CI = [1.69; 2.12]) and also an increased odds of bipolar disorder (OR = 1.62 [1.50; 1.75]). These results remained in the sib pair analysis.
In sensitivity analyses, the odds of diabetes (OR = 0.99 [0.92; 1.06]) were not increased in students of artistic subjects, and students of law and jurisprudence had no increased odds of schizophrenia (0.93 [0.76; 1.14]) or bipolar disorder (0.92 [0.81; 1.04]).
These associations remained when we conducted sib-pair analyses on siblings discordant for psychotic disorders, indicating that the associations exist within families and are thus not confounded by familial factors.
Finally we adjusted for IQ (in males only) which had a negligible effect on the estimates.
Discussion: Compared to the general population, students of artistic subjects at university have approximately double the odds of developing schizophrenia and 1.6 times the odds of developing bipolar disorder. Sensitivity analyses, using different exposures and outcomes, found no associations, confirming the specificity of the findings to psychosis and indicating that these results are unlikely to have arisen through biases in the study design. Furthermore, there was no evidence of confounding by familial factors or IQ. It appears that these associations are genuine and warrant further study to understand what may underlie this association.

O3.2 Children of parents with severe psychiatric disorders: with whom do they grow up? - a prospective, population-based study

Anne Ranning[*1], Thomas Munk Laursen[2], Carsten Hjorthøj[3], Anne Thorup[4], Merete Nordentoft[5]*

[1]Mental Health Centre Copenhagen, Copenhagen, Denmark, [2]Aarhus University; The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH); Mental Health in Primary Care (MEPRICA); Institute of General Medical Practice, Aarhus, Denmark, [3]Mental Health Center Copenhagen, University of Copenhagen, Copenhagen, Denmark, [4]Child and Adolescent Mental Health Center and The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), Aarhus, Denmark, [5]Mental Health Center and The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), Aarhus, Denmark

Background: Severe psychiatric disorders, especially schizophrenia, have been associated with impaired parenting capacities in multiple studies. The children are at increased risk of experiencing adversities and of developing dysfunctions and mental illness in childhood and adult life. This being a highly vulnerable population, more comprehensive knowledge is needed for public health strategies to provide helpful services and interventions. To date the basic question of where and with whom these children live during upbringing has only been addressed superficially and based on low-quality data.
Methods: We used information from Danish registers on children's addresses and calculated the proportion living in different household living arrangements in the course of childhood: in conjugal families, single-parent households, reconstituted families, or without their parents. The study was conducted as a prospective, register-based cohort study covering all children in the entire Danish population born after 1982 ($N = 1{,}823{,}625$) and their parents with a diagnosis of schizophrenia, bipolar disorder, depression, or none of these disorders. Regression analyses were performed assessing risk of dissolution of conjugal family. Compared to the general population both mothers and fathers with severe psychiatric disorders were more likely to live alone with their children.
Results: Of children of mothers with severe psychiatric disorders 20% lived alone with a mother with schizophrenia 20%, and 25% ($P < 0.00001$) lived alone with their mother with bi-polar disorder or severe depression. Compared to parents in the general population, both mothers and fathers with psychiatric disorders were more likely to live alone with their children. Parents' psychiatric illness strongly predicted dissolution of the conjugal family. This pattern was most pronounced if parents had a diagnosis of schizophrenia, especially for mothers; 63% of children lived with both parents at age 1 compared to 88% in the general population ($P < 0.00001$) and 24% at age 17, compared to 60% in the general population ($P \leqslant 0.00001$). The regression analyses showed parents' psychiatric disorders, low socio-economic position and substance abuse to predict dissolution of conjugal families.
Discussion: Our finding that a large proportion of these children live in single parent-headed households raises concern for the wellbeing of the children. Children are more vulnerable in the absence of a second adult, who could otherwise compensate for the affected parent's caregiving resources, monitor his/her mental health state, and advocate on behalf of the family. Studies document that children who experience emotional or physical neglect and abuse can be invisible in the social system in the absence of a second parent. More knowledge is needed about the conditions and specific needs for support of these single-parent headed households.
Our finding that conjugal families dissolve with higher rates when parents have severe psychiatric disorders imply that relationships in the nuclear family are especially difficult in these families. Family discord is stressful for children and stressors in childhood are part of the developmental pathway of psychopathology. Our results substantiate the importance of intervention on a family level in prevention strategies targeting children at familial high risk for severe psychiatric disorders.

O3.3 Phenotypic manifestation of genetic risk for schizophrenia during adolescence in the general population

Stanley Zammit[*1], Hannah Jones[2], Evie Stergiakouli[2], Katherine Tansey[2], Leon Hubbard[3], Jon Heron[2], Mary Cannon[4], Peter Holmans[3], Glyn Lewis[5], David Linden[3], Peter Jones[6], George Davey Smith[2], Michael O'Donovan[3], Michael Owen[3], James Walters[3]*

[1]Cardiff University & University of Bristol, [2]University of Bristol, Bristol, UK, [3]Cardiff University, Cardiff, UK, [4]Royal Collegeof Surgeons in Ireland, Dublin, Irelang, [5]University College London, London, UK, [6]University of Cambridge, Cambridge, USA

Background: Schizophrenia is a highly heritable, polygenic condition characterized by a relatively diverse phenotype, and frequent comorbid conditions such as anxiety and depression. There is currently limited evidence on how high genetic risk for schizophrenia is manifest in the general population. We aimed to investigate the extent to which genetic risk for schizophrenia is associated with different phenotypes during adolescence in a population-based birth cohort.
Methods: We used data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a population-based UK birth cohort. Polygenic risk scores (PRSs) for schizophrenia were generated for individuals in ALSPAC using results of the second Psychiatric Genomics Consortium Schizophrenia genome-wide association study as a training set.
Logistic regression was used to assess associations between schizophrenia PRS ($N = 3673$ to 5444 depending on outcome investigated) and the following outcomes during adolescence: a) psychotic experiences (using the semi-structured PLIKSi at 12 and 18 years), b) negative symptoms (questionnaire based on CAPE at 16.5 years), c) depressive disorder (semi-structured DAWBA interview at 15.5 years) and d) anxiety disorder (DAWBA at 15.5 years).
Results: PRSs created using single nucleotide polymorphisms with a training set P value ≤ 0.05 showed strong evidence of association ($P < 0.001$) with negative symptoms (OR per SD increase in PRS = 1.21, 95% CI = 1.09, 1.36; R2 = 0.007) and anxiety disorder (OR per SD increase in PRS = 1.17, 95% CI = 1.06, 1.29; R2 = 0.005). No evidence was found of an association between schizophrenia PRS and psychotic experiences (OR per SD increase in PRS = 1.08, 95% CI = 0.98, 1.19; R2 = 0.001), or depressive disorder (OR per SD increase in PRS = 1.02, 95% CI = 0.91, 1.13; R2 = 0.00005).
Associations with negative symptoms and anxiety disorder were independent of each other and other psychopathology examined. Results were mostly consistent across different training set P value thresholds and using different cut-offs and measures of the psychopathology examined.
Discussion: We demonstrate polygenic overlaps between common genetic polymorphisms associated with schizophrenia and both negative symptoms and anxiety disorder, but not with psychotic experiences or depression. I will discuss a number of possible explanations for these findings, and what they might mean for both genetic studies of schizophrenia and population-based studies of psychotic experiences. One implication of our findings is that, as schizophrenia genetic risk appears to be manifest as anxiety and negative symptoms during adolescence, a greater focus on these phenotypes rather than on psychotic experiences might be required for prediction of transition in at-risk samples.

O3.4 Toxic social environments and psychosis: the role of violence and multiple adversities in childhood

Craig Morgan[*1], Charlotte Gayer-Anderson[1], Kathryn Hubbard[1], Stephanie Beards[1], Ulrich Reininghaus[2], Valeria Mondelli[1], Simona Stilo[1], Marta Di Forti[1], Carmine Pariante[1], Robin Murray[1], Paola Dazzan[1]*

[1]King's College London, London, UK, [2]Maastricht University, Maastricht, Netherlands

Background: There is consistent evidence that various forms or markers of childhood adversity are associated with around a 2 to 3 fold increased odds of psychosis, e.g., family breakdown, peer bullying, and physical and sexual abuse. However, much of the research has been on low-level psychotic experiences in general population samples, not psychotic disorder, and has used crude

measures of adversity without consideration of severity, frequency, timing, or duration. Further, studies have tended to focus on specific forms of adversity in isolation, despite the fact that such adversities frequently co-occur. Using data from a population based case-control study of first episode psychosis, we sought to extend previous research by examining in detail associations between various forms of childhood adversity and psychotic disorder, focusing in particular on timing and severity of exposure and on how these combine to increase risk.
Methods: The Childhood Adversity and Psychosis (CAPsy) study is a population based case-control study of first episode psychosis conducted in south London, UK. During a four year period in a defined catchment area, we identified and recruited a sample of cases with a first episode psychotic disorder aged 18–64 years and, using a combination of quota and random sampling, a sample of controls aged 18–64 years. We collected extensive information from cases and controls, using a validated semi-structured interview (Childhood Experiences of Care and Abuse (CECA)), on the timing and severity of exposure to various forms of adversity before age 16 years, including family breakdown, household financial problems, household discord, bullying, and psychological, physical, and sexual abuse. We used logistic regression to estimate odds ratios for each form of adversity, overall and by timing and severity, adjusted for age, gender, ethnicity, and history of psychosis in a first degree relative. We further used latent class analyses to identify groups characterized by extent of exposure to multiple adversities.
Results: We identified and collected extensive data from 303 cases (men, 63%; mean age, 29 years) and 301 controls (men, 51%; mean age, 35 years). First, exposure to each form of childhood adversity was associated with a 2 to 4 fold increased odds of psychotic disorder, independent of potential confounders including a history of psychosis in a first degree relative. Second, the strongest effects were for the most severe level of each exposure, i.e. involving violence; e.g., the odds ratio for physical bullying was 2.64 (95% CI 1.39-5.03), compared with an odds ratio for non-physical (verbal) bullying of 1.39 (95% CI 0.88-2.22). Third, the timing of exposure was important for some forms of adversity, e.g. psychological abuse that began in childhood (age 0–11 years) had a stronger effect on odds of psychosis (i.e., odds ratio [OR] 5.14 for age 0–11 vs. OR 2.09 for age 12–16); by contrast, bullying that began in adolescence (age 12–16 years) had a stronger effect (i.e., OR 1.94 for age 12–16 vs. OR 1.34 for age 0–11). Finally, we identified three classes characterized by different probabilities of exposure to the range of childhood adversities measured: 1) low exposure; 2) high exposure to family breakdown, low exposure to abuse; 3) high exposure to all. Compared with controls, cases were around 3 times more likely to be in Class 2 (OR 3.56, 95% CI 1.50–8.50) and 5 times more likely to be in Class 3 (OR 5.03, 95% CI 2.55–9.93).
Discussion: Our findings are important for understanding the nature of the relationship between childhood adversities and psychosis. They suggest that, for psychotic disorder, it may be exposure to severe (i.e., involving violence) and multiple forms of adversity throughout childhood that particularly increase risk.

O3.5 Exposure to anti-infective agents and the risk of severe mental disorders – a nationwide study

Ole Köhler[*1], Liselotte Petersen[2], Ole Mors[1], Preben Bo Mortensen[2], Robert H. Yolken[3], Christiane Gasse[2], Michael Eriksen Benros[4]*

[1]Psychosis Research Unit, Aarhus University Hospital, Aarhus, Denmark, [2]National Centre for Register-Based Research, Aarhus University, Aarhus, Denmark, [3]Johns Hopkins School of Medicine, Baltimore, Maryland, USA, [4]Mental Health Centre Copenhagen, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark

Background: Severe infections requiring hospitalization are associated with increased risks of schizophrenia and affective disorders. However, no large-scale studies have investigated the associations of the more commonly occurring infections treated with anti-infective agents in primary care settings.
Methods: Nationwide cohort-study including all individuals born in Denmark 1985–2002 without hospitalization with infections or a registered mental disorder before 1995 and with prescription information available since 1995. The association between prescription of anti-infective agents and the subsequent risk of schizophrenia and affective disorders were studied during 1995–2013. COX regression analyses were adjusted for important covariates.
Results: We included 1,028,291 individuals, of whom 1,013,019 (98.0%) redeemed at least one prescription for anti-infective agents during follow-up. Anti-infective agents, particularly antibiotics, were associated with subsequent increased risks of schizophrenia by a hazard rate ratio (HRR) of 1.36 (95% CI = 1.19–1.55) and affective disorders by a HRR of 1.72 (95% CI = 1.56–1.90), fitting a dose-response and temporal relationship ($P < 0.001$). The population-attributable risk associated with anti-infective agents was 27% for schizophrenia and 42% for affective disorders. In particular, prescription for antibiotics increased the risk of schizophrenia by a HRR of 1.41 (95% CI = 1.28–1.56) and affective disorders by a HRR of 1.75 (95% CI = 1.59–1.94). These results were supported by sub-analyses on 544,439 individuals (99.2% used anti-infective agents) with life-long prescription information.
Discussion: Anti-infective agents, particularly antibiotics, were associated with an increased risk of schizophrenia and affective disorders. These risks may be mediated via effects of infections on the brain, alterations of the microbiome due to anti-infective agents, genetics, or other environmental factors. The prevention of infections through immuno-prophylactic measures and limitation of unnecessary exposure to antibiotics may represent considerations in the reduction of the risks of mental disorders.

O3.6 Incidence of psychotic disorders in England, France, Italy, the Netherlands, Spain and Brazil: data from the eu-gei study

Hannah Jongsma[*1], Craig Morgan[2], Andrei Szoke[3], Alice Mule[4], Jean-Paul Selten[5], Ilaria Tarricone[6], Julio Bobes[7], Jim Van Os[8], Bart Rutten[8], Domencio Berardi[6], Robin Murray[2], Antonio Lasalvia[9], Paulo Menezes[10], James Kirkbride[11], Peter B. Jones[1], EU-GEI Work Package 2[12]*

[1]University of Cambridge, Cambridge, USA, [2]Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK, [3]CMP ADULTES CRETEIL, Créteil, France, [4]AOUP Paolo Giaccone, Palermo, Italy, [5]Maastricht University; Rivierduinen Mental Health Care Institute, Maastricht, Netherlands, [6]Bologna University, Bologna, Italy, [7]University of Oviedo, Oviedo, Spain, [8]Maastricht University Medical Centre, Maastricht, Netherlands, [9]University of Verona, Verona, Italy, [10]Universidade de Sao Paulo, São Paulo, Brazil, [11]University College London, London, UK, [12]EU-GEI, Maastricht, The Netherlands

Background: The incidence of psychotic disorders varies across countries and settings. However, it is unclear which factors underpin this variation, such as for instance the higher rates in urban and migrant populations. The EU-GEI study was established to investigate the incidence as well as genetic and environmental determinants of first episode psychosis in a multi-national setting. The aim of the present study was to estimate the crude, age-sex standardized, and age-sex-ethnicity standardized incidence of psychotic disorders using the same methodology across 16 centers in 6 countries (England, France, Italy, the Netherlands, Spain, and Brazil).
Methods: We conducted a population-based study of the incidence of ICD-10 psychotic disorders (F10-33) over a 3-year period. Inclusion criteria were: (1) presence of an untreated first episode of non-organic psychosis; (2) aged between 18-64 at the time of first contact; (3) resident in one of the clearly defined catchment areas; (4) no previous psychotic disorder or treatment with anti-psychotic drugs. Research-based diagnoses were based on an OPCRIT assessment.. Demographic data (age, sex, ethnicity) and OPCRIT diagnosis were collected. Denominator data was estimated from official government sources. Crude as well as directly standardized (age-sex, an age-sex-ethnicity) incidence rates were estimated, and for the latter the population from the 2011 English Census was used as the standard population.
Results: We identified 2458 incidence cases over 13,385,089 person-years at-risk (PYAR), corresponding to an overall crude incidence rate of 18.4 (17.7–19.1) per 100,000 PYAR. Preliminary crude incidence rates varied between centers, from 6.8 (5.0–9.3) in rural Spain (Santiago) to 47.0 (41.9–52.7) per 100,000 PYAR in Amsterdam. The crude incidence in England was 23.9 (22.0–26.0) per 100,000 PYAR, in France it was 33.8 (30.4–37.6), in Italy 12.5 (11.5–13.7), in the Netherlands 29.7 (22.0–32.7), in Spain 14.5 (13.1–15.9), and in Brazil 13.7 (12.2–15.6) per 100,000 PYAR. Crude incidence in rural areas was 12.9 (12.0–13.9) per 100,000 PYAR, and in urban areas this was 22.3

(21.3–23.4) per 100,000 PYAR. The corresponding incidence rate ratio was 1.66 (1.53–1.83) (rural as reference category). This was statistically significant ($P < 0.001$). Standardization for age, sex, and ethnicity did not alter these associations.
Discussion: Crude incidence rates of psychotic disorders appear to be lower than expected on the basis of previous studies. However, variance remained high and familiar patterns emerged. For example, incidence was higher in Northern European countries (France, the Netherlands, and England) compared to Southern Europe. Furthermore, incidence was higher in urban compared to rural areas.

O3.7 Is there a cumulative effect of social disadvantage on risk of psychosis?

Simona Stilo[*1], Charlotte Gayer-Anderson[1], Stephanie Beards[1], Kathryn Hubbard[1], Adanna Onyejiaka[1], Francois Bourque[1], Valeria Mondelli[1], Paola Dazzan[2], Carmine Pariante[1], Marta Di Forti[1], Robin Murray[1], Craig Morgan[1]*

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

Background: A growing body of evidence suggests that experiences of social disadvantage are associated with an increased risk of psychosis. However, only a few studies have specifically looked at cumulative effects and long-term associations. We compared the prevalence of specific markers of social disadvantage at, and prior to, first contact with psychiatric services in patients suffering their first episode of psychosis and in a control sample and explored long-term associations, cumulative effects, and directions of associations.
Methods: We collected information from 332 patients and from 301 controls recruited from the local population in South-East London. Three indicators of social disadvantage in childhood and six indicators of social disadvantage in adulthood were analyzed.
Results: Compared with controls, cases were approximately two times more likely to have had a parent die before the age of 17 (OR 1.95, 95% CI 0.9–3.8) and approximately three times more likely to have experienced a long-term separation from one or both parents before the age of 17 (OR 3.04, 95% CI 2.1–4.3). Cases were also more likely than controls to report two or more markers of adult social disadvantage, not only at first contact with psychiatric services (OR 9.5, 95% CI 5.4–16.7), but also at onset (OR 8.5, 95% CI 4.8–15), one year pre-onset (OR 4.5, 95% CI 2.8–7), and five years pre-onset (OR 2.9, 95% CI 1.8–4.6).
Discussion: Greater numbers of indicators present and long-term exposure were associated with progressively greater odds of psychosis. There is some evidence that social disadvantage tends to cluster and accumulate.

O3.8 Mortality and deliberate self-harm during clozapine use in treatment-resistant schizophrenia: results from the crestar collaboration

Theresa Wimberley[*1], James H MacCabe[2], Thomas M Laursen[1], Aske Astrup[1], Henriette T Horsdal[1], Holger J Sørensen[3], Christiane Gasse[1], Henrik Støvring[4]*

[1]National Centre for Register-Based Research, Aarhus University, Aarhus, Denmark, [2]Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK [3]Mental Health Centre Copenhagen; University of Copenhagen, Copenhagen, Denmark, [4]Aarhus University, Aarhus, Denmark

Background: Treatment-resistant schizophrenia affects approximately 30% of patients with schizophrenia. Clozapine is the most effective second-generation antipsychotic treatment recommended for treatment-resistant schizophrenia. It is however often substituted by alternative treatment strategies such as switching or augmenting with other antipsychotics, despite lack of evidence for the efficacy and safety of such strategies. Several studies have demonstrated a decreased mortality rate in clozapine users in schizophrenia. However, the mortality and suicidal behavior in clozapine users compared to non-clozapine use in patients suffering from treatment-resistant schizophrenia have not yet been studied. We aim to describe the rates of all-cause mortality and deliberate self-harm in association with clozapine use in patients with treatment-resistant schizophrenia.
Methods: We linked population-based Danish registers to identify patients diagnosed with schizophrenia between 1996 and 2013 who met criteria for treatment-resistant schizophrenia. The criteria were that they initiated clozapine treatment or were admitted to psychiatric hospital after two subsequent periods of different antipsychotic monotherapy. Patients were followed from the date of meeting the criteria for treatment resistance (baseline) until death/deliberate self-harm, emigration, or June 1, 2013. Hazard ratios were estimated for baseline clozapine exposure as well as for time-varying clozapine exposure. Analyses were adjusted for sex, age, history of deliberate self-harm, and substance abuse.
Results: We identified 2,248 patients meeting criteria for treatment-resistant schizophrenia (46% females, median age at baseline was 30 years (inter-quartile range: 25–37 years)). Among these, 51% initiated clozapine at baseline and 61% initiated clozapine during the entire follow-up, comprising a total of 15,932 person-years at risk of death. In total, 145 (6.5%) died and 398 (17.7%) committed deliberate self-harm during follow-up. The mortality rates per 100 person-years were 1.42 (during antipsychotic-free periods), 0.78 (during antipsychotic monotherapy), 0.67 (during antipsychotic polypharmacy), and 0.54 (during clozapine treatment, partially augmented). For the time-varying clozapine exposure (non-clozapine-exposed periods as reference) the adjusted hazard ratios were 0.53 (95% CI: 0.35–0.81) for all-cause mortality and 0.56 (0.44–0.71) for deliberate self-harm. For the baseline clozapine exposure (non-clozapine users as reference) adjusted hazard ratios were 0.99 (95% CI: 0.71–1.38) for all-cause mortality and 0.68 (0.56–0.83) for deliberate self-harm.
Discussion: Our results corroborate findings from previous research of decreased all-cause mortality during clozapine use. In a cohort of all patients with TRS we applied a study design which, at least in part, could account for confounding by indication and channeling, which have been major issues in previous observational studies. Additionally we detected a decreased rate of deliberate self-harm during clozapine use, which may suggest a potential pathway of effect of clozapine in the prevention of deaths in patients with treatment-resistant schizophrenia.

O4. Phenomenology and dimensional discussion

O4.1 Exploring the applicability of a network approach to psychosis

Johanna Wigman[*1], Stijn de Vos[1], Marieke Wichers[1], Jim Van Os[2], Annegien Bartels-Velthuis[3]*

[1]Groningen University, Groningen, Netherlands, [2]Maastricht University Medical Centre, Maastricht, Netherlands, [3]University of Groningen, University Medical Center Groningen, Groningen, Netherlands

Background: Our ability to accurately predict development and outcome of early expression of psychosis is limited. To elucidate the mechanisms underlying psychopathology, a broader, transdiagnostic approach that acknowledges the complexity of mental illness is required. The application of the novel network paradigm may be fruitful here.
Methods: We explore the applicability of a transdiagnostic network approach to psychosis. Data pertain to the third wave (second follow-up) of a sample of adolescents originally recruited at age 7–8 years (the PSYCHE study). At baseline, $N = 347$ children with auditory verbal hallucinations (AVH) as well as $N = 347$ control children were included. $N = 293$ of these $N = 694$ children participated in the second follow-up (mean age 18.9 years; 59% women). Participants completed the Community Assessment of Psychic Experiences (CAPE) and the Depression, Anxiety and Stress Scale (DASS-21). A specific type of network model, the Ising model, was applied to dichotomized CAPE and DASS items.
Results: Our results show that it is possible to map the multi-dimensional experiences of the CAPE and the DASS as a network, and that examination of interconnectedness of experiences provides information that cannot be easily distilled from composite scores, e.g. correlations of sum scores. Interconnections of experiences within the same domain were observed, as well as interconnections between experiences of multiple psychopathological domains. The many

domain-crossing links, especially between depressive and negative experiences, underline the need to work cross-diagnostically and to examine the relation of symptom (domains) not only within one certain diagnostic construct, but also in relation to other domains.
Quantitative and qualitative differences in network architecture were found in networks of experiences in individuals with or without AVH at age 7–8 years. These differences in network architecture could not be explained by current differences in CAPE or DASS sum scores. It showed for example that in the group with previous AVH, positive psychotic experiences are more interconnected compared to the group without previous AVH, even when the sum scores on this dimension were similar. Apparently, dynamics between psychological experiences have different patterns in individuals who as children are exposed to psychotic phenomena. In addition to information on individual experiences, network analysis also yields important information on the full network. The presence of different communities demonstrates other ways of grouping experiences than according to their original domain that may provide information on their co-occurrence.
Discussion: The current paper is, to our knowledge, one of the first to examine the interconnectedness of psychotic experiences with other psychopathological domains. Mapping the dynamics between subclinical psychopathological experiences may help us to better understand the processes that may lead to the development of clinical disorders. Shifting our focus from symptoms per se to the dynamics between symptoms seems to yield important information, as it allows us to examine roles and/or contributions of individual items. This study showed that it is possible to map transdiagnostic experiences of psychopathology as a network, and that important information can be derived from this approach in comparison to regular approaches. In future research, parameters derived from network analysis (e.g. centrality indices) could be used to predict important variables, such as course or outcome of early psychopathological symptoms or levels of psychosocial functioning.

O4.2 Childhood trauma and social stress reactivity in psychosis: a virtual reality study

Wim Veling[*1], *Roos Pot-Kolder*[2], *Jacqueline Counotte*[3], *Jim Van Os*[4], *Mark van derGaag*[5]

[1]*University Medical Center Groningen, Groningen, Netherlands,* [2]*VU University Amsterdam, Amsterdam, Netherlands,* [3]*Parnassia Psychiatric Institute, The Hague, Netherlands,* [4]*Maastricht University Medical Centre, Maastricht, Netherlands* [5]*Parnassia Psychiatric Institute, VU University Amsterdam*

Background: Childhood trauma may be related to risk for psychosis by the mechanism of sensitization to social stress. It leads to negative cognitive schemas that may be activated in the context of social stress. Virtual Reality (VR) provides the opportunity to test this mechanism by controlled experimental exposure to different social environments.
Methods: Fifty-five patients with recent onset psychotic disorder (FEP), 20 patients at ultra-high risk for psychosis (UHR), 42 siblings of patients with psychosis and 53 controls walked five times in a virtual bar with different levels of environmental social stress. Virtual social stressors were population density, ethnic density, and hostility. Social stress sensitivity was measured with paranoia and subjective distress in response to virtual social stress exposures, childhood trauma and self-esteem were assessed at baseline. Multilevel random intercept regression analyses were used to test childhood trauma as predictor and moderator of paranoia and subjective distress in VR. Social stress sensitivity was tested as mediator between childhood trauma and symptoms of psychosis.
Results: Childhood trauma was significantly associated with higher paranoia and subjective distress in the virtual social stress experiments. There was a positive and linear interaction between childhood trauma and degree of environmental social stress on paranoia and subjective distress. Social stress sensitivity measures mediated associations between childhood trauma, (minor) psychotic and affective symptoms, and psychosis liability.
Discussion: Childhood trauma is associated with heightened social stress sensitivity and contributes to psychotic and affective dysregulation later in life by sensitized paranoid and stress response to social stressors.

O4.3 Premorbid and social determinants of formal thought disorder in early psychosis

Eric Roche[*1], *Ricardo Segurado*[2], *Brian O'Donoghue*[3], *Felicity Fanning*[1], *Laoise Renwick*[4], *Kevin Madigan*[1], *Caragh Behan*[1], *John Lyne*[5], *Mary Clarke*[1]

[1]*DETECT Early Intervention in Psychosis,* [2]*CSTAR, University College Dublin, Dublin, Ireland,* [3]*Orygen Youth Health, Melbourne, Australia,* [4]*University of Manchester & DETECT Early Intervention in Psychosis Service, Manchester, United Kingdom,* [5]*Dublin North Mental Health Services, Ireland & DETECT Early Intervention in Psychosis Service*

Background: Language is essential for everyday functioning and its use is influenced by social context. Formal thought disorder (FTD) is the most frequent type of language disturbance evaluated by psychiatrists, however we understand very little about its social determinants. Social adjustment may be evaluated in relation to the premorbid period or the post-illness phase of psychosis. There has been minimal investigation of the social determinants of FTD at any stage of psychotic illness and none has evaluated this association longitudinally. We aimed to: 1) evaluate the prognostic value of premorbid adjustment (PA) in relation to FTD at first episode psychosis (FEP) and investigate whether this relationship persists over the first year of illness and 2) compare the relative influence of premorbid vs. post-illness social adjustment in relation to FTD occurrence 1 year post-FEP.
Methods: Participants were recruited through the DETECT Early Intervention in Psychosis Service in Dublin, Ireland between February 2005 and July 2014; they were evaluated at FEP presentation and 1 year later. Those aged between 16 and 65 years old and presenting with affective and non-affective psychotic disorders were included in this study. Dimensions of FTD were established by factor analysis of SAPS and SANS items and included: disorganized, verbose, and impoverished dimensions (disFTD, verFTD, and povFTD respectively). Dimensions of PA were also established and included premorbid social, academic, and socio-sexual domains of PA. Social adjustment in the year following FEP was established with the "Quality of Social Relationships" item of the Strauss-Carpenter Level of Functioning Scale. Predictors of each FTD dimension at FEP and at 1 year were evaluated with hierarchical regression; other clinical variables controlled for in the analysis included: age, gender, duration of untreated illness (DUI), inattention and negative symptoms, and reality distortion. Funding for this study was provided by the Health Research Board of Ireland.
Results: A total of $n = 623$ participants were evaluated at FEP presentation and of these $n = 397$ were re-assessed at 1 year (i.e. 64% follow-up rate). Fifty one percent of the sample had evidence of at least one FTD dimension at FEP and 30% did so at 1 year assessment. At FEP presentation the presence of povFTD was predicted by poor premorbid socio-sexual development (OR 3.93, 95% CI 1.19–12.98, $P < 0.05$). Neither verFTD nor disFTD at presentation were predicted by any domain of premorbid social adjustment. The association between premorbid socio-sexual development and povFTD at 1 year became non-significant when the quality of social relationships during the 1st year post-FEP was added into the regression model. Lower quality of social relationships significantly predicted the presence of disFTD at 1 year (OR 0.66, 95% CI 0.44–0.97, $P < 0.05$), but not povFTD (OR 0.54, 95% CI 0.55–1.03, $P = NS$) when controlling for other clinical variables. In a sub-sample of those with a schizophrenia diagnosis, lower quality of social relationships significantly predicted the presence of povFTD but not disFTD at 1 year assessment.
Discussion: Social adjustment is a significant predictor of FTD in early psychosis. FTD evolves in the year following FEP and post-illness social adjustment becomes more influential than premorbid adjustment in determining the presence of FTD following FEP. There appears to be a bi-directional relationship between FTD/social functioning and social milieu/FTD in early psychosis. This is relevant given that communication disorders have been proposed as a potential target of intervention in psychotic disorders.

O4.4 A dimensional approach to elucidating the neural basis of psychotic spectrum traits

Samantha Abram[*1], Krista Wisner[1], Colin DeYoung[1], Matthew Smith[2], Angus MacDonald, III[1]*

[1]University of Minnesota, Minneapolis, USA, [2]Northwestern University, Evanston, Illinois, USA

Background: Emerging evidence suggests that two dimensions can capture the negative symptoms of schizophrenia: experiential symptoms characterized as internal motivational impairments (e.g., anhedonia, apathy) and expressive symptoms characterized by external communicative impairments (e.g., alogia). Although research suggests that these symptom domains may be supported by separable neural substrates, the underlying neural correlates of negative symptoms remain poorly understood. The medial prefrontal cortex and ventral striatum (e.g., nucleus accumbens) are promising targets for such neural investigations, given their roles in reward processing and motivation. In the present study, we examined whether resting-state connectivity in these areas predicted experiential negative symptoms. Driven by psychopathology's dimensional characteristics, we examined these associations in a community sample and a sample of individuals with schizophrenia.
Methods: We included two samples of resting-state fMRI: 1) a community sample ($N = 218$) who completed the Personality Inventory for DSM-5 (PID-5), and 2) a schizophrenia sample ($N = 30$) who completed the Scale for the Assessment of Negative Symptoms (SANS). Experiential negative symptom traits were captured using the withdrawal, intimacy avoidance, and anhedonia PID-5 domains. An equivalent experiential negative symptom score was computed for schizophrenia patients using the affective flattening, avolition-apathy, and asociality-anhedonia SANS domains. Intrinsic connectivity networks were generated using Independent Component Analysis in the community sample and applied to both samples to derive comparable subject-level coherence metrics (or within-network connectivity metrics). Analogous regression models were built for each sample that included the hypothesized networks, as well as age, gender, cognition, head motion, and medication covariates. To assess the specificity of these neural-symptom associations, we built additional regression models that included the same neural predictors with either expressive negative or positive symptoms as the criterion (again, creating parallel criterion using PID-5 and SANS domains).
Results: Reduced ventral striatum coherence predicted higher experiential negative symptoms in community controls ($\beta = -0.19$, $P = 0.01$) and individuals with schizophrenia ($\beta = -0.94$, $P = 0.004$). Among individuals with schizophrenia, greater medial prefrontal cortex coherence also predicted more severe experiential negative symptoms ($\beta = 0.91$, $P = 0.003$).
These effects remained when accounting for the aforementioned covariates. Moreover, medial prefrontal and ventral striatum coherence did not predict expressive negative or positive symptoms in either sample, suggesting phenotypic specificity for experiential negative symptoms. Lastly, medial prefrontal and ventral striatum between-network connectivity did not predict experiential negative symptoms in either sample, indicating methodological specificity for the within-network coherence metric.
Discussion: These results suggest that ventral striatum coherence is implicated in the experiential negative symptoms/traits present across the psychosis spectrum, whereas, medial prefrontal coherence may be more relevant to the negative symptoms observed in schizophrenia. Moreover, connectivity within (but not between) these networks may be specifically implicated in psychosis-related motivational impairments but not communicative deficits. Collectively, this work encourages a dimensional approach to elucidating the neural basis of severe psychopathology.

O4.5 Conversion from psychosis like experiences in the community to not only psychotic disorders; but also to depression and anxiety disorders: six years follow-up study in a community based population

Umut Kirli[*1], Tolga Binbay[1], Hayriye Elbi[1], Bülent Kayahan[1], Hüseyin Onay[1], Ferda Özkınay[1], Nesli Zağlı[2], Kübra Yıldırım[2], Jim van Os[3], Koksal Alptekin[2]*

[1]Ege University, Bornova, Turkey, [2]Dokuz Eylul University, İzmir, Turkey, [3]Maastricht University, Maastricht, Netherlands

Background: There is strong evidence that psychosis like experiences (PLE) are strongly related to clinical psychosis (CP). However its relation to any other mental disorders has not yet identified. The main aim of this study is to assess the conversion rate from psychosis like experiences to mental disorders as well as psychotic disorder and related psychosocial risk factors during a 6 years follow-up in a community sample
Methods: Addresses were contacted in multistage clustered area probability sampling frame covering 11 districts and 302 neighborhoods at baseline (T0 n: 4011) and 6 years after (T1 n: 2185). PLE were screened with Composite International Diagnostic Interview in both steps. Individuals reporting PLE in any steps were re-interviewed with SCID-I at T0 and T1. Relations were tested using logistic regression models.
Results: Of PLE which are related to a degree of distress and help-seeking behavior at T0, 6.4% transitioned to CP; 44.9% to affective disorders without psychotic features, 38.9% to other DSM disorders (mostly anxiety disorders); only 9.8% didn't meet the criteria of any DSM disorders at T1. Most of the people with newly onset CP at T1 had PLE at T0 (62.8%). Psychosocial risk factors related to developing CP in T1 were having baseline PLE with both distress and help-seeking behavior (OR: 34.3, CI: 11.5–101.8, $P < 0.001$), cannabis abuse in both T0 and T1 (OR: 33.2, CI: 6.1–181.6, $P < 0.001$), alcohol abuse in both T0 and T1 (OR: 5.1 CI: 1.4–18.2, $P < 0.001$) and number of stressful life events (β: 7.8, CI: 0.01–0.02, $P < 0.001$). 23.3% of individuals having PLE which are related to a degree of distress and help-seeking behavior and having a first degree relative with plausible psychosis transitioned to CP; 100% of individuals with PLE with distress and help seeking+family history of plausible psychosis+cannabis use transitioned to CP.
Discussion: Risk factors synergistically affect the clinical psychosis risk. Psychosis like experiences take attention for the risk to develop not only psychosis but also any other mental disorder especially depression and anxiety disorder in future.

O4.6 Auditory hallucinations in adults with hearing impairment

Mascha Linszen[*1], Bert van Zanten[1], Rob Teunisse[2], Iris Sommer[1]*

[1]UMC Utrecht, Utrecht, Netherlands, [2]Dimence, Deventer

Background: Visual hallucinations can be triggered by visual impairment, a phenomenon known as the Charles Bonnet syndrome. A hypothetical explanatory mechanism for this phenomenon is often referred to as cortical deafferentiation, which states that understimulation of the central visual system leads to spontaneous neuronal activation within these areas. Likewise, hearing impairment is associated with auditory hallucinations, often with a musical content. However, research on the relation between hearing impairment and hallucinations is limited. In this study we aim to determine prevalence, risk factors, and phenomenology of auditory hallucinations in adults with hearing impairment.
Methods: All adult patients that were referred to the audiology department for audiometric testing were screened for the presence of auditory hallucinations, using a screening list to distinguish auditory hallucinations from tinnitus, illusions, and obsessions. Subjects with hearing impairment who screened positive for hallucinations in the last month were subsequently interviewed with the Questionnaire for Psychotic Experiences (QPE) to further assess the phenomenology of hallucinations and comorbid psychotic symptoms. Hearing impairment was assessed with pure tone audiometry and defined as a High Fletcher Index (mean hearing loss at frequencies of 1, 2 and 4 kHz) of at least 25 decibel in at least at one ear.
Results: One thousand and six individuals participated, 831 of whom had hearing impairment. 126 subjects (15.2%) with hearing

impairment had experienced auditory hallucinations in the last month, versus 7 subjects (4.0%) in the group without hearing impairment ($P < 0.0001$). Interestingly, the prevalence of recent auditory hallucinations increased with increasing levels of hearing impairment severity. Prevalence rates were 12% in persons with mild impairment, 19% in persons with moderate impairment, 21% in persons with severe impairment and 23% in persons with very severe impairment.
Within the group of hearing impairment, tinnitus in the past month occurred significantly more often in the group with hallucinations (84.8%) compared to those without (69.7%; $P = 0.009$), but did not differ in distribution of age and sex. Phenomenologically, the content of the auditory hallucinations included music or melodies ($n = 47$; 37.3%) voices ($n = 65$; 51.6%), phones or doorbells ($n = 30$; 23.8%), sounds of vehicles or sirens ($n = 29$; 23%),and other sounds ($n = 13$; 10%). One third of the participants suffered from their hallucinations (33%). A quarter (25%) had decreased insight in the unreal character of their hallucinations to at least some extent, and 15% had comorbid delusion-like ideas.
Discussion: Our findings reveal an increased risk of auditory hallucinations in patients with impaired hearing. In current clinical practice, it is therefore important to acknowledge hearing impairment as a highly prevalent and potentially reversible risk factor for auditory hallucinations. Hearing impairment can be easily diagnosed with audiometry and often improves with the use of adequate hearing aid equipment. The co-occurrence of delusion-like ideas and reduced insight in some persons with hallucinations suggest a phenomenological overlap between auditory hallucinations in our studied group and in patients with schizophrenia. This illustrates the essence of a transdiagnostic approach to hallucinations. Lastly, our findings shed new light on mechanisms that possibly underlie auditory hallucinations. The association between hallucination prevalence and hearing impairment severity are suggestive for auditory deafferentiation as an underlying mechanism for hallucinations in patients with hearing impairment.

O4.7 Cognitive heterogeneity on the schizophrenia – bipolar spectrum

Tamsyn Van Rheenen[1], Kathryn Lewandowski[2], Lesley Norris[3], Dost Ongur[2], Anil Malhotra[4], Susan Rossell[5], Katherine Burdick[6]*

[1]Melbourne Neuropsychiatry Centre, University of Melbourne; Brain and Psychological Sciences Research Centre, Swinburne University; Monash Alfred Psychiatry Research Centre, The Alfred Hospital and Monash University, [2]McLean Hospital and Harvard Medical School, Massachusetts, USA, [3]McLean Hospital, Massachusetts, USA, [4]Zucker Hillside Hospital, New York, USA, [5]Brain and Psychological Sciences Research Centre, Swinburne University; Monash Alfred Psychiatry Research Centre, The Alfred Hospital and Monash University; St Vincents Mental Health, [6]Icahn School of Medicine at Mount Sinai, New York, USA

Background: Cognitive dysfunction is a core characteristic of schizophrenia (Sz) and bipolar disorder (BD), with current evidence suggesting quantitative, but not qualitative differences between the two. Such evidence draws on outcomes of group-level analysis, despite increasing recognition that a substantial amount of cognitive within-group heterogeneity exists in both of these disorders. It currently remains unclear as to whether between-group comparisons of performance in cognitive clusters emerging from within these nosological categories uphold this finding; we aimed to address this by empirically identifying discrete cognitive clusters and comparing their qualitative cognitive profiles both within and between diagnoses.
Methods: Preliminary data from 294 healthy controls (HC), 156 Sz and, 193 BD participants that completed the MATRICS Consensus Cognitive Battery (MCCB) was available. Hierarchical cluster analyses using the age and gender corrected T scores of the 7 MCCB domains were performed on the data in two steps; the first analyzing the whole sample regardless of diagnosis and the second analyzing within each group. Cognitive performance of the emergent clusters was compared within and between diagnostic categories using MANOVA.
Results: The first analysis resulted in 3 clusters; 2 comprising a mix of BD, SZ, and HC participants characterized by cognitive performance either at or within +.8 SD of the normative mean, and a third comprising mainly Sz and BD patients with more profound performance reductions (performance 1.5 - 2 SDs below normative mean). When analyzed by diagnostic category, HC's clustered into 2 groups; 1 with performance equivalent to the normative mean and 1 with performance 1-1.5 SDs above it. In contrast, 3 discrete clusters emerged within each clinical group. These included two qualitatively similar, globally impaired clusters characterized by profound impairments across several cognitive domains that differed in magnitude between diagnoses only in social cognition;, and two qualitatively similar, moderately impaired groups with intact social cognition that differed in magnitude between diagnoses on processing speed, verbal/visual learning, and problem solving. A third cluster of Sz patients formed a 'selective' deficit group with mild impairments on processing speed, attention/vigilance, and social cognition. This cluster did not differ significantly from the third cluster of BD patients that were spared of patient-control performance deficits completely.
Discussion: Sz and BD patients can be clustered into discrete groups that meaningfully account for within-group cognitive heterogeneity. As general cognitive performance between the globally and most profoundly impaired clusters from within each diagnostic group failed to differentiate between Sz and BD, it is possible that these groups are manifesting a shared etiology

O4.8 Outcomes of non-transitioned cases in a sample at ultra-high risk for psychosis

Ashleigh Lin[1], Stephen Wood[2], Barnaby Nelson[3], Amanda Beavan[2], Patrick McGorry[3], Alison Yung[4]*

[1]Telethon Kids Institute, Subiaco, Australia, [2]University of Birmingham, Birmingham, England, [3]Orygen Youth Health Research Centre, Melbourne, Australia, [4]Institute of Brain Behaviour and Mental Health, University of Manchester, Manchester, UK

Background: Two thirds of individuals identified as ultra-high risk (UHR) for psychosis do not develop a psychotic disorder over the medium-term. This highlights the need to examine outcomes other than psychosis in this population. The aim of this study was to examine the medium- to long-term outcome of a large UHR cohort from the PACE Clinic in Melbourne. We investigated the presence of persistent attenuated psychotic symptoms, and incident and persistent non-psychotic disorders.
Methods: Participants were help-seeking individuals identified as being at UHR risk for psychosis between two and 14 years previously (median = 5.7). The current sample is drawn from the PACE400 Study and consists of 226 participants (125 females; 101 males) who completed follow-up assessment and had not developed a psychotic disorder. Mean age at follow-up was 25.5 years (SD = 4.8).
Results: Significant psychopathology was found. In this non-psychotic sample, 28% reported attenuated psychotic symptoms at follow-up. 68% of participants experienced non-psychotic disorder over the follow-up period - 48% experienced mood disorder, 34% anxiety disorder, and 29% a substance use disorder. For a majority of the participants, non-psychotic disorder was present at baseline (90%), and was persistent for 57% of them. Over the follow-up period, 26% of the cohort remitted from a disorder, but 37% developed a new (incident) disorder. Only 7% did not experience any psychiatric disorder over the follow up period. The incidence of non-psychotic disorder was associated with higher negative symptoms at baseline. Females experienced higher rates of persistent/recurrent disorder. Meeting the brief limited intermittent psychotic symptoms (BLIPS) UHR criteria at intake was associated with lower risk for persistent/recurrent non-psychotic disorder.
Discussion: UHR individuals who do not develop psychosis are at significant risk for continued attenuated psychotic symptoms. They also have a high risk for persistent, recurrent, and incident non-psychotic disorders. The UHR phenotype, while relatively specific to incident psychosis, also captures patients with a range of emerging or chronic psychopathology. These finding have important implications for on-going clinical care. Findings confirm the need to examine and treat non-psychotic psychopathology in young people who present as UHR for psychosis.

O5. Brain imaging-i: molecules, structures, and functions

O5.1 Accelerated gray and white matter aging in schizophrenia

Vanessa Cropley[*1], Paul Klauser[1], Rhoshel Lenroot[2], Jason Bruggemann[3], Suresh Sundram[4], Chad Bousman[1], Avril Pereira[5], Thomas Weickert[6], Cynthia Shannon Weickert[3], Christos Pantelis[1], Andrew Zalesky[1]*

[1]Melbourne Neuropsychiatry Centre, The University of Melbourne, Melbourne, Australia, [2]University of New South Wales, New South Wales, Australia, [3]Neuroscience Research Australia: Schizophrenia Research Laboratory, New South Wales, Australia, [4]Florey Institute of Neuroscience and Mental Health, Victoria, Australia, [5]Florey Institute of Neuroscience and Mental Health, The University of Melbourne, [6]University of New South Wales/NeuRA, New South Wales, Australia

Background: Schizophrenia has been hypothesized to be a disorder of accelerated aging. However, although deficits in gray and white matter have been consistently observed, less is known about their progression with age. Using neuroimaging techniques and a pseudo-longitudinal design, this study aimed to determine whether the rate of gray matter loss and white matter deterioration with aging is comparable to that seen in healthy individuals of the same age, or whether the rate is accelerated, or diminished, in individuals with schizophrenia.
Methods: Structural magnetic resonance imaging and diffusion weighted imaging data was obtained from 326 individuals diagnosed with schizophrenia or schizoaffective disorder (SZ) and 197 healthy controls registered in the Australian Schizophrenia Research Bank. Participants were aged 18-65 years. Gray matter volume (GMV) at each voxel was calculated with voxel-based morphometry using Statistical Parametric Mapping 8. Fractional anisotropy (FA), a measure sensitive to fiber density, axonal diameter and myelination in WM, was generated using tract-based spatial statistics. Polynomial regression was used to model the influence of age on GMV and FA at a whole-brain (averaged across all voxels across the brain) and voxel level. The explanatory variables were diagnostic status (dx), age (a), age squared (a^2) as well as the interactions ($dx \times a$) and ($dx \times a^2$). The second interaction term models a between-group difference in the rate at which GMV or FA changes with time. Nuisance covariates included sex and scanner location. The regression was run separately with age centered at a range of ages between 20 and 65 years. This enabled age-specific determination of between-group differences (i.e. dx main effect) and between-group differences in the rate of change (i.e. $dx \times a^2$ interaction effect).
Results: GMV and FA were significantly reduced in SZ compared to controls in all cortical lobes and white matter, respectively. GMV and FA decreased with age in both SZ and controls. Across the whole brain, a polynomial model was significant for GMV ($P = 0.018$) but not for FA ($P = 0.36$). Age-specific comparisons showed that GMV was significantly lower in SZ at nearly each age studied but at the earliest age this loss was confined to fronto-temporal regions and became widespread with increasing age. Rate of GMV loss in SZ significantly exceeded the rate of loss seen in controls from young adulthood until about 45 years. In contrast, FA was significantly reduced, and its rate of loss was steeper, in SZ patients from approximately 35 years and this deterioration increased year to year thereafter.
Discussion: Deterioration in gray and white matter in SZ does not occur in parallel but occurs at different ages. Loss of gray matter in SZ is evident from early adulthood but rapidly declines during middle age and then stabilizes. Once this gray matter loss stabilizes, white matter deficits are evident and accelerate with age thereafter. These findings suggest that SZ is characterized by an initial reduction in gray matter, followed by age-related accelerated white matter deterioration. Future studies that examine the genetic and/or environmental mechanisms underlying these differential neurostructural trajectories with age and their clinical associations are warranted.

O5.2 Structural connectivity correlates of planning and executing goal-directed behaviour in schizophrenia

Ishraq Siddiqui[*1], Sarah Saperia[1], Gagan Fervaha[1], Jon Pipitone[1], Joseph Viviano[1], Eliyas Jeffay[1], Konstantine Zakzanis[1], Ofer Agid[1], Aristotle Voineskos[1], Gary Remington[1], George Foussias[1]*

[1]Centre for Addiction and Mental Health, University of Toronto, Toronto, Ontario, Canada

Background: Motivation is a complex construct of processes that culminate into the planning and execution of goal-directed behavior. While loss of motivation is recognized as a prominent feature of schizophrenia, these critical final steps of realizing motivation into action have not been extensively studied by objective and ecologically valid means. The neurobiological underpinnings of this process also remain largely unknown. In an attempt to address these shortcomings, we administered a novel virtual goal-planning and action task, the Multitasking in the City Test (MCT), and assessed associations between task performance and structural brain connectivity using diffusion tensor imaging (DTI).
Methods: The MCT requires subjects to fulfill eight pre-specified errands (e.g., budgeting for and purchasing items, attending an appointment, and going to the post office) within 15 minutes in a virtual city. The main performance indicators are the number of errands completed, completion time, errors committed (repeated and failed attempts), and distance traveled. In an initial behavioral validation phase, 49 schizophrenia patients (SZ) and 55 healthy controls (HC) completed the MCT and underwent comprehensive characterization of clinical symptoms, cognition, and, medication side-effects. A subsample of 20 SZ and 19 HC additionally completed a neuroimaging phase, whereby fractional anisotropy (FA) values were computed based on the (Enhancing NeuroImaging Genetics through Meta-Analysis) ENIGMA DTI protocol. Fiber tracts associated with the motivation and reward system were of primary interest.
Results: Analysis of the behavioral data indicated that SZ participants completed fewer errands (Mann-Whitney $U = 1039.5$, $Z = -3.49$, $P < 0.001$), took longer ($U = 784.0$, $Z = -3.67$, $P < 0.001$), traveled farther ($U = 922.0$, $Z = -2.77$, $P = 0.006$), and had more failed attempts ($U = 928.5$, $Z = -2.80$, $P = 0.005$) compared to HC. Motivation correlated with MCT performance, in SZ with completion time and distance (Spearman $|\rho| = 0.430–0.451$, $P \leqslant 0.002$), and in the overall sample with completions, failures, time, and distance ($|\rho| = 0.245–0.310$, $P \leqslant 0.012$). In the imaging subsample, partial correlations between MCT metrics and FA values, controlled for age, showed significant associations between several task measures and the right external capsule ($|\rho| = 0.387–0.459$, $P \leqslant 0.016$), and bilaterally the anterior internal capsule ($|\rho| = 0.332–0.463$, $P \leqslant 0.042$) and uncinate fasciculus ($|\rho| = 0.333–0.487$, $P \leqslant 0.041$). Further, repeated attempts correlated with the left external capsule ($\rho = -0.385$, $P = 0.017$) and right saggital striatum ($\rho = -0.354$, $P = 0.029$), and distance traveled correlated with the left superior longitudinal fasciculus ($\rho = -0.362$, $P = 0.026$).
Discussion: The behavioral findings suggest that motivational impairments in SZ, in the context of simulated everyday settings, may manifest not only as incapacity to fulfill goal-directed activities (errand completions and errors), but also as reduced efficiency in applying motivation towards this end (completion time and distance). The preliminary imaging findings support the notion that these aspects of motivation may overlap substantially but not completely, potentially at a neurobiological level. Further understanding the intricacies of translating motivation into real-world action may help guide the development of targeted therapeutics to improve outcomes in schizophrenia.

O5.3 Differences in global brain abnormalities between offspring, siblings, cotwins and parents of patients with schizophrenia

Sonja de Zwarte[*1], Rachel Brouwer[1], Manon Hillegers[1], Wiepke Cahn[1], Hilleke Hulshoff Pol[1], René Kahn[1], Neeltje van Haren[1]*

[1]Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, Netherlands

Background: Convergent neuroimaging evidence has shown abnormalities in patients with schizophrenia (SZ) throughout the brain, and to

some extent also in first-degree relatives (Boos *et al.*, 2007). However, MRI studies have shown varying results depending on the generational relationship of the first-degree relatives with the proband. A possible explanation could be that, although first-degree relatives share on average 50% of their genes with the proband (except for monozygotic twins who share almost 100%), they differ in relative risk (RR) to develop SZ (Gottesman, 1991). Here, we compare siblings, cotwins, parents, and offspring of patients with SZ to healthy controls (HC) and patients on global measures of the brain, and investigate whether these brain abnormalities vary among the different types of relatives.
Methods: A total of 868 participants were included from 4 SZ family MRI studies: Dutch Bipolar and Schizophrenia Offspring study (SZ offspring $n=29$ [not affected with SZ], HC $n=44$), Utrecht Parents Study (parents $n=67$, HC $n=55$), Genetic Risk and Outcome of Psychosis study (siblings $n=211$, HC $n=170$, patients $n=174$), and Schizophrenia Twin study (DZ $n=14$, MZ $n=13$, HC $n=58$, patients $n=33$). MRI scans were processed with the FreeSurfer software package. Age and gender effects were regressed out in each cohort individually and standardized residuals were calculated. Combining these data, linear mixed model analyses were performed comparing patients, HC and relatives, taking family relatedness into account, for cortical GM, cerebral white matter (WM) volume, total surface area and mean GM cortical thickness. Effect sizes were calculated for the total relatives group and the individual relative groups as compared with HC.
Results: The relatives showed an intermediate cortical GM volume as compared with patients ($B=0.251$, $P=0.001$) and HC ($B=-0.192$, $P=0.021$). Cerebral WM volume and surface area were significantly reduced in both patients and their relatives as compared with HC (cerebral WM volume, respectively, $B=-0.322$, $P<0.001$ and $B=-0.273$, $P=0.001$; surface area, respectively, $B=-0.329$, $P<0.001$ and $B=-0.242$, $P=0.005$), but did not differ between patients and relatives. Cortical thickness was significantly lower in patients as compared with HC ($B=-0.362$, $P<0.001$), but the relatives did not differ from HC. In a preliminary analysis comparing the different types of relatives, SZ offspring showed the greatest effect sizes compared to HC for all phenotypes studied.
Discussion: This study compared different types of first-degree relatives of patients with SZ, both combined and separately, with HC and patients. Relatives showed an intermediate decrease of global cortical GM volume. Cerebral WM volume and total surface area were both decreased in patients and relatives compared to HC, suggesting a familial (probably genetic (Boos *et al.*, 2007)) component to these decreases. In contrast, cortical thinning was only observed in patients, implicating that cortical thickness is an effect of illness rather than a familiar (possibly genetic) marker. Preliminary results indicate that SZ offspring show more abundant brain abnormalities compared to parents, siblings, and twins. Interestingly, RR for the disease is indeed relatively high for offspring. We are currently increasing our sample size in collaboration with the ENIGMA consortium.

O5.4 Increase in extracellular free water in first-episode schizophrenia patients is related to improved cognitive outcomes

Amanda Lyall[*1], Ofer Pasternak[1], Delbert Robinson[2], Dominick Newell[1], Joey Trampush[2], Juan Gallego[2], Katherine Karlsgodt[3], Anil Malhotra[2], Philip Szeszko[4], Marek Kubicki[1]*

[1]Harvard Medical School, Boston, Massachusetts, USA, [2]The Zucker Hillside Hospital, New York, USA, [3]University of California, Los Angeles, USA, [4]ICAHN School of Medicine, New York, USA

Background: Recent years have brought renewed interest regarding the involvement and role of neuroinflammation in psychiatric diseases. Psychosis, especially during its first episode, is characterized by acute symptoms, and, according to some reports, increased levels of pro-inflammatory cytokines in CSF and blood. Limited evidence also suggests that anti-inflammatory drugs might alter the course of psychosis during the first break. Yet, despite this renewed interest, the cause, location, or exact timing of the neuroinflammatory response in patients with psychosis is still unclear. Previous neuroimaging studies have reported increased extracellular free-water (FW), a potential indicator of neuroinflammation, in recent-onset schizophrenia patients (Pasternak *et al.*, 2012). Here, we extend this approach to a new cohort of first episode patients with psychosis to better understand the timing and functional significance of the increased FW.
Methods: High-resolution diffusion weighted imaging (DWI) data was acquired on a 3-Tesla scanner in 63 patients experiencing a first-episode of psychosis and 70 healthy control subjects recruited from the Zucker Hillside Hospital, part of the North Shore-LIJ Health System in NY. We applied free-water imaging analysis, which deconstructs the diffusion signal into two maps: free water (FW), a measure of the fractional volume of extracellular water that is free to diffuse in each voxel, and the fractional anisotropy of the tissue (FA-t) in each voxel (Pasternak *et al.*, 2009). In addition, a conventional fractional anisotropy (FA) map was calculated and the white matter skeleton was generated using a whole brain, automated analytic pipeline (TBSS). Group comparisons of FA, FW, and FA-t projected onto the skeleton were calculated using nonparametric permutation-based tests with a threshold free cluster enhancement and family-wise error correction. The FW and FA-t values for patients were also correlated with scores from the MATRICS Consensus Cognitive Battery that were collected at baseline and 12 weeks.
Results: Our study revealed lower FA across the whole brain in first episode psychosis patients compared to healthy controls. Similar to prior published findings, FA changes were primarily mediated by significant increases in FW. These FW effects were relatively widespread, encompassing regions previously implicated in the neurobiology of psychotic disorders. In contrast, lower FA-t was also observed in patients, but only in small segments of the corpus callosum, left corona radiata, and left superior longitudinal fasciculus. Moreover, in patients, higher FW at the time of the scan was correlated with better neurocognitive functioning 12 weeks later. There were no significant differences between previously treated versus antipsychotic drug-naïve patients suggesting that the observed effects were not influenced by prior treatment.
Discussion: This is the first study to show that increased FW in white matter tracts during the initial presentation of psychosis correlates with improved follow-up neurocognitive scores, which may represent a potentially beneficial neuroinflammatory response to the underlying biological cause of psychosis. Moreover, our findings of increased FW in white matter tracts at the first-episode of psychosis are highly consistent with prior work (Pasternak *et al.*, 2009). Specifically, the FW effects observed in the current study were widespread throughout the brain and more pronounced compared to signs of axonal degeneration, which were observed in relatively circumscribed regions. In summary, the use of FW imaging provides a first step towards a more complete understanding of the potential relationship between early inflammation and cognitive outcomes in psychosis.

O5.5 Cortical thickness changes with age in a subset of first episode psychosis patients presenting with persistent negative symptoms: a longitudinal mri study

Carolina Makowski[*1], Michael Bodnar[1], Ashok Malla[1], Ridha Joober[1], Martin Lepage[2]*

[1]McGill University, Montreal, Québec, Canada, [2]McGill University, Douglas Mental Health University Institute, Montreal, Québec, Canada

Background: Recent work from our group and others has clearly established that persistent negative symptoms (PNS) can be observed following a first episode of psychosis (FEP), and can negatively affect functional outcome. Given that a FEP often occurs during a period of ongoing brain development and maturation, neuroanatomical changes may have a specific age-related component. We previously reported cortical thinning specific to PNS relative to non-PNS patients in temporal and temporo-parietal brain regions. Here we further our results by examining cortical thickness and trajectories with age using longitudinal structural imaging in a larger sample of patients.
Methods: Structural T1 volumes were acquired at three time points (baseline, one-year and two-year follow-up) for non-PNS ($N=76$), PNS ($N=21$) patients, and Controls ($N=48$). Images were processed using the CIVET pipeline (Version 2.0). Linear mixed models were applied to test for a) the main effect of time, b) interaction between time and group membership, and c) interaction between age and group membership.

Results: PNS patients showed significant cortical thinning within the right middle temporal gyrus from baseline to two-year follow-up, after controlling for age. No significant 'group × time' interaction effects were found. A significant 'age × group' interaction was found between the PNS and non-PNS patient subgroups, such that the PNS group showed significantly increased cortical thickness with age compared to the non-PNS group in clusters within the left dorsolateral prefrontal cortex and inferior frontal gyrus, extending to orbitofrontal cortex (all $P < 0.01$, RFT corrected). Furthermore, the PNS group had significantly different regression slopes from both controls and non-PNS when examining the mean cortical thickness of the four aforementioned regional clusters (all $P < 0.001$).
Discussion: FEP patients with PNS show significantly thinner cortex over time within the right temporal cortex when controlling for age. Furthermore, PNS patients showed significantly different cortical trajectories with age compared to their non-PNS peers. A positive relationship between age and cortical thickness in the PNS group could be linked to potential disruptions in cortical maturation processes within higher order brain regions, which may reflect late or protracted brain development. Future work examining the effects of age on brain correlates in FEP are needed to confirm these observations and refine their interpretation. The current study identifies a unique subgroup of FEP patients that are differentiated at both the clinical and neuroanatomical level, providing future avenues within clinical programs to better identify and treat individuals with psychosis presenting with PNS.

O5.6 A sensitized prefrontal dopamine response to psychosocial stress in the early stage of psychosis

Huai-Hsuan Tseng[*1], Miran Kenk[1], Gary Remington[2], Pablo Rusjan[1], Alan Wilson[3], Sylvain Houle[1], Romina Mizrahi[1]*

[1]PET Centre, Centre for Addiction and Mental Health, [2]Centre for Addiction and Mental Health (CAMH) and the University of Toronto, [3]University of Toronto, Toronto, Ontario, Canada

Background: While the underlying neurobiological causes of increased vulnerability for psychosis remains unclear, environmental stress modulates the dopaminergic system critical to pathogenesis of psychosis, and contributes to the development and aggravation of psychotic symptoms. Recent evidence suggests decreased prefrontal cortex (PFC) dopamine release during amphetamine challenge, however psychosocial stress-induced dopamine release in PFC in psychosis remains unexplored. The current study aims to examine PFC dopamine release during psychosocial stress in drug-naïve schizophrenia (SCZ) and clinical high risk for psychosis (CHR) as compared to matched healthy volunteers (HV).
Methods: To examine stress-induced dopamine release outside the striatal regions, we used a very high-affinity dopamine D2/3 PET radiotracer: [11C]-FLB 457. Stress-induced DA release under a validated psychosocial stress task was estimated as the percent change in binding potential (BP) between conditions (displacement of [11C]-FLB 457, calculated as: (BP[control] - BP[stress])/BP[control]) in the PFC areas.
Results: 14 HV, 16 CHR (7 cannabis users) and 20 SCZ (9 users) subjects were included so far. We found a significant group difference of baseline binding potential (BP[control]) in the anterior cingulate after controlling for cannabis use ($F = 3.41$, df = 2,46, $P = 0.041$). After controlling for the baseline binding potential, a significant group difference ($F = 3.22$, df = 2,45, $P = 0.049$) was found with a higher displacement of [11C]-FLB457 in SCZ patients (6.33% ± 3.56) and an intermediate response in CHR participants (−2.58% ± 3.76) relative to HV (−8.52% ± 4.42). A significant negative association was observed between the level of displacement in PFC and severity of overall ($r = -62$, $P < 0.01$) and negative psychotic symptoms ($r = -57$, $P < 0.02$) in SCZ patients.
Discussion: We report higher dopamine release under social stress in anterior cingulate in drug-naïve SCZ, which is associated with fewer negative psychotic symptoms. The finding suggest that in the early stage of psychosis, a sensitized prefrontal DA response to social stress may exist, particularly in individuals with less manifestation of negative symptoms.

O5.7 Cellular and extracellular abnormalities in healthy subjects with auditory verbal hallucinations

Ofer Pasternak[*1], Marek Kubicki[2], Rene Mandl[2], Iris Sommer[2]*

[1]Brigham and Women's Hospital, Harvard Medical School, [2]University Medical Centre Utrecht, Utrecht, Netherlands

Background: Auditory verbal hallucinations (AVH) are one of the characteristic symptoms of psychotic disorders. Nevertheless AVH also appear in healthy individuals with a prevalence of 5–10%, suggesting the possibility of a continuum, ranging from rare occurrences in healthy individuals to psychotic patients with frequent occurrence at the other end. Imaging studies, and notably diffusion MRI, have found various abnormalities associated with AVH in schizophrenia (SZ), which may suggest complex pattern of white matter alterations that result in AVH. However, the majority of previous studies were performed on psychotic patients, where hallucinations are one of many clinical symptoms complicated by the influence of medication. Here we set to identify whether or not AVH are associated with microstructural abnormalities that can be identified using diffusion MRI in medication free non-psychotic subjects. Further, we ask whether or not abnormalities in healthy subjects with AVH are associated with the severity of symptoms in psychotic patients with AVH.
Methods: Diffusion MRI data was acquired on a 3-Tesla scanner in 40 non-psychotic subjects experiencing AVH (AVH-noPS), in 40 patients diagnosed with SZ experiencing AVH (AVH-SZ), and in 45 healthy controls (HC). The three groups were matched for age and gender, which nevertheless were used as covariates in the statistical analysis. The diffusion MRI data was corrected for motion, eddy currents and EPI distortions. Then, the free-water imaging analysis was applied in order to separate extracellular contributions from cellular contributions to the diffusion MRI signal. The analysis yielded a free-water (FW) map, sensitive to changes in the extracellular space, such as atrophy and neuroinflammation, along with a corrected fractional anisotropy (FA) map that is more specific to cellular changes occurring in the brain tissue, such as degeneration.
Results: Comparing AVH-noPS with HC, we find higher extracellular FW averaged over the entire brain ($P = 0.023$), and in the following ICBM-DTI atlas based regions: left internal capsule (L-IC; $P = 0.036$), left posterior limb of the IC ($P = 0.001$), left superior fronto-occipital fasciculus ($P = 0.021$), left corona radiata (L-CR $P = 0.040$), left posterior CR ($P = 0.029$), and the genu of the corpus callosum ($P = 0.046$). Cellular abnormalities were evident as decreased FA in the right uncinate (R-UNC; $P = 0.014$). Within the AVH-SZ subjects we found significant correlation with AVH severity score for FW in the fornix ($P = 0.022$), and for FA in the fornix ($P = 0.028$), R-UNC ($P = 0.0156$) and left UNC ($P = 0.040$).
Discussion: Our findings demonstrate that AVH in healthy and SZ subjects is associated with both cellular and extracellular abnormalities. In healthy subjects experiencing AVH the extracellular abnormalities have larger extent, and the cellular abnormalities are limited to the R-UNC. Further, the R-UNC is associated with AVH severity in AVH-SZ. Therefore, our results suggest that AVH-noPS subjects may have nonspecific neuroinflammatory response, accompanied with damage or degeneration to the uncinate fasciculus, which also plays a role in psychotic subjects with AVH. Previous studies of psychotic subjects have identified an association of the uncinate fiber with AVH, along with several other fibers. However, the ability to separate extracellular from cellular contributions, as well as the investigation of healthy subjects experiencing AVH allowed increased specificity to abnormalities that may be closer related to AVH, and less affected by the chronicity of SZ. The increased specificity highlights a focal degeneration in the uncinate, accompanied with a more elaborated extracellular - possibly neuroinflammatory – response, as pathological sources for AVH.

O5.8 Glutamate in psychosis: a meta-analysis of proton magnetic resonance spectroscopy (1h-mrs) studies

Kate Merritt[*1], Alice Egerton[1], Matthew Kempton[1], Matthew Taylor[1], Philip McGuire[1]*

[1]King's College London, London, UK

Background: Alterations in glutamatergic neurotransmission may be fundamental to the pathophysiology of schizophrenia and the

glutamatergic system may be a target for new therapeutic interventions. To investigate the nature of brain glutamate alterations in schizophrenia we present a meta-analysis of glutamate proton magnetic resonance (1H-MRS) studies.
Methods: Electronic databases were searched to identify journal articles reporting 1H-MRS glutamate, its metabolite glutamine or Glx (total glutamate+glutamine) in schizophrenia patients in comparison to healthy volunteers. Effect sizes were calculated for glutamate, glutamine, and Glx in brain regions reported in at least 3 studies. Secondary analysis grouped studies into those examining different illness stages (at risk, first episode psychosis or chronic schizophrenia).
Results: 59 eligible studies were identified. In schizophrenia, there were significant elevations in glutamate in the basal ganglia ($P = 0.01$, $g = 0.63$), glutamine in the medial frontal cortex ($P = 0.04$, $g = 0.35$), thalamus ($P = 0.04$, $g = 0.56$) and medial temporal lobe ($P = 0.04$, $g = 0.41$) and Glx in the basal ganglia ($P = 0.01$, $g = 0.39$), and medial temporal lobe ($P = 0.002$, $g = 0.32$). No region showed a reduction in glutamate metabolites in schizophrenia. Sufficient studies were available to show that these glutamatergic elevations were present at different illness stages in some regions.
Discussion: Schizophrenia is associated with elevations in glutamatergic metabolites across several brain regions. This supports the hypothesis that schizophrenia is associated with excess glutamatergic neurotransmission in several limbic areas, and further indicates that compounds that reduce glutamatergic transmission may have therapeutic potential.

O6. Cognition: multifaceted approach

O6.1 Polygenic mir-137 pathway scores explain variability in cognitive performance in patients with schizophrenia and controls

Donna Cosgrove[*1], Denise Harold[2], Ric Anney[3], Omar Mothersill[1], Matthew Hill[3], Nicholas Bray[3], Michael Gill[2], Aiden Corvin[2], Derek Morris[1], Gary Donohoe[1]*

[1]National University of Ireland, Galway, Ireland, [2]Institute of Molecular Medicine, Trinity College Dublin, Dublin, Ireland, [3]Institute of Psychological Medicine and Clinical NeuroSciences, Cardiff University, Cardiff, UK

Background: Variants at MIR137, one of the genetic loci most strongly associated with increased schizophrenia risk to date, are reported to explain variation on behavioral and cortical measures relevant to cognition. As miR-137 is known or predicted to regulate the expression of ~1800 other genes, including several that are independently associated with schizophrenia risk (e.g. ZNF804A, CSMD1, and CACNA1C), we tested whether this gene set was also associated with variation in cognitive performance.
Methods: Our analysis was based on an empirically derived list of genes whose expression was altered by manipulation of MIR137 expression. This list was then cross referenced with the data from the largest genome-wide association study of schizophrenia published to date to construct individual polygenic scores for a range of schizophrenia risk *P*-value thresholds (ranging from 0.00001 to 0.5). We then tested, in a sample of 808 patients and 192 controls, whether these polygenic risk scores were associated with altered neuropsychological performance on cognitive functions known to be affected in schizophrenia (namely general cognitive ability [IQ], working memory, episodic memory, attentional control, and social cognition). A subgroup of the healthy participants also underwent functional imaging during a spatial working memory task ($n = 108$) and a facial processing task ($n = 83$).
Results: Increased polygenic risk scores within the MIR137 pathway were observed to be associated with significantly lower performance on multiple measures of IQ, working memory, and episodic memory. These effects were observed most clearly at a polygenic threshold of $P = 0.05$, although significant results were observed at all three thresholds. Furthermore, analysis of the spatial working memory fMRI task suggested that increased MiR-137 polygenic risk score (thresholded at $P = 0.00001$) was significantly associated with increased activation of the right inferior occipital gyrus.
Discussion: These data suggest that increased polygenic risk in a gene set whose expression was altered by manipulation of MIR137 expression consisting of observed interactors of miR-137 was associated with decreased cognitive performance. Notably, the strength of association was stronger for the gene set as a whole than for the most strongly associated MIR137 SNP. These data are consistent with emerging evidence that at least some of the genetic risk for schizophrenia conferred by MIR137 relates to its broader downstream genetic effects.

O6.2 Neuropsychological functioning over time in the North American prodrome longitudinal study (napls)-2 clinical high risk cohort

Kristen A Woodberry[*1], William S Stone[1], Daniel I Shapiro[1], Cole M Chokran[2], Anthony J Giuliano[3], Caitlin Bryant[2], Jean Addington[4], Carrie Bearden[5], Kristin Cadenhead[6], Tyrone Cannon[7], Barbara Cornblatt[8], Thomas McGlashan[7], Diana Perkins[9], Ming Tsuang[6], Elaine Walker[10], Scott Woods[7], Larry J Seidman[11]*

[1]Beth Israel Deaconess Medical Center; Harvard Medical School, Boston, USA, [2]Beth Israel Deaconess Medical Center, Boston, USA, [3]Worcester Recovery Center and Hospital, Worcester, USA, [4]University of Calgary, Calgary, Canada, [5]University of California, Los Angeles, USA, [6]University of California, San Diego, USA, [7]Yale University, New Haven, USA, [8]The Zucker Hillside Hospital, New York, USA [9]University of North Carolina, North Carolina, USA, [10]Emory University, Georgia, United States, [11]Harvard Medical School, Boston, Massachusetts, USA

Background: Given the robust relationship between cognition and real life functioning in schizophrenia and related psychotic disorders, the prevention and remediation of cognitive deficits in those impacted by these illnesses has become a high research priority. Delineating trajectories of cognitive functioning during the prodromal phase is critical to identifying treatment targets, timing, and strategies. Age, sociodemographic, and illness factors would all be expected to impact neuropsychological development in adolescents and adults at clinical high risk (CHR) for psychosis.
Methods: The North American Prodrome Longitudinal Study (NAPLS) -2 assessed functioning on an extensive battery of neuropsychological (NP) tests at baseline, one year, two years, and, post-conversion in a CHR sample followed clinically for up to 2 years. NP data were available for 689 subjects (90% of total) at CHR and 265 (95% of total) healthy comparison subjects, 43% of whom (both samples) were assessed at least three times.
Results: Those who transitioned to a psychotic disorder over the course of follow-up generally performed below those who did not and significantly below healthy comparisons. Tasks reliant on attention, visual and auditory working memory, visuospatial and verbal memory, and processing speed best differentiated those who transitioned from those who did not at one year (Cohen's d from −0.32 to −0.53). Discrepancies from normal functioning on these tests were generally large (Cohen's d from −0.66 to −1.01), consistent with findings for first episode samples. However, clinical outcome was not associated with a significantly different trajectory over time. Linear mixed models analyses will examine the role of age, time since prodromal syndrome onset, gender, socioeconomic and clinical variables, and baseline functioning in predicting change over time. We will further examine clinical and sociodemographic characteristics of those who showed a significant decline or improvement in cognitive functioning over time.
Discussion: Although the majority of subjects who transitioned to psychosis did so prior to the one year NP assessment, limiting the examination of change prior to transition, these data from one of the largest CHR studies to date examining neuropsychological functioning over time, support a growing consensus that much of the neuropsychological dysfunction in major psychotic disorders is present early in the course of illness and prior to its full expression. The relevance of these findings for understanding the role of cognition in psychotic disorders and for remediation efforts will be discussed.

O6.3 Educational achievement in psychiatric patients and their siblings; a register-based study in 30 000 individuals in the Netherlands

Wanda M. Tempelaar[1], Fabian Termorshuizen[*2], Marco P.M. Boks[1], René S. Kahn[1]*

[1]University Medical Centre Utrecht, Utrecht, Netherlands, [2]Universtiy Medical Centre Utrecht, Institute for Mental Health Care, Utrecht, Netherlands

Background: Poor educational achievement is associated with a range of psychiatric disorders. Several studies suggest that this

underperformance is due to cognitive deficits that commence before disease onset and reflect a genetic risk for this disorder. However, the specificity and the familial contribution of this cognitive deficit are not clear. We analyzed lifetime educational achievement of psychiatric patients diagnosed with schizophrenia, bipolar or depressive disorder, and their unaffected siblings.
Methods: In a register-based case-control study, 1,561 patients with schizophrenia, 813 patients with bipolar disorder, 8,112 patients with depression, and their siblings were each matched with eight population controls. Patients, siblings, and controls were compared on the highest educational stream they completed.
Results: Lower educational performance was present in schizophrenia patients from primary school onwards (completing primary school: OR 0.69, completing secondary school: OR 0.69, completing academic education: OR 0.46), compared to patients with bipolar disorder or depression. Siblings of schizophrenia, bipolar, or depressed patients showed no underachievement at primary or secondary school, but siblings of schizophrenia patients as well as siblings of depressed patients were less successful in their educational achievement after secondary school (completing academic education: schizophrenia siblings: OR 0.90, depressive disorder siblings: OR 0.91).
Discussion: Educational underperformance from primary school onwards is specifically related to schizophrenia and not to bipolar disorder or depression. Moreover, it appears to be a harbinger of the illness, since it is not found in their siblings. These results add to evidence that early cognitive deficits are a distinct feature of the schizophrenia phenotype.

O6.4 Source memory distortions may be related to attenuated psychotic experiences in young offspring of parents affected by major psychoses

Elsa Gilbert[*1], Marie-Anne Gariépy[1], Michel Maziade[1], Nathalie Gingras[1], Caroline Cellard[1], Nancie Rouleau[1]*

[1]*Université Laval, Quebec, Canada*

Background: Episodic memory (EM) deficits are reported to be among the most severe cognitive impairments, both in schizophrenia (SZ) patients and in at risk populations. We have previously reported that EM deficits analogous to those in adult patients can be detected in children born to parents affected by SZ or bipolar disorder (BP), many years before the disease incidence (Maziade *et al.*, Schiz Bull, 2011; 2009). More recently, research have suggested that commonly observed EM deficits in patients with psychoses may be explained by source memory dysfunction. Source memory refers to the attribution of the origin under which specific events or facts are acquired in EM (Johnson, Psychol Bull, 1993). Interestingly, studies reported that difficulties in source memory correlate with hallucinations in psychotic patients suggesting an etiologic role in the development of psychotic symptoms. It is still unknown whether source memory alterations occur at the onset of psychosis or precede it, therefore being an early marker of risk. Accordingly, our aims were to 1) characterize source memory in youths at high genetic risk of major psychoses, 2) verify if impairments are similar in nature and intensity to those documented in patients and 3) examine the relationship between source memory and attenuated psychotic symptoms in this at risk population.
Methods: We have followed up across 25 years, 48 large families densely affected by major psychoses (Maziade, Mol Psychiatry, 2005). Extensive cognitive and clinical evaluations were collected on 84 offspring born to an affected parent descending from these kindred. Amongst those, 27 offspring aged 9–25 years old, i.e., still under the mean age of psychosis onset, were also assessed with a source memory task and the Launay-Slade Hallucination Scale (LSHS) along with 30 healthy controls without positive family history of SZ or BP and matched on age and gender. The Source Memory Task is a validated measure developed by our group (Doré, Cogn Neuropsychiatry, 2007) to assess episodic item recognition and several source memory processes and distortions (i.e. attribution of origin: temporal/ internal/external source; response bias; relational binding; metacognition).
Results: High-risk offspring showed impaired source memory functioning compared to healthy control, specifically in temporal context attribution ($P < 0.001$, $d = -1.07$). Attribution of internal/external source was preserved ($P = 0.38$, $d = -0.24$) suggesting it would be affected only in psychotic state. Furthermore, offspring showed more memory distortions, namely reduced relational binding and alterations in metacognition, than controls. Furthermore, offspring reported more hallucinatory-like experiences than controls ($P = 0.04$). The latter were significantly associated with source memory distortions ($P = 0.016$, $d = 1.03$).
Discussion: Findings support the presence of source memory dysfunctions in offspring at high genetic risk of SZ and BP that would be similar to those previously documented in psychotic patients. Source memory would represent an early risk marker of psychosis since dysfunctions would be observable many years before illness onset. Moreover, even if these children and adolescents were clinically healthy, they nonetheless were more likely to report subclinical hallucination-like experiences. Our data suggest that source memory distortions could be implicated in the developmental mechanisms of psychotic symptoms. To our knowledge, this is the first study on source memory in offspring of parents affected by major psychoses. Our findings call for more in-depth developmental understanding of the cognitive architecture in childhood that increases vulnerability to psychosis.

O6.5 Relational and item specific memory markers of psychosis risk

Sarah White[1], Tara Niendam[1], Cameron Carter[1], J. Daniel Ragland[*1]*

[1]*University of California at Davis, California, USA*

Background: People with schizophrenia have disproportionate memory impairments when encoding relational versus item-specific information, and when using recollection rather than familiarity during retrieval. It has not been determined whether this pattern is present in individuals at clinical high risk for psychosis and represents a trait marker of psychosis risk, or if this pattern is present only following illness onset and is reflective of clinical state. To investigate the role of state and trait factors we administered the Relational and Item-Specific memory task (RiSE) to individuals at clinical high risk for psychosis (CHR) and people with schizophrenia.
Methods: 181 individuals; 58 healthy controls (HC), 101 first episode psychosis participants (FE) (78 on atypical, 2 on typical antipsychotics), and 22 CHR (7 on atypical antipsychotics) participants completed the (RiSE) following clinical assessment. Because CHR participants were younger than FE and HC participants (who were age matched), we compared the CHR group's performance to both the full sample and to an age matched subsample of 23 HC, and 34 FE individuals. Measures of recognition accuracy (d') familiarity (F) and recollection (R) were examined with ANOVA for task effects and group differences, and Spearman correlations examined relationships with clinical symptoms (disorganization, positive, and negative symptom factors).
Results: Overall recognition accuracy (d') was equally impaired in CHR and FE groups [$F(1,123) = 3.20$, $P = 0.08$]–who did not differ from each other regardless of age-matching. As in previous studies, familiarity was less impaired, and did not significantly differ between groups for either the age-matched or full samples [$F(2,178) = 0.57$, $P = 0.57$]. However, when recollection was compared between patient groups and HCs, there was a significant group by condition interaction for the CHR [$F(1,76) = 7.45$, $P < 0.01$], but not for the EP groups [$F(1,158) = 1.86$, $P = 0.175$]. In the CHR contrast, recollection was impaired following relational [$t(76) = 3.30$, $P < 0.01$] but not following item-specific encoding [$t(54.06) = 0.84$, $P = 0.40$]. In contrast, the EP group had impaired recollection following both item-specific [$t(142.49) = 2.53$, $P = 0.01$] and relational encoding [$t(154.11) = 4.23$, $P < 0.01$]. Examination of clinical factors revealed that worse recollection in FE, but not in CHR groups, was associated with more severe positive symptoms ($r = 0.25$, $P = 0.02$). Structural equation modeling will also be used to further investigate the role of clinical symptoms, medication, and potential moderating effects of age and IQ on this pattern of memory impairments in CHR and FE individuals.
Discussion: Examination of RiSE performance in FE and CHR individuals suggests that both trait and state factors contribute to frequently observed disproportionate impairments in recollection following relational encoding and relative sparing of item-specific encoding

and familiarity-based retrieval. Impaired recollection following relational encoding may serve as a trait marker of psychosis risk, as dysfunction was equally present in CHR and FE participants. In contrast, impaired recollection following item-specific encoding may reflect the deleterious effect of being in a psychotic state as this impairment was present only in the FE group and was associated with severity of positive symptoms. Relational memory, therefore, appears to be an important target for early intervention.

O6.6 Schizophrenia patients with delusions show a specific deficit in updating beliefs from positive but not negative new evidence

Ilinca Angelescu[1], Mariam Haque[1], James Gilleen[1]*

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

Background: Delusions are the prototypical symptom of schizophrenia and psychosis. Both formation and maintenance factors are thought to contribute to delusions. Resistance to contradictory may serve as a maintenance factor, and this has been investigated with simple data-gathering tasks on which patients with schizophrenia are impaired. Recently a novel paradigm which assesses capacity to update beliefs–which are more proximal to delusions - has shown that patient and healthy groups have specific deficits in the capacity to update beliefs from new information. We investigated belief updating in schizophrenia (predominantly with paranoid delusions) and healthy volunteers and hypothesized that patients would show a resistance to update beliefs compared to healthy people - consistent with models of delusions.
Methods: 56 patients with schizophrenia and 63 healthy controls were asked the likelihood that they would experience 40 negative life events. After rating the likelihood, the real likelihood was shown, and the patients were asked again the chance of experiencing it. The relative values allowed separation of trials where updating was required from positive or negative information ('good news' or 'bad news'); and the amount of updating for either type of information could be quantified.
Results: A 2×2 ANOVA revealed a significant valence of news effect ($F(1, 74) = 17.59$, $P < 0.001$), and a significant interaction of news and group ($F(1, 74) = 4.02$, $P < 0.05$; group effect n.s.). Both groups updated equally from bad news (n.s.) and while healthy people updated significantly more from good news that bad news, critically, schizophrenia patients showed a significantly impaired capacity to update from good news. Mood and memory did not moderate this effect.
Discussion: These results indicate that patients with schizophrenia fail to allow positive information ('good news') to update beliefs. Paranoid delusions are a negative self-relevant mental states, and so evidence that contradicts these delusions constitutes positive information. A resistance to update mental schema from positive evidence may constitute a maintenance factor in delusions.

O6.7 Self assessment of social cognition in schizophrenia: impairments in evaluating task difficulty and adjusting effort accordingly

Philip Harvey[1], Amy Pinkham[2], David Penn[3]*

[1]University of Miami Miller School of Medicine, Miami, USA [2]University of Texas at Dallas, Dallas, USA [3]University of North Carolina, North Carolina, USA

Background: Patients with severe mental illnesses manifest substantial deficits in self-assessment, which has been shown to impact on everyday functioning. In addition, people with schizophrenia have substantial impairments in the ability to judge the difficulty of tasks and rewards associated with task performance. Our research found that mis-estimation of an individual's level of cognitive impairment impacted everyday functioning at least as much as cognitive impairments themselves. In this study, we expand these efforts to self-assessment of social cognitive functioning, comparing people with schizophrenia to healthy individuals on their social cognitive performance, their assessment of that performance, and their ability to adjust effort to task difficulty.
Methods: Patients with schizophrenia ($n = 55$) and healthy controls ($N = 35$) were examined with the Bell-Lysaker Emotion Recognition Test (BLERT). The BLERT is a computerized assessment of emotion recognition with 21 items. The task was modified to measure self assessment of performance and the ability to adjust effort to the task demands and feedback. Participants were asked after they completed each item to rate their confidence in their correctness on a 0–100 scale. Then they were given immediate feedback (Correct/incorrect). Dependent variables included comparisons of performance on the test, confidence in performance (hard vs. easy items; correct vs. incorrect responses, and time to response for each item examined as a function of difficulty of the item and accuracy of the response.
Results: Patients with schizophrenia performed more poorly on the BLERT then HC, as expected. HC were more confident on items that they correctly answered than for items with errors. When items were examined in terms of their difficulty (easiest 6 vs hardest 6), the HC responded more rapidly to easy items ($P < 0.05$), were more confident in their responses ($P < 0.001$), and took longer to respond when making an error than a correct response ($P < 0.001$). In contrast, patients responded at the same speed to hard and easy items, were no more confident for easy items than hard ones, and were no more confident when correct than when incorrect. In fact, for patients there was an extremely high correlation ($r^2 = 0.64$) between confidence and response times ($r^2 = 0.60$) for easy and hard items. This correlation was much lower in HC ($r^2 = 0.17$); ($r^2 = 0.44$).
Discussion: Schizophrenia patients appeared to have difficulty judging the level of difficulty of social cognitive tests and had difficulty adjusting their effort accordingly. These data suggest impairments in assessing situational demands and are consistent with previous reports of impairments in self assessment and effort based decision making in schizophrenia patients. These results are convergent with recent research suggesting that schizophrenia patients fail to adjust their effort in response to rewards, suggesting that self-assessment may be interacting with reward sensitivity in order to produce performance that fails to adapt to situational demands.

O6.8 Long-term cariprazine treatment for the prevention of relapse in patients with schizophrenia: additional analyses from a randomized, double-blind, placebo-controlled trial

W Wolfgang Fleischhacker[1], Suresh Durgam[2], Willie Earley[1], Rui Li[2], Dayong Li[2], Kaifeng Lu[2], István Laszlovszky[3], Henry A. Nasrallah[4]*

[1]Medical University Innsbruck, Innsbruck, Austria, [2]Forest Research Institute, Dehradun, India, [3]Richter Gedeon Plc., [4]Saint Louis University, Saint Louis, USA

Background: Cariprazine, a dopamine D3/D2 receptor partial agonist with preference for D3 receptors, is approved by the FDA for the treatment of schizophrenia. Cariprazine has a unique pharmacokinetic profile, with 2 active metabolites, desmethyl- and didesmethyl-cariprazine, and a half-life of the total active moieties of about 1 week. This long half-life may confer additional protection against relapse in cases of sporadic nonadherence. This study evaluated the efficacy, safety, and tolerability of cariprazine versus placebo in the prevention of relapse in patients with schizophrenia. The time to onset of relapse following discontinuation of cariprazine treatment in patients randomized to the placebo arm was also investigated.
Methods: This was a multinational, randomized, double-blind, placebo-controlled, parallel-group study in adult patients with schizophrenia (NCT01412060); the total study duration was up to 97 weeks. Symptoms were stabilized during an 8-week, flexible-dose, run-in phase and a 12-week, fixed-dose, stabilization phase with cariprazine (3–9 mg/d). Patients who completed the 20-week open-label treatment phases were randomized to continue cariprazine (3, 6, or 9 mg/d) or switch to placebo for up to 72 weeks of double-blind treatment. The primary efficacy parameter was time to relapse, defined as worsening of symptom scores, psychiatric hospitalization, aggressive/violent behavior, or suicidal risk. Time to relapse between the placebo and cariprazine groups was compared using the log-rank test and hazard ratio (HR) with 95% confidence interval (CI); the cumulative distribution function of time to relapse was estimated by Kaplan-Meier curves. Additional efficacy parameters included change in Positive and

Negative Syndrome Scale (PANSS) total score and Clinical Global Impression-Severity (CGI-S) score. Safety assessments included adverse events (AE), clinical laboratory parameters, vital signs, and extrapyramidal symptom scales.
Results: A total of 264/765 (35%) patients completed the open-label treatment phase; 200 met eligibility criteria and were randomized to placebo ($n = 99$) or cariprazine ($n = 101$) treatment. The time to relapse was significantly longer in patients who continued cariprazine than in patients switched to placebo ($P = 0.0010$ [log-rank test]). Relapse occurred in nearly twice as many placebo- (47.5%) as cariprazine-treated patients (24.8%); the HR (95% CI) was 0.45 (0.28, 0.73). At week 2, few placebo- or cariprazine-treated patients had relapsed (two [2%] each group); at week 4, only 3 (3%) placebo-treated patients had relapsed despite discontinuing cariprazine. The Kaplan-Meier analysis indicated separation of the cariprazine and placebo curves started at almost 50 days. The placebo group showed greater mean worsening in PANSS and CGI-S scores relative to the cariprazine group during double-blind treatment. The most common AEs (≥10%) during open-label treatment were akathisia (19.2%), insomnia (14.4%), and headache (12.0%). There were no treatment-emergent AEs that occurred at an incidence of ≥10% in the cariprazine group during the double-blind treatment phase.
Discussion: Long-term cariprazine treatment was significantly more efficacious than placebo for the prevention of relapse in patients with schizophrenia. The low relapse rate during the first few weeks of double-blind treatment in patients switched to placebo may suggest a sustained treatment effect for cariprazine that is related to the long effective half-life. The safety profile of cariprazine in this long-term study was comparable to that observed in the acute cariprazine studies.

O7. Neurobiology

O7.1 Pathogenic neuronal autoantibodies in patients with a psychotic disorder: results of screening three large cohorts

Hans van Mierlo[*1], *Lot de Witte*[1], *M.J. Titulaer*[2], *M.H. van Coevorden-Hameete*[3], *E. de Graaff*[3], *C. Hoffmann*[4], *P. Martinez-Martinez*[4], *René S. Kahn*[1]

[1]*University Medical Center Utrecht, Utrecht, Netherlands,* [2]*Erasmus Medical Center, Rotterdam, Netherlands,* [3]*Utrecht University, Utrecht, Netherlands,* [4]*School for Mental Health and Neuroscience, Maastricht, Netherlands*

Background: After the discovery of anti-NMDA receptor encephalitis, which often debuts with psychiatric symptoms, it has been hypothesized that autoantibodies directed against neuronal surface antigens might play a role in the pathogenesis of various psychotic disorders including schizophrenia.
Methods: Using three different study designs we set out to examine the prevalence of neuronal antibodies in patients with a psychotic disorder. 1) Plasma samples of 475 patients diagnosed with a schizophrenia spectrum disorder were screened for the presence of IgG antibodies against the GluN1 subunit of the NMDA receptor using a cell based assay and immunohistochemistry. 2) Plasma samples of 104 patients diagnosed with schizophrenia were screened for the presence of various neuronal surface antibodies using cultured hippocampal neurons and transfected HeLa cells. 3) Serum samples of 127 patients with a psychotic disorder, of which 64% had a first episode psychosis, were screened for the presence of IgG GluN1 antibodies in a similar way as cohort 1.
Results: Using different screening methods in three cohorts we were unable to discover any patient with a psychotic disorder that tested positive for the presence of pathogenic neuronal antibodies. In cohort 1, two plasma samples showed a false positive result when using a commercial cell-based assay to screen for GluN1 antibodies.
Discussion: Our results suggest that the presence of pathogenic neuronal antibodies in patients with a psychotic disorder is very rare, although further studies using cerebrospinal fluid and samples from acutely ill patients are needed. Attention should also be given to the experimental methods used to screen for these antibodies and positive results should be validated using different testing methods or CSF.

O7.2 Exposure to childhood physical and sexual abuse is associated with divergent cortical abnormalities in first episode psychosis patients and controls and with diurnal cortisol concentration only in controls

Simone Ciufolini[*1], *Valeria Mondelli*[2], *Matthew Kempton*[2], *AAT Simone Reinders*[2], *Tiago Reis Marques*[2], *Craig Morgan*[2], *Marta Di Forti*[2], *Robin Murray*[2], *Anthony David*[2], *Carmine Pariante*[2], *Paola Dazzan*[2]

[1]*Sapienza University, Rome, Italy,* [2]*Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK*

Background: Experiencing physical or sexual abuse during childhood is a major risk factor for psychosis. There is mounting evidence that childhood trauma is associated with brain alterations in psychosis and that these may be linked with a dysfunction of the Hypothalamic-Pituitary-Adrenal (HPA). However, the relationship between these factors remains unclear. Also, it remains to be established whether and how the biological consequences associated with childhood abuse in patients with psychosis differ from those observed in individuals with the same exposure who do not develop psychosis.
Methods: Brain structure was evaluated with an MRI scan in a 3 T scanner in 86 first episode psychosis (FEP) patients (49 positive for moderate/severe childhood abuse) (mean age: 27.8 SD ± 9.1 years) and 64 healthy controls (30 positive for moderate/severe childhood abuse) (mean age 29.1, SD ± 8.6 years). First, a two-way ANCOVA General Linear Model analysis using FreeSurfer was performed, vertex-by-vertex, to explore differences in cortical thickness related to case or control status, and exposure or no exposure to childhood abuse. Finally, Cortisol Production During the Day (CPD) levels were correlated with measures of cortical thickness in those regions in which a significant effect of abuse was identified.
Results: Individuals who reported moderate/severe childhood abuse, irrespective of the presence of psychosis, presented cortical thinning of the right medial-orbital-frontal gyrus and the lingual gyrus (all $P < 0.001$ FWE corrected). FEP patients with abuse had cortical thinning of the right cuneus, right latero-orbito-frontal gyrus, right post-central gyrus, right pre-central gyrus, right superior-frontal gyrus and right inferio-parietal gyrus, while controls with abuse showed an increased thickness in these areas (all $P < 0.001$ FWE corrected). This is suggestive of an interaction between group (patient/control) and abuse. Thickness of the areas associated with abuse (right medial-orbital-frontal gyrus and in the lingual gyrus) was negatively correlated with the CPD ($r = -0.30$; $P = 0.003$ and $r = -0.24$; $P = 0.02$, respectively). Among the areas displaying significant interaction between group and abuse, the right post-central gyrus and the right pre-central gyrus were not correlated with CPD in cases or in controls. In contrast, the right cuneus, right latero-orbito-frontal gyrus, right superiofrontal, and the right inferio-parietal gyrus were negatively correlated with CPD in controls ($r = -0.48$; $P = 0.003$; $r = -0.45$; $P = 0.005$; $r = -0.59$; $P < 0.001$; and $r = -0.43$; $P = 0.008$, respectively) but not in cases.
Discussion: These results suggest that exposure to childhood abuse has a long-term effect on the adult brain, in areas involved in social adjustment, mood control, and drive. Interestingly, this effect is different in cases and controls, suggesting a specific vulnerability in individuals who would eventually develop psychosis. The negative correlation between cortisol and cortical thickness in areas sensitive to abuse exposure suggests a link between brain and HPA axis in response to environmental stressors, potentially related to a negative effect of excessive concentration of corticosteroid on the brain. This relationship was found only in controls resilient to abuse exposure suggesting possibly an adaptive mechanism to environmental stress.

O7.3 Protein pathology in chronic mental illnesses–towards a biological definition

Carsten Korth[*1], *Verian Bader*[1], *Svenja Trossbach*[1], *Rita Marreiros*[1], *Nichoals Bradshaw*[1]

[1]*University of Düsseldorf, Düsseldorf, Germany*

Background: Disruption of proteostasis is a common cellular phenotype after a genetic or exogenous lesion of postmitotic neurons. In the

most extreme examples, the neurodegenerative diseases, proteostasis disturbance leads to microscopically visible protein deposits. However, it is reasonable to assume that also in other chronic brain conditions, for example mental illnesses like residual schizophrenia or chronic depression, proteostasis occurs, even though clearly not accompanied by massive neuronal loss.
The hypothesis of my laboratory was therefore to investigate the occurence of proteostasis in the context of chronic mental illnesses like schizophrenia, exemplified by the occurrence of protein pathology, i.e. proteins insoluble in ionic detergents.
Methods: Post mortem brains from patients with schizophrenia, bipolar disorder, depression, or healthy controls were obtained from the Stanley Research Foundation (Consortium collection; $n = 60$), and the insoluble proteome purified by biochemical fractionation. The insoluble proteome of each patient was then either immunoblotted for candidate genes or pooled by diagnosis ($n = 15$) and injected into mice for the generation of monoclonal antibodies that would selectively recognize only schizophrenia brains but not healthy brain (epitope disovery); epitopes of such antibodies were determined on protein arrays. Finally, we also performed proteomics of the insoluble proteome. For positive hits, genetic studies were performed to gather independent evidence. Candidate proteins for which misassembly was firmly established animal models were generated by modest overexpression (Molecular Psychiatry, in press).
Results: For the rare candidate gene Disrupted-in-Schizophrenia 1 (DISC1), we could show insolubility in a subset of patients with mental illness crossing clinical diagnoses. When we modeled DISC1 aggregation in a novel transgenic rat model, we observed disruption of dopamine homeostasis with amphetamine hypersensitivity aberrant dopamine reuptake (Molecular Psychiatry, in press), validating the notion of DISC1 protein pathology for chronic mental illness. Using epitope discovery we identified two candidate proteins, CRMP1 and TRIOBP1 as aggregated in subsets of cases with chronic mental illness. Proteomics of the insoluble proteome of schizophrenia yielded more novel candidates that are currently validated.
Discussion: Protein pathology is a novel way of classifying chronic mental illnesses such as schizophrenia, complementing the currently prevailing genetic view. In fact, in the classical neurodegenerative diseases, the same proteins aggregate in sporadic cases, that are mutant in the minority of familial cases. More specifically, insoluble DISC1 assemblies seem to regulate dopamine homeostasis, a brain central metabolic disturbance during psychosis. Using this transgenic rat model, a number of reverse translational approaches are possible like the identification of diagnostic biomarkers for chronic mental illnesses related to DISC1.

O7.4 Tak-063, a phosphodiesterase 10a inhibitor with balanced activation of direct and indirect pathways, provides potent and dose-dependent antipsychotic-like effects in multiple paradigms

Haruhide Kimura[*1], Akina Harada[1], Hirobumi Suzuki[1], Maki Miyamoto[1], Kazunori Suzuki[1]*

[1]*Takeda Pharmaceutical Company, Osaka, Japan*

Background: Phosphodiesterase 10A (PDE10A) inhibitors are expected to be novel drugs for schizophrenia through their activation of both direct and indirect pathway medium spiny neurons (MSNs). However, in rats with methamphetamine (METH)-induced hyperactivity, excessive activation of the direct pathway by the dopamine D1 receptor agonist SKF-82958 cancels antipsychotic-like effects of the dopamine D2 receptor antagonist haloperidol. Thus, balanced activation of these pathways is critical for the efficacy of PDE10A inhibitor in schizophrenia. We investigated how to achieve balanced activation using MP-10 (Pfizer's PDE10A inhibitor), TAK-063 (novel PDE10A inhibitor discovered at Takeda), and compound 1, which has a chemical structure similar to TAK-063 and an off-rate similar to MP-10.
Methods: Male ICR, C57BL/6J mice, Sprague-Dawley rats, and homozygous Pde10a-knockout mice were used in this study. Paraformaldehyde-fixed rat coronal sections were immunostained with mouse monoclonal anti-cAMP antibody and rabbit polyclonal anti–substance P antibody. Off-rates of TAK-063, MP-10, and compound 1 from PDE10A in rat brain sections were determined by measuring their PDE10A occupancy using [3H]T-773 as a tracer. The binding of TAK-063 and MP-10 to PDE10A in the presence of various concentrations of cyclic nucleotides (cAMP and cGMP) in rat brain sections was also evaluated using [3H]T-773. The activation of MSN pathways in rats was evaluated by quantitative polymerase chain reaction to determine the induction of genes as pathway-specific markers: enkephalin for the indirect pathway, and substance P for the direct pathway. Striatal PDE10A occupancy by PDE10A inhibitors was measured using T-773 as a tracer. Suppression of METH-induced hyperactivity was assessed by measuring locomotor activity for 2 hours after METH administration. Improvement of prepulse inhibition (PPI) was investigated in a C57BL/6 J low-PPI mouse model.
Results: An immunohistochemical analysis showed that >90% of cAMP-positive cells were co-immunostained with the anti–substance P antibody in the rat striatum. The binding affinities of TAK-063 and MP-10 to PDE10A were similar (Ki values: 3.2 nM for TAK-063, 4.3 nM for MP-10). The off-rate of TAK-063 from PDE10A was faster than that of MP-10; after 60 minutes' incubation following saturation, the PDE10A occupancies of TAK-063 and MP-10 in rat brain sections were reduced to 23.09 and 49.85%, respectively. In general, faster off-rate enzyme inhibitors are more sensitive than slower off-rate inhibitors to binding inhibition by enzyme substrates. As expected, TAK-063 was more sensitive than MP-10 to binding inhibition by higher concentrations (6-60 mM) of cyclic nucleotides. Both compounds activated the indirect pathway to a similar extent, whereas activation of the direct pathway by TAK-063 was partial compared with that by MP-10. TAK-063, but not MP-10, dose-dependently suppressed METH-induced hyperactivity in rats and increased PPI in C57BL/6 J mice. Compound 1 (slower off-rate with TAK-063–like chemical structure) had an MP-10–like pharmacologic profile.
Discussion: Off-rates from PDE10A may characterize the pharmacologic profile of PDE10A inhibitors; slow off-rate PDE10A inhibitors may lose antipsychotic-like effects by excessive activation of the direct pathway. TAK-063, with its balanced activation of the direct and indirect pathways, produced antipsychotic-like effects in multiple animal models. A clinical proof-of-concept study is ongoing (ClinicalTrials.gov Identifier: NCT02477020).

O7.5 Hyperprolactinaemia in first episode psychosis- a longitudinal assessment

John Lally[*1], Olesya Ajnakina[1], Brendon Stubbs[1], Hugh R Williams[2], Marco Colizzi[1], Elena Carra[1], Poonam Gardner- Sood[1], Kathryn Greenwood[3], Zerrin Atakan[1], Valeria Mondelli[1], Khalida Ismail[1], Oliver Howes[4], David Taylor[5], Shubulade Smith[1], Robin Murray[1], Fiona Gaughran[1]*

[1]*Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK,* [2]*Lewisham Promoting Recovery Neighbourhood 3 Team, South London and Maudsley NHS Foundation Trust,* [3]*University of Sussex, Brighton, UK,* [4]*King's College London, Institute of Psychiatry; Medical Research Council Clinical Sciences Centre, Hammersmith Hospital, Imperial College London, UK,* [5]*Maudsley Hospital and Institute of Pharmaceutical Science, King's College London, London, UK*

Background: Little is known about hyperprolactinaemia (HPL) in first episode psychosis (FEP) patients. To investigate longitudinal changes in serum prolactin in FEP, and the relationship between HPL, and antipsychotic medication and stress.
Methods: Given the paucity of longitudinal research investigating HPL in people with early psychosis, we set out to investigate the prevalence of HPL during the first year of treatment for psychosis. Specifically, we set out to examine a) the relationship between HPL and antipsychotic medication use, gender, ethnicity, age, smoking, and psychopathology at the time of the study recruitment; b) to evaluate any differences in serum prolactin levels, c), and HPL among antipsychotic naïve and antipsychotic treated patients. For the first time, we aimed to elucidate any associations of perceived stress and stressful life events with serum prolactin in antipsychotic naïve patients. Serum prolactin was recorded in FEP patients at recruitment and again, 3 and 12 months later. HPL was defined as a serum prolactin level greater than 410 mIU/L (~19.3ng/ml) for males, and a serum prolactin level greater than 510 mIU/L (~24.1ng/ml) females
Results: From a total of 174 people with serum prolactin measurements at study recruitment, 43% ($n = 74$) had HPL, whilst 25% ($n = 21/78$) and 28% ($n = 31/133$) had HPL at 3 and 12 months respectively. We observed higher serum prolactin levels in females versus males ($P < 0.001$), and in antipsychotic treated ($n = 68$) versus

antipsychotic naïve patients ($P < 0.0001$). Prolactin levels were consistently raised in FEP patients taking risperidone, amisulpride, and FGAs compared to other antipsychotics. Forty nine percent ($n = 68$) of antipsychotic treated patients had HPL at study recruitment ($n = 68$), which was significantly higher than 11% ($n = 3$) of the antipsychotic naïve patients with HPL (OR = 7.9 (95% CI 2.29–27.49) $P < 0.001$). There was no significant association between the mean DDDs of antipsychotic medication in those with HPL at study recruitment compared to those with no HPL (T1 HPL-DDD = 0.95 (SD = 0.64); T1 No HPL- DDD = 0.96 (0.67) ($t = 0.130$, df = 137, $P = 0.897$). Similarly at follow up (T3), the mean DDD was not significantly different in those with HPL (mean DD = 1.05 (SD = 0.60)) compared with those with no HPL (mean DDD = 1.08 (SD = 0.54)) ($t = 0.181$, df = 57, $P = 0.857$).Those with HPL at study recruitment had similar durations of antipsychotic treatment (mean = 46.6 days (SD 41.8)) compared to those without HPL (mean = 53.3 days (SD 45.3) ($t = 0.896$, df = 133, $P = 0.37$). Neither was duration of antipsychotic use associated with HPL at follow up (T3) (T3 HPL: mean duration of antipsychotic use = 391.6 days(SD = 153.2); T3 with no HPL: mean duration of antipsychotic use = 421.3 days (SD = 177.3) ($t = 0.726$, df = 81, $P = 0.47$). No significant relationship was observed between perceived stress scores ($\beta = 7.13$, $t = 0.21$, df = 11, $P = 0.0.84$ 95% CI -72.91–87.16), or objective life stressors ($\beta = -21.74$, $t = -0.31$, df = 8, $P = 0.77$ 95% CI −218.57–175.09), and serum prolactin.
Discussion: This is the largest naturalistic study in FEP to report on the prevalence of HPL over the first year of illness. Our study found elevated rates of HPL over the course of the first 12 months of illness. We found no relationship between HPL and perceived stress, thus failing to provide support for the prolactin/stress model of early psychosis. HPL is associated with the use of all antipsychotics, and is more prominent with the use of amisulpride, FGAs, and risperidone, with rates plateauing at 12 months but remaining high. This has been a consistent finding in studies of maintenance treatment in schizophrenia, and while emerging evidence indicates that it occurs in FEP populations as well, this study confirms these findings.

O7.6 Early treatment non-response as a predictor of lack of clinically significant antipsychotic effect in youth with a first episode of psychosis: 12-week results from a randomized controlled trial

Pia Jeppesen[*1], Marie Stentebjerg-Olesen[1], Ditte Rudå[1], Dea Klauber[1], Karsten Gjessing Jensen[1], Anders Fink-Jensen[2], Jens Richardt Jepsen[3], Birgitte Fagerlund[4], Christoph U Correll[5], Anne Katrine Pagsberg[6]*

[1]Child and Adolescent Mental Health Center, [2]Psychiatric Centre Copenhagen, Mental Health Services, [3]Center for Neuropsychiatric Schizophrenia Research; Child and Adolescent Mental Health Center, [4]Center for Neuropsychiatric Schizophrenia Research, Psychiatric Center Glostrup; University of Copenhagen and The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), [5]The Zucker Hillside Hospital; Hofstra North Shore-LIJ School of Medicine; Albert Einstein College of Medicine; The Feinstein Institute for Medical Research, [6]Child and Adolescent Mental Health Centre

Background: Early response (ER) versus early non-response (ENR) to antipsychotics two weeks after initiation of treatment has proven to be a robust predictor of a clinically significant ultimate response (UR) versus ultimate non-response (UNR) in adults with schizophrenia. The early antipsychotic response paradigm is far less studied in youth. The present study explored the predictive values of various definitions and time points for measurement of the ER/ENR as predictors of UR/UNR and of symptomatic remission in treatment of youth with a first episode of psychosis.
Methods: Patients aged 12–17 years and included in the Tolerability and Efficacy of Antipsychotics in Children and Adolescents with Psychosis (TEA)-trial were randomized to a 12-week, blinded intervention with quetiapine vs aripiprazole, and assessed after week 2, 4, and 12. ER was defined as ≥ 20% reduction of the Positive and Negative Syndrome Scale (PANSS)-total-score after week 2, or after week 4. Alternative measures of ER were "minimally improved" on the Clinical Global Impressions-Improvement scale (CGI-I) after week 2, or after week 4. UR in the TEA trial was a priori defined as a PANSS-total-score reduction of ≥ 30% and a score of "much improved" or "very much improved" on the CGI-I at week 12. Cross-sectional symptomatic remission was defined as score of ≤ 3 on 8 selected PANSS-items (P1, P2, P3, N1, N4, N6, G5, and G9) at week 12. Analyses included calculations of the sensitivity, specificity, positive and negative predictive values of ER/ENR with regard to the UR/UNR and remission, using two different scales (PANSS or CGI-I) and two different time points (2 weeks or 4 weeks) for the measurement of the ER/ENR.
Results: Altogether, 109 patients with recent-onset psychosis (mean age = 15.3 (SD = 1.4) years, 72 (66%) diagnosed with schizophrenia) were compliant with treatment and assessments during the first 2 or 4 week visits, and thus were included in the present analyses. The frequencies of ER, UR and remission were low, each within the range of 22–24%. The negative predictive values of ER/ENR for UR/UNR were above 80% regardless of the scale and time point used to define the ER/ENR. The sensitivity of the ER/ENR generally increased from week 2 to week 4, but all positive predictive values were low, likely due to the low rates of UR and remission. The CGI-I-based ER/ENR after week 2 and 4 showed predictive values in the same range as the corresponding PANSS-based ER/ENR. Statistically and clinically significant differences were found for ER-patients versus ENR-patients in endpoint scores of PANSS-total-, PANSS-negative-, and PANSS-general symptoms, in change-scores of PANSS-total, and PANSS-general symptoms, and in use of co-medications. All analyses showed a more favorable course and outcome for ER-patients compared with ENR-patients.
Discussion: The study replicated and extended the evidence of the clinical value of ER/ENR already 2 weeks after initiation of antipsychotic treatment as a predictor of UR/UNR in youth with first-episode psychosis. Especially ENR proved highly predictive of UNR, absence of remission and an overall less favorable treatment outcome 12 weeks after treatment initiation. Monitoring ENR with the brief and easy-to-use CGI-I scale may be a useful tool for clinicians to detect a high risk of UNR and therefore consider abortion or change of the antipsychotic medication after only 2 or 4 weeks, in order to limit exposure of the individual patient to inefficient and potentially harmful antipsychotic medication.

O7.7 Thalamic reticular nucleus dysfunction as a driver of thalamo-prefrontal dysconnectivity in nmda receptor antagonist and disc1 schizophrenia models

Judith Pratt[*1], Brian Morris[2], Neil Dawson[3]*

[1]University of Strathclyde, Strathclyde Institute Pharmacy & Biomedical Science, Glasgow, Scotland, [2]University of Glasgow, Glasgow, Scotland, [3]Lancaster University, Lancaster, UK

Background: The importance of disrupted thalamic connectivity in schizophrenia is emerging with evidence of reduced thalamic–prefrontal cortex connectivity. A key modulator of thalamic nuclei is the thalamic reticular nucleus (TRN). The TRN is a thin sheet of GABAergic neurones that surrounds other thalamic nuclei and hence occupies an anatomically strategic position to control neural communication between thalamic nuclei and their respective cortical connections. Because of its thin shape the TRN is difficult to delineate in human imaging studies. We have therefore examined its potential role in schizophrenia through examination of the impact of risk factors for schizophrenia upon TRN function in relation to thalamocortical circuitry in rodent models.
Methods: To model schizophrenia 'risk' factors, we selected NMDA receptor antagonist models and a DISC1 genetic model. We employed 2-deoxyglucose (2-DG) imaging to assess regional rates of cerebral glucose metabolism and we applied partial least squares regression (PLSR) analysis and graph theory analysis to this functional brain imaging data in order to gain insight into the altered functional connectivity of brain regions in the context of brain networks.
Results: Both acute and repeated administration of NMDA receptor antagonists, altered function related changes in 2-DG uptake in rat prefrontal cortex and thalamic circuits. We found that acute ketamine produced hyperfrontality but that repeated phencyclidine (PCP) produced metabolic hypofrontality. Thalamic hypometabolism was evident in the anteroventral, medio-dorsal, and TRN after acute ketamine. Similarly subchronic PCP resulted in hypometabolism in both the TRN and the centromedial nucleus. Notably, thalamic-prefrontal functional connectivity and TRN functional connectivity to

the prefrontal cortex (PFC)was reduced following repeated PCP treatment. Furthermore, graph theory measures showed that the TRN lost its important hub status in functional brain networks after subchronic PCP. In keeping with the hypothesis that the TRN plays a central role in driving PFC changes, we found reductions in parvalbumin expression and other GABAergic cell markers in the TRN prior to similar changes in the PFC after repeated PCP. The importance of the TRN is corroborated in a Disc1 transgenic mouse model. Disc1tr transgenic mice showed hypofrontality and TRN hypofunction and reduced functional connectivity between the TRN and PFC.
Discussion: These data strongly suggest that the TRN may have a prominent role in the dysregulation of neural communication between the thalamus and the PFC in schizophrenia and a central role in driving the long term changes in thalamic–prefrontal cortex connectivity seen in the disorder. The question of how disrupted functional connectivity signatures develop during the course of illness and how they may represent biomarkers for symptom development and early intervention therapies will also be addressed.

O7.8 The dsm-5-defined attenuated psychosis syndrome and conversion to full scale schizophrenia spectrum disorders, an institution-wide retrospective review

Zachary Zuschlag[*1], Alyssa Kennedy[1], Jeff Korte[1], Laura Franko-Tobin[1], Karen Hartwell[1], Mark Hamner[1]*

[1]Medical University of South Carolina, South Carolina, USA

Background: It has been proposed that a diagnosis of prodromal psychosis, termed the Attenuated Psychosis Syndrome (APS), should be added to the DSM. Although not included in the main body of the DSM-5, it was included in Section III: Conditions for Further Study. This has lead to an increasing interest in prodromal psychosis. To date, research on prodromal psychosis has focused on individuals identified by structured interviews and specialized clinician rating scales. Although ideal for the research setting, the application of this research in standard clinical practice has limitations. There remains a lack of studies looking at patients seen in ordinary clinical practice and diagnosed with unstructured interviews, including a lack of studies specifically examining the reliability and predictive validity of the APS as defined in the DSM-5. The aim of the current study was to determine whether the DSM-5-defined APS would identify individuals with prodromal psychosis and predict conversion to schizophrenia spectrum disorders at a rate analogous to previous studies that utilized structured interviews/specialized rating scales. An additional aim was to analyze covariates to see if their inclusion to the APS criteria increased conversion rates.
Methods: A retrospective review of the medical record was utilized to identify individuals meeting diagnostic criteria for the APS, followed by further evaluation at the 2–3 years following their initial diagnosis, to determine if they converted to schizophrenia spectrum disorders. Covariate information was also obtained to determine if the addition of certain variables to the APS criteria would increase rates of conversion. A 5-year period was analyzed, and our entire university system was included. Descriptive statistics were performed to compare our results to previous studies.
Results: Of the 152 individuals included in the final analysis, 66 converted to schizophrenia spectrum disorders at a period between 2-3 years following their initial diagnosis of APS, a 43.4% conversion rate. At the 3 year mark, comparison to previous studies yielded a z-score = 1.841 with a P-value = 0.066, indicating that there was no significant difference between our observed rates of conversion and previously published rates from studies which utilized structured interviews/specialized rating scales. Analysis of the covariates showed 3 that significantly increased the rates of conversion when added to the basic APS criteria: cannabis use ($P = 0.048$), lack of previous axis I diagnosis ($P = 0.005$), and lack of previous treatment with psychotropic medications ($P = 0.009$).
Discussion: Studies are needed examining the potential utility of the APS diagnosis in standard clinical practice. Specifically, the reliability in diagnosis and predictive validity of conversion to full-scale schizophrenia spectrum disorders must be determined. The current study aimed to examine the latter, by retrospectively looking at the APS in a standard psychiatric patient population and tracking conversion rates to schizophrenia spectrum disorders over a period of time. To our knowledge, this is the first reported study showing that the DSM-5-defined Attenuated Psychosis Syndrome can accurately predict conversion to full scale schizophrenia spectrum disorders at a rate analogous to that observed in previous studies utilizing research populations, structured interviews, and specialized rating scales. Our results also suggest that adding variables to the basic APS criteria may increase the predictive rates of conversion. These findings suggest that the DSM-5-defined APS does indeed have potential clinical utility for identifying prodromal individuals and predicting their conversion to schizophrenia and related disorders.

O8. Clinical trials

O8.1 Cariprazine as monotherapy for the treatment of predominant negative symptoms of patients with schizophrenia: a double-blind, active comparator-controlled phase-3 trial

W. Wolfgang Fleischhacker[*1], György Németh[2], István Laszlovszky[2], Pál Czobor[3], Balázs Szatmári[2], Erzsébet Szalai[2], Ágota Barabássy[2], Judit Harsányi[2], Marc Debelle[2], Suresh Durgam[4], István Bitter[3], Rene Kahn[5]*

[1]Medical University Innsbruck, Innsbruck, Austria, [2]Richter Gedeon Plc., Gyömrői, Hungary, [3]Semmelweis University, Budapest, Hungary, [4]Forest Research Institute, Dehradun, India, [5]University Medical Center Utrecht, Utrecht, Netherlands

Background: Persistent and predominant negative symptoms of schizophrenia are burdensome and disabling for schizophrenic patients while no real treatment options exist at the moment. Cariprazine is a potent dopamine D3 and D2 receptor partial agonist with preferential binding to D3 receptors approved by FDA for the treatment of schizophrenia and manic and mixed episodes associated with bipolar I disorder. Post hoc analysis of 6-week efficacy trials on a subset of patients with high levels of negative symptoms demonstrated significant improvement relative to placebo. The objective of this clinical trial was to evaluate the efficacy, safety, and tolerability of cariprazine relative to risperidone in patients with predominant negative symptoms of schizophrenia.
Methods: This study was a multinational, randomized, double-blind, risperidone-controlled, parallel group clinical trial in adult patients with predominant, negative symptoms of schizophrenia. To be enrolled into study and randomized, patients had to have predominant negative symptoms, defined as PANSS factor score for negative symptoms (PANSS-FSNS) ≥ 24 and at least 2 of the 3 core negative symptoms scored at least 4; PANSS factor score for positive symptoms (PANSS-FSPS) ≤ 19; no clinically relevant depressive symptoms and no or limited extrapyramidal symptoms; assessed as stabilized with predominant negative symptoms for a retrospective 6-month period prior to screening, and for a prospective 4-week period prior to randomization. Following 2 weeks of cross-titration patients were treated with either cariprazine target dose 4.5 mg/d, or with risperidone target dose 4 mg/d for 24 weeks. The primary efficacy parameter was the improvement in negative symptoms, defined as change from baseline (CfB) to endpoint in PANSS-FSNS. The secondary efficacy parameter was functional improvement, defined as CfB to endpoint in Personal and Social Performance Scale (PSP) total score.
Results: 461 Patients were randomized 1:1 to double-blind cariprazine ($n = 230$) or risperidone ($n = 231$). PANSS-FSNS, PSP total score and PANSS-FSPS were similar at baseline in the two treatment groups. 77.4% of the patients completed the 26-week study treatment in both groups. CfB at Week 26 in the primary parameter, PANSS-FSNS, was significantly larger in the cariprazine than in the risperidone treatment group (LSMD = −1.46; 95% CI: [−2.39, −0.53]; $P = 0.002$; MMRM, ITT) and favored cariprazine at each visit with statistically significant differences from Week 14 onward. CfB at week 26 in the secondary parameter, PSP total score, showed also a significantly greater improvement with cariprazine compared to risperidone (LSMD = 4.63; 95% CI: [2.71, 6.56]; $P < 0.001$; MMRM, ITT) and favored cariprazine at each visit with statistically significant differences from Week 10 onward. The CfB at Week 26 was statistically significant in favor of cariprazine in the PSP sub-domains of self-care score ($P = 0.004$), socially useful activities ($P < 0.001$), and personal and social relationships ($P < 0.001$) while not significant in case of

disturbing and aggressive score. Clinical Global Impression-Severity ($P = 0.005$) and -Improvement ($P < 0.001$) scores also showed significant changes in favor of cariprazine. Patients tolerated the treatment well, as reflected by low discontinuation rates due to adverse events (AEs). The most common AEs (≥10%) during treatment were insomnia (10.0%), and headache (10.4%), both in the risperidone treatment group.
Discussion: 26-Week cariprazine treatment, given as monotherapy, was significantly more effective on negative symptoms and on functioning than risperidone in patients with predominant negative symptoms of schizophrenia.

O8.2 The neurapro-e study: a multicentre rct of omega-3 fatty acids and cognitive-behavioral case management for patients at ultra-high risk of psychosis

Patrick D McGorry[*1], Sherilyn Goldstone[1], Gregor Berger[2], Eric Yu Hai Chen[3], Lieuwe de Haan[4], Ian Hickie[5], Connie Markulev[1], Nilufar Mossaheb[6], Barnaby Nelson[1], Dorien Nieman[4], Merete Nordentoft[7], Anita Riecher-Rössler[8], Miriam Schaefer[1], Stefan Smesny[9], Andrew Thompson[1], Swapna Verma[10]*

[1]Orygen - The National Centre of Excellence in Youth Mental Health, Parkville, Australia, [2]Clienia Schoessli, Oetwil am See, Swizterland, [3]The University of Hong Kong, Hong Kong, China, [4]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [5]Brain & Mind Research Institute, University of Sydney, Sydney, Australia, [6]Medical University of Vienna, Vienna, Austria, [7]Mental Health Centre Copenhagen, Copenhagen, Denmark, [8]University of Basel Psychiatric Clinics, [9]University Hospital Jena, Jena, Germany, [10]Institute of Mental Health

Background: Recent meta-analyses have indicated that preventive intervention is likely to benefit patients 'at risk' for psychosis, in terms of symptom reduction, improved functioning, and delay or even prevent the onset of full-threshold psychotic disorder. Strong preliminary results from a single-site RCT of the effectiveness of omega-3 polyunsaturated fatty acids (PUFA), coupled with the reduced transition rate in ultra-high risk (UHR) samples, mean that further study of such benign potentially neuroprotective interventions is clinically and ethically required. We designed and conducted a large international multicentre RCT to seek to replicate the results of the initial RCT of omega-3 PUFAs in the UHR stage of illness.
Methods: The trial was a 6-month, double-blind, randomized, placebo controlled trial of 1.4 g/day omega-3 PUFAs in UHR patients aged between 13 and 40 years. The primary hypothesis was that UHR patients receiving omega-3 PUFAs plus cognitive behavioral case management (CBCM) would be less likely to transition to psychosis over a 6-month period compared to treatment with placebo plus CBCM. Secondary outcomes examined the 12-month transition rates and symptomatic and functional outcomes, as well as whether candidate risk factors and biomarkers predicted the response to omega-3 PUFAs treatment in the UHR group.
Results: 977 subjects were screened at 10 international centers, and 304 were randomized; randomization was stratified by recruitment site and MADRS score (< 21 and ≥ 21), as depression and antidepressant treatment can impact prodromal symptoms and illness progression. 78% of participants were retained at 6 months. The mean age was 19.1 years and 50% were at least moderately ill on CGI. The Kaplan-Meier estimated transition rates at 12 months were 11.2% in the omega-3 group and 11.5% in the placebo group ($P = 0.76$). There were no significant differences in symptomatic and functional change between the two groups at 6 months and 12 months. Compliance rates (based on pill count) were 43% in the omega-3 group and 41% in the placebo group. A *post hoc* analysis compared outcome in the omega-3 compliant group with the placebo group and the omega-3 non-compliant participants combined. This analysis indicated a trend level ($P = 0.11$) lower transition rate in the omega-3 compliant group.
Discussion: The transition rates in this trial were lower than expected (10.5%). Therefore, longer term (2 year +) follow-up of this cohort is currently being conducted. There were no significant differences in outcomes between the two treatment groups. Compliance was reasonably poor in the trial, which may have contributed to the negative finding. Analyzing the group by compliance levels indicated a lower transition rate in the omega-3 compliant participants, although this did not reach statistical significance. Further analyses, including cell membrane fatty acid profiling and analysis of outcomes based on compliance status are currently underway and will be presented.

O8.3 The randomized, double-blind switch study: do non-improvers benefit from a change of the antipsychotic after 2 weeks of treatment?

Stefan Leucht[1], Diana Cirajliu[2], Liana Dehelean[3], Michael Dettling[4], Wolfgang Gaebel[5], Andreas Heinz[4], Markus Jäger[6], Georg Juckel[7], Michael Landgrebe[8], Markus Leweke[9], Valentin Matei[10], Delia Podea[11], Michael Riedel[12], Dorina Sima[13], Lynne Stecher[1], Stephan Heres[1]*

[1]Technische Universität München, Munich, Germany, [2]Spilatal Judetean Constanta, Constanta, Romania, [3]Timisoara University of Medicine, Timisoara, Romania, [4]Charite Berlin, Berlin, Germany, [5]Universität Düsseldorf, Düsseldorf, Germany, [6]Universität Ulm, Ulm, Germany, [7]Universität Bochum, Bochum, Germany, [8]Universität Regensburg, Regensburg, Germany, [9]Universität Mannheim, Mannheim, Germany, [10]Spitalul Clinic de Psihiatrie Obregia, Bucharest, Romania, [11]Vasile Goldis Western University of Arad, Arad, Romania, [12]LMU München, Munich, Germany, [13]Spitalul Clinic de Psihiatrie Obregia, Bucharest, Romania

Background: Current treatment guidelines often recommend maintaining an antipsychotic treatment attempt in an acute episode of schizophrenia for 4–8 weeks. These recommendations are based on the "delay of onset of action" hypothesis of antipsychotic drugs which was, however, clearly rejected by a landmark meta-analysis. 1 Moreover, since this review numerous studies have shown that those patients who have not really improved after 2 weeks of antipsychotic treatment (usually defined as $< 20\%/25\%$ BPRS or PANSS total score reduction from baseline), are unlikely to ultimately fully respond if they keep taking the same antipsychotic, and this has recently been confirmed by a meta-analysis. 2 But the question remains whether switching the antipsychotic is an effective strategy in such cases.
Methods: In the SWITCH trial 347 patients were randomized to double blind treatment with either olanzapine or amisulpride for 2 weeks. Those patients who reached the a priori defined cut off of at least 25% PANSS total score reduction from baseline stayed on the assigned double-blind treatment for another 6 weeks. The 'non-improvers', however, were again randomized (2nd randomization) to either staying on double-blind treatment with the identical compound for another 6 weeks (control group) or to switching over to the alternative double-blind antipsychotic (intervention group). The primary outcome parameter was remission rates between the control and the intervention group after 8 weeks of treatment.
Results: In the group of patients initially meeting non-response criteria and randomized to stay on the assigned compound (control group) 41.6% reached remission. In the patients switched to the alternative compound after initial non-response 63.2% reached remission ($P = 0.006$, ITT dataset, logistic regression, multiple imputation, adjusted for PANSS total score at baseline). This finding was robust irrespective of the compound initially used (i.e. drug-independent). Secondary efficacy outcomes did not reach statistical significance.
Discussion: Our data suggest that switching the antipsychotic after two weeks of an effective dose to a compound with a very different side-effect profile can be an effective strategy. Moreover, double-blind trials with two randomizations within two weeks are possible in schizophrenia research.

References:

1. Agid O, Kapur S, Arenovich T, Zipursky RB. Delayed-onset hypothesis of antipsychotic action - A hypothesis tested and rejected. ArchGenPsychiatry 2003; 60(12): 1228-35.
2. Samara MT, Leucht C, Leeflang MM, *et al.* Early Improvement As a Predictor of Later Response to Antipsychotics in Schizophrenia: A Diagnostic Test Review. Am J Psychiatry 2015; 172(7): 617-29.

O8.4 Positive phase 3 clinical trial of iti-007 for the treatment of schizophrenia: efficacy results from a randomized, double-blind, placebo-controlled trial

Kimberly Vanover[*1], Robert Davis[1], Cedric O'Gorman[1], Jelena Saillard[1], Michal Weingart[1], Sharon Mates[1]*

[1]*Intra-Cellular Therapies, Inc., New York, USA*

Background: ITI-007 is a first-in-class investigational new drug in clinical development for the treatment of schizophrenia. Through synergistic actions via serotonergic, dopaminergic and glutamatergic systems, ITI-007 represents a novel approach to the treatment of schizophrenia and other neuropsychiatric disorders. ITI-007 is a potent antagonist at 5-HT2A receptors, a mesolimbic/mesocortical dopamine phosphoprotein modulator (DPPM) with activity as a pre-synaptic partial agonist and post-synaptic antagonist at dopamine D2 receptors, a mesolimbic glutamate GluN2B receptor phosphoprotein modulator and a serotonin reuptake inhibitor. Phase 2 clinical trial (ITI-007-005) data indicated that 60 mg ITI-007 was effective in reducing symptoms of schizophrenia with a safety and side effect profile similar to placebo (Lieberman *et al.*, Biological Psychiatry, 2015 online ahead of print). A Phase 3 clinical trial (ITI-007-301) was conducted to evaluate the efficacy and safety of ITI-007 for the treatment of schizophrenia.
Methods: In the Phase 3 trial (ITI-007-301) patients with an acutely exacerbated episode of schizophrenia were randomized to receive one of three oral treatments once daily for 4 weeks: 60 mg ITI-007, 40 mg ITI-007, or placebo in a 1:1:1 ratio. The primary endpoint was change from baseline on the Positive and Negative Syndrome Scale (PANSS) total score at Day 28 compared to placebo. The key secondary endpoint was the Clinical Global Impression scale for Severity of Illness (CGI-S). Other exploratory endpoints included the PANSS Positive Symptom subscale score and the Personal and Social Performance (PSP) scale.
Results: In this trial, once-daily ITI-007 60 mg met the primary endpoint and demonstrated efficacy with statistically significant superiority over placebo at Day 28 as measured by the PANSS total score ($P = 0.022$). Moreover, ITI-007 60 mg showed significant efficacy as early as week 1 on both the PANSS total score and PANSS Positive Symptom subscale score, which was maintained at every time point throughout the entire study. ITI-007 60 mg also met the key secondary endpoint of statistically significant improvement on the CGI-S ($P = 0.003$) and improved psychosocial function as measured by the PSP. ITI-007 showed a dose-related improvement in symptoms of schizophrenia with the 40 mg dose approximating the trajectory of improvement seen with the 60 mg dose, but the effect with 40 mg did not reach statistical significance on the primary endpoint, but did statistically separate from placebo on the PANSS Positive Symptom Subscale and the CGI-S. Consistent with previous studies, ITI-007 was safe and well-tolerated. [Please see companion abstract/poster for more details on safety.]
Discussion: These findings confirm and extend the positive results demonstrated at 60 mg in the Phase 2 study. Taken into context with data from another clinical trial (ITI-007-008) in which ITI-007 60 mg was associated with a mean of approximately 40% striatal dopamine D2 receptor occupancy using positron emission tomography (PET), ITI-007 demonstrated efficacy at relatively low striatal D2 receptor occupancy, lower than the occupancy range required by most other antipsychotic drugs. Unlike any existing schizophrenia treatment, this dopamine receptor phosphoprotein modulator, or DPPM, acts as a pre-synaptic partial agonist and post-synaptic antagonist at D2 receptors. This mechanism along with potent interactions at 5-HT2A receptors, serotonin reuptake inhibition, and indirect glutamatergic modulation likely contributes to the efficacy with improved psychosocial function. As such, ITI-007 represents a novel approach to the treatment of schizophrenia.

O8.5 Effects of estrogen and serm augmentation on symptom severity and cognition in schizophrenia: a meta-analysis

Sophie Heringa[*1], Marieke Begemann[1], Angelique Goverde[1], Iris Sommer[1]*

[1]*University Medical Center, New Orleans, UK*

Background: Sex differences in favor of women in incidence, onset, and course of schizophrenia suggest that estrogens play a protective role in the pathophysiology of the disease. Indeed, in women, higher levels of estrogens are associated with less severe symptoms. This has motivated investigators to study the potential of estrogens in the treatment of schizophrenia. Currently, particular interest exists in selective estrogen receptor modulators (SERMs). SERMs have an agonistic action on estrogen receptors in the brain but with a more beneficial side effects profile compared to estrogens, which may thus open the door to long term treatment. This has led to recent large trials investigating potential treatment effects of the SERM raloxifene in both men and women with schizophrenia. Present evidence is summarized of the efficacy of estrogens and SERMs for improving symptoms and cognition in schizophrenia.
Methods: Double-blind, placebo-controlled, randomized studies were included, examining augmentation with estrogens or SERMs. Outcome measures were total symptom severity, positive and negative symptom subscores, and cognition. In meta-analyses, combined weighted effect sizes (Hedges' g) were calculated for all estrogen action, as well as separately for estrogens and SERMs.
Results: Twelve studies were included, examining 761 patients. Six studies examined estrogens in postmenopausal women, and one in men. Four studies examined the SERM raloxifene in postmenopausal women, and one in both men, and (premenopausal) women. Significant effects were found for all estrogen action regarding total symptoms (Hedges' $g = 0.90$, $P = 0.017$), positive (Hedges' $g = 0.51$, $P = 0.004$), and negative symptoms (Hedges' $g = 0.36$, $P < 0.001$). Subgroup analyses yielded significant results for estrogens in premenopausal women (6 studies) for total, positive, and negative symptoms, and for raloxifene in women and men (5 studies) only for total symptoms. Cognition was assessed in one study using estrogen and two studies using raloxifene. Only both raloxifene studies found significant improvements, in the domains memory, attention, and verbal fluency.
Discussion: Estrogens and the SERM raloxifene could be effective augmentation strategies in the treatment of schizophrenia. Given the potential side effects of estrogens, partially associated with longer duration use, the SERM raloxifene is preferred for long term treatment. Importantly, raloxifene is has shown promising results with regard to improving cognition. Future trials are needed to replicate these effects, in particular with regard to long-term treatment and treatment of cognition. Based on the present results, a new RCT will start in 2016 at the University Medical Center Utrecht, studying the effect of 120 mg raloxifene daily for 12 weeks, in addition to antipsychotic treatment. We aim to include 148 premenopausal women, postmenopausal women, and men with schizophrenia. Primary outcomes are symptom severity and cognition, expected results are due in 2019.

O8.6 Rtms for the treatment of schizophrenia negative symptoms - clinical, neurocognitive and imaging results from a large-scale multicentric trial

Alkomiet Hasan[*1], Birgit Guse[2], Joachim Cordes[3], Berthold Langguth[4], Wolfgang Gaebel[3], Wolfgang Woelwer[3], Thomas Schneider-Axmann[1], Peter Falkai[1], Nikolaos Koutsouleris[1], Thomas Wobrock[2], RESIS Core Group*

[1]*Ludwig-Maximilians University, Munich, Germany,* [2]*Georg-August-University Göttingen, Göttingen, Germany,* [3]*Heinrich-Heine University, Düsseldorf, Germany,* [4]*University of Regensburg, Regensburg, Germany,* [5]*Psychiatric University Hospital Munich, Munich, Germany*

Background: The development of new treatment for predominant negative symptoms is a major goal in schizophrenia research. Pharmacological and psychosocial interventions are effective with low to moderate effect sizes, but there is still a desperate search for new treatment option that are rooted in the pathophysiology of schizophrenia. Repetitive transcranial magnetic stimulation (rTMS) applied to the left dorsolateral prefrontal cortex (DLPCF) has been discussed to be such a treatment options. However, despite many trials available, no large-scale multi-centric trial has yet evaluated the efficacy and biological impact of this intervention.
Methods: From 2007 to 2011, we performed a randomized, sham-controlled, rater-blinded and patient-blinded clinical trial on three sites. 175 patients with schizophrenia and predominant negative symptoms were randomly assigned either to active or sham rTMS (3 weeks, 1000 stimuli per session, 10 Hz, 110% resting motor

threshold). Primary outcome was change in PANSS Negative subscale. Secondary outcomes included several psychopathological assessments (other PANSS subscales, Depression-related scales, global functioning), a broad cognitive battery (Rey Auditory Verbal Learning Test, Trail Making Test A and B, Wisconsin Card Sorting Test, Digit Span Test, and the Regensburg Word Fluency Test), and structural MRI. Assessments were performed before and after the intervention.
Results: Analyses did not reveal statistic significant differences in psychopathological or neurocognitive measures between active and sham rTMS. Both groups improved over time, but effect sizes indicated for cognitive measures at least a numeric, but non-significant superiority of the intervention compared to sham rTMS. Imaging analyses indicate that rTMS applied to the left DLPFC has the potential to induce brain volume increases in interconnected areas.
Discussion: In contrast to promising meta-analyses, this first large-scale multi-scale clinical trial indicate that 10 Hz rTMS applied to the left DLPFC is not effective for the treatment of predominant negative symptoms. As the sample size of this trial exceeds the sample sizes of other available trials, these results will impact effect sizes in future meta-analyses. However, the pattern of neurocognitive and brain structural changes indicate that active rTMS has the potential to improve functionality in schizophrenia and to restore impaired neural plasticity. Further research is warranted to disentangle the biological and clinical impact of rTMS in schizophrenia. First results of the Repetitive Transcranial Magnetic Stimulation (rTMS) for the Treatment of Negative Symptoms in Schizophrenia (RESIS) trial (NCT00783120) have already been published: Wobrock *et al.* (2015) – Biological Psychiatry; Hasan *et al.* (2015)–Schizophrenia Bulletin.

O8.7 Antipsychotic medication continuity following housing first: results of a randomized trial

Julian Somers[*1], *Stefanie Rezansoff*[1], *Akm Moniruzzaman*[1]

[1]*Simon Fraser University, Burnaby, Canada*

Background: Psychotic disorders are particularly overrepresented among homeless people. Non-adherence to prescription medication may be especially problematic among homeless individuals, and homelessness has been found to be highly predictive of poor adherence to psychotropic medication in particular. Non-adherence has been linked to a variety of patient (e.g., cognitive impairment, substance abuse, and symptom severity), medication (e.g., side effects and complexity of dosing regimen), and environmental (e.g., access to health services, living situation, and stigma) factors. Housing First (HF) is an approach to ending homelessness among people with serious mental illness and has expanded internationally. Little research has examined the association between HF on medication adherence. The current study used an experimental design and examined the impact of HF on continuity of antipsychotic medication use.
Methods: Eligible individuals were: at least 19 years old; met criteria for at least one current mental disorder; and were absolutely homeless or precariously housed. Following a screening interview ($n = 800$), eligible participants were designated as high needs (HN; $n = 297$) based on a score of 62 or lower on the Multnomah Community Assessment Scale and current bipolar disorder or schizophrenia. Participants were randomized to congregate housing with on site 24×7 supports, scattered site Housing First with Assertive Community Treatment (or Treatment as Usual, consisting of existing services and supports available to homeless adults with mental illness living in Vancouver. Detailed records of antipsychotic prescription medications were received for consenting participants ($n = 213$). Medication Possession Ratios (days of medication received divided by days since initial dose) for antipsychotics were calculated for the pre and post-randomization periods. Both intervention conditions were compared with Treatment As Usual (reference) post randomization.
Results: There were no sociodemographic or health-related differences between participants randomized to the three study arms. Participants were on average 40 years of age, white (52%), male (73%), and had been homeless for 10 years. Medication possession ratios (MPR) for antipsychotics in the pre-randomization period were 0.43. Total follow up time post randomization was 555 person years. MPRs in the post periods were as follows (mean, standard deviation): Housing First (0.68, 0.31); Congregate (0.57, 0.33), Treatment as Usual (0.49, 0.38). One-way ANOVA indicates that Housing First resulted in a significant increase in MPR (0.19) compared to Treatment as Usual ($P = 0.004$). The MPR in the Congregate condition did not differ significantly or meaningfully (0.08) from Treatment as Usual.
Discussion: Continuity of antipsychotic medication use was very low in our sample of homeless mentally ill adults. Medication Possession Ratio (MPR) indicated that participants received antipsychotics on 43% of days pre-randomization. Our experimental findings indicate that Housing First resulted in a significant increase in antipsychotic MPR (to 0.68), while congregate housing did not produce an similar increase relative to treatment as usual. These findings confirm the urgent need to deliver supported housing for mentally ill people who are homeless, and show that Housing First can meaningfully improve medication adherence among people receiving antipsychotics. The finding that Congregate housing did not result in an improvement in MPR (despite very frequent episodes of dispensing) may be a reflection of the culture among residents, and that fact that medication adherence was voluntary by participants in both experimental conditions.

O8.8 A double-blind, randomised, placebo-controlled, parallel group trial of cannabidiol as adjunctive therapy in the first line treatment of schizophrenia or related psychotic disorder

Philip McGuire[*1], *Philip Robson*[2], *Wieslaw J. Cubala*[3], *Daniel Vasile*[4], *Paul Morrison*[1], *Stephen Wright*[2]

[1]*Institute of Psychiatry Psychology & Neuroscience, Kings College London, London, UK,* [2]*GW Pharmaceuticals plc, Salisbury, UK* [3]*Medical University of Gdańsk, Gdańsk, Poland,* [4]*University Emergency Military Central Hospital*

Background: Cannabidiol (CBD) has antipsychotic effects in both animal and human models of schizophrenia. This randomized, double-blind, placebo-controlled trial explored the efficacy of CBD as an add-on therapy to conventional antipsychotic medication in participants with schizophrenia or related disorders.
Methods: Participants with schizophrenia or related psychotic disorder aged 18 to 65 who had been treated with stable dose of antipsychotic medication for a minimum of 4 weeks were randomized 1:1 to receive either adjunctive CBD (GWP42003) ($n = 43$) or placebo ($n = 45$). Inclusion required a PANSS Total score > 60 at baseline. Participants received either oral 500 mg CBD twice daily or matched placebo for 6 weeks, and continued with their existing antipsychotic medication. The PANSS, SANS, BACS, GAF, and CGI were used to assess symptom levels, cognitive performance, level of functioning, and the clinician's overall impression at baseline and 6 weeks. Statistical tests were two-sided at the 5% significance level.
Results: GWP42003 was superior to placebo at improving positive symptoms of schizophrenia, as measured by PANSS 'P' ($P = 0.0188$ intention to treat analysis set [ITT]; $P = 0.0093$ per protocol analysis set [PP]). PANSS Total scores showed greater symptom improvement in the GWP42003 group ($P = 0.1332$ [ITT], $P = 0.0768$ [PP]), and twice as many GWP42003 participants were treatment responders ($\geq$ 20% improvement in baseline PANSS Total score) ($P = 0.0896$ [ITT], $P = 0.0781$ [PP]). CGI improvement and symptom severity assessments both showed GWP42003 as being superior to placebo (CGI-I $P = 0.0182$; CGI-S $P = 0.0443$). There were no significant group differences for changes in negative and general symptoms. There were trends for greater improvements with GWP42003 in cognitive performance, ($P = 0.0677$), and level of functioning ($P = 0.0839$). The incidence of treatment emergent adverse events in the two groups was very similar (34.9 and 35.6%), and the great majority of these events were mild. Only one participant in each group withdrew because of an adverse event.
Discussion: To our knowledge, this is the first randomized trial of cannabidiol as an adjunctive treatment in schizophrenia. The addition of cannabidiol to antipsychotic medication was associated with an improvement in positive psychotic symptoms and in the global clinical impression, and there were trends for improvements in cognitive performance and the overall level of functioning. Addition of cannabidiol was not associated with adverse effects. The data suggest that cannabidiol can have beneficial effects in patients with schizophrenia, over and above those of conventional antipsychotic medication. The findings are consistent with previous reports of antipsychotic effects of cannabidiol in schizophrenia (Zuardi *et al.*,

2006) (Leweke *et al.*, 2012). Beneficial effects of cannabidiol in patients in whom conventional treatment has been only partially effective may reflect its action on the central endocannabinoid rather than the dopamine system.
ClinicalTrials.gov ID: NCT02006628
Funding: GW Research Ltd.

O9. Psychosocial functioning

O9.1 Persistent or recurrent course of co-morbid disorders is associated with functional impairment at 6-year follow-up in patients at clinical high risk for psychosis

Grazia Rutigliano[*1], Lucia Valmaggia[2], Paola Landi[3], Marianna Frascarelli[4], Marco Cappucciati[5], Victoria Sear[6], Matteo Rocchetti[5], Andrea De Micheli[5], Ceri Jones[1], Philip McGuire[1], Paolo Fusar-Poli[5]*

[1]King's College London, Institute of Psychiatry Psychology and Neuroscience, London, UK, [2]King's College London, Institute of Psychiatry Psychology and Neuroscience, South London and the Maudsley NHS Foundation Trust, London, UK, [3]King's College London, Institute of Psychiatry Psychology and Neuroscience; University of Pisa, [4]King's College London, Institute of Psychiatry Psychology and Neuroscience; Sapienza University of Rome, [5]King's College London, Institute of Psychiatry Psychology and Neuroscience; University of Pavia, [6]South London and the Maudsley NHS Foundation Trust, Beckenham, UK

Background: Patients at clinical high risk for psychosis (CHR) have an average 36% risk of transition at 3 years (1). Although up to 70% of CHR patients do not transition to full-blown psychosis, about half of them continue suffering from attenuated psychotic symptoms (APS) (2) and present substantial role and social functional impairment over the follow-up period (3). Moreover, several psychiatric disorders co-occur together with the CHR state, impacting baseline global functioning and quality of life (4) and triggering help-seeking behaviors (5). Little is known about the impact of comorbidities on long-term clinical and functional outcomes of CHR patients.
Methods: The sample included 154 CHR help-seeking patients (identified with the CAARMS, Comprehensive Assessment of the At-Risk Mental State). We assessed baseline psychopathology using the HAM-D, HAM-A (Hamilton Depression/Anxiety Rating Scale), and PANSS (Positive and Negative Syndrome Scale). 74 patients completed the 6-year follow-up assessment (mean = 6.19, SD = 1.87). We used the SCID I and II to formulate diagnoses of co-morbid disorders at follow-up. We rated global functioning on the Global Assessment of Functioning (GAF) scale.
Results: We found a 28.4% risk of transition to psychosis at 6-year follow-up. Of those who did not transition, 26.4% continued reporting APS. Less than half of the present sample (43.4%) achieved functional remission (GAF > 60). We found that 56.8% patients were affected by at least one co-morbid disorder at follow-up. 61.5% of co-morbid disorders present at baseline had persistent or recurrent course. Of those without comorbidities at baseline, 45.4% developed a new disorder over the follow-up period. Only 16.5% of the entire sample never experienced any co-morbid disorder. The persistence or recurrence of co-morbid disorders was associated with significantly poorer global functional outcomes at follow-up (OR = 4.359, 95% CI for OR = 1.214–15.655, $P = 0.024$).
Discussion: Persistence or recurrence of non-psychotic comorbidities in CHR patients is associated with adverse functional outcomes. As persistent disability in non-transitioned patient may better account for the overall clinical and economic burden of the CHR state, treating comorbidities early could have a broader impact on future psychopathological trajectories than focusing only on prevention of schizophrenia.

O9.2 Personalized predictions of global functioning in chronic patients across 17 European sites

Dominic B. Dwyer[*1], Janos Kalman[2], Monika Budde[2], Heike Anderson-Schmidt[3], Katrin Gade[3], Urs Heilbronner[2], Peter Falkai[1], Thomas G. Schulze[2], Nikolaos Koutsouleris[1]*

[1]Ludwig Maximilian University, Munich, Germany, [2]Institute of Psychiatric Phenomics and Genomics, Ludwig Maximilian University, Munich, Germany, [3]University Medical Centre Göttingen, Göttingen, Germany

Background: Individuals diagnosed with schizophrenia or bipolar disorders have different social, occupational, and psychiatric illness courses: some experience relative stability, while others fluctuate over time. These courses can be difficult to predict clinically, which highlights a need for prognostic tools. This study tested whether machine learning could provide clinically useful prognoses using standard clinical tests in individuals with established schizophrenia, schizoaffective, and bipolar disorders over a 6-month period.
Methods: Participants were selected from a longitudinal, naturalistic, multi-site project designed to investigate psychiatric illness course and outcomes. A total of 276 participants (age(SD) = 45.23(12.4); 130 females) with a DSM-IV diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder were included from 17 centers across Germany and Austria. A standard clinical battery measuring socio-demographic, illness history, symptom, and functional outcomes (251 variables) used to predict each individual's score on the global assessment of functioning (GAF) scale during a 6-month follow-up assessment. Machine learning techniques included linear support vector regression with ensemble learning wrapped into a comprehensive cross-validation framework that controlled for possible center and diagnostic biases.
Results: Results demonstrated that GAF scores decreased over the 6-mth period across all diagnoses ($t(284) = -6.85$, $P < 0.001$). Each individual's score could be robustly predicted with a mean absolute error of 7.4 GAF units—i.e., within one level of functioning ($R2 = 0.46$, $t = 15.43$, $P < 0.001$). The predictive clinical signature included variables related to the patient's current level of functioning, quality of life, work status, and positive/negative psychotic symptoms. The results generalized across centers and diagnoses.
Discussion: This study demonstrates that global functioning can be robustly predicted at a single-subject level across 17 independent sites and three diagnoses. The prognostic accuracy was within a clinically useful range and the clinical signature included measures that agree with existing literature. These results highlight the potential of automated prognostic tools to assist in psychiatric care.

O9.3 Mechanisms of formal thought disorder in first episode psychosis and psychometric schizotypy: the role of affective and cognitive systems

Kyle Minor[*1], Matthew Marggraf[1], Beshaun Davis[1], Paula DeCrescenzo[1], Nicole Mehdiyoun[2], Alan Breier[2]*

[1]Indiana University, Purdue University, [2]Indiana University School of Medicine, Indianapolis, USA

Background: Although Formal Thought Disorder (FTD) has been described since early conceptualizations of psychosis, its underlying mechanisms are poorly understood. Previous studies suggest that FTD may be influenced by affective and cognitive systems; however, few have examined these relationships in schizophrenia-spectrum populations. In this project, we examined FTD by assessing 'reactivity'—a change in FTD in experimental compared to baseline conditions—at two different points on the schizophrenia-spectrum: 1) Psychometric schizotypy (i.e., people at putative high risk for developing psychotic disorders); and 2) First episode psychosis (i.e., people who have already experienced their first psychotic episode). We expected FTD would be significantly greater in the schizotypy and first episode groups when negative affect and cognitive load were induced (i.e., group by condition interactions). Additionally, we expected that FTD and reactivity would be negatively linked with social functioning in both groups.
Methods: FTD and reactivity were measured in two separate cohorts. First, psychometric schizotypy ($n = 47$) and non-schizotypy groups

($n = 50$) were compared. Next, FTD was measured in sex- and race-matched FEP ($n = 19$) and healthy control ($n = 19$) groups. Both FTD and reactivity were assessed across baseline, affective, and cognitive conditions using a novel speech paradigm. Using this paradigm, subjects spoke for approximately two minutes about negatively-(affective condition) and neutrally-valenced (baseline, cognitive conditions) memories. In the cognitive condition, subjects completed a one-back visual working memory task while simultaneously generating speech. Relationships between FTD, reactivity, and social functioning were also examined within each group.
Results: Five key findings emerged: 1) the first episode group displayed significant, large differences (all P-values < 0.01, d-value range: 0.90–1.30) in FTD compared to healthy controls; 2) those with first episode psychosis exhibited significant affective reactivity compared to all other groups ($P < 0.01$); 3) greater FTD coincided with decreased cognitive performance from baseline to cognitive conditions in the first episode group; 4) FTD and affective reactivity were linked with poor real-world social functioning in first episode—but not control—groups, accounting for as much 56% of social functioning's variance; and 5) those displaying psychometric schizotypy did not significantly differ from the non-schizotypy group on FTD or reactivity.
Discussion: Affective and cognitive systems appear to play critical roles in FTD—but only once a person crosses the threshold into psychosis. Whereas those with schizotypy did not differ from the non-schizotypy group, the first episode cohort exhibited levels of FTD in line with what has been observed in chronic schizophrenia—suggesting FTD is already nearing peak severity shortly after psychosis emerges. Greater FTD and affective reactivity were also linked with poor social functioning. Affective reactivity, in particular, may be one method of predicting which young adults with first episode psychosis will develop severe social impairments. From a treatment perspective, our finding may signal a need to teach emotion regulation strategies that can be implemented to reduce FTD when emotionally loaded topics are discussed. Although few current treatments have exhibited effectiveness for reducing FTD, interventions focusing on integrating information (e.g., cognitive remediation, metacognitive therapy) could hold promise. Future work should focus on evaluating these treatments in schizophrenia-spectrum populations.

O9.4 Using ehealth technology to detect barriers to social functioning in people with schizophrenia

Matteo Cella[*1], *Rachel Potterton*[1], *Megan Lawrence*[1], *Til Wykes*[1]

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

Background: A reduction in social functioning is commonly observed in people with schizophrenia. Novel technologies offer the possibility of assessing social functioning in everyday life and exploring the mechanisms responsible for its severity. The current study investigates the contribution of emotion regulation, social cognition, and symptoms to social functioning through a novel assessment method integrating wearable technology and portable digital devices.
Methods: Twenty-five people with schizophrenia (SZ) and 33 healthy controls (CTRL) were assessed for social behavior, mood, and galvanic skin conductance (SCR) for six consecutive days. The portable device recorded social behavior and mood ratings semi-randomly 7 times per day. SCR was recorded continuously by a wrist worn device. Participants were also assessed with measures of social cognition and for symptom severity.
Results: There were no significant differences in the average daily number of completed assessments between groups (SZ 4.5; CTRL 4.9). Participants with schizophrenia reported being more alone than controls (71 vs 28%), being less in the company of friends and family (20 vs 43%) and strangers (8 vs 26). People with schizophrenia reported higher levels of negative emotions compared to controls in social and non-social situations. SCR magnitude was significantly higher in people with schizophrenia in social situations with strangers and was only associated with one social cognitive measures emotional intelligence ($r = -0.28$). Negative symptoms severity was also associated with SCR magnitude ($r = 0.54$, $P = 0.01$)
Discussion: Portable devices may represent a useful way of assessing social behavior and it associated physiological signature in everyday life. Increased physiological arousal, high negative symptoms and poor emotional intelligence were associated with poor social engagement, particularly with strangers. Tackling negative symptoms, emotional intelligence, and emotion regulation may be important to improve social functioning and reduce barriers to recovery.

O9.5 Persistent negative symptoms in first episode psychosis: prevalence, predictors and long term prognosis

Stephen Austin[*1], *Carsten Hjorthøj*[2], *Ole Mors*[3], *Rikke Gry Secher*[2], *Mette Bertelsen*[2], *Pia Jeppesen*[2], *Lone Petersen*[2], *Anne Thorup*[2], *Merete Nordentoft*[2]

[1]*North Zealand Psychiatric Centre, University of Copenhagen, Copenhagen, Denmark,* [2]*Mental Health Center Copenhagen, University of Copenhagen, Denmark,* [3]*Aarhus University Hospital, Aarhus, Denmark*

Background: Negative symptoms are a core component of schizophrenia, impact on outcomes and often are resistant to treatment. The goal of this study was to investigate the prevalence, baseline predictors and long term impact of persistant negative symptoms (PNS) within a large representative cohort of people with first episode psychosis.
Methods: The study had prospective design. Patients recruited into the OPUS trial (1998-2000) with a first time diagnosis within the schizophrenia spectrum (F20–28) were included. People were classified with persistent negative symptoms, if they experienced enduring negative symptoms that were not secondary to psychotic symptoms, depression, or due to medication side effects. Clinical data collected at baseline, 1 year, 2 years, and 10 years was used to identify predictors of PNS and long term outcomes.
Results: Full clinical data was available on 369 people. A total of 90 people (24%) displayed PNS, two years after diagnosis. Significant univariable predictors of PNS at baseline were low functioning, male sex, cannabis use, poor pre-morbid social functioning, and high levels of negative symptoms. People that displayed PNS had significantly lower functioning and higher levels of psychopathology at 10 year follow-up. A total 3% of people with PNS were recovered at 10 year follow-up compared to rate of 20% recovered without PNS (OR 7.42, $P < 0.01$).
Discussion: A significant proportion of the cohort displayed persistent negative symptoms and these symptoms significantly impacted on long-term outcomes. Researchers and clinicians need to continue to develop effective interventions that can ameliorate these symptoms and potentially impact on illness prognosis within schizophrenia.

O9.6 The core role of metacognition in mediating between cognition, functional capacity and real-life function in first-episode psychosis

Geoff Davies[*1], *Kathy Greenwood*[2]

[1]*University of Sussex, Brighton, UK,* [2]*University of Sussex and Sussex Partnership NHS Foundation Trust, Brighton, UK*

Background: Neurocognitive and functional outcome deficits have long been acknowledged in schizophrenia and are considered a core feature of the disorder. Neurocognition has been found to account for functional disability to a greater extent than psychopathology however much of the variance in functional outcome still remains unexplained. Metacognition has been found to relate to both neurocognition and functional outcome and may account for the unexplained variance in functional outcome through mediating the relationship between neurocognition and functional outcome. Metacognition may further account for the relationship between functional capacity and real-world functioning. Understanding how individuals translate cognitive and functional skills into the real-world may offer valuable guidance to cognitive remediation programmes. By investigating the relationship between neurocognition and functional outcome in first-episode psychosis (FEP) much can be learned about the trajectory of disability and the course of illness in schizophrenia.
Methods: 80 FEP participants were recruited from Early Intervention services in Sussex, UK and completed measures of neurocognition (memory, executive function, and IQ), metacognition (Beck Cognitive Insight Scale, Metacognitive Awareness Interview), psychopathology (PANSS), and both functional capacity (UPSA) and objective real-life function (The Time Use Survey). Path analyses investigated the relationships between variables through Structural Equation Modeling.

Results: Factor analysis was run to determine construct properties prior to inclusion in models. A series of path models demonstrate that metacognition and negative symptoms partially mediate the relationship between neurocognition and functional capacity. A second model demonstrated that metacognition fully mediates the relationship between functional capacity and objective function.
Discussion: The present study suggests that metacognition and negative symptoms partially account for the relationship between neurocognition and functional capacity and that metacognition fully accounts for the relationship between functional capacity and real-world functioning. This latter finding suggests that metacognition solely accounts for the translation of performance-based skills that relate to everyday tasks into the real-world contexts. This finding is important to models of recovery as it suggests that cognitive remediation programmes that focus on enhancing metacognitive abilities may have the greatest potential impact in real life settings.

O9.7 The daily activity report to assess productive activity

Dawn Velligan[*1], Jim Mintz[2], Cynthia Sierra[2], Mona Martin[3], Megan Fredrick[2], Greg Maglinte[4], Patricia Corey-Lisle[5]*

[1]University of Texas Health Science Center, School of Medicine, San Antonio, USA, [2]University of Texas Health Science Center, San Antonio, USA, [3]Health Research Associates, Mountlake Terrace, USA, [4]Amgen Inc., California, USA, [5]EMD Serono, Rockland, USA

Background: The assessment of real-world functional outcomes in clinical trials for medications targeting negative symptoms and cognitive impairment is extremely important. Current measures rely on intact insight and memory, require collateral information which can complicate clinical trials or assess capacity rather than real-world functioning. In response to this need, we developed the Daily Activity Report (DAR), a novel measure to assess everyday functional activity. The DAR records a person's daily activity for seven consecutive days based upon phone calls made three times a day. A total score and scores in three domains; instrumental, social, and nondomestic work or school activities are generated.
Methods: Following a comprehensive review of existing instruments, and instrument development which included focus groups with individuals with schizophrenia, and caregivers, and pilot testing, we examined the psychometric properties of the DAR in 50 patients with schizophrenia and 25 controls. Patients were assessed with DAR for a week prior to in- office ratings at baseline and one week prior to in-office assessments one month later. Assessments included the Social and Occupational Functioning Scale (SOFAS), Schizophrenia Objective Functioning Instrument (SOFI), UCSD Performance-Based Skills Assessment (UPSA-B), Positive and Negative Syndrome Scale (PANSS), and the Brief Cognitive Assessment (BCA). To determine whether the DAR added to the prediction of outcome scores over and above simply knowing the person was awake, we examined whether the change in R2 was significant when adding DAR scores to sleep hours.
Results: Inter-item consistency was high.89-.94 for each domain and.88 overall. Test retest reliability across one month for the total DAR score was.67 $P < 0.0001$. The total DAR score as well as scores for social activity and non-domestic work/school differed significantly between control and patient participants ($P < 0.0001$). DAR domain scores were associated with negative symptoms and functional outcomes, with the DAR predicting as much as 54% of the variance in negative symptom measures of daily activity and as much as 33% of the variance in functional outcome. The primary DAR score related to these measures was the work/school dimension suggesting that global assessments of functional outcome typically used in trials are really assessing whether or not people work and are not capturing much about social contact and independent living. DAR scores were only weakly and non-significantly related to positive symptoms. Results were nearly identical when sleep hours were excluded.
Discussion: The study provides preliminary support for the reliability and validity of the DAR and suggests that further refinement and investigation of such an instrument may be valuable. The 3 items represent fairly independent domains. The DAR total score was significantly correlated with negative symptoms and not positive symptoms, and was correlated with global social and occupational functioning demonstrating both convergent and discriminant validity. Results suggest that the DAR captures motivation, initiation and doing which may be important initial targets in studies of compounds designed to improve negative symptoms. Moderate test-retest reliability may suggest that the DAR is more likely to change in short term clinical trials than are global measures of functional outcome. This would make the DAR important in trials of novel compounds targeting negative symptoms. The development of a patient reported version of the DAR using smart phone technology with automatic scoring is the next step in development.

O9.8 Prediction of longer-term functional outcome in the Vienna omega-3 study

G. Paul Amminger[*1], Monika Schlögelhofer[2], Claudia M. Klier[2], Patrick D. McGorry[1], Miriam R. Schäfer[1]*

[1]Orygen - The National Centre of Excellence in Youth Mental Health, Parkville, Australia, [2]Medical University of Vienna, Vienna, Austria

Background: Psychosocial functioning is an important outcome in young people at ultra-high risk (UHR) for psychosis, independent of psychosis conversion. Most studies examining predictors of poor functioning in UHR subjects have reported 1–3 year follow-up data. We sought to examine longer-term predictors of functional outcome in the participants of the Vienna omega-3 study (Amminger *et al.*, 2015), utilizing demographic, clinical, and biomarker information.
Methods: Participants were aged 13–25 years at first presentation and met criteria for one or more of the three operationally defined groups of risk factors for psychosis: attenuated positive psychotic symptoms; transient psychosis; and genetic risk plus a decrease in functioning. A range of sociodemographic, erythrocyte membrane fatty acid (FA) measures, and clinical variables were determined at baseline. Baseline measures included the Positive and Negative Syndrome Scale (PANSS), the Montgomery–Asberg Depression Rating Scale (MADRS) and the Global Assessment of Functioning (GAF). Other potential predictors investigated in this analysis were: sex; duration of attenuated psychotic symptoms; tobacco use; alcohol use and illicit drug use. Fatty acid measures included values for following omega-6 (n-6) and omega-3 (n-3) polyunsaturated FAs (PUFAs): 18:2n-6, 18:3n-6, 20:3n-6, 20:4n-6, 22:2n-6, 22:4n-6, 18:3n-3, 20:5n-3, 22:5n-3, 22:6n-3 and the ratio of the sum of long-chain (LC) n-6 to n-3 PUFAs. Functioning at follow-up was assessed using the Social and Occupational Functioning Assessment Scale (SOFAS). The length of follow-up was 7 years (median).
Results: Eighty-one individuals were enrolled in the study. In 69 individuals (85.2%, 69/81), a SOFAS score could be determined as a measure of functioning a median of 7 years after baseline. Significant predictors of poor functioning at longer-term follow-up (P values < 0.05) in univariate analyses were male sex, high levels of PANSS symptoms (i.e. positive, negative, and general symptoms), high levels of MADRS depressive symptoms, poor functioning at baseline, lower levels of 18:3-n (alpha-linolenic acid), and a higher LCn-6 to LCn-3 ratio. The GAF and PANSS measures were highly correlated and therefore further investigated in to separate multivariate models. In the first model when significant predictors were entered simultaneously, low baseline GAF score and the higher ratio of LCn-6 to LCn-3 ratio were independent significant predictors of functional outcome. In the second model, high scores on PANSS total and the higher ratio of LCn-6 to LCn-3 were independent significant predictors of functional outcome.
Discussion: A high n-6 to n-3 ratio promotes the pathogenesis of many diseases, including cardiovascular disease, cancer, and inflammatory diseases, whereas increased levels of n-3 PUFA, exert suppressive effects (Simopoulos 2008). This follow-up study of the Vienna omega-3 study examined risk factors for poor functioning in the long term. The results are consistent with previous studies in UHR samples which reported baseline functioning and symptom severity as predictors. This analysis for the first time revealed a significant relationship between cell membrane lipid composition i.e. a higher ratio of LCn-6 to LCn-3 and functional outcome independent of baseline symptoms and functioning.

References:

1. G.P. Amminger, M.R. Schäfer, M. Schlögelhofer, C.M. Klier, P.D. McGorry, Longer-term outcome in the prevention of psychotic disorders by the Vienna omega-3 study. Nature Communications, vol. 6, p. 7934, 2015.

2. A.P. Simopoulos. The importance of the omega-6/omega-3 fatty acid ratio in cardiovascular disease and other chronic diseases. Experimental Biology & Medicine, vol. 233, no. 6, pp. 674–688, 2008.

O10. Treatment and clinical service

O10.1 Can non-invasive brain stimulation improve working memory in schizophrenia?

Kate Hoy[*1], Neil Baiely[1], Sara Arnold[1], Paul Fitzgerald[1]*

[1]Monash University, Melbourne, Australia

Background: Cognitive deficits in schizophrenia, and in particular working memory impairments, underlie more functional disability than any other symptom of the illness. Existing treatments show limited effectiveness and do not address the underlying pathophysiology of these symptoms. Working memory impairments in schizophrenia have been reliably associated with impaired neural synchrony in the prefrontal cortex, specifically gamma synchrony. In the healthy population gamma synchrony is required for successful performance in the face of increasing working memory load and is thus thought to be reflective of increased cognitive effort. It has been repeatedly shown that patients with schizophrenia are not able to modulate gamma synchrony within the prefrontal cortex, and that this lack of gamma modulation may indeed underlie their working memory deficits. An approach that is able to address this pathophysiology could have considerable clinical significance. Non-invasive brain stimulation, in particular transcranial Direct Current Stimulation (tDCS) has shown potential in this regard, however to date there has been relatively little research into the use of tDCS for enhancing cognitive performance in schizophrenia.
Methods: We investigated the effects of a single session of tDCS on cognitive performance over time in a repeated measures, double-blind placebo-controlled design in 18 patients with schizophrenia, in particular looking at the effects of dose of stimulation. Specifically, we investigated the impact of anodal left DLPFC tDCS (1mA, 2mA, sham) on performance of the 2-back post-stimulation across three time points (0, 20, and 40 minutes). We also recorded EEG concurrently with the 2-back in order to investigate the impact of tDCS on task-related gamma activity.
Results: We found a significant overall effect of stimulation dose on 2-back performance ($F(2,34) = 3.868$, $P = 0.031$), with 2mA producing great improvement than either 1mA (Mean Difference = 0.236, $P = 0.022$) or sham (Mean Difference = 0.249, $P = 0.027$). We also found a significant effect of time for 2mA ($F(2,34) = 3.586$, $P = 0.039$), with performance improving over the 40 minutes post stimulation. There was no change over time for 1mA ($F(2,34) = 0.281$, $P = 0.756$) or sham ($F(2,34) = 0.238$, $P = 0.790$). With respect to task related gamma activity, there was a significant increase in gamma event-related synchronisation in the left DLPFC following 2mA ($t(15) = 1.851$, $P = 0.042$; $d = 0.68$) which correlated with behavioral improvement (rho = +0.426 $P = 0.050$).
Discussion: These results show that tDCS is able to enhance working memory in patients with schizophrenia, and provide initial evidence that it may be doing so by restoring normal gamma oscillatory function. We are now extending this work to investigate the effects of repeated sessions of tDCS in order to assess the duration of improvement and subsequent impact on functional outcomes, the preliminary outcomes of this data will also be presented.

O10.2 Smartphone-enhanced symptom management and relapse prevention: a randomised controlled trial

Shon Lewis[*1], Matt Machin[1], Richard Hopkins[2], Caroline Sanders[1], Zhimin He[3], Charlotte Stockton-Powdrell[1], John Ainsworth[1], Eve Applegate[1], Pauline Whelan[1], Charlotte Bamford[1], Andy Bowen[1], Chris Roberts[1], Til Wykes[3]*

[1]The University of Manchester, Manchester, UK, [2]Manchester Mental Health and Social Care Trust, Manchester, UK, [3]Kings College London, London, UK

Background: Improving recovery from acute symptoms and preventing relapse are two major challenges in serious mental illness. We developed a smartphone-based personalized technology to monitor symptoms in real time and have already shown proof of concept, with good acceptability, safety, reliability, and validity for active remote monitoring of symptoms in a series of previous published studies (www.clintouch.com). We report a randomized trial testing its efficacy in improving psychotic symptom control, and its potential as an early warning system for relapse when embedded into the ICT systems of mental health provider organizations.
Methods: Participants with SMI receive a semi-random beep 2–4 times per day on their smartphone app and answer 14 key symptom rating items using a touchscreen slider. Responses are uploaded wirelessly in real time to a central server and build into a graphical readout on the handset, allowing active symptom monitoring and attempts at self-management. We built this into an end-to-end system in two NHS Hospital Trusts (Manchester and South London) to stream data into electronic care records and enable detection by the clinical team of early signs of relapse in people with SMI when key symptoms exceeded a personalized severity threshold. We conducted an open randomized controlled trial of this active symptom monitoring (ASM) using the smartphone app compared to usual management with the aim of assessing: (i) acceptability of continuous monitoring over 3 months; (ii) impact of active self-monitoring on PANSS positive symptoms and Empowerment Rating Scale score assessed at 6 and 12 weeks; (iii) efficiency of detecting early warning signs of relapse. Eligible participants with a DSM5 diagnosis of schizophrenia and related disorders and a history of relapse within the previous two years were included from an early intervention team (early psychosis group) and a community team (chronic psychosis group).
Results: Of 181 eligible, 81 were randomized to either active symptom monitoring or management as usual. 90% stayed in the trial for 12 weeks. Of the 38 in the ASM arm who completed 12 week follow up, adherence defined as responding to $>33\%$ of alerts was 84, $>50\%$ of alerts was 60%. At 12 weeks, ASM compared to usual management was associated with no difference on empowerment scale. PANSS positive subscale score showed a significant mean reduction in the ASM group over 12 weeks in the early psychosis group ($n = 22$, mean age 26 years; planned ANCOVA $P < 0.02$), but no effect in the chronic psychosis group ($n = 18$, mean age 46 years). Early warning sign alerts generated by the system occurred in 92% of cases and blind comparison with electronic case record data suggested good sensitivity and lower specificity, but with clear indications of how to adjust the gain of the system to improve future event-detection efficiency. Qualitative analyses supported the acceptability of the system to participants and staff.
Discussion: The active smartphone monitoring system is feasible and acceptable over three months in people with schizophrenia and related disorders. It was associated with psychotic symptom improvement in recent onset participants, supporting the notion of improved self-management. When built into clinical management workflows to enable personalized alerts of symptom deterioration, it was shown to have potential use in promoting earlier intervention for relapse.
Funded by UK Medical Research Council grants G901434, MR/K0155161, 2010-2015.

O10.3 Adding aerobic exercise to cognitive training enhances the impact on cognition and work functioning: a ucla pilot rct in first episode schizophrenia

Keith Nuechterlein[*1], Sarah McEwen[1], Joseph Ventura[1], Kenneth Subotnik[1], Livon Ghermezi[1]*

[1]University of California, Los Angeles, USA

Background: Systematic cognitive training has been shown to significantly improve the core cognitive dysfunctions of schizophrenia, but a substantial cognitive deficit remains. Aerobic exercise induces neurogenesis and synaptic plasticity in healthy individuals and shows promise for improving cognition in schizophrenia. We hypothesize that aerobic exercise increases learning potential and thereby will enhance the impact of neuroplasticity-based cognitive training in schizophrenia. This enhancing effect may be particularly large in the initial stages of the illness.
Methods: In an ongoing pilot randomized controlled trial, we have thus far assigned 32 first-episode schizophrenia patients to either

Cognitive Training & Exercise (CT&E) or Cognitive Training (CT) for a 6-month period. We used neuroplasticity-based computerized cognitive training programs from Posit Science (BrainHQ and SocialVille) for both groups, two days a week, two hours a day. The CT&E group also participated in aerobic exercise for 150 minutes per week, including 45 minutes at UCLA two days a week and 30 minutes at home two days a week. The MATRICS Consensus Cognitive Battery (MCCB) was used to assess cognitive functioning. The Global Functioning Scale: Role was used as the primary index of work/school functioning.
Results: For the primary cognitive outcome, the MCCB Overall Composite T score, the Group X Time (baseline, 3 months, 6 months) interaction results suggest that CT&E improves cognition substantially more than CT alone (Cohen's f = 0.36, comparable to Cohen's d = 0.72, $P < 0.09$). The more rapid gains in cognition are particularly evident in the first 3 months (mean change: CT&E: 6.5 ± 6.5 T-score points; CT: 2.2 ± 4.2 T), a contrast that is already statistically significant ($P = 0.03$) in this ongoing RCT. The effect size for the rating on the Global Functioning Scale: Role, based on the Group X Time (baseline, 3 months, 6 months) interaction, suggests that the CT&E group is likely to improve more than the CT alone group (Cohen's f = 0.31, comparable to $d = 0.62$). The contrast at 3 months is already statistically significant (mean gain: CT&E: 1.15 ± 1.73; CT: −0.40 ± 0.83, $P = 0.005$).
Discussion: Our preliminary results in this ongoing RCT suggest that the addition of regular aerobic exercise enhances the impact of computerized cognitive training on overall cognitive functioning to a notable degree. In addition, this combination appears to produce improvements in work/school functioning to a greater extent than cognitive training alone. This initial efficacy signal clearly supports moving to a fully powered confirmatory clinical trial.

O10.4 Antipsychotic treatment algorithm for first episode schizophrenia – a guide for clinicians

Ofer Agid[*1], Gagan Fervaha[2], Robert Zipursky[3], Cynthia Siu[4], Hiroyoshi Takeuchi[2], George Foussias[2], Huma Shireen[2], Gary Remington[1]*

[1]Centre for Addiction and Mental Health, The University of Toronto, [2]Centre for Mental Health and Addition, Toronto, Canada, [3]McMaster University, Hamilton, Canada, [4]Data Power, Inc.

Background: Clinicians treating patients with first episode schizophrenia are faced with numerous choices in terms of antipsychotic, dose, formulation, etc. In addition, assessing response can be difficult due to lack of clarity regarding definition of response, remission, and the appropriate time to achieve each. These factors can compromise treatment optimization, which in turn can negatively impact outcome. To date, there has been very little evidence that both systematically and collectively evaluates these different levels of decision-making.
Methods: We developed and adapted a treatment algorithm for first episode schizophrenia spectrum disorder in our clinic, using standardized clinical rating scales to evaluate response. The algorithm assumes that early and effective disease management during the earliest stages may favorably influence outcome for patients. Further assumptions guiding the algorithm's development include: early onset of action of antipsychotics; early response/non-response predicts later response/non-response; treatment resistant schizophrenia (TRS) can be identified during the illness' earliest stages; and, relapse prevention efforts should be implemented as soon as possible. The algorithm progresses according to response, moving patients through two non-clozapine second generation antipsychotic (SGA) trials followed by clozapine in the case of suboptimal response. Each trial consists of 3 stages (low, full, or high-dose), lasting up to 4 weeks at each stage and adjusted according to response/tolerability. Clinical response is defined as Clinical Global Impression-Improvement (CGI-I) < 3 (much or very much improved) during the first 12 weeks of treatment and Brief Psychiatric Rating Scale (BPRS) Thought Disorder subscale < 3 (mild or less for each core psychotic item) later on.
Patients achieving relative (CGI-I) or absolute (BPRS-Thought Disorder subscale) response are advised to switch to SGA-long acting injectable (LAI) formulations.
Results: From 2009–2014, 457 patients were treated according to the algorithm for their first episode of schizophrenia. Of these, 119 (26%) declined treatment, while 338 (74%) commenced treatment and completed at least one antipsychotic trial. Demographics of this latter group are as follows: age (mean) 22.5 ± − 3.8, range 18–34 years; gender, male = 257 (76%); diagnosis, schizophrenia/schizoaffective 274/64 = 81.2%/18.8%. At 6-month follow-up antipsychotic treatment was: oral SGA 154 (45.6%); LAI 100 (29.5%); clozapine 79 (23.3%); FGA/Polypharmacy 5 (1.5%).
Discussion: We provide findings from an established algorithm that is evidence based and addresses practical issues often not captured by randomized clinical trials (RCTs). The advantages of such a treatment algorithm include standardized treatment to guide clinical decision making and enhance timely treatment. Arguably, use of such a strategy will accelerate early treatment optimization and, ultimately, measures of outcome. The algorithm has taken steps to ensure clear definitions for relative/absolute response and remission, focusing solely on the positive symptom domain since the goal is one of evaluating antipsychotic response. It addresses both oral and LAI formulations, as well as clozapine early in the course of treatment, and relapse prevention to improve long-term outcomes. Our own experience with algorithm based treatment of first episode schizophrenia indicates that approximately 50% of patients will be treated with an oral SGA, 30% with a LAI SGA, and 20% with clozapine. This distribution might serve as an index for good clinical practice in first-episode schizophrenia clinics.

O10.5 Ultra high risk for psychosis is not associated with greater rates of transition to psychosis compared to those not at such risk

Agatha Conrad[1], Terry Lewin[2], Sean Halpin[3], Ulrich Schall[3], Ketrina Sly[1], Vaughan Carr[*4]*

[1]Hunter New England Mental Health Service, [2]Priority Research Centre for Translational Neuroscience and Mental Health, Newcastle, UK, [3]University of Newcastle, Newcastle, UK, [4]University of New South Wales, New South Wales, Australia

Background: Although screening and assessment have improved, the rates of transition to psychosis in ultra high risk (UHR) patients have decreased over time, with an average transition rate of 32% at 3 year follow up. Rates of transition to psychosis by patients presenting to clinical services who do not meet UHR criteria are not often compared against those who meet those criteria. Here we focus on just such a comparison.
Methods: A 10 year audit (1997–2007) was completed of all presentations ($N = 1{,}997$) to the Psychological Assistance Service (PAS) in Newcastle, an early psychosis service specializing in assessment and treatment of young people aged 12–25 years who are at risk of developing a psychotic disorder or who are in the early stages of a first episode of psychosis. Service level data, together with baseline assessment and diagnostic information, was used to examine relationships between UHR status, subsequent illness episodes, community contacts and hospital admissions.
Results: All presentations were classified into six clinical groups: 14.4% pre-existing psychosis, 19.7% recent onset psychosis, 9.5% UHR, 35.3% non-psychotic disorders with no psychiatric hospital admissions, 8.3% non-psychotic disorders with at least one psychiatric hospital admission, and 12.5% labeled undetermined. Using non-psychotic disorders and no psychiatric hospital admissions as the reference group (14.6% transition to psychosis), there were no significant differences in transition rates compared to the UHR (17.3%), non-psychotic disorders with at least one psychiatric hospital admission (25.9%), and the undetermined (15.2%) groups. There were significantly higher rates of subsequent psychosis episodes among those with pre-existing psychosis (62.3%, AOR = 6.28) and recent onset psychosis (49.9%, AOR = 4.16) compared to the reference group.
Discussion: The findings highlight the non-predictive value of UHR criteria for transition to psychosis. Additional analyses indicate the importance of monitoring and treating those who do not meet UHR criteria in that they experience psychiatric morbidity at comparable levels to those who do meet UHR criteria.

O10.6 How many psychiatric beds per capita do we need?

Richard O'Reilly[*1], John Gray[1], Jerry Shum[1]*

[1]*University of Western Ontario, Faculty of Medicine, Ontario, Canada*

Background: Since the 1950s, psychiatric services in most developed countries have undergone radical change from a system almost exclusively hospital-based to one that now operates primarily in community settings. The decline in the absolute number of psychiatric beds has been accentuated by significant population expansion in many countries. As bed numbers have decreased, there are fewer beds available to treat people experiencing acute exacerbations of schizophrenia and other psychotic illnesses. Few attempts have been made to identify a minimal or optimal number of psychiatric beds per capita. Many administrators reasonably contend that the optimal number of psychiatric beds depends on the quantity and quality of the community psychiatric services. However, we should at least have a range for the required minimum and optimum number of beds in a similar way that we have for other elements of the service system such as numbers of psychiatrists and community-based teams. In this study, we make our first attempt to put parameters around what these ranges might be.
Methods: We extracted reported psychiatric bed numbers for nations in the databases of the World Health Organization and the Organization for Economic Cooperation and Development. The Canadian data from the above databases was first verified using data in the Canadian Institute for Health Information (CIHI) database. We further verified the Canadian data, which is hospital specific, by contacting each hospital in three Canadian provinces. We established the cause of all noted inconsistencies in hospital specific data. These procedures identified several areas that are likely to be a source of confusion when comparing data within and between jurisdictions. Finally, we polled Canadian jurisdictions to determine if there were established targets for psychiatric beds.
Results: Remarkable variation exists in bed numbers amongst similar nations. Germany, Canada and Italy have respectively 87, 35, and 10 psychiatric beds/100,000 population. We will focus our further analysis on these three nations as representative examples of countries with a high, medium and, low rate of psychiatric beds per capita. The initial due diligence comparison of the CIHI data with figures obtained directly from hospitals yielded hospital specific differences as great as 20%. Uncertainty over whether to include beds used for detoxification and those used for more formal addictions treatment accounted for much of these variances. In Canada, only the province of Ontario has established a psychiatric bed target (35/100,000). In contrast, the Canadian Psychiatric Association recommended 50 acute beds and 15 long-stay beds/100,000.
Discussion: Countries with similar levels of development appear to have markedly differing amounts of inpatient services for people with psychiatric disorders. We are currently undertaking a more detailed analysis of the types of services included in the reported bed numbers in Germany and Italy to ensure that they are comparable with Canada. In view of the degree of the variances found thus far, it seems likely that there are real differences. If there are, it would raise important questions of how Italy manages the types of individual who are treated as inpatients in Germany and Canada and whether the outcomes are equivalent.

O10.7 An investigation of the potential specificity of childhood maltreatment trauma in patients with non-affective psychosis as compared to other mental health disorders

Nina Mørkved[*1], Mathilde Endsjø[2], Dagfinn Winje[2], Erik Johnsen[3], Anders Dovran[4], Kjersti Arefjord[2], Rune Kroken[3], Siri Helle[5], Liss-Gøril Anda-Ågotnes[6], Maria Rettenbacher[7], Nathalie Huber[7], Else-Marie Løberg[8]*

[1]*Mosjoen District Psyciatric Centre, Helgeland Hospital,* [2]*University of Bergen, Bergen, Norway,* [3]*University Hospital; University of Bergen,* [4]*University of Bergen; Sørlandet Hospital Health Enterprise,* [5]*Haukeland University Hospital, Bergen, Norway,* [6]*Stavanger University Hospital, Stavanger, Norway,* [7]*Innsbruck Medical University, Innsbruck, Austria,* [8]*University of Bergen; Haukeland University Hospital*

Background: Childhood maltreatment trauma (CMT) might be a potential risk factor in psychosis, and the prevalence of CMT may be higher in patients with psychosis as compared to other mental health disorders. However, research also shows an increase in general psychopathology and a variety of mental health disorders following CMT, raising the question of specificity between CMT and psychotic disorders. The aim of the study was to investigate the potential specificity of CMT in psychosis. We hypothesized that there would be more CMT in patients with non-affective psychosis as compared to other mental health disorders.
Methods: The sample consisted of 52 patients with non-affective psychosis and 52 matched patients with other mental health disorders. All patients in the psychosis group ($n = 52$) met the ICD-10 diagnostic criteria for non-affective psychosis (F20–F29; Schizophrenia, schizotypal, and delusional disorders), and had a score of □4 on at least one of the items Delusions, Hallucinatory behavior, Grandiosity, Suspiciousness/Persecution, or Unusual thought content on the PANSS. The non-psychosis group consisted of ICD-10 diagnosis F10–19 Mental and behavioral disorders due to psychoactive substance use, F30–39 Mood disorders, F40–48 Neurotic, stress-related and somatoform disorders, F50–59 Behavioral syndromes associated with physiological disturbances and physical factors, F60–69 Disorders of adult personality and behavior, and F80–89 Disorders of psychological development. CMT was measured by the Childhood Trauma Questionnaire Short-Form (CTQ-SF) assessing physical, emotional and sexual abuse, and physical and emotional neglect. We compared the two groups on CTQ-SF sum score and subscale scores indicating rates of CMT, in addition to rates of none/low vs. moderate/severe levels of CMT.
Results: The psychosis group had significantly higher CTQ-SF sum scores $U = 893.50$, $P = 0.003$, $r = -0.29$, and scored significantly higher on three of five subscales; physical abuse, $U = 1069.50$, $P = 0.039$, $r = -0.20$, sexual abuse, $U = 1043.50$, $P = 0.004$, $r = -0.28$, and physical neglect, $U = 773.50$, $P = 0.000$, $r = -0.38$. Patients in the psychosis group were more likely to have experienced moderate/severe levels of CMT. Emotional neglect and emotional abuse were no more frequent in the psychosis group than in the non-psychosis group. In the psychosis group, 67.3% had cut-off scores for one or more subtypes of CMT as compared to 38.5% in the non-psychosis group, and 9.6% had cut-off scores for four or more subtypes of CMT compared to 0% in the non-psychosis group.
Discussion: Patients with psychosis reported a history of more CMT, both in terms of severity and frequency, compared to non-psychotic patients. Thus, our results mainly confirmed our hypothesis of a link between CMT and psychosis. However, the prevalence of some CMT also in the non-psychosis group, as well as non-significant differences in two subtypes of CMT indicated a graded specificity of CMT in psychosis. Our results are consistent with previous research on CMT and psychosis. Limitations regarding the present study relate to fairly small sample sizes and retrospective data. Strengths of the study include the use of matched pairs and the comparison of CMT in psychosis to other mental health disorders instead of the general population. Future research is needed to explore possible causal directions, developmental sequences and mediating or moderating factors on the relationship between CMT and psychosis, as well as a prospective and longitudinal design. We conclude that CMT might have an especially strong effect on the development of psychosis, and assessment of trauma history should be included in psychosis interventions.

O10.8 12-Year follow-up study of mortality due to suicide among first episode psychosis cohort: is the early intervention program more effective in reducing excess mortality due to suicide in psychosis

Kit Wa Sherry Chan[*1], Wing Yan Stephanie Chan[1], Lai Ming Christy Hui[1], Wing Chung Chang[1], Ho Ming Edwin Lee[1], Yu Hai Eric Chen[1]*

[1]*The University of Hong Kong, Hong Kong, China*

Background: The mortality gap between the general public and people with psychotic disorders remains large. Despite the excess mortality particularly due to suicide observed in people with psychosis, little has been done to investigate measures that may effectively prevent premature deaths. It remains unclear if early intervention (EI) for psychosis can have sustainable effect to prevent excess mortality. This study compared the mortality rates at 12-year between first-episode

psychosis patients from the EI program, and those who received standard care service.
Methods: Seven hundred consecutive patients who received the EI service between 2001 and 2003 in Hong Kong, and 700 matched patients who received the standard care (SC) service between 1998 and 2001 were traced over a 12-year period following their first presentation. The EI service in Hong Kong (EASY) provides phase specific intervention to patients with first episode psychosis of age 15–25. All deaths within the cohort were identified via the centralized digital patient records system. Official verdict on cause of death was then obtained from the Coroner's Court.
Results: Of all 1,400 patients, 80 (5.7%) people had died within the follow-up period, 74 (5.3%) cases committed suicide. There were 4.1% ($N = 29$) among the EI group and 7.3% ($N = 51$) among the SC group. The difference of suicide rates between the two groups was statistically significant, χ^2 (1) = 4.71, $P < 0.03$. Multivariate Cox-proportional hazards regression analysis revealed that, EI patients were at reduced risk of mortality than those in the SC group (adj. rate ratio [RR] 1.68, 95% CI 1.05–2.69). However, when suicide occurred within the first three years following the initial onset were excluded, there was no significant difference between the two groups (adj. rate ratio [RR] 1.08, 95% CI.60–1.97), with 1.5% ($N = 21$) from the EI group and 1.5% ($N = 22$) from the SC group. Compared with the general population, the standardized mortality ratios for suicide [SMR] for EI (SMR 31.5, 95% CI 21.52–44.71) and SC (SMR 51.4, 95% CI 38.64–66.99) were both very high.
Discussion: This study investigated mortality among 1,400 individuals with first-episode psychosis at 12-year follow-up. Significantly more deaths were observed within people in the EI program than in those who received the SC service. After controlling for the gender difference, the analyses revealed that the EI program is more effective than the SC service in reducing mortality rates in psychosis patients, especially for the first three years of illness. However, the excess mortality in psychosis patients yet remains large. These points to the need in refining the EI service in targeting the tractable clinical and social risk factors that underlie excess mortality in psychosis.

O11. Brain imaging-ii: molecules, structures, and functions

O11.1 Aberrant salience and dysfunctional neural processing of self-reference in unmedicated schizophrenia patients

Teresa Katthagen[*1], Jakob Kamniski[1], Norbert Kathmann[2], Henrik Walter[1], Andreas Heinz[1], Florian Schlagenhauf[3]*

[1]Campus Charité Mitte, Charité - Universitätsmedizin, Berlin, Germany, [2]Humboldt-Universität zu Berlin, Berlin, Germany, [3]Campus Charité Mitte, Charité - Universitätsmedizin; Max Planck Institute for Human Cognitive and Brain Sciences

Background: A disturbed sense of self is a core symptom in schizophrenia and can be experimentally probed via self-referential processing (Kelley *et al.*, 2002; Nelson, Whitford, Lavoie, & Sass, 2014). The latter process is accompanied by activation in the cortical midline structures (van der Meer, Costafreda, Aleman, & David, 2010). Previous work revealed blunted ventromedial prefrontal cortex/anterior cingulate cortex (vmPFC/ACC) activation during self-referential processing correlated with aberrant salience attribution towards irrelevant events in patients with schizophrenia (Pankow, *et al.*, 2015). However, since these patients were medicated studies in unmedicated patients are warranted. To our knowledge, this is the first study to investigate aberrant salience and the neural correlates of self-referential processing in unmedicated schizophrenia patients.
Methods: In the present study, 18 schizophrenia patients (mean age: 34.83 years, 6 females) who did not receive antipsychotic medication as well as 18 healthy controls (mean age: 33.44 years, 6 females) completed the self-referential paradigm during fMRI. In this task, they applied trait words to themselves (self) or to Angela Merkel (other). Outside the scanner, they completed the Salience attribution test (SAT; Roiser *et al.*, 2009), an instrumental learning paradigm probing aberrant salience. The latter was defined as the individual reaction time difference between trials of equally irrelevant cue features. Parameter estimates from the t-contrast self > other were extracted using an ACC/vmPFC mask and correlated with aberrant salience scores in each group.
Results: Schizophrenia patients displayed increased aberrant salience compared to healthy controls (t(32) = 3.132, $P = 0.004$). In the fMRI paradigm, the t-contrast self > other revealed the typical response pattern comprising the anterior cortical midlines structures and the midbrain (at pFWE corrected < .05). In this contrast, groups differed in their vmPFC response ([338–2], F (1, 68) = 17.20, pSVC for bilateral ACC/vmPFC = 0.026). *Post hoc* t-test revealed that unmedicated schizophrenia patients displayed reduced vmPFC activation compared to healthy controls ([338–2], t (1, 68) = 4.15, pSVC for bilateral ACC/vmPFC = 0.013). There was a statistical trend for the negative correlation between vmPFC/ACC activation and aberrant salience in schizophrenia patients ($r = -0.411$, $P = 0.09$).
Discussion: Similar to results in medicated patients (Pankow *et al.*, 2015), unmedicated schizophrenia patients showed increased aberrant salience and dysfunctional self-referential processing in the vmPFC/ACC. Thus, the differentiation of relevance attribution during self-compared to other-referencing might be blunted in unmedicated schizophrenia patients. In line with the aberrant salience hypothesis (Heinz, 2002; Kapur, 2003, 2005), unmedicated patients attributed meaningfulness to irrelevant events. However, the association between aberrant salience and self-referential processing did not approach significance which might have been due to the relatively small sample size. Our results stress the importance of investigating schizophrenia related concepts at varying clinical stages of the disorder. Future studies should focus on the idionsycratic aspects and underlying mechanisms of aberrant salience and self-reference.

O11.2 Single dose of cannabidiol attenuates neurofunctional abnormalities present in individuals at high risk of psychosis

Sagnik Bhattacharyya[*1], Cathy Davies[1], Robin Wilson[1], Elizabeth Appiah-Kusi[1], Matthijs Bossong[1], Paul Allen[1], Vincent Giampietro[1], Philip McGuire[1]*

[1]King's College London, London, UK

Background: Cannabidiol (CBD), a major ingredient in the extract of cannabis, may have antipsychotic and anxiolytic properties.[1–3] It may also protect from impairments in memory induced by delta-9-tetrahydrocannabinol and has been shown to modulate the neural substrates of verbal memory in healthy individuals.[2] However, the precise mechanism underlying the potential antipsychotic-like effects of CBD is unclear. Here, we investigate this in individuals at ultra-high risk of psychosis (UHR), using a combination of acute pharmacological challenge and functional magnetic resonance imaging (fMRI). UHR individuals experience low-grade psychotic symptoms and have a very high-risk of making a transition to frank psychosis. Our objective was to test whether an acute oral dose of CBD can modulate functioning of the neural substrates of verbal memory in individuals at UHR of psychosis using functional magnetic resonance imaging (fMRI).
Methods: We employed a randomized, double-blind, placebo-controlled, parallel-arm, between-subject design to examine the acute effect of CBD in 28 UHR individuals who were randomized to receive either an acute oral dose of CBD (600 mg; UHR-CBD) or placebo (UHR-Placebo; $n = 14$ per arm). A separate healthy control group ($n = 19$) was studied under identical conditions but without any drug administration. Each participant was studied on one occasion using fMRI whilst performing a verbal paired associates learning task.
The outcome measures of interest were regional brain activation (blood-oxygenation-level-dependent response) during encoding and recall conditions of the verbal paired associates learning task, recall performance in the task, and levels of positive psychotic symptomology.
Results: Relative to healthy controls, UHR subjects under placebo conditions displayed enhanced engagement ($P < 0.005$) in the parahippocampal gyrus, inferior parietal lobule, precuneus and caudate head during the encoding condition, and attenuation of engagement ($P < 0.005$) of the parahippocampal gyrus and inferior frontal gyrus during cued recall. Severity of psychotic symptoms in the UHR individuals under placebo condition were correlated with recall task performance ($r = 0.7$, $P = 0.002$) and functional alterations in the parahippocampal gyrus (rho = 0.58, $P = 0.018$) and caudate (rho = 0.53, $P = 0.031$). Acute Cannabidiol treatment in UHR individuals modulated activation in each of these regions ($P < 0.005$), such that activation in the UHR-CBD group was intermediate between that of healthy

controls and UHR-placebo. These differences occurred in the absence of difference in recall performance between the groups.
Discussion: These results suggest that acute CBD treatment may attenuate neurofunctional abnormalities present in individuals at UHR of psychosis. Regions modulated by CBD subserve verbal memory and include the key neural substrates altered in psychosis. Together, these results complement existing evidence suggesting a role for CBD as an antipsychotic and support a therapeutic role in individuals at UHR of psychosis.

O11.3 Hippocampal perfusion and novelty-dependent learning in individuals at ultra high risk for psychosis

Mathilde Antoniades[*1], Paul Allen[1], Matthijs Bossong[2], Gemma Modinos[1], Matilda Azis[1], Carly Samson[1], Jesus Perez[3], Oliver Howes[1], James Stone[1], Philip McGuire[1]*

[1]Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK, [2]Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, Netherlands, [3]University of Cambridge, Cambridge, UK

Background: Data from both animal models and human studies suggest that increased activity in the hippocampus plays a critical role in the development of psychosis. In healthy subjects, the hippocampus mediates novelty-dependent learning. The aim of the present study was to examine whether novelty-dependent learning is impaired in subjects at ultra high risk (UHR) for psychosis, and whether this is related to increased resting hippocampal activity.
Methods: Resting cerebral blood flow (CBF) was measured in bilateral hippocampal regions of interest (ROI) using continuous Arterial Spin Labelling in 57 UHR subjects and 26 healthy controls (HC). Participants also completed a contextual memory task outside the scanner. First, they were presented with a series of scenes, some of which were shown twice. During a subsequent encoding stage, familiar scenes (previously shown once) were presented with either novel scenes or with very familiar scenes (previously presented twice). This difference in context is thought to affect recognition memory for familiar scenes and was tested in the recognition stage, when participants indicated whether they "know", "recognise" or, "have never seen" each scene before. Recognition accuracy was defined as the sum of "know" and "recognise" responses.
Results: There was a main effect of encoding context on recognition accuracy ($P = 0.003$), suggesting that both groups benefited from the novel encoding context. There was a trend for a group effect ($P = 0.069$), with UHR subjects less accurate than controls. There were significant interactions between the effects of group and recognition accuracy on perfusion in both the left ($P = 0.018$) and right ($P = 0.043$) hippocampal/subiculum ROIs. In UHR subjects, as hippocampal/subiculum rCBF increased, recognition accuracy decreased, whereas the opposite relationship was evident in HC.
Discussion: Hippocampal hyperactivity is thought to drive dopamine dysfunction and the development of psychotic symptoms through projections to the striatum. The findings from the present study suggest that increased hippocampal activity may also contribute to the episodic memory deficits that are evident in UHR subjects.

O11.4 Does dopaminergic function underlie clinical response in first episode psychosis: an 18f-dopa pet study

Sameer Jauhar[*1], Mattia Veronese[1], Fiona Pepper[1], James Stone[1], Alice Egerton[1], Federico Turkheimer[1], Philip McGuire[1], Shitij Kapur[1], Oliver Howes[2]*

[1]King's College London, London, UK, [2]MRC Clinical Sciences Centre, London, UK

Background: Between 15–30% of patients show limited response to treatment. One recent F-DOPA study found higher levels of striatal dopamine synthesis capacity in people whose illness had responded to treatment with antipsychotic medication, compared to those whose illness does not respond, and recent fMRI studies have shown cortico-striatal connectivity predicts treatment response. However, to date, no study has examined the relationship between dopamine synthesis capacity and subsequent response to treatment in first episode patients who have never received antipsychotic medication.
Methods: Drug naïve/ minimally treated patients experiencing their first psychotic episode underwent 18F-DOPA PET scans at baseline, and clinical assessments before and after treatment.
Results: Of the 17 subjects recruited (9 drug naïve, 5 off medication, 3 minimally treated for less than 14 days), there was a significant positive correlation between baseline Whole Striatal influx rate (Kicer) and change in PANSS positive symptoms (pearson's correlation $r = 0.62$, $P < 0.01$ (two-tailed), PANSS negative symptom change (pearson's $r = 0.60$, P-0.02 (two-tailed), and PANSS total symptom change (pearson's $r = 0.753$, $P < 0.01$ (two-tailed), $P < 0.01$ (two-tailed)).
Discussion: Baseline dopamine synthesis capacity is related to clinical response to antipsychotic medication, as measured by the PANSS. This has potential implications for personalizing pharmacological treatments for psychotic symptoms in clinical practice.

O11.5 Altered glutamine, glutamate and gaba levels in schizophrenia patients and their healthy first-degree relatives: a 1h-mrs study at 7t

Lara Rösler[*1], Katharine N. Thakkar[1], Jannie P. Wijnen[1], Vincent O. Boer[1], Dennis W.J. Klomp[1], Wiepke Cahn[1], René S. Kahn[1], Sebastiaan F.W. Neggers[1]*

[1]University Medical Center Utrecht, Utrecht, The Netherlands

Background: In the past decade, the NMDA-receptor hypofunction hypothesis of schizophrenia has gained increasing recognition as it can successfully explain the heterogeneity of symptoms. This model suggests decreased functioning of glutamatergic NMDA receptors resulting in altered glutamatergic and GABAergic transmission. In the present study, we investigated this hypothesis by measuring glutamate (Glu), glutamine (Gln), Glx (Glu+Gln) and γ-aminobutyric acid (GABA) levels in patients with schizophrenia, their unaffected first-degree relatives, and healthy controls, using magnetic resonance spectroscopy (1H-MRS) at 7 Tesla. The use of an ultra-high field strength enables the separation of metabolites which are overlapping at lower field strengths. Additionally, the inclusion of healthy relatives allowed us to examine whether altered metabolism is associated with genetic vulnerability towards the disease.
Methods: We measured Glu, Gln, Glx, and GABA concentrations in 21 medicated patients with schizophrenia, 23 unaffected first-degree relatives, and 24 healthy controls using 1H-MRS at 7 Tesla. Measurements were conducted in the bilateral basal ganglia and in the occipital cortex, using a semi-Laser sequence for Glu, Gln, and Glx, and a Mega-press sequence for GABA.
Results: Reduced GABA was observed in the occipital cortex of patients with schizophrenia when compared with the combined sample of unaffected relatives and healthy controls. Unaffected relatives and patients with schizophrenia, when grouped together, showed reduced Glu and Glx in the occipital cortex. No group differences were found in the basal ganglia.
Discussion: Our findings indicate that changes in GABAergic transmission, as observed in patients with schizophrenia, might either be a biomarker of the illness or reflect medication effects. Reduced glutamatergic concentrations, on the other hand, might be associated with illness liability. These results help elucidate the pathophysiology of schizophrenia and can aid the facilitation of novel therapeutic interventions.

O11.6 Environmental influences on white matter integrity in psychotic disorder: a longitudinal family-based dti study

Patrick Domen[*1], Stijn Michielse[1], Sanne Peeters[1], Wolfgang Viechtbauer[1], Jim Van Os[1], Machteld Marcelis[1]*

[1]Maastricht University, Maastricht, The Netherlands

Background: Diffusion tensor imaging (DTI) studies suggest disease-related dysconnectivity or disease-related differential sensitivity to the environment in psychotic disorder. However, most studies are cross-sectional, and do not inform on the time course of these changes, which is what the current study set out to do.
Methods: DTI scans were obtained from 85 patients with a psychotic disorder, 93 non-psychotic siblings and 80 healthy controls, of which 60% was rescanned 3 years later. In a whole-brain voxel-based

analysis, associations between change in fractional anisotropy (ΔFA) and environmental exposures (cannabis use and childhood trauma exposure) as well as interactions between group and environmental exposure in the model of FA and ΔFA were investigated. Analyses were adjusted for a priori hypothesized confounding variables.
Results: At baseline, there were no significant associations between FA and both environmental risk factors. Over the 3-year interval, significant interactions between group and respectively cannabis exposure ($\chi^2 = 6.2$, $P = 0.04$) and trauma exposure ($\chi^2 = 11.0$, $P = 0.004$) in the model of ΔFA were found. Patients showed more FA decrease over time compared to both controls and siblings when exposed to higher levels of cannabis or childhood trauma.
Discussion: Higher levels of cannabis or childhood trauma may compromise connectivity over the course of the illness in patients, but not in individuals at low or higher than average genetic risk for psychotic disorder, suggesting interactions between the environment and illness-related factors.

O11.7 Heterogeneity- a novel way to study microstructural gray matter organization in schizophrenia?

Johanna Seitz[*1], Yogesh Rathi[1], Amanda Lyall[1], Ofer Pasternak[1], Elisabetta Del Re[2], Margaret Niznikiewicz[3], Paul Nestor[4], Larry Seidman[2], Tracey Petryshen[5], Raquelle Mesholam-Gately[6], Joanne Wojcik[6], Robert McCarley[7], Martha Shenton[1], Inga Koerte[8], Marek Kubicki[1]*

[1]Brigham and Women's Hospital, Harvard Medical School, Boston, USA, [2]Harvard Medical School, Boston, USA, [3]Harvard Medical School/BHCS, Boston, USA, [4]VA Boston Healthcare System, Boston, USA, [5]Massachusetts General Hospital, Boston, USA, [6]Beth Israel Deaconess Medical Center, Boston, USA, [7]Harvard/VAMC,[8]Ludwig- Maximilians- Universität, Munich, Gemany

Background: Neuroimaging has widely been used to examine brain alterations in patients with schizophrenia (SCZ). Most evidence comes from magnet resonance imaging (MRI) studies investigating macrostructural gray matter features (volume, thickness) or from diffusion tensor imaging (DTI) studies exploring microstructural white matter abnormalities. Studies which allow the investigation of microstructural gray matter organization are lacking. Therefore, we propose the use of a novel DTI based measure- heterogeneity. First we aim to find potential differences of microstructural gray matter organization between patients with SCZ and healthy control individuals (HC). If present we than aim to study when these differences occur and how they develop over the course of disease. Gray matter alterations, if occurring at early ages, would suggest a neurodevelopmental pathology, however a progression of brain abnormalities would support the assumption that SCZ is a neurodegenerative disease.
Methods: High resolution 3D T1 and DTI sequences were acquired on a 3 Tesla scanner. The 46 patients and 37 HC were matched on age (range: 15.63-56.92), sex, parental socioeconomic status, estimated premorbid IQ and handedness. The T1s were parcellated using FreeSurfer and registered to the diffusion images. We applied a free water correction to remove the extracellular free water component from the data and ensure that we investigate only cellular gray matter structure. Fractional anisotropy (FA) and mean diffusivity (MD) were calculated for each voxel, and afterwards heterogeneity for the four cortical lobes. Heterogeneity captures the variability of FA or MD over a predefined brain area. The correlation of heterogeneity of FA (HFA) and heterogeneity of MD (HMD) with age were calculated for patients with SCZ and HC. We than explored group differences by using an ANCOVA. Finally, we investigated this further by splitting (mean split) our cohort into younger and older subgroups.
Results: Both groups showed significant positive correlations of heterogeneity with age and significant negative correlations of gray matter volume with age. We found significant group differences ($F = 6.58$, $df = 1$, $P = 0.012$) for HFA for the frontal lobe between patients and HC. After splitting the cohort in a younger and an older group we found that only younger patients exhibit higher heterogeneity in the frontal lobe ($t = 4.29$, $df = 40$, $P < 0.0001$). No significant volume differences between patients and HC were found.
Discussion: The increase of heterogeneity with age in patients and HC indicates that the cortex loses its highly ordered cellular organization when aging. Patients and HC showed a similar age dependent pattern, no group differences between older patients and HC were found. This suggests that the loss of microstructural cellular gray matter organization is not accelerated in SCZ. On the other hand, higher heterogeneity in the frontal lobe in early SCZ might suggest a neurodevelopmental gray matter pathology, and might be considered a biomarker for SCZ risk.

O11.8 Frontal white matter tract profiles underpin continuous individual differences in positive schizotypy: evidence from a large nonclinical sample

Rachael Grazioplene[*1], Aldo Rustichini[1], Colin DeYoung[1]*

[1]University of Minnesota

Background: Psychotic-spectrum psychopathology is increasingly modeled as continuous and multidimensional. To this end, an important goal of research is to examine whether schizotypal personality trait dimensions associate with features of neural structure and function in ways that resemble established neural markers of clinical psychosis and/or psychosis-proneness. The present study used both a classic (FSL's TBSS) and a novel (Automated Fiber Quantification) method for diffusion imaging analyses to examine whether the structural connectivity profiles in frontal, fronto-temporal, and fronto-thalamic white matter tracts predict positive schizotypy in a community sample.
Methods: The sample was comprised of 233 psychiatrically healthy adults between the ages of 20–40. Subjects completed several questionnaire measures that assess both clinical and subclinical variation in the psychotic spectrum, including MPQ Absorption (Tellegen & Waller, 1984) and PID-5 Psychoticism (Krueger *et al.*, 2012); these measures were used to create an index of positive schizotypy. Diffusion imaging scans were collected on a 3 T Siemens Trio scanner; scans were 12 minutes long and measured 71 diffusion directions. Analyses were carried out using FSL for preprocessing and Tract-Based Spatial Statistics (TBSS); Automated Fiber Quantification (AFQ; Yeatman *et al.*, 2012) was used to create subject-specific tract-wise fiber quantification for the bilateral uncinate fasciculi, anterior thalamic radiations, and forceps minor. These fiber quantification maps allow for the comparison of Fractional Anisotropy values across subjects without the need to warp subjects to a common template. In TBSS and AFQ, respectively, Fractional Anisotropy was regressed against a positive schizotypy index, controlling for Sex, Age, and IQ. Results from TBSS and AFQ were compared.
Results: Whole-brain TBSS results demonstrated a significant negative association between the positive symptom index and Fractional Anisotropy in the left frontal lobe ($b = -0.25$, $P < 0.001$); this is consistent with findings from meta-analytic studies of white matter connectivity in schizophrenia and in first-degree relatives of probands with psychosis. Preliminary results from AFQ suggest that the observed FA decreases are present in spatially specific locations along the left uncinate fasciculus and the bilateral forceps minor.
Discussion: The present findings demonstrate that schizotypy-linked white matter connectivity patterns mimic the structural connectivity results observed in first-episode psychosis and in first-degree relatives of people with schizophrenia. The inclusion of AFQ results represents a novel finding in the schizotypy literature: AFQ allows for a more nuanced measurement of Fractional Anisotropy changes over and above what is possible with TBSS. While preliminary, the AFQ results point to Fractional Anisotropy differences at specific anterior locations in the left uncinate fasciculus and forceps minor, providing novel information about the specific within-tract nature of white matter endophenotypes for psychosis. Overall, these findings suggest that characteristics of frontal white matter partially underpin positive schizotypal tendencies in nonclinical samples, and thus the present study supports the notion that liability to psychosis is best modeled along a continuum and is evident in brain structure.

O12. Biomarkers

O12.1 Anti-inflammatory and antioxidant effects of risperidone on drug naïve first episode psychosis

Cristiano Noto[*1], Vanessa Ota[2], Eduardo Gouvea[1], Marcos Leite Santoro[2], Lucas Rizzo[2], Cinthia Higuchi[1], Decio Barbosa[3], Patricia Moretti[1], Belangero Sintia[1], Quirino Cordeiro[4], Rodrigo Bressan[1], Ary Gadelha[1], Michael Maes[5], Elisa Brietzke[1]*

[1]Universidade Federal de São Paulo, São Paulo, Brazil, [2]UNIFESP, São Paulo, Brazil, [3]UEL, London, UK, [4]Santa Casa de misericordia de São Paulo, São Paulo, Brazil, [5]Deakin University, Victoria, Australia

Background: There is robust evidence that schizophrenia is characterized by immune-inflammatory and oxidative/antioxidant abnormalities. The results of previous studies, however, are heterogeneous due to several confounding factors, as the effect of antipsychotic drugs. Therefore, research on antipsychotic naïve first-episode psychosis (FEP) patients is essential to elucidate the role of immune and oxidative processes in the disorder. The objective of this study is to determine cytokines levels and the oxidative stress status in drug naïve FEP patients, compared to healthy controls and to delineate the effects of treatment with risperidone on these biomarkers.
Methods: 55 drug naïve FEP patients and 61 healthy controls were enrolled; FEP patients were reassessed after 10 weeks of risperidone treatment. Seven cytokines, i.e. IL-2, IL-10, IL-4, IL-6, IFN-γ, TNF-α, and IL-17, three oxidative stress biomarkers, i.e. lipid hydroperoxides (LOOH), NO metabolites (NOx), and advanced oxidation protein product (AOPP), and two antioxidant biomarkers, i.e. total radical-trapping antioxidant parameter (TRAP), and paraoxonase 1 (PON1), were measured. The Positive and Negative Syndrome Scale (PANSS) and the Calgary Depression Scale for Schizophrenia (CDSS) were used to measure symptoms' severity.
Results: We found that FEP patients had significantly higher IL-6, IL-10, and TNF-α levels, and significantly lower PON1 activity and increased TRAP values than healthy controls. After risperidone treatment, the three altered cytokines and additionally IL-4 decreased significantly. Moreover, PON1 activity increased and LOOH levels decreased. These effects of risperidone were not significantly associated with the clinical response and risperidone dosage.
Discussion: In conclusion, our results show a specific cytokine and antioxidant profile in FEP patients and that treatment with risperidone lead to immunoregulatory effects, characterized by suppressant effects on monocytic, Th2 and T regulatory functions, and antioxidant effects by lowering lipid peroxidation and increasing the antioxidant defenses against lipid peroxidation related to PON1. Such results highlight possible interconnections between psychosis, stress response immune-inflammatory pathways and antipsychotic treatment.

O12.2 Dose-related target occupancy and engagement of the glycine transporter-1 inhibitor pf-03463275, in healthy humans subjects and schizophrenia subjects

Deepak D'Souza[*1], Mohini Ranganathan[2], Naomi Driesen[2], Jason Johannesen[3], Kyung-huep Ahn[3], Yiyun Huang[4], Richard Carson[4], John Krystal[3], Yale NCATS STudy Team[2]*

[1]Yale University School of Medicine, VA Connecticut Healthcare System, New Haven, USA, [2]Yale University School of Medicine, New Haven, USA, [3]Yale University, VA Connecticut Healthcare System, New Haven, USA, [4]Yale PET Center, New Haven, USA

Background: There is a need to develop treatments for the cognitive impairments associated with schizophrenia (CIAS). Deficits in NMDA receptor (NMDAR) function contribute to the neurobiology of CIAS by interfering with the integrity of brain functional connectivity and neuroplasticity. Therefore, facilitation of NMDA-R function via the glycine site is one potential treatment approach for CIAS. Glycine transporter-1 inhibitors (GlyT1Is) such as PF-03463275 act by raising synaptic glycine levels and increasing glycine occupancy of the high-affinity (glycineB) coagonist site of NMDA-receptor (NMDA-R) thus, enhancing NMDA-R function. However, with higher doses of GlyT1Is there is some evidence suggesting a plateauing and/or worsening of effects suggestive of an inverted 'U' dose response regulation of NMDA-R function. A series of studies in healthy controls ($n = 24$) and schizophrenia subjects ($n = 9+10$) were conducted to determine the dose/s of the GlyT1I, PF-03463275 that 1) produces optimal occupancy at the GlyT1, and 2) facilitates NMDA-R function with the goal of selecting the best possible dose for a clinical trial combining PF-03463275 with cognitive remediation to address CIAS.
Methods: The dose-related occupancy of PF-03463275 (10, 20, 40, and 60 mg BID) was determined in both medicated schizophrenia subjects (SZs) and healthy controls (HCs) using 18 F-CFPyPB and PET. In parallel, enhancement of NMDAR function was assayed using two approaches. In the first, the dose-related (0, 20, and 40 mg BID) effects of PF-03463275 on ketamine-induced impairments in working memory-related cortical activation and psychosis-like effects was assessed only in HCs. In the second, the dose-related (0, 20, 40, and 60 mg BID) effects of PF-03463275 on a visual Long Term Potentiation (LTP) paradigm (persistent enhancement of visual-evoked potentials following high-frequency stimulation) was assessed in both HCs and SZs.
Results: All doses of PF-03463275 were well tolerated by subjects in this study. All doses of PF-03463275 exceeded the pre-specified occupancy threshold of 10%. Specifically, 10, 20, 40, and 60 mg BID PF-03463275 produced GlyT1 occupancies of 44, 61, 76, and 83%, respectively. In HCs, PF-03463275 did not attenuate the ketamine-induced reductions prefrontal circuit activation during working memory nor did it ameliorate ketamine-associated deficits in working memory accuracy. PF-03463275 attenuated ketamine-induced psychosis-like symptoms in HCS ($P = 0.03$) but these effects did not survive correction for multiple comparisons. PF-03463275 enhanced LTP in SZs with peak effects at 40 mg BID but no effects at 60 mg BID.
Discussion: The relationship between PF-03463275 dose and GlyT1 occupancy is linear. PF-03463275 did not attenuate effects of ketamine in the working memory assay but may reduce ketamine-induced psychosis-like effects in HCs. In the LTP paradigm, the effects of PF-03463275 in patients with schizophrenia suggest an inverted U dose-response relationship, with peak efficacy observed at 40 mg BID. Together, these data provide evidence supporting the testing of PF-03463275 for its ability to increase neuroplasticity in schizophrenia with the aim of enhancing the impact of cognitive remediation.

O12.3 Maternal markers of inflammation during pregnancy and schizophrenia in the offspring

Håkan Karlsson[*1], Linnea Widman[1], Brian K. Lee[2], Renee Gardner[1], Göran Wadell[3], Christina Dalman[1]*

[1]Karolinska Institutet, Solna, Sweden, [2]Drexel University, Philadelphia, USA, [3]Umeå University, Umeå, Sweden

Background: Chronic, as well as acute, infections during pregnancy have been associated with the later development of schizophrenia and other non-affective psychoses in the offspring. While the mechanisms underlying these associations remain to be established, experimental studies suggest that maternal immune activation or inflammation can be involved. Few studies have, however, investigated maternal sera obtained during pregnancies of future cases for signs of ongoing inflammation or activation of the innate immune system. The studies published to date report somewhat contradictory observations suggesting elevated levels of tumor necrosis factor α, interleukin 8, complement factor 1q and C-reactive protein in sera from mothers of cases of psychosis as compared to control pregnancies. An inflammatory response is normally a tightly regulated chain of events involving a large number of inter-correlated components. It is therefore very likely that molecular patterns based on many of these components are more informative than individual markers in terms of predicting psychosis in the offspring.
Methods: We here report on a nested case-control study where we employed maternal serum samples collected from 137 cases and 394 controls, as part of the Swedish rubella screening program and stored, since 1975. We used commercially available Bio-Plex panels that assayed nine different acute phase proteins (APPs) and 17 different cytokines. We considered potential confounding by factors such as maternal age and gestational length at the time of sampling as well as sex of the child.
On this highly inter-correlated data, we constructed an inflammatory risk score consisting of the weighted linear sum of immune marker

coefficients as estimated by ridge regression. Ten-fold cross-validated ridge regression was performed using the R package glmnet. Model fit was examined using AIC (Akaike's information criterion). We compared ridge regression models with 1) APPs only; 2) cytokines only; 3) APPs and cytokines.
Results: A risk score using information from the acute phase proteins only significantly predicted non-affective psychoses in the offspring (OR 1.50, CI 1.21–1.88). A risk score based on cytokines appeared to have slightly better predictive power (OR 1.76, CI 1.42–2.20). Combining information from the nine different APPs with information from the 17 different cytokines in a total risk score performed better than the individual scores in predicting psychosis in the offspring (OR 2.06, CI 1.63–2.63).
Discussion: We conclude that levels of a range of cytokines and acute phase reactants in maternal sera obtained during the early second trimester appear to contain information relevant for the prediction of the later development of non-affective psychosis in the offspring. While data from the cytokine panel appeared to contain slightly more information than the APP panel, the combination of the two provided the most information. These observations suggest that adding more biological markers will further improve the prediction of disease in the offspring and contribute to the identification of mechanisms involved in the causation of schizophrenia and other psychoses.

O12.4 Event-related potentials changes associated with violence in violent patients with schizophrenia

Menahem Krakowski[*1], *Pál Czobor*[2]

[1]*Nathan Kline Institute for Psychiatric Research, New York, USA,* [2]*Semmelweis University, Budapest, Hungary*

Background: Our goal was to understand important factors associated with violence in schizophrenia, including abnormalities in neurophysiological mechanisms underlying response inhibition and emotional processing, as increased susceptibility to negative emotional triggers and poor response inhibition are important in the etiology of violence in schizophrenia.
Methods: We compared violent patients with schizophrenia (VS; $N = 35$) to non-violent patients (NV; $N = 24$), healthy controls (HC; $N = 28$), and non-psychotic violent subjects (NPV; $N = 31$). We recorded high-density Event-Related Potentials (ERPs) and behavioral responses during an Emotional Go/NoGo Task. We evaluated psychiatric symptoms with the Positive and Negative Syndrome Scale and impulsivity with the Barrat Impulsiveness Scale (BIS-11). We investigated the univariate differences among these groups in ERP and behavioral parameters. In addition, we considered violence as a common dimension across subjects who were classified on the basis of presence/absence of violence and presence/absence of psychosis. We investigated the multivariate relationship of N2 and P3 with these 2 dimensions through canonical correlation analysis.
Results: Behavioral and neural deficits on the Go/NoGo were most pronounced in VS when they were presented with negative stimuli. There was an overall difference in commission errors for negative valence ($F = 13.9$,df = 3,115, $P < 0.001$) with worse performance in VS. They responded faster than NV ($P = 0.02$) when making these errors and evidenced larger N2 increases ($P = 0.01$) and greater P3 decreases ($P = 0.01$). N2 increases were related to P3 decreases (Spearman rho = 0.63, $N = 35$, $P < 0.001$; rho = 0.39, $P = 0.02$; rho = 0.46, $P = 0.005$, in frontal, central, and temporal areas). The N2 and P3 changes were associated with greater impulsivity in frontal, central, and temporal areas ($P < 0.01$). In contrast, NV showed little change in reaction time or ERP amplitudes with emotional stimuli. VS and NPV presented with more severe substance abuse and antisocial behavior than HC and NV ($P = 0.01$). In the canonical analyses, we obtained 2 significant sets of correlations between ERP components and the binary dimensions ($P < 0.0001$ for psychosis; $P = 0.04$ for violence). These dimensions were independently related to the ERP components. The psychosis dimension was associated with large N2 reductions in all scalp areas. The violence dimension was associated with large P3 reductions in all scalp areas.
Discussion: Negative affective triggers have a strong impact on violent patients with schizophrenia, both at the behavioral and neural levels. The resulting enhanced emotional activation is reflected in increased N2, which is present only in VS and with negative emotional stimuli. This activation interferes with response inhibition, which is reflected in decreased P3. The N2 changes are related to the P3 changes. Some of the ERP changes are also found in NPV when we look at violence as a dimension across groups. The NPV share also various historical and behavioral disturbances with the VS. The affective disruption of response inhibition, which we found in this study, may index an important pathway to violence and suggests new modes of treatment.

O12.5 Clinical staging and profiling in psychiatry

Dorien Nieman[*1], *Stephan Ruhrmann*[2], *Mirjam van Tricht*[3], *Patrick McGorry*[4], *Lieuwe De Haan*[5]

[1]*Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands,* [2]*University Hospital-University of Cologne, Cologne, Germany,* [3]*Academic Medical Center, Amsterdam, Netherlands,* [4]*Orygen Youth Health Research Centre, Parkville, Australia,* [5]*AMC-Academisch Psychiatrisch Centrum, Amsterdam, The Netherlands*

Background: The inconvenient truth is that the disease burden caused by psychiatric disorders has increased in the past decennia whereas in many other medical specialties, it has decreased. The improved prognosis in e.g. oncology and cardiology is partly due to early detection and treatment. In light of limited treatment possibilities in late stages of major mental disorders, early detection and treatment in psychiatry is promising. Accumulating evidence, as marshaled in a recent review in The Lancet Psychiatry, suggests that a blend of clinical staging and profiling, which naturally incorporates an At-Risk Mental State (ARMS), might be a better guide for treatment of patients in different stages of psychiatric illness than the categorical DSM and ICD diagnostic systems.
Methods: In a profiling study, 61 ARMS subjects were assessed at baseline with instruments yielding data on neuropsychology, symptomatology, environmental factors, premorbid adjustment, and neurophysiology. The follow-up period was 36 months.
Results: At 36 months, 18 participants (29.5%) had made a transition to psychosis. Premorbid adjustment ($P = 0.001$, hazard ratio [HR] = 2.13) and parietal P300 event-related potential amplitude ($P = 0.004$, HR = 1.27) remained as predictors in the Cox proportional hazard model. The individual prognostic scores (calculated with an algorithm that includes these predictors) were stratified into 3 risk classes, establishing a prognostic index. In the risk class with the worst social-personal adjustment and information-processing impairment (as assessed with the P300 biomarker), 74% of the subjects made a transition to psychosis whereas in the lowest risk class, transition rate was only 4%. Furthermore, transition emerged on average more than 17 months earlier in the highest risk class compared to the lowest risk class [1].
Discussion: Perhaps objective biomarkers combined with clinical symptoms, existential concerns, and psychosocial functioning could be used in the future in a clinical staging and profiling model to assess a patients' individual risk and need for particular types of care instead of the current characterization of the patients' symptoms with respect to the broad DSM or ICD criteria by the clinician [2]. First results will also be presented of a comprehensive, transdiagnostic biomarker study in more than 500 patients with various psychiatric diagnoses.
An advantage of implementation of a clinical staging and profiling model would be that in the earliest stages, symptoms would not have to be labeled as a specific disease with a formal diagnosis or even as an at-risk stage, but instead as a mild-to-moderate mental ill health situation. Optimal individual prognosis and early, personalized treatment of mental illness with benign interventions could lead to substantial gains in outcome, quality of life, and health-care costs.

O12.6 Glutamatergic dysfunction is associated with feedback learning dysfunction and myelination deficiency in schizophrenia: multi-modal imaging evidence from 1h-mrs, mcdespot and functional mri

Elias Mouchlianitis[*1], *Lucy Vanes*[1], *Sukhi Shergill*[1]

[1]*King's College London, London, UK*

Background: Glutamatergic dysfunction as a result of NMDA receptor hypofunction has been implicated in the development of psychosis, by inducing both functional and structural alterations that result to abberant information processing. However, the neurobiology of this

hypothesis not yet clearly understood. Here we use a multimodal approach and novel imaging methods to investigate the association between glutamate, myelination, and feedback learning in schizophrenia.
Methods: We studied 40 patients with a DSM-IV diagnosis of schizophrenia and 20 healthy controls matched for age and sex. 17 patients were diagnosed with treatment-resistant schizophrenia (by modified Kane criteria) and 13 were classified as treatment-responsive. During an MRI scan where we acquired: i) proton magnetic resonance spectroscopy (1H-MRS) at 3 Tesla from the anterior cingulate cortex (ACC); ii) mcDESPOT sequence to measure myelination deficits; iii) an fMRI feedback learning task. 1H-MRS data were analyzed using a standard basis function within LC-Model and glutamate was scaled to creatine. fMRI data were analyzed using a standard preprocessing pipeline within SPM. At the first-level individual data were analyzed with a trial-by-trial approach, using prediction error (PE) for each trial derived from the behavioral data as a parametric modulator. The mcDESPOT data were analyzed by deriving myelin water fraction (MWF) maps. Glutamate data were integrated with mcDESPOT and fMRI data by using individual glutamatate to creatine ratio values as a covariate within the general linear model of each analysis and testing for group interactions by first contrasting all patients to controls and then with *post hoc* group comparisons.
Results: For the fMRI data, a contrast between patients and controls showed that there was a significant group interaction between glutamate and PE-related BOLD activation in the posterior cingulate (MNI = 4, −34, 32) and right putamen (MNI = 0 24, 10, 0). For the posterior cingulate, healthy controls showed a significant negative correlation between glutamate and BOLD activation, $R = -0.62$, $P = 0.01$ while there was no significant correlation for patients, $R = 0.283$, $P = 0.15$. Importantly, there was a significant positive correlation between PE-related BOLD activation in the posterior cingulate and Total PANSS scores, $R = 0.53$, $P < 0.01$. In the right putamen healthy controls showed a negative correlation between Glu/Cr and PE-related BOLD activation, $R = -0.48$, $P = 0.06$, while the patients a positive correlation, $R = 0.39$, $P = 0.06$ There was also a positive correlation between PE-related BOLD and total PANSS score, $R = 0.64$, $P < 0.01$. For mcDESPOT the contrast between all patients and controls showed that there was a significant group interaction between glutamate MWF in the right corticospinal track. Healthy controls showed a positive glutamate and MWF, $R = 0.69$, $P < 0.001$, while the patients a negative correlation, $R = -0.41$, $P < 0.05$, with higher glutamate values associated with decreased MWF.
There were no differences in the post-hoc group comparisons
Discussion: We show for the first time, using novel multimodal imaging methods, that glutamatergic dysfunction is associated with abberant feedback learning in the posterior cingulate and the right putament, both regions widely implicated in schizophrenia. Importantly increased abberant learning in both regions was strongly associated with increased symptomatology. Furthermore, increased glutamate in patients was associated with myelination decreases. Taken together these data suggest that glutamatergic dysfunction is potentially a key modulator of dysconnectivity and associated abberant information processing, and warrants further investigation in relation to treatment-response.

O12.7 Causal relationships between cannabis use and psychotic-like experiences in young adult twins

Ragnar Nesvåg[*1]*, Ted Reichborn-Kjennerud*[1]*, Nathan A. Gillespie*[2]*, Gun Peggy Knudsen*[1]*, Jørgen G. Bramness*[3]*, Kenneth Kendler*[2]*, Eivind Ystrom*[1]

[1]*Norwegian Institute of Public Health,, Oslo, Norway,* [2]*Virginia Commonwealth University, Virginia, USA,* [3]*University of Oslo, Oslo, Norway*

Background: The relationship between cannabis use disorders (CUD) and psychotic symptoms and disorders may be explained by common etiological factors, uni- or bidirectional causal mechanisms or a combination of the two. The objective of the current study was to investigate the contribution of genetic and environmental risk factors and direction of causation for the association between symptoms of CUD and psychotic-like experiences (PLEs) in young adult twins.
Methods: A population-based sample of 2793 Norwegian twins (43.4% of those eligible, 63.5% female, mean age 28.2 years, ranging 19–36 years) were assessed for symptoms of CUD and PLEs by the Composite International Diagnostic Interview. Item Response Theory models were fitted separately to estimate the latent risk for having symptoms of CUD and PLEs, respectively. Co-twin control analysis was performed to estimate the relative risk of PLEs given symptoms of CUD in the total sample, and within twin pairs. Biometric models were fitted to estimate the heritability of the latent traits, evidence for common genetic and environmental factors, and to determine direction of causation for the association between symptoms of CUD and PLEs.
Results: 10.4% reported lifetime use of cannabis, and 25.4% reported at least one PLE. The relative risk of PLEs in the presence of symptoms of CUD was 6.49 (95% CI, 4.06, 10.39) in the total sample and 3.92 (95% CI, 1.57, 9.76) within twin pairs. The heritability of symptoms of CUD was 88% in men and women, and the heritability of PLEs was 77% in men and 43% in women. Symptoms of CUD and PLEs had 55% overlap in genetic risk factors and 52% overlap in environmental risk factors. The model specifying symptoms of CUD to cause PLEs had better fit than models specifying causality in the opposite direction or reciprocal causation.
Discussion: The association between symptoms of CUD and PLEs is explained by common genetic and environmental risk factors, but also direct causal effects primarily from symptoms of CUD to PLEs. The results provide support for cannabis as an independent risk factor for psychotic symptoms.

O12.8 Cannabis-induced attenuated psychotic symptoms: implications for prognosis in young people at ultra-high risk for psychosis

Meredith McHugh[1]*, Patrick D McGorry*[1]*, Alison Yung*[2]*, Ashleigh Lin*[3]*, Stephen Wood*[4]*, Jessica Hartmann*[1]*, Barnaby Nelson*[*1]

[1]*Orygen, The National Centre of Excellence in Youth Mental Health, Parkville, Australia,* [2]*Institute of Brain Behaviour and Mental Health, University of Manchester, Manchester, UK,* [3]*Telethon Kids Institute, Subiaco, Australia,* [4]*University of Birmingham, Birmingham, UK*

Background: Cannabis use shows a robust dose-dependent relationship with psychosis risk within the general population and can induce transient attenuated psychotic symptoms in up to 50% of users. Given these effects, it is surprising that 8 of 9 studies examining cannabis use among young people at Ultra-High Risk (UHR) for psychosis find no relationship to risk for transitioning to a psychotic disorder. Critically, most of these studies treated individuals with a history of cannabis use as a homogenous group, ignoring variability in patterns and consequences of cannabis-use. Therefore, the present study examined how variability in characteristics of cannabis use contributes to transition risk in UHR individuals. It was expected that heavier and more problematic cannabis use, an earlier age of first use and a history of cannabis-induced attenuated psychotic symptoms would be all be associated with an increased risk of transitioning to a psychotic disorder at follow-up.
Methods: Participants were 190 UHR individuals (76 males) recruited at entry to the Personal Assessment and Crisis Evaluation (PACE) clinic, Melbourne Australia, between September 2000 and May 2006. They completed a comprehensive baseline assessment including a survey of cannabis and other drug use characteristics during the period of heaviest use. We developed a novel measure of severity of cannabis abuse based on frequency of use, subjective need for cannabis, impaired capacity to control use, impaired capacity to stop use, social problems and risk taking behavior associated with use. Outcome was transition to a psychotic disorder, with mean time to follow-up of 5.0 years (range 2.4–8.7 years).
Results: A history of cannabis abuse was reported in 58% of the sample. Of these, 26% reported a history of cannabis-induced attenuated psychotic symptoms. These individuals were 4.7 times more likely to transition to a psychotic disorder ($P = 0.001$). Severity of cannabis abuse also contributed to psychosis risk ($P = 0.036$), but this effect was fully mediated by higher abuse severity among individuals with a history of cannabis-induced attenuated psychotic symptoms. Individuals with a history of cannabis-induced attenuated psychotic symptoms also reported greater intensity of positive psychotic

symptoms at treatment entry, a younger age of first use, greater use frequency, and a greater proportion of daily nicotine users at baseline. Importantly, history of cannabis-induced attenuated psychotic symptoms remained a significant predictor of transition after controlling for these factors (adjusted HR = 3.75, $P = 0.030$). Daily nicotine use and other drug use were not related to transition risk in this sample (ps > 0.20).
Discussion: These findings suggest that cannabis use poses risk in a subpopulation of UHR individuals who manifest cannabis-induced attenuated psychotic symptoms. This pattern is consistent with previous studies showing that cannabis use increases psychosis risk only among individuals with an underlying genetic vulnerability. Our findings also corroborate previous evidence that the risk posed by cannabis use may peak in adolescence. In the present study, 88 percent of individuals with a history of cannabis-induced attenuated psychotic symptoms reported an age of first use of 15 years or younger. Future studies should examine the extent to which cannabis-induced attenuated psychotic symptoms reflect risk within the general population. Overall, findings reveal an important early marker of risk, and a potential proxy measure of underlying genetic vulnerability, with significant prognostic utility for UHR individuals.