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ABSTRACTS OPEN

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Poster Session/Lunch III

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T1. Using a stratified approach in psychiatry – implications for treatment and the search for underlying mechanisms of mental illness

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Background: Previous work has shown that across different patient samples, patients exposed to childhood trauma are more likely to have co-occurrence of affective, anxious, and psychosis symptoms than non-traumatized patients. However, the clinical relevance of trauma-related admixture remains to be established. Furthermore, a possible underlying mechanism linking childhood trauma to psychopathology is not well understood
Methods: We examined patients with mood disorder ($n = 1260$), anxiety disorder ($n = 896$) or psychotic disorder ($n = 532$) in terms of symptom profiles, quality of life (QOL) and social functioning. In a separate general population sample ($n = 563$), daily life stress sensitivity was investigated, using the Experience Sampling Method (ESM).
Results: Mood disorder patients exposed to childhood trauma and with an admixture of affective, anxious and psychosis symptoms (Trauma +/ADM+) had a lower QOL (B -12.6, 95% CI -17.7- -7.5, $P < 0.001$), more help-seeking behaviour (Odds Ratio[OR] 2.5, 95% CI 1.1-5.7, $P = 0.031$), and higher prevalence of substance use disorders (OR 7.8, 95% CI 1.1-58.0, $P = 0.044$), compared with patients without a trauma history and symptom admixture (Trauma-/ADM-). Similar results were found in patients with an anxiety disorder. Traumatized patients with a psychotic disorder and admixture of symptoms showed lower QOL (B -0.6, 95% CI -0.9- -0.4, $P < 0.001$), higher prevalence of drug disorders (OR 2.2, 95% CI 1.2-3.9, $P = 0.008$), and lower global assessment of functioning (B -12.8, 95% CI -17.1- -8.5, $P < 0.001$) than Trauma-/ADM- patients. Individuals from the general population who had experienced trauma and have co-occurring (subclinical) symptoms showed an increased emotional reactivity to daily life hassles (B 0.09, 95% CI 0.02-0.15, $P = 0.008$), compared with Trauma-/ADM- individuals.
Discussion: Using a stratification approach, based on trauma exposure and symptom profiles, uncovers a clinically meaningful subgroup of patients who are more treatment-resistant. Additional trauma-treatment may be beneficial, even in patients who are not suffering from clear posttraumatic stress symptoms. Increased daily life stress sensitivity may be the underlying mechanism trough which some, but not all, individuals who are exposed to trauma develop psychopathology. In future studies attempting to find underlying biological or psychological mechanisms in mental illness, utilizing a stratification approach based on environmental exposure and symptom phenotype, rather than on diagnostic category, may be necessary.

T2. Relationship between clozapine induced EEG abnormalities and the serum concentration of clozapine in Japanese patients with schizophrenia

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Background: Clozapine-induced electroencephalography (EEG) abnormalities are common. It has been reported that clozapine-induced EEG abnormalities occur in a dose-dependent manner and correlate with the serum concentration of clozapine (C-CLZ). However, the oppositional results were also reported. The objective of this study is to investigate the relationship between serum level of clozapine and EEG abnormalities.
Methods: Twenty-eight patients were recruited in this study, but five patients were excluded because clozapine was discontinued before post-treatment EEG measurement or measurement of C-CLZ. Ultimately, 23 patients (6 males, 17 females) with an average age of 35 years were enrolled. The subjects were divided into EEG normal and abnormal group. C-CLZ and the serum concentration of metabolite of clozapine (N-CLZ) were measured. The correlation between C-CLZ and daily dose of CLZ (D-CLZ), N-CLZ and D-CLZ were evaluated in each group. C-CLZ per D-CLZ (C/D), N-CLZ per D-CLZ (N/D) and the ratio of C-CLZ to N-CLZ (C/N) were compared between the two groups.
Results: 74 serum levels were measured. All patients had normal baseline EEGs, and 10 patients later showed EEG abnormalities. There were a significant correlation between C-CLZ and D-CLZ (EEG normal: rs 0.58, $P < 0.01$, EEG abnormal: rs 0.56, $P < 0.01$) and between N-CLZ and D-CLZ (EEG normal: rs 0.53, $P < 0.01$, EEG abnormal: rs 0.57, $P < 0.01$). There were no significant differences between the EEG normal and EEG abnormal groups in C/D, N/D, C/N.
Discussion: It has been reported that clozapine-induced EEG abnormalities occur in a dose-dependent manner and correlate with the serum level of clozapine. (Welch *et al.* 1994, Freudenreich *et al.* 1997, Haring *et al.* 1994). However, Centorrino *et al.* (2002) did not find a relationship between dose and EEG abnormalities. Goyal *et al.* (2011) reported EEG abnormalities in 61.9% of patients received clozapine at a dose of 100 mg or less. Haring *et al* described EEG abnormalities in 52% of patients and reported that these were dependent on plasma levels; they also determined that dose was not statistically related to EEG abnormalities.
In this study, there were a moderate correlation between C-CLZ and D-CLZ and between N-CLZ and D-CLZ. On the other hand, there were no significant difference between EEG abnormal and EEG normal group in C/D, N/D and C/N. These results indicates that EEG abnormalities may occur independently of dose of clozapine or the serum level of clozapine.

T3. Extrapyramidal symptoms during risperidone maintenance treatment in schizophrenia: a prospective, multicenter study

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Background: The risperidone maintenance treatment in schizophrenia (RMTS) study was designed to identify the duration of maintenance treatment required with the initial therapeutic dose, in constant to a reduced dose. The current study investigated extrapyramidal

symptoms (EPS) in different risperidone maintenance treatment paradigms over one year.
Methods: Clinically stabilized patients with schizophrenia ($N = 374$) were randomized to a no-dose-reduction group and 4-week and 26-week reduction groups, in which the dose was gradually reduced to 50% over 8 weeks and maintained. EPS were assessed at baseline and monthly for six months, followed by every two months. The Simpson-Angus Scale of Extrapyramidal Symptoms (SAS)-Chinese version assessed EPS severity. Data were analyzed via a generalized Linear Mixed Model (GLMM).
Results: The frequency of EPS at baseline was 23.2%, 20.0%, and 21.3% in the 4-week, 26-week, and no-dose-reduction groups, respectively. Risperidone dose, positive symptoms, and disorganized thoughts at baseline predicted development and maintenance of EPS. The GLMM indicated the significant decrease in EPS was maintained, and different trajectories occurred over time across groups. In the 235 patients who continued treatment after 1-year, the incidence of EPS decreased to 4.1%, 2.8%, and 10.0% in the 4-week, 26-week, and no-dose-reduction groups, respectively, whereas the numbers of dropouts because of intolerable EPS were not significantly different (4.8%, 6.7%, and 6.2%, respectively).
Discussion: These novel findings indicate that EPS were tolerable and differentially decreased depending on the dose paradigm during the one-year treatment period. Future studies should implement a GLMM to investigate antipsychotic side effects during long-term treatment.

T4. Threshold of dopamine D2/3 receptor occupancy for hyperprolactinemia in older patients with schizophrenia

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Background: Although hyperprolactinemia carries a long-term risk of morbidity, the threshold of dopamine D2/3 receptor (D2/3R) occupancy for hyperprolactinemia has not been investigated in older patients with schizophrenia. This study included 42 clinically stable outpatients with schizophrenia (DSM-IV) (mean ± SD age: 60.2 ± 6.7 years) taking olanzapine or risperidone. Subjects underwent [11C]-raclopride positron emission tomography (PET) scans to measure D2/3R occupancy before and after reducing their dose of antipsychotic by up to 40%. Blood samples were collected before each PET scan to measure prolactin (PRL) levels.
Methods: The present study was conducted in conjunction with a 12- to 24- week prospective PET study to examine the effects of antipsychotic dose reduction in older, stable patients with schizophrenia. Stepwise multiple regression analyses were performed to examine the effects of the following variables on PRL levels: age, gender, antipsychotics (olanzapine or risperidone), and D2/3R occupancy. To evaluate the D2/3R occupancy threshold for hyperprolactinemia in this population, Fisher's exact tests were employed with increments of 1% between 60% and 70% in D2/3R occupancy.
Results: PRL decreased following dose reduction (mean ± SD, 24.1 ± 30.2 to 17.2 ± 15.1, $P < 0.001$). 16 subjects showed hyperprolactinemia at baseline and 11 subjects still had hyperprolactinemia after dose reduction. PRL levels were associated with female gender ($\beta = 0.32$, $P = 0.006$, vs. male), antipsychotics ($\beta = 0.23$, $P = 0.02$, risperidone vs. olanzapine), and D2/3R occupancy ($\beta = 0.23$, $P = 0.04$). Those with D2/3R occupancy higher than 66% were more likely to have hyperprolactinemia than those with D2/3R occupancy lower than 66% ($P = 0.03$). Sensitivity, specificity, positive predictive value, and negative predictive value of this threshold were 0.44, 0.81, 0.78, and 0.48, respectively. We identified a D2/3R occupancy threshold for hyperprolactinemia of 66% in older patients with schizophrenia that is lower than that in younger patients (~73%).
Discussion: Our results suggest a higher sensitivity to antipsychotics in older patients. Thus, clinicians are advised to regularly monitor PRL levels and try to minimize exposure to antipsychotics while maintaining their clinical effectiveness in stable older patients with schizophrenia.

T5. Childhood neglect differentially affects psychotic patients in comparison to healthy siblings and controls

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Background: Life-threatening traumatic events (CT) encountered early in life may be mediated by affective dysregulation (distress proneness, i.e. neuroticism-N) and related to psychosis proneness (i.e. positive and negative symptoms). The confirmation that association between CT and psychosis has been apparent across subjects with different levels of psychosis risk was recently published and replicated, showing a true association rather than reporting bias, reverse causality, or passive gene-environment correlation. Literature is inconsistent if any sub-type of trauma in particular was associated with psychosis.
We aimed to descriptively evaluate self-reports of childhood trauma, abuse and neglect in Serbian sample and to examine the correlation of abuse and neglect with neuroticism and psychotic symptoms in the cases vs. sibling and controls.
Methods: The study included Serbian clinical patient population-Pt ($n = 52$, age = 29.3 ± 6.0, male 59.6%, illness duration 62.8 ± 56.7 months), their healthy siblings-HS ($n = 55$, age = 28.6 ± 6.8, male 41.8%) and controls-C ($n = 51$, age = 29.8 ± 6.3, male 45.1%) and assessed cross-sectionally Childhood Trauma Questionnaire (CTQ, scores: total, abuse and neglect), neuroticism scale from Eysenck Personality Questionnaire-103 (EPQ-N) and Community Assessment of Psychic Experiences (CAPE, scores P and N). The data collection in Serbia was performed in collaboration with EU-GEI research network.
Results: The patients reported more EPQ-N, P and N ($P = .000$ in all comparisons with the other subgroups). Pt had more trauma than C (means: total CT 1.28 and 1.12, $P = .001$; abuse 1.12 and 1.00, $P = .029$; neglect 1.40 and 1.20, $P = .005$), while HS reported more neglect in comparison to C (means: 1.20 and 1.12, $P = .020$) and less abuse in comparison to patients (1.07 and 1.13, $P = .05$). Pt and HS had the same levels of neglect (mean 1.40, both). Positive significant correlation between childhood abuse, distress proneness and psychosis proneness was confirmed in all sub-samples. However, positive significant correlation between neglect and two aforementioned domains was evident only in non-patient population. In Pt, the neglect in childhood was associated neither with present levels of neuroticism, nor with positive/negative symptoms ($r = .108$; $r = .221$ and $r = .215$, respectively).
Discussion: Evidence that childhood exposure to both sub-types of trauma is the highest in the patients with schizophrenia is consistent with the similar studies from other countries, while the finding that patients' reaction to neglect is different in comparison to general population is unexpected finding. Possibility that there are specific underlying mechanisms which alter sensitivity towards neglect in subjects at highest risk for psychosis deserves further attention, firstly the consideration of disorganized symptom dimension and related domains.

T6. Immigration and community mental health services: an example of an effective outreach drug treatment program.

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Background: The prevalence of mental health problems on homeless population, especially drug abuse disorders, is higher than the general population. In the other hand, some surveys have shown that the access to drug- treatment of immigration-population with drug-abuse problems in Spain is lower than natives. This characteristic: to be homeless-immigrant in Spain, are risk factors of drug-abuse and conversely that requires outreach programs and street-work interdisciplinary teams. The objective of this survey is to describe the effect on immigration homeless population of a qualitative outreach intervention addressed to motivate the introduction of drug treatment in public-ambulatory drug-services.

Methods: This is a survey was made in the city of Girona (Catalonia, Spain), with about 100,000 people in a region of a 39 km2. There's only one homeless public shelter in the city, and only one mental health and addictions institution. These characteristics made the city special for to investigate the homeless. The design of the survey was observational, transversal and analytic. Measures of location and dispersion, correlation for quantitative variables, contingence tables for qualitative variables, t student or ANOVA or U-Mann Whitney for to compare means (depending on normality) there were used. There were analysed two samples. First of all, we used the data since 2010 until 2014 (included) about all the homeless population of Girona ($n = 737$) in these years to contextualize the phenomenon. We compare this population with some sociodemographic characteristics to contextualize differences among origin. In a second step, we had analysed severity of dependence using the Severity Dependence Scale (SDS) on a representative experimental sample of 154 homeless during the year 2014 (cut-off point indicating presence of dependence for alcohol and cocaine (=/>3), cannabis (=/>4) and heroin (=/>5). We compare the results of SDS to the treatment doing for the subjects (immigrants or not) to compare the access to the public services. Also, we compared this population with some sociodemographic characteristics to contextualize differences and we described the effect of the street-work outreach intervention.
Results: About the homeless population of Girona ($n = 737$): The gender distribution was 613 males (83.2%) and 123 females (16.7%). The median of age was 44 years old (Z of K.S. = 8.45, $P = < .001$), without significative differences among genders (men = 45, women = 42, U Mann-Whitney = .072).
Immigration population was established in 51,3% of the sample ($n = 326$), 20.5% from Maghreb, ($n = 75$). Immigrant featured more mental health diagnoses (X2 = 25.1, df = 1, $P < .001$), especially psychotic disorders (X2 = 4,8, df = 1, $P = .004$) and more drug dependence diagnoses (X2 = 18,5, df = 1, $P = .033$) than native population. In consequence, immigrant population was registered more on the public mental health services than native population (X2 = 46.3, df = 1, $P < .001$). About the severity of dependence analysis ($n = 154$). The results of the SDS showed 51.2% of the sample ($n = 79$) obtained points higher than the cut-off punctuation. In addition, consulting the clinic expedient, it found 36,4% (36.4%) was registered. Therefore 23 subjects (14.8%) had dependence criteria and didn't have contact with drug abuse services. Immigrants of the intervention group presented more treatment introductions than native population (X2 = 11,4, df = 1, $P = .001$).
Discussion: The relationship among results of SDS and diagnose suggest a significative number of subjects with dependence was in treatment process and indicate the good results of the outreach street-work, especially the immigrant treatment results when we organize specific integration objectives and methodologies.

T7. Risk of suicide among homeless women: gender differences in the streets of Girona (Catalonia)

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Background: The scientific evidence clarifies the relation establishing among homeless population and some different mental health problems included severe mental disorders and drug abuse disorders. Mental health problems are involved with the suicide behaviour among others risks factors included gender (to be men in general populations), alcohol consumption or tentative of suicide. The objective of this survey is to analyse gender differences among the homeless population of Girona.
Methods: This is a survey was made in the city of Girona (Catalonia, Spain), with about 100,000 people in a region of a 39 km^2. There's only one homeless public shelter in the city, and one only mental health and addictions institution. These characteristics made the city special for to investigate the homeless. The design of the survey was observational, transversal and analytic.
Measures of location and dispersion, correlation for quantitative variables, contingence tables for qualitative variables, t student or ANOVA or U-Mann Whitney for to compare means (depending on normality) there were used. There were analysed two samples. First of all, we used the data since 2010 until 2014 (included) about all the homeless population of Girona ($n = 737$) in these years. We compare this population with some sociodemographic characteristics to contextualize differences among genders. In a second step, we had analysed the suicide risk on a representative sample of 154 homeless during the year 2014, using the Plutchik Suicide Risk Scale (cut-off point indicating substantial suicide risk = 6).
Results: About the homeless population of Girona ($n = 737$): The results indicated that there were 613 males (83,2%) and 123 females (16,7%). The median of age was 44 years old (Z of K. S. = 8.45, $P = < .001$), without significative differences among genders (men = 45, women = 42, U Mann-Whitney = .072). There were 411 (55.8%) persons with open expedient in the Mental Health Public Network and 72 (9.8%) were diagnosed of psychotic disorders, 32 (4.3%) of paranoid schizophrenia. Women had a significative high level of diagnosed mental disorders (X2 = 3.81, df = 1, $P = .036$), specially personality disorders (fisher = .002) and dual pathology (X2 = 6.89, df = 2, $P = .032$). About the suicide risk analysis ($n = 154$)
The age average of the sample was 42.8 years old (ED = 11.7, Rank = 18-77) and there are no differences among genders (Men = 42.4, ED = 11.6 vs. Women = 45.2, ED = 12.1; t = -1.036, df = 152, $P = .31$). There were 66 subjects (45.2%) with a significative point of substantial suicide risk, and 38 (24.7%) had an experience of tentative of suicide. Women had high score on Plutchik test (= 7.3, ED = 3.2 vs. = 5.1, ED = 3.3; t = -3.1, df = 144, $P = .003$) and the logistic regression results that to be woman is a high predictive factor of suicide risk (OR = 1.38, $P = .021$). Women had been more experience of tentative of suicide than men (X2 = 11.2, df = 1, $P = .001$).
Discussion: Different studies referred that the victimization of the women living in the streets by the men, is an important risk factor of to get worse mental health symptoms, including suicide risk. This survey has demonstrated that women homeless are a especially risky collective that the public services need to protect and offer specific services for them.
In addition, some countries started alternative programs for to care the homeless population with severe mental health problems like schizophrenia, like housing first programs. This programs conclude that provide house first and don't using the Continuum of Care model, the homeless people have less harms associated with mental health.

T8. Effect of brexpiprazole on weight and metabolic parameters: an analysis of short- and long-term trials in schizophrenia

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Background: Approximately one-third of new cases of diabetes in patients with schizophrenia were seen in patients exposed to olanzapine, risperidone, or quetiapine in a US Veterans Health Administration cohort.[1] Brexpiprazole is a serotonin-dopamine activity modulator that is a partial agonist at 5-HT1A and dopamine D2 receptors at similar potency, and an antagonist at 5-HT2A and noradrenaline alpha1B/2C receptors.[2] Brexpiprazole was approved in July 2015 by the FDA for treatment of schizophrenia. Here we evaluate the effect of brexpiprazole on weight and metabolic parameters in patients with schizophrenia based on pooled data from two pivotal studies;[3,4] and pooled data from the open-label extension to these studies [NCT01397786] (data cut-off May 2015), and a phase 2, open-label extension study [NCT01649557].
Methods: In the two similarly designed pivotal studies, patients with acute schizophrenia were randomly assigned to fixed once-daily doses of brexpiprazole 2 mg, 4 mg or placebo for 6 weeks (an additional treatment group was included in each study [0.25 mg and 1.0 mg]; these doses are not presented). The long-term studies were open-label, 52-weeks, flexible-dose (1 to 4 mg/day and 1 to 6 mg/day) studies with brexpiprazole. The long-term studies enrolled de novo patients, patients who had completed one of the two pivotal studies, as well as patients who had completed a phase 2 study. We report here weight and fasting metabolic parameters including glucose, and lipid metabolism-related laboratory measurements at Week 6 of the placebo-controlled studies and at Week 26 of the open-label studies.
Results: In the short-term studies, mean change in weight from baseline to Week 6 was 1.7 ($N = 253$), 1.4 ($N = 251$), and 0.4 kg ($N = 227$)

for the 2 mg, 4 mg brexpiprazole and placebo groups, respectively. In the long-term studies, the mean change in weight from baseline to Week 26 was 1.5 kg ($N = 485$). For fasting metabolic parameters, mean changes from baseline to last visit in the short-term studies were (brexpiprazole 2 and 4 mg vs placebo): total cholesterol 2.22 and 2.97 vs 3.21 mg/dL; high-density lipoprotein cholesterol (HDL) 1.51 and 0.46 vs -1.78 mg/dL; low-density lipoprotein cholesterol (LDL) 0.36 and 2.35 vs 1.82 mg/dL; triglycerides -1.39 and 0.75 vs 0.38 mg/dL; and glucose -0.23 and 1.64 vs 0.42 mg/dL. Mean changes from baseline to Week 26 in the long-term studies were: total cholesterol 2.97 mg/dL; HDL 1.01 mg/dL; LDL 0.92 mg/dL; triglycerides 4.00 mg/dL; and glucose 3.11 mg/dL.
Discussion: A moderate weight increase was observed after treatment with brexpiprazole with small changes in lipid profiles and other metabolic parameters.
Uncited references
1CINS; 1Karolinska; 1National; 1Universitat
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T9. The interaction between bullying and FKBP5 haplotype on psychotic-like experiences and reactivity to stress: does it matter in real life?

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Background: Research indicates that exposure to psychosocial stressors, such as bullying, is associated with an increased risk for clinical and subclinical psychosis phenotypes. Bullying is a form of childhood adversity that may lead to feelings of social defeat. Evidence also suggests that daily life stressors play an important role in the expression of psychotic-like and paranoid symptoms. Individual variation in symptoms in response to stress is likely to be moderated by genetic variability. In particular, single nucleotide polymorphisms (SNPs) on the FKBP5 gene may moderate the association between momentary stress and psychotic-like symptoms. However, there are no studies investigating whether FKBP5 SNPs and bullying are associated with the real-world expression of symptoms. The present study employed Experience Sampling Methodology to assess gene–momentary environment (GxE) interactions in daily life. Specifically, the study examined the impact of genetic variation in the FKBP5 gene, bullying, and their interaction (FKBP5 x bullying) on (i) levels of paranoid and psychotic-like experiences (PLEs) and (ii) paranoid and psychotic-like reactivity to different forms of momentary stress (situational and social stressors).
Methods: Two hundred and six nonclinical young adults were interviewed for bullying with the Childhood Experiences of Care and Abuse. They were also prompted randomly eight times daily for one week to complete assessments of their current experiences, symptoms, and two types of stress appraisals: situational and social (being alone because people do not want to be with you). Participants were genotyped for the main FKBP5 SNPs (rs3800373, rs9296158 and rs1360780) reported in previous studies. Analyses were conducted with the haplotype derived from these three SNPs.
Results: Bullying, but not FKBP5 haplotype, was associated with PLEs. Neither was associated with paranoia. However, the GxE interaction indicated that bullying was associated with increased paranoia and PLEs for participants with the risk haplotype but not for those with the non-risk haplotype. In addition, bullying moderated the association of situational, but not social, stress with paranoia. The risk haplotype did not moderate the associations of situational or social stress with symptoms. The GxE interaction indicated that the association between social stress and PLEs was significantly increased by exposure to bullying in participants with the risk haplotype, but not for those with the non-risk haplotype.
Discussion: To our knowledge, this is the first examination of the interaction between FKBP5 variability with bullying on the expression of psychotic phenomena in daily life. The findings support and extend previous research indicating an interaction between FKBP5 SNPs and childhood trauma in the prediction of symptoms in several mental disorders. Consistent with the stress-sensitivity model of the positive dimension of psychosis, momentary stressors were associated with PLEs and paranoid experiences. Although genetic variability by itself did not moderate these associations, bullying exposure in carriers of the risk haplotype was associated with psychotic-like reactivity to social stress. The findings are consistent with the increasing relevance given to socially defeating schemas in the experience of reality distortion. Furthermore, they suggest that the interplay between bullying and FKBP5 variability plays a role in increasing the likelihood of psychotic-like reactivity to socially defeating appraisals in the real word.

T10. Mismatch negativity and P3A amplitude in young adolescents with first episode psychosis: a comparison with attention-deficit/hyperactivity disorder

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Background: Deficient mismatch negativity (MMN) has been proposed as a candidate biomarker in schizophrenia and may therefore be potentially useful in early identification and intervention in early onset psychosis. In this study we explored whether deficits in the automatic orienting and reorienting responses, measured as MMN and P3a amplitude, are present in young adolescents with first episode psychosis and whether findings are specific for psychosis compared to young adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD).
Methods: MMN and P3a amplitude were assessed in young adolescents (age 12-17 years) with either first episode psychosis ($N = 27$) or with ADHD ($N = 28$) and age and gender matched healthy controls ($N = 43$). The MMN paradigm consisted of a four-tone auditory oddball task with deviant stimuli based on frequency, duration and their combination.
Results: The results showed significantly less MMN in patients with psychosis compared to healthy controls in response to frequency deviants. A trend level difference between these two groups was seen in MMN elicited by duration deviants. MMN amplitudes in the group of patients with ADHD were not significantly different from patients with psychosis or healthy controls. No significant group differences were found on P3a amplitude.
Discussion: In conclusion, young adolescents with first episode psychosis showed impaired MMN compared to healthy controls while intermediate and overlapping levels of MMN were observed in adolescents with ADHD. The findings suggest that young FEP patients already exhibit preattentive deficits that are characteristic of schizophrenia albeit expressed on a continuum shared with other neuropsychiatric disorders.

T11. The fecal microbiota of patients with first episode psychosis and healthy controls

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Background: The possible effects of gut microbiota on the central nervous system and psychiatric disorders have received increasing

attention, but it has not been studied in first-episode psychosis before. Here, we investigated if fecal microbiota of patients with first-episode psychosis (FEP) differs from healthy matched controls and if the possible differences correlate with symptom severity.
Methods: We assessed FEP-patients three times (baseline, two, and 12 months) and controls twice (baseline and 12 months). Each assessment consisted of an interview, questionnaire, and collection of blood and fecal samples. Fecal samples were collected from 42 patients and 20 controls for polyphasic microbiological analysis (real-time PCR, denaturing gradient gel electrophoresis and metagenomics). Blood was sampled to study metabolic and inflammatory measures. Symptoms were measured with the Brief Psychiatric Rating Scale – Extended and self-report questionnaires (Beck Depression Inventory, Beck Anxiety Inventory and the Obsessive-Compulsive Inventory, Revised).
Results: Numbers of Lactobacillus group bacteria were higher in FEP-patients than in controls at baseline and two months ($P < 0.05$) and the numbers significantly correlated with severity of symptoms in patients at all measurement points. The correlation was strongest for positive psychotic symptoms, but was also present for self-reported depressive and anxiety symptoms. The numbers of Lachnospiraceae were lower ($P < 0.05$), whereas the predominant bacterial diversity was higher in the FEP-patients than in the controls at baseline and at one-year follow-up ($P < 0.05$). Based on our metagenomic analysis results, microbial community identification detected two clusters associated with case-control status and levels of TNF-alpha ($P < 0.05$). Patients were more likely to belong to the cluster associated with higher TNF-alpha levels. Differences in gut microbiota in patients with FEP compared to controls were not explained by diet.
Discussion: Fecal microbiota of FEP-patients differs from healthy controls in numbers and composition. Lactobacillus group bacteria are persistently elevated in FEP-patients as compared to controls and associate with severity of psychotic symptoms.

T12. Associations of neonatal markers of inflammation and risk of autism spectrum disorders

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Background: Animal models indicate that early life immune disturbances can influence neurodevelopmental outcomes relevant to autism. While prenatal exposures such as maternal infection are implicated in the etiology of autism, the role of perinatal immune exposures are less clear.
We here aimed to measure acute phase proteins in neonatal dried blood spots, as markers of neonatal inflammation, and determine associations with later risk of autism.
Methods: We performed a case-control study of 779 autism cases and 1,050 control born 1998-2000 in Sweden, with case ascertainment as of December 2011. Blood spots were collected from a central biobank. Nine acute phase proteins were measured using a magnetic bead-based multiplex panel: α-2 microglobulin, C-reactive protein, haptoglobulin, serum amyloid P, procalcitonin, ferritin, tissue plasminogen activator, fibrinogen, and serum amyloid A. We examined logistic regression models of the inflammatory markers adjusted for total protein content, sex of child, maternal age, and birth year. Inflammatory markers were individually examined, as well as combined into an inflammation index score based on ridge regression coefficients.
Results: All acute phase proteins were moderately to highly correlated, ranging from Spearman correlations of 0.31 (fibrinogen and C-reactive protein) to 0.79 (ferritin and α-2 microglobulin). Higher levels of 6 of the 9 acute phase proteins were individually associated with increased risk of autism. Per doubling of acute phase protein concentration, adjusted individual odds ratios ranged from 1.05, 95% CI: 0.94-1.17 (procalcitonin) to 1.15, 95% CI: 1.03-1.28 (tissue plasminogen activator). A 1SD increase in the inflammation index score was associated with a 19% increase in odds of autism, OR: 1.19, 95% CI 1.07-1.33.
Discussion: Because acute phase proteins are not thought to cross the placenta, the results suggest that the perinatal innate immune system may influence later risk of autism.

T13. Episodic memory impairments are associated with functional alterations within the memory network in schizophrenia

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Background: Schizophrenia (SZ) is a severe mental disease that is associated various with cognitive deficits. For instance, episodic memory deficits are commonly found in- and are therefore characteristic for schizophrenia. In this study, we used a face-name-association task in order to elucidate the biological underpinnings of episodic memory function in SZ.
Methods: 32 healthy subjects, 34 SZ patients and 30 first-degree relatives underwent T2- weighted fMRI assessments on a 3D Tesla Siemens Magnetom Scanner while a face-name-association task was presented. An anatomical t1 weighted scan was acquired using the 3D-MDEFT sequence. The groups were matched for age, gender and years of education. In order to evaluate cognitive performance we tested participants on the multiple-choise-word comprehension test, a test for verbal intelligence, and the MATRICS Consensus Cognitive Battery which considers seven cognitive domains. Additionally, we assessed current psychopathology in patients using the PANSS.
The functional pattern of the three groups were analyzed in a statistical group comparisons. Additionally, we performed correlation analysis between individual psychopathology, accuracy and reaction time of the face-name association task and the beta scores of the functional brain pattern.
Results: SZ patients showed a significantly lower response accuracy and a significant increase of reaction time during the retrieval of Face-Name-Pairs compared to controls. We also observed slightly lower accuracy in relatives compared with controls. However, this contrast did not reach statistical significance. During retrieval, schizophrenia patients displayed significant altered neuronal activation patterns within the episodic memory network when compared with functional activation in the control group. The relatives' functional activation pattern during retrieval was comparable to that of the patient group, indicating altered functional response during retrieval of face-name pairs. Impaired performance in various cognitive domains, predominantly in the memory, were significantly associated with altered functional activation within the memory network. However, individual psychopathology did not correlate to the neuronal activation during the encoding or retrieval of face-name pairs.
Discussion: Both the accuracy of memory performance as well as the functional activation pattern during retrieval revealed alterations in SZ patients, and to a lesser degree, in relatives of schizophrenia patients. The results are subsequently meant to be integrated in a comprehensive model of memory function that is of interest for the treatment of cognitive symptoms in SZ, as persistent cognitive impairment may hamper full rehabilitation.

T14. Corpus callosum integrity disruption in treatment resistant schizophrenia

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Background: Patients with schizophrenia (SCZ) are classified as treatment- resistant schizophrenia (TRS) when they fail to respond

to at least two antipsychotic drugs trial with adequate dose and length. Despite recent advances in the development of new antipsychotic medications, up to 20-30% of SCZ patients still report disabling treatment-resistant symptoms. TRS patients may constitute a specific neurobiological profile due its pharmacological distinct features. In general, neuroimage studies report more severe abnormalities in TRS patients compared to non treatment-resistant schizophrenia (Non-TRS). The aim of this study was to evaluating white matter fiber tracts interconnecting brain regions between Non-TRS and TRS patients.
Methods: Diffusion MRI data were obtained on 44 TRS patients and 58 Non-TRS patients, collected on a Siemens 1.5T MRI scanner. Whole-brain analysis of fractional anisotropy (FA) was performed using tract-based spatial statistics (TBSS); TFCE (Threshold-Free Cluster Enhancement) was applied to find clusters, significance level was set at p less than 0.01. To investigate the potential confounding effect of age and gender on FA, we performed analyses investigating their effect, and found no significant correlation.
Results: No age, gender or duration of illness differences were observed between TRS and Non-TRS patients, respectively (35,09 y ±8,75 vs 37,52y ±11,52)(40M/18F vs 28M/16F) (14,27y±6,37 vs 13,59y±8,77). There was a significant difference on age of onset between groups (20,89y±6,11y vs 23,97y±6,75y). A significant reduction in FA values was observed in several white matter tracts in TRS, mainly at the genu, body, and splenium of the corpus callosum (CC).
Discussion: This is the first study to compare white-matter integrity between TRS and Non-TRS patients. A previous study reported similar findings comparing TRS patients and healthy controls. Further studies will be required to replicate these results and to explore the significance of white matter changes elsewhere in the brain in order to determine whether these changes occur before definition of TRS or are consequence of disease progression related to clozapine exposure.

T15. Post-mortem evidence for increased microglia activity in schizophrenia

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Background: Although the precise pathogenesis of schizophrenia is unknown, genetic, biomarker and imaging studies suggest involvement of the immune system. It remains unsure whether the immune system is involved in the pathophysiology of all patients or just in a subgroup.
Methods: In this study we analyzed evidence from studies assessing immune-factors in post-mortem brains of schizophrenia patients and healthy controls. Thirty-nine studies were included, reporting on 665 patients and 628 controls. We divided these studies into those pertaining to cells and those assessing molecular parameters and meta-analyses were performed on both categories.
Results: Our pooled estimate on cellular level showed a significant increase in microglia ($P=0.0014$) in the brains of schizophrenia patients compared to controls. Meta-regression on brain regions demonstrated this increase was most pronounced in the temporal cortex. Numbers of macroglia (astrocytes or oligodendrocytes) did not differ significantly. There was substantial heterogeneity of molecular parameters, therefore this category was divided into pro- and anti-inflammatory according to their association with increased or decreased activity of the immune system. A significant increase in the overall protein expression of the pro-inflammatory molecular components was observed.
Discussion: The significant increase in microglia density in postmortem brains of schizophrenia patients together with the increase in pro-inflammatory molecular markers observed in our meta-analysis strengthens the hypothesis that neuro-inflammation plays a role in the pathogenesis. A focus on this component of the pathogenesis may open up new strategies for effective prevention and treatment, for instance with immune-modulating drugs, stress or sleep modulation, exercise, food supplements or probiotics.

T16. A systematic review on the neural correlates of apathy within multiple patient populations, including schizophrenia

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Background: Apathy is a debilitating symptom present in many neuropsychiatric, neurodegenerative, and neurological disorders (Caeiro *et al.*, 2013; Theleritis *et al.*, 2014; van Reekum *et al.*, 2005). Apathy is commonly defined as a syndrome of diminished motivation that is persistent over time and which comprises a loss of goal-directed behavior, goal-directed and cognitive actions, and loss of expression of emotions (Marin, 2009). In schizophrenia, apathy is one of the core negative symptoms and the strongest predictor of poor cognitive, functional and occupational outcome, reduced medication compliance, increased caregiver burden, and diminished quality of life (Chase *et al.*, 2011; Clark *et al.*, 2011). Despite consistency in the diagnosis and phenomenology of apathy over various patient populations, the underlying neurobiology is unclear. The aim of this review is to provide insights into potential shared and unique neural correlates of apathy within separate patient groups.
Methods: Current neuroimaging literature (i.e. MRI, PET, SPECT and EEG research) on apathy in various patients populations (i.e. neurodegenerative, acquired brain injury, and psychiatric disorders) was gathered and reviewed. PubMed and Web of Knowledge databases were searched and a total of 99 articles, published between June 1990 and June 2014, were included. To visualize the results related to gray matter abnormalities, we constructed brain maps representing a selection of the imaging findings of the included articles in this review.
Results: Results suggest that structural abnormalities within fronto-striatal circuits are most consistently associated with apathy across the different pathological conditions, primarily involving mediodorsal prefrontal regions, the anterior cingulate cortex, and the mediodorsal basal ganglia. Of note, abnormalities within the inferior parietal cortex, a region previously not included in neuroanatomical models of apathy, was also found to be consistently associated with apathy. Furthermore, within neurodegenerative disorders and patients with acquired brain injury temporal regions were additionally associated with apathy. Results from functional studies suggest a disruption in reward anticipation and processing (measured with reward-related paradigms), and also report abnormalities within the fronto-striatal circuit. Of note, most of these functional studies were performed in schizophrenia patients.
Discussion: Our review suggests that the structural and functional neuroanatomy of apathy may be similar across different patient groups. However, because of a rather selective use of either structural or functional neuroimaging methods and apathy measures within each patient group, a distinctive pathophysiology for apathy in different patient groups cannot be ruled out. The implication of a range of brain regions suggest that different routes towards apathy are possible, and that different population specific pathologies are associated with different types of apathy, as previously hypothesized by Levy & Dubois (2006). In order to increase our understanding of the etiology of apathy, we recommend a more diverse use of neuroimaging methods and a more detailed assessment on apathy across different pathology classes.

T17. Cognition and psychopathology in first episode of psychosis: are they related to inflammation?

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Background: Cognitive deficits are present from the onset of psychosis and are considered a core feature of the disorder. Increasing evidence

suggests that cognitive function is associated with inflammatory processes. This study evaluated the association between cognition and inflammatory biomarkers in first episode of psychosis (FEP), in order to identify cognitive phenotypes from inflammatory expression profiles.
Methods: Case-control study of 92 FEP and 80 matched controls. Neurocognitive assessment, including verbal ability, sustained attention, verbal memory, working memory and executive function, was performed. The expression of pro- and anti-inflammatory mediators of a main inflammatory pathway related to stress was measured.
Results: FEP patients performed worse in all cognitive domains compared to controls and had higher expression of pro-inflammatory levels and lower expression of anti-inflammatory ones. In the FEP group, cognition and psychopathology were associated with inflammation. Hierarchical regression analysis showed that association between the anti-inflammatory prostaglandin 15d-PGJ2 and sustained attention on one hand, and COX-2 expression and executive function on the other, were statistically significant.
Discussion: 15d-PGJ2 plasma levels and COX-2 expression may be useful as biomarkers of cognition in FEP and would allow the stratification of patients based on these measures. The identification of subgroup of patients could be useful to guide treatment programs by providing tools to select a personalized treatment approach and would facilitate clinicians to monitor the course of cognitive impairment and therapeutic response. Determination of the inhibitory protein of the inflammatory transcription factor NFκB (IκBα) could be useful in early phases for assessing clinical severity.

T18. Response to clozapine treatment and neurotrophic factors level among schizophrenia patients

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Background: Clozapine is the only effective therapy for about 30% of schizophrenia patients otherwise refractory to anti-psychotics. However, not only it is associated with numerous side effects, some could be fatal, there is a substantial portion of this population who will not respond to clozapine. Therefore, there is an unmet need to find biomarkers for successful clozapine therapy. Neurotrophins, such as Brain Derived Neurotrophic Factor (BDNF), which are regulated by monoamines, including serotonin, are implicated in many psychiatric disorders. It was previously shown that serum BDNF levels tend to be low in schizophrenia patients in relation to healthy controls and that there might be an association between clozapine daily dose and the level of serum BDNF.
Methods: Blood samples of 86 chronic clozapine-treated schizophrenia patients were analyzed for serum neurotrophins in a cross-sectional design. Serum BDNF, Vascular Endothelial Growth Factor (VEGF), Neurotrophic Growth Factor (NGF) and Glial Derived Neurotrophic Factor (GDNF) were determined using standard ELISA kits. For each patient clozapine clinical responsiveness was determined using PANSS and other clinical measures (both longitudinal from history records and current state).
Results: Our sample consisted of 49 (57%) responders (67.3% males, mean age 43.6 ± 10.4 years) and 37 (43%) non-responders (73% males, mean age 43.6 ± 10.7 years). There was a significant difference between groups on total-PANSS (53.7 ± 13.7 vs. 85.2 ± 13.3, $P < 0.0001$, respectively). Responders had higher mean BDNF level than non-responders (2066 ± 814.4 pgr vs. 1668 ± 820.7 pgr, $P < 0.05$. respectively). There was no significant difference between responders and non-responders in mean VEGF, NGF and GDNF. VEGF was, however, significantly correlated with age ($r = 0.23$, $P < 0.05$). There was no significant correlation between the other neurotropins and gender, age, clozapine daily dose or PANSS
Discussion: Our findings suggest association between serum BDNF and response to clozapine among schizophrenia patients. Since BDNF readily crossed the blood-brain barrier, the serum levels may reflect brain levels, therefore suggesting BDNF involvement in clozapine mechanism of action. Moreover, this might imply that patients with higher levels of BDNF tend to response to clozapine, however this should be tested in a prospective longitudinal design and not cross-sectional as in our study. Based on these findings, we believe that there is a need to expand the search for other domains of clozapine activity as potential biomarkers for response. Eventually we believe it will enable us to construct a combined predictive model for clozapine response.

T19. Impairments in pre-attentive auditory processing and the cortical thickness of its structural correlates in schizophrenia

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Background: The automatic auditory change detection response observed through the mismatch negativity (MMN) component of event-related potentials has been methodically studied in schizophrenia. MMN amplitude attenuation is a consistent finding in this population, and sustains interest of researchers with its potential in predicting conversion and reflecting disease progression after onset. Its generators are said to be localized in temporal, contributing to auditory perception and discrimination, and frontal, attention-switching, cortices. Studies of brain structure in schizophrenia have reported abnormalities in several areas, including those that are known as the generators of MMN. However, the potential relationship between MMN and the characteristics of related brain areas is unclear and warrant further exploration.
Methods: We conducted a magnetoencephalography study of MMN in 16 schizophrenic patients and 18 healthy control subjects. Through source reconstruction, we extracted whole-brain current source density (CSD) strengths using minimum norm estimation, and focused on areas previously reported as potential generators of MMN. We also went on to examine structural MRI using Freesurfer for surface-based cortical analysis of thickness and vertex-based GLM for group comparisons.
Results: Through extracting CSD values from MMN-relevant areas, we found significantly decreased CSD strengths of both temporal and frontal areas in patients compared to healthy subjects. Preliminary data will be presented on cortical thickness, as well as that with regard to CSD values in the two groups.
Discussion: The results will be discussed in terms of potential neuroanatomical underpinnings of MMN and how it may provide further insight on the nature of MMN deficits consistently observed in schizophrenia.

T20. Glutamate-related aminoacids before and after 10 weeks of antipsychotic treatment in drug naïve first-episode psychosis

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Background: The dysfunctions in glutamatergic neurotransmission and glutamate-related amino acids have been investigated in the pathophysiology of schizophrenia. Glutamine, glutamic acid, asparagine, proline and hydroxyproline are associated with glutamate metabolism and serine can be served as a neuromodulator by coactivating NMDA receptors. The aim of this study is to indicate the relationship between plasma glutamate-related amino acids levels and the severity of psychotic symptoms and treatment response in drug naïve first episode psychotic patients before and after 10 weeks and 18-24 months followed-up periods.
Methods: Drug naïve first episode psychotic patients ($n = 41$) were recruited to the study and followed up for 10 weeks. The blood samples were obtained before initiating the treatment and at the end of 10 weeks treatment. LC/MS/MS method was used to be able to measure plasma levels of these biological variables. To evaluate the psychotic symptoms, SANS, SAPS and BPRS inventories were applied before and after 10 weeks treatment period. A decrease in BPRS score more than 40% was used to indicate treatment response. Healthy volunteers ($n = 30$) matched for age, sex and education levels were used as the control group. A long term follow-up was performed 36 of the patients by using the global assessment of functioning (GAF) score after 18-24 months from the acute episode.

Results: The plasma serine, asparagine, glutamine, glutamic acid, proline and hydroxyproline levels were significantly higher compared to healthy controls in the first-episode psychotic patients ($P < 0.0001$). After the treatment, plasma glutamic acid, proline and hydroxyproline levels were significantly increased ($P < 0.05$) while the asparagine level was decreased with the treatment ($P < 0.05$). The serine and glutamine levels remained similar ($P > 0.05$). The initial plasma glutamine levels were negatively correlated with the initial SAPS score (r = -0.45, $P < 0.01$) and the BPRS score evaluated at the end of 10 weeks (r = -0.36, $P < 0.05$). The initial plasma proline levels were negatively correlated with the SAPS score not only before the treatment but also at the end of the 10-week antipsychotic treatment (r = -0.51 and r = -0.39, respectively; $P < 0.05$). The initial plasma proline and hydroxyproline levels were both negatively correlated with the initial BPRS score (r = -0.37 and r = -0.33, $P < 0.05$). Moreover the serine and asparagine levels measured at 10th week were significantly correlated with the global assessment of functioning (GAF) scores obtained during the follow-up after 18-24 months (r = 0.36 and 0.38, respectively, $P < 0.05$). A linear regression analysis revealed that the asparagine was the main predictor for GAF score (beta = 0.38, $P < 0.05$). Depending on the partial correlation coefficients 14% of the variance in GAF score can be explained by a statistically valid model [$F(1,34) = 5.68$; $P < 0.05$].
Discussion: Glutamate-related amino acids may play an important role in the pathophysiology of first episode psychosis. Their plasma levels were significantly correlated with the several symptom scales and they differentially changed with the treatment. Asparagine levels measured at the end of 10 weeks of antipsychotic treatment could be used as a predictive variable to estimate the long-term outcome.

T21. Aberrant tyrosine transport across plasma membrane - an endophenotype marker in schizophrenia

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Background: Studies of associations between biological markers, candidate genes and clinical characteristics such as symptoms and cognitive functioning may disentangle homogeneous subgroups in a heterogeneous disorder such as schizophrenia. Aberrant tyrosine transport across the cell membrane in patients with schizophrenia is a biological marker with bearing on the genetic susceptibility for schizophrenia. The aim of the present study was to investigate the occurrence of aberrant tyrosine transport across the fibroblast membrane in first-degree relatives to patients with schizophrenia to find indications of genetic transmission.
Methods: Twenty-three consecutively recruited patients with schizophrenia, both first-episode ($n = 10$) and chronic patients ($n = 13$), 23 mothers, 13 fathers and 10 controls entered the cross-sectional study. They were clinically characterized (diagnosis, PANSS, GAF, Socio-demographics, family history), underwent a neuropsychiatric investigation (WAIS-R NI) and skin biopsies were obtained for fibroblast cultivation and assessment of tyrosine transport kinetics in vitro.
Results: A high and significant correlation was found between mothers and patients for the tyrosine kinetic parameter Km ($r_{xy} = 0.504$, $P = 0.024$). The correlations between the patient and the mothers became even stronger when the analyses were confined to the 10 families with both parents included in the study ($r_{xy} = 0.741$, $P = 0.014$). Mothers with a low Km had worse cognitive functioning as compared to those with a high Km; a finding going in the same direction as in patients. Patients with low Km ($n = 18$) performed worse than patient with high Km ($n = 18$) and the healthy controls ($n = 51$).
Discussion: Aberrant tyrosine transport across plasma membrane may offer a biological marker that delineates a subgroup of patients with a heritable form of schizophrenia. A plausible mechanism is maternal inheritance for a subgroup of patients with low cognitive functioning.

T22. Structural brain correlates of stress reactivity in the at-risk mental state

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Background: Stress is thought to be a risk factor for psychosis, but the psychological and biological mechanisms underlying this association remain unclear. One psychological mechanism that is thought to be relevant is stress reactivity, characterised by intense emotional reactions and psychotic-like experiences in response to routine daily hassles and minor stressful experiences. This study investigated associations between stress reactivity and the volume of stress-related brain structures in people at clinical high risk for psychosis. It was hypothesized that the association between minor stressors and increased negative effect, positive affect and intensity of psychotic-like experiences would be stronger in those with smaller hippocampal and amygdala volume.
Methods: The Experience Sampling Method (ESM) was used to measure minor stressful experiences (event stress, social stress and activity stress), negative and positive affect and psychotic experiences in daily life. Structural MRI data was used to calculate the volume of the hippocampus and amygdala. In initial analyses on the association between volume of stress-related brain structures and elevated reactivity to minor stressors, linear mixed models were used to account for the multilevel structure of ESM data, treating multiple observations as nested within subjects.
Results: Smaller hippocampal volume was associated with: greater positive affective and negative affective reactivity to event stress; greater psychotic reactivity to activity stress; and greater negative affective reactivity to social stress. Smaller amygdala volume was associated with: greater positive affective, negative affective and psychotic reactivity to event stress; negative affective and psychotic reactivity to activity stress; and negative affective reactivity to social stress.
Discussion: Smaller volumes of two stress-related brain structures are markers for greater affective and psychotic reactivity to different forms of stress in people at clinical high risk for psychosis.

T23. Low serum nogo-a, UCH-l1 and α-synuclein levels in patients with schizophrenia compared to healthy controls

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Background: Determining whether schizophrenia is a neurodegenerative illness with progressive structural changes in the brain after debut of the illness, or a neurodevelopmental disorder starting in early life, is of significant importance for understanding the pathophysiology of the illness and its treatments. Therefore, in this study we aimed to show the relation of neuromodulatory proteins with schizophrenia, and compared serum Nogo-A, UCH-L1 and α-synuclein levels of schizophrenia patients with healthy controls.
Methods: This study was performed in Psychotic Disorders Unit of Istanbul University, Cerrahpaşa Faculty of Medicine, department of psychiatry. 44 Patients with schizophrenia who is followed by psychotic disorders unit, and 40 healthy control was included in this study. Socio-demographic form and PANSS was applied to patients, and sociodemographic form was applied to both groups. Fasting bloods were collected and Nogo-A, UCH-L1 and α-synuclein levels were measured by ELISA method.
Results: In study group, mean age onset of psychosis was 22,8 (±5,4), and mean number of hospitalization was 2,95 (±1,3). Serum Nogo-A, UCH-L1 and α-synuclein levels of the patients with schizophrenia were significantly lower than healthy controls.
Discussion: Serum levels of Nogo-A, UCH-L1 and α-synuclein in patients with schizophrenia was lower than healthy controls. Our study results supported the neurodevelopmental and neurodegenerative models for ethiopathogenesis of schizophrenia. As our

knowledge there is no study in the literature measuring serum levels of these molecules in patients with schizophrenia, therefore these preliminary study findings should be replicated by new researches.

T24. Mismatch negativity: alterations in nonclinical adults from the general population who report subclinical psychotic symptoms

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Background: Deficits of mismatch negativity (MMN) in schizophrenia and individuals at risk for psychosis have been replicated many times. Several studies have also demonstrated the occurrence of subclinical psychotic symptoms within the general population. However, none has yet investigated MMN in individuals from the general population who report subclinical psychotic symptoms.
Methods: The MMN to duration-, frequency-, and intensity deviants was recorded in 217 nonclinical individuals classified into a control group ($n = 72$) and three subclinical groups: paranoid ($n = 44$), psychotic ($n = 51$), and mixed paranoid-psychotic ($n = 50$). Amplitudes of MMN at frontocentral electrodes were referenced to average. Based on a three-source model of MMN generation, we conducted an MMN source analysis and compared the amplitudes of surface electrodes and sources among groups.
Results: Significant differences in MMN generation among the four groups were revealed at the frontal source for duration-deviant stimuli ($P = 0.01$). We also detected a trend-level difference ($P = 0.05$) in MMN activity among those groups for frequency deviants at the frontal source.
Discussion: Individuals from the general population who report subclinical psychotic symptoms are a heterogeneous group. However, alterations already exist in their frontal MMN activity. This increased activity might be an indicator of more sensitive perception regarding changes in the environment for individuals with subclinical psychotic symptoms.

T25. Clinical and cognitive performance and the RS53576 SNP of oxitocine receptor gene (OXTR) in recent onset psychosis and at risk mental state (ARMS) subjects

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Background: There is an increasing interest in investigating the role of the central oxytocinergic system in the expression of psychotic disorders. In that sense, some studies have indicated a relationship between genetic variations in Oxitocine Receptor Gene (OXTR) and the risk of schizophrenia. OXTR SNP rs53576 has been shown as particularly promising candidate. However, inconclusive results in studies investigating the association between SNP rs53576 and clinical features in schizophrenia warrants further research in this area.
We aimed to investigate the relationship between rs53576 SNP and clinical and cognitive characteristics in early psychosis and At Risk Mental State (ARMS) subjects
Methods: One-hundred and nine participants (4.9% of females and mean age of 23.4 (5.6) years) were recruited from the outpatient Early Intervention Psychosis team in Reus, Spain. Seventy-six presented their first-episode of psychosis in the last two years and thirty-three fulfilled ARMS criteria assessed by CAARMS.
The MATRICS Consensus Cognitive Battery (MCCB) which evaluate 7 separable cognitive domains (Speed of Processing, Attention /Vigilance, Working Memory, Verbal Learning, Visual learning and Social Cognition domains) and an overall composite was administered to all participants. Symptom severity in the recent onset psychosis group was assessed by PANSS consensus five- factor model (positive, negative, disorganized, excited and depressed factors) Potential differences in psychopathological and cognitive domains between A-allele carriers (AG and AA) and homozygote GG -carriers of the rs53576 SNP of OXTR gene were evaluated by t- tests or U-Mann-Whitney tests when appropriate. Multivariate analysis of covariance (MANCOVA) was performed to determine the effects of rs53576 genotypes as factor, covariating for gender and the significant clinical domains found in the univariate analysis as dependent variables.
Results: Recent onset psychotic subjects presented worse cognitive performance in speed processing domain ($t = -3.65$; $p < 000$), solving problem domain ($t = -2.88$; $p = .005$) and overall composite ($t = -2.04$; $P = .044$) of the MCCB corrected by age and gender. No statistically significant differences were found in any of the 7 cognitive domains of the MCCB between A-allele carriers and GG carriers in both recent onset psychosis and ARMS groups. However, within the psychosis group, A-allele carriers were more likely to present greater scores in the positive ($Z = -2.38$; $P = .017$) and depressive ($Z = -2.06$; $P = .03$) dimensions of the PANSS than GG-carriers. When correcting for gender in multivariate analysis, only associations between the A allele and higher positive symptoms remained significant ($\beta = 1.81$, $P = .03$)
Discussion: To our knowledge, previous OXTR genetic molecular studies included only chronic schizophrenia patients. In addition, this is the first study investigating the association of genetic variations of OXTR and cognition in ARMS subjects.
Despite negative findings regarding the association of cognitive performance and social cognition and OXTR SNP rs53576, our results however are in accordance with previous findings indicating a relationship between the A-allele in 53576 and higher rates of psychopathology, specially positive symptoms and depressive symptoms. Although the small sample size prevent us to make further conclusions, our results support the notion that specific variation in the OXTR gene might play a role in the clinical expression of patients with psychotic disorders.

T26. Dysregulated 14-3-3 family in schizophrenia

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Background: The 14-3-3 family is implicated in the regulation of several key biological processes such as cell signaling, gene transcription, metabolism, neurodevelopment and apoptosis. In humans, there are seven highly conserved members of this family expressed which are β, ε, γ, η, θ, ζ and σ. During the past two decades, this family has been found to be associated with schizophrenia by human genetic studies and postmortem gene expression studies. Linkage analysis studies identified SNPs of 14-3-3ε, 14-3-3η and 14-3-3ζ in various populations with schizophrenia and some postmortem studies reported altered mRNA expression levels of 14-3-3 family in different brain regions of patients with schizophrenia. To date, all of the studies published on the 14-3-3 family expression levels in schizophrenia were still focused on postmortem samples. Therefore, it is necessary to targetedly quantitate the 14-3-3 family expression at both transcript and translation levels in drug naïve first-episode patients with schizophrenia and to relate this family to disease status.
Methods: This study chose peripheral blood leukocytes as the clinical samples to targetedly investigate the mRNA and protein expression levels of the 14-3-3 family in drug naïve first-episode patients with schizophrenia and their matched controls by qRT-PCR and ultra performance liquid chromatography-multiple reaction monitoring mass spectrometry. PANSS ratings were completed through face-to-face interviews with trained raters. A Student's t-test was performed to determine statistically significant changes in mRNA or protein abundances. Pearson correlation analysis was performed to test the correlations between mRNA expression levels and protein expression levels and Spearman correlation analysis was performed to test the correlations between relative mRNA/protein expression and PANSS

scores. *P*-value < 0.05 was considered to be a statistically significant difference.
Results: In targeted transcriptome, 14-3-3σ exhibited a significant increase; 14-3-3β, 14-3-3ε, 14-3-3γ and 14-3-3θ were significantly decreased; 14-3-3η and 14-3-3ζ showed no notable alterations in patients with schizophrenia compared with the healthy controls, respectively. In targeted proteome, 14-3-3β, 14-3-3ε, 14-3-3γ, 14-3-3θ and 14-3-3ζ were all significantly decreased and 14-3-3η showed no alterations in patients with schizophrenia. In Pearson correlation analysis, a significant positive correlation between mRNA and protein expression levels of the 14-3-3 family in schizophrenia was found. In Spearman correlation analysis, a remarkably negative correlation between mRNA expression levels of ε, θ, ζ isoforms and positive symptoms of schizophrenia was found as well.
Discussion: We employed the targeted transcriptomics and proteomics to characterize the 14-3-3 family in schizophrenic patients and the matched controls and to relate this family to disease status. The decreased expression of the 14-3-3 family and the unique increased 14-3-3σ as well as protein expression levels positively correlated with mRNA expression levels of most 14-3-3 family members may be the characteristics of schizophrenia. Besides, selected members of this family may have effect on disease severity of schizophrenia. Albeit observing its abnormal expression at both mRNA and protein levels, it is still difficult to precisely illustrate the role of 14-3-3 family in schizophrenia. Therefore, the potential functional role of this family and its effect on schizophrenic symptoms are recommended for future explorations and larger sample cohorts are encouraged to validate the expression levels of this family.

T27. Aerobic exercise increases BDNF and predicts enhanced cognitive and global functioning in first episode schizophrenia: a UCLA pilot RCT

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Background: Cognitive deficits in schizophrenia (SZ) are viewed as having the strongest influence on everyday functioning and are a critical target for new treatment development. Physical, aerobic exercise has been shown to induce neurogenesis and synaptic plasticity, which is mediated by brain-derived neurotrophic factor (BDNF). BDNF is released from activated muscles and centrally in the brain during exercise leading to improved cognitive functioning. Thus, aerobic exercise provides a neurochemical boost that, when combined with cognitive training, has the potential to enhance the impact of neuroplasticity-based cognitive training.
Methods: In an ongoing pilot RCT, nine patients with a recent first episode of SZ were assigned to Cognitive Training & Exercise (CT&E) and eight to Cognitive Training (CT) for a 6-month period. We used neuroplasticity-based computer programs from Posit Science (BrainHQ and SocialVille) for cognitive training. Both treatment groups participated in these cognitive training sessions at UCLA two days a week, two hours a day. To examine the hypothesized role of neurotrophin-releasing physical exercise in enhancing learning, the CT&E group also participated in an aerobic conditioning exercises for 150 minutes per week, including 45 minutes at UCLA two days a week and 30 minutes at home two days a week. Blood samples were collected from participants prior to randomization, 2 weeks after intervention onset, and 3 and 6 months after intervention onset. We chose the 2-week point to examine the role of BDNF as an early indicator of target engagement. We administered the YMCA Fitness Assessment protocol half sit-up test (the total number of properly executed repetitions (reps) in 1 minute) to operationalize muscular strength and endurance.
Results: Serum BDNF concentrations clearly and significantly increased from baseline to 6 months in CT&E (35%) relative to CT (-2.4%) (Cohen's f = 0.91). BDNF also tended to increase as early as 2 weeks to a greater extent in CT&E (17%) than CT (2.6%) (f = .21). Using data from both CT&E and CT groups we see that 2-week gains in BDNF correlated with cognitive improvement (MCCB Overall Composite) at 3 months (r = .36) and with improvement in everyday functioning (mean Global Functioning Scale scores) at 6 months (r = .51). We also examined the effect of the intervention on physical fitness outcomes. Muscular endurance showed greater improvement from baseline to 3 months in the CT&E group (+10 reps) than in the CT group (+0.14 reps) (f = .38) and from baseline to 6 months in CT&E (+13 reps) compared to CT (+0.13 reps) (f = .61). In exploratory analyses we found a positive relationship between the change in BDNF from baseline to 6 months and change in muscular strength from baseline to 6 months (r = .58).
Discussion: We have clear evidence of target engagement and indications that it starts to occur early in treatment. In addition to BDNF increasing more in CT&E than CT, as hypothesized, we find correlations between early BDNF gain and later cognitive and functional outcome improvement that are consistent with BDNF as an early target predictive of later outcomes. Aerobic exercise produces neurotrophic factors that boost synaptic plasticity and learning potential, raising the likelihood that it may increase the impact of neuroplasticity-based cognitive training. These preliminary results help to elucidate the neurobiological pathways by which a CT&E intervention impacts a critical biological target to lead to improved cognitive and everyday functioning in SZ. This pilot RCT is currently ongoing at UCLA.

T28. Correlation between BDNF serum levels and basal clinical characteristics in first episode psychosis

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Background: Brain-derived neurotrophic factor (BDNF) is the most widely distributed neurotrophin in the central nervous system and is highly expressed in the hippocampus and the prefrontal cortex, areas implicated in schizophrenia symptoms. Recent studies have found that BDNF levels were moderately reduced in schizophrenia samples, including drug naïve and medicated patients, when compared with age-matched healthy controls. They also found an accelerated decrease with age, although they observed a high heterogeneity in BDNF levels between the different studies. Furthermore, their results could not support the greater decrease in men than in women that had previously been observed. The reasons for the heterogeneity in BDNF levels between different studies could be due in part by the fact that some patients were evaluated while on antipsychotic treatment. Atypical antipsychotics may increase, whereas treatment with conventional antipsychotics may decrease, peripheral BDNF levels. Moreover, they did not take into account illness characteristics, such as illness stage. Therefore, the aim of the present study is identify which factors may affect BDNF levels heterogeneity. We will study the relationship between clinical characteristic at baseline and BDNF serum levels at baseline in a sample of drug - naive first episode psychosis.
Methods: 45 drug – naive first episode psychosis patients were consecutively admitted to Hospital del Mar since January 2013 to April 2015 and entered the first episode programme of the institution. The included evaluation were sociodemographic and clinical data. Moreover we did fasting blood analysis to measure BDNF serum levels before the administration of antipsychotic treatment. We did a T student test to compare BDNF serum levels in relation to gender, cannabis use, tobacco use and diagnosis of affective psychosis. Furthermore we studied the correlation between BDNF serum levels and clinical variables at baseline using Pearson Correlation.
Results: The mean age at onset of illness was 24,71 years (ds = 5.758) and most of the subjects were male (64,3%). The mean DUP was 124,74 days and the most frequent diagnosis was Psychosis NOS (57,1%). The BDNF serum levels at baseline did not show any correlation with clinical characteristics at baseline (age of onset, tobacco use and PANSS). Moreover, we did not find any differences in BDNF serum levels at baseline in relation to gender (56,75 ± 26,17 vs 57,11 ± 36,07, t = -0,034, *P* = 0,973), tobacco use (62,05 ± 29,13 vs 50,42 ± 27,64, t = 1,284, *P* = 0,207) and cannabis use (63,46 ± 33,78 vs 50,17 ± 21,39, t = 1,486, *P* = 0,145) and affective and non – affective psychosis (54,81 ± 29,83 vs 76,04 ± 24, 92, t = -1,498, *P* = 0,144).
Discussion: In our sample of first episode psychosis, there aren't any clinical characteristic at baseline in relation to BDNF serum levels at baseline.

Although, it seems to be a tendency to have a higher BDNF levels in patients without tobacco and cannabis use, and affective psychosis. These results are in agreement with some recent studies which describe that acute cannabis use can initially increase, whereas chronic use can decrease, peripheral BDNF levels. In relation to tobacco use, it has been shown that nicotine use is associated with the alteration of BDNF levels in serum, and an association between smoking and the BDNF Val(66)Met polymorphism has also been found. But the effects of this association are still unclear. The hypothesis that FEP with affective psychosis have higher BDNF serum levels could be explained by the fact that patients with higher BDNF levels have a better prognosis, like patients with affective psychosis. However, more studies should be done to clarify the association between BDNF and clinical characteristics of schizophrenia.

T29. Platelet serotonin concentrations and depressive symptoms of schizophrenia

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Background: Depressive symptoms seem to be frequent in schizophrenia, but so far have received less attention than other symptom domains. Impaired serotonergic neurotransmission has been implicated in the pathogenesis of depression and schizophrenia. The objectives of this study were to investigate platelet serotonin concentrations in schizophrenic patients with and without depressive symptoms, as well as to investigate the association of platelet serotonin concentrations with symptoms of schizophrenia, mostly depressive symptoms.
Methods: A total of 364 patients were included in the study, 237 of which had significant depressive symptoms. Significant depressive symptoms were defined by the cut-off score of 7 or more on Calgary Depression Rating Scale (CDSS). Platelet serotonin concentrations were assessed by the enzyme-linked immunosorbent assay (ELISA).
Results: Prevalence of depression in patients with schizophrenia was 65.1%. Schizophrenic patients with depressive symptoms showed lower platelet serotonin concentrations compared to schizophrenic patients without depressive symptoms. An inverse correlation was found between platelet serotonin and depressive symptoms, with those symptoms being associated with lower platelet serotonin concentrations in patients with depressive symptoms (mean ± SD; 490.6 ± 401.2) compared to patients without depressive symptoms (mean ± SD; 660.9 ± 471.5).
Discussion: Depressive symptoms in schizophrenic patients may be associated with reduced concentrations of platelet serotonin.

T30. Is P300 an endophenotype for schizophrenia or a state marker of neurocognitive deficit? Evidence from inter-trial variability analysis

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Background: The P300 component, which reflects cognitive processes, is a candidate endophenotype for schizophrenia. However, the state-dependent property of averaged P300 amplitudes has been an obstacle for defining P300 as a definitive endophenotype. Thus, we aimed to investigate whether P300 is a genetic vulnerability marker or a state-dependent marker through inter-trial variability analysis.
Methods: Forty-five patients with schizophrenia, thirty-two subjects with genetic high risk (GHR), and fifty-two healthy control (HC) subjects participated in P300, clinical symptoms, and neurocognitive function assessments. Both conventional averaging and inter-trial variability analysis were conducted for P300 and results were compared across groups using analysis of variance. Pearson's correlation was performed to find the association between P300 inter-trial variability and measurements of current symptomatic, neurocognitive status.
Results: Average P300 amplitude at Pz was reduced in both GHR and schizophrenia groups compared with healthy control subjects. Meanwhile, P300 inter-trial variability was increased only in schizophrenia patients and was relatively preserved in subjects with GHR similar to that of HC subjects. Schizophrenia patients showed impaired performance in the measurements of executive function, attention, verbal memory, and verbal fluency. Furthermore, we found a significant relationship between neurocognitive performance results, which showed deficits in schizophrenia, and P300 inter-trial variability in schizophrenia patients.
Discussion: Increased inter-trial variability, owing to cognitive impairment, can make the averaged P300 seemingly state-dependent. From these results, we suggest that the P300 amplitude may be an endophenotype for schizophrenia, with inter-trial variability as a possible state marker for current cognitive deficits in schizophrenia.

T31. Examining the relationship between glutamate and auditory mismatch negativity (MMN) in antipsychotic-naïve/free patients with schizophrenia: preliminary findings from an (1)H-MRS-EEG study

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Background: Mismatch negativity (MMN), an event-related potential (ERP) component elicited by the occurrence of an infrequent deviant stimulus in a series of standard stimuli, has been suggested to be associated with the excitatory glutamatergic neurotransmission. Although both glutamate and MMN are considered to be of high relevance to schizophrenia pathophysiology, the relationship between them has not been evaluated in schizophrenia patients. We report preliminary findings from a study examining whether in-vivo glutamate concentration in the left temporoparietal junction (TPJ), a region implicated in the pathogenesis of auditory hallucinations, correlates with MMN amplitude in antipsychotic-naïve /antipsychotic-free patients.
Methods: *In vivo* magnetic resonance spectroscopy (MRS) at a field strength of 3T was used to acquire single-voxel (2cm × 2cm × 2cm) spectra from the left TPJ of right-handed acutely symptomatic schizophrenia patients [*N* = 12; 9 antipsychotic-naïve; age = 32.7 ± 7.4 years, 7 male, duration of untreated psychosis (DUP): 30.6 ± 36.6 months; duration of illness 4.1 ± 3.9 years; Scale for Assessment of Positive Symptoms (SAPS) total score: 24.1 ± 10.7; Scale for Assessment of Negative Symptoms (SANS) total score: 21.2 ± 20.7]. Immediately after the scan, for eight of the subjects, auditory MMN in response to duration deviants was assessed over the midline fronto-central region of the scalp (Fz, FCz, and Cz) using gold plated electrodes. LCModel was used to estimate the glutamate/creatine ratio (Glu/Cr) in subjects' spectra. The Cramer-Rao lower bound (CRLB) for glutmate and creatine was set at 20%. No subjects' data exceeded the CRLB. The signal to noise ratio (SNR) for all subjects was ≥ 25. EEG data was analyzed using Curry7, and MMN values from the lead with the strongest waveform across subjects were used for correlational analysis.
Results: Mean Glu/Cr among the subjects was 0.68 ± 0.05. Mean MMN amplitude was -3.97 ± 1.15. We found a significant positive correlation between Glu/Cr and MMN peak amplitude (r = 0.72, *P* = 0.04); higher glutamate level was associated with lower (less negative) MMN amplitude.
Discussion: To the best of our knowledge, this study reports, for the first time, the presence of an association between glutamate level and duration-MMN peak amplitude in schizophrenia patients. Our preliminary findings support the view that MMN is dependent on the glutamatergic neurotransmitter system. Given the importance of glutamate in information processing, cortical plasticity, and schizophrenia pathophysiology, our finding adds to the accumulating evidence supporting the role of MMN as a biomarker in schizophrenia.

T32. Interpersonal sensitivity, bullying and paranoid ideation among help-seeking adolescents and young adults.

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Background: The effects of a negative interpersonal experience such as bullying in childhood and adolescence can be strong and long lasting. Bullying may be associated with paranoid ideation and suspiciousness. Individuals at high risk to develop psychosis reported significantly more experiences of bullying than healthy controls together with increased paranoid ideation in later life. Not many studies focused upon the possible correlation between pre-existing personality aspects and more severe psychological consequences of bullying. Interpersonal sensitivity (IS) is a personality trait defines as an extreme sensitivity to interpersonal interactions (i.e. subjects have the constant perception of self-deficiencies in relation to others and the feeling of having a bothersome core-self that needs to be hidden from others. IS is correlated to subtle suspiciousness and persecutory ideations. Therefore, having high level of IS may be a fertile ground upon which an adverse experience, as bullying, may produce the development of paranoid thoughts.
Methods: Data were collected in six Adult (AMHS) and Child and Adolescent Mental Health Services (CAMHS) located in one of the eight Local Health Districts of Rome, Italy, i.e. the Rome H area, between January 2012 and January 2015 as part of the early detection project "Liberiamo il Futuro" (LIF). The sample consisted of 147 adolescents and young adults selected after a screening phase (Prodromal Questionnaire 92 was used as screening instrument) and evaluated with the Structured Interview for Psychosis-risk Syndromes (SIPS). All participants were specifically asked if they had experienced either psychological bullying or physical bullying and completed the Interpersonal sensitivity measure (IPSM).
Results: Of the whole sample, 30 (20%) subjects had experienced psychological bullying or physical bullying at least once in the life. Performing a multiple regression, bullying was found to be an independent predictor of subtle paranoid ideation and suspiciousness (measured with the SIPS). However, IS was also found to be an independent predictor of subtle paranoid ideation; in particular two IPSM subscales, fragile inner-self and separation anxiety, resulted significantly correlated with paranoid ideation.
Discussion: Our results confirmed that bullying is a negative interpersonal experiences associated with paranoid ideation and suspiciousness. However, being overly sensitive and having negative beliefs about the self as fragile and vulnerable to threat also lead to a tendency to attribute experiences as externally caused and, in turn, facilitate the formation and maintenance of paranoid ideation (4). In conclusion, having high level of IS may represent a predisposing factor for the developing of suspiciousness when facing a negative experience like bullying. Together with information and preventing campaigns about bullying into primary and secondary schools, assessing levels of interpersonal sensitivity and planning targeted psychotherapeutic interventions to fight potential difficulties in interpersonal relationships may be an important psychosis prevention action.

T33. Management of psychiatric symptoms in pediatric anti-nmda receptor encephalitis: case report and systematic review

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Background: Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is an autoimmune condition that causes serious psychiatric symptoms, prominently including psychosis, catatonia, and agitation. Nearly 40% of affected patients are in the pediatric age range, but few publications detail management of psychiatric symptoms for pediatric patients diagnosed with anti-NMDA receptor encephalitis. We present a systematic review of literature and an illustrative case report of a 17-year-old girl who presented with psychosis, agitation, and insomnia, and underwent treatment with olanzapine, clonazepam, and clonidine.
Methods: PUBMED was searched for all publications in the English language describing anti-NMDA encephalitis from 2007 to November 2015. Publications were included if they met all of the following criteria: 1) presented novel data, 2) reported treatment of psychiatric phenomena for one or more patients aged up to and including 18 years, and 3) full text was available. Thirty-four publications detailing 38 unique cases were included.
Results: Cases were 3 to 18 years of age and 66% female. The most commonly reported psychiatric symptoms were agitation ($n = 32$, 84%), followed by psychosis ($n = 27$, 71%), sleep disturbance ($n = 18$, 47%), catatonia ($n = 17$, 45%), mood disturbance ($n = 15$, 40%), and anxiety ($n = 7$, 18%). A total of 32 cases (84%) reported treatment with antipsychotic medications; first generation antipsychotics were used in 6 cases (16%), second generation antipsychotics were used in 15 cases (39%), a combination of first and second generation were used in 7 cases (18%), and the antipsychotic was not specified in 4 cases (11%). The most common antipsychotics used were risperidone ($n = 16$, 57%), haloperidol ($n = 10$, 36%), and olanzapine ($n = 10$, 36%). Benzodiazepines were used in 24 cases (63%), and lorazepam was most common ($n = 12$, 55%). Some utilized medications including melatonin, clonidine, trazodone, anticholinergics, fluoxetine and zolpidem. A wide range of doses was reported. Additionally, non-pharmacologic interventions targeted at psychiatric symptoms were described in 11 cases, and electroconvulsive therapy (ECT) was administered in 5 cases. Significant adverse effects occurred, with neuroleptic malignant syndrome diagnosed with high probability in 4 cases (13%), and suspected in 5 additional cases (16%). Dystonia, rigidity, tremors, and bradykinesia were also linked to medication side effects. All reported adverse events occurred coincidentally with antipsychotic administration.
Discussion: Psychiatric symptoms in pediatric cases of anti-NMDA receptor encephalitis were frequently managed with antipsychotics and benzodiazepines. Though antipsychotic medication may be necessary to control agitation and psychosis, serious side effects are concerning. Unlike in delirium resulting from other causes, benzodiazepines do not seem to be contraindicated in altered mental status secondary to anti-NMDA receptor encephalitis. ECT may also be of utility and was well-tolerated in reported cases.

T34. Predicting the next three years: testing multivariate psychosis-risk outcome algorithms in an unselected adolescent psychiatric sample

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Background: Several multivariate algorithms have been proposed for predicting psychosis among individuals at Clinical High Risk (CHR) for psychosis, as attempts to improve over current CHR criteria. These algorithms have typically been based on samples from specialized clinics, with a high base risk of transition to psychosis. In this study, we test existing models in an unselected adolescent psychiatric sample, to determine the generalizability of previous findings to clinical practice. In addition, we generate our own exploratory model.
Methods: A total of 162 new psychiatric patients aged 15-18, of whom 59 fulfilled CHR criteria, underwent an extensive baseline assessment including the SIPS and a large neurocognitive battery. Clinical status 3 years after baseline was based on diagnoses in comprehensive national hospital registers and case reports.
Previously published multivariate logistic regression algorithms for predicting transition to functional psychosis were ranked by model fit and, where appropriate, AUC. In secondary analyses, the prediction of psychiatric hospitalization in the CHR subsample was used as a proxy for determining how well the models predict deterioration of general functioning. In the corresponding exploratory analyses, all previously proposed predictors were entered in a regression analysis with a stepwise backward algorithm. All analyses were weighted to compensate for under-sampling of questionnaire screen negatives.

Results: All models performed worse than in the samples they were derived from, even when applied only to the CHR subsample. The best models avoided dichotomization of baseline variables and explicitly included the severity of positive symptoms. At best, Nagelkerke R2 reached 0.8 in the CHR subsample, and AUC reached.8 in both the whole sample and in the CHR subsample.
Discussion: In this unselected adolescent psychiatric sample, extended psychosis-risk algorithms presented an improvement in overall accuracy over current standard CHR criteria, at the expense of lower sensitivity. Keeping the full information in symptom ranges as part of the risk estimation proved beneficial, which was to be expected in a sample with greater variation than in specialized clinics. The applicability of psychosis-risk classifications to psychiatric practice appears limited, despite these advances.

T35. Schizotypy in the early- to mid-teens predicts passive suicidal ideation two years later

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Background: For many years, self-reported schizotypy has been regarded as a nonclinical state of liability for schizophrenia. Its principal utility has been as a nonclinical window on mechanisms and processes that characterise the developmental course of schizophrenia. However, evidence emerging over the past five years suggests that features of self-reported schizotypy measured in non-help-seeking children and adolescents are strongly associated with general psychological distress, negative effect, and suicidal ideation and behaviour. I sought to test whether taxometric schizotypy classification during the early to mid teenage years predicted self-reported suicide-related thinking and behaviour two years later.
*Meth*ods: In the first phase of a two-phase study, $n = 387$ high-school pupils (12 to 16 years, M = 14.7 years; 35% male) were classified as schizotypal ($n = 39$) or non-schizotypal ($n = 288$) by taxometric analysis of self-reported psychotic and psychosis-like experiences. In the second phase approximately 2 years later (age M = 16.9 years), a subset of schizotypal ($n = 16$) and non-schizotypal ($n = 31$) group members participated in a comprehensive follow-up assessment during which they reported on passive and active suicidal ideation and suicide-related behaviour.
*R*esults: Compared to the complement group, schizotypy was associated with higher odds of passive suicidal ideation (OR = 8.41, p = .011; 95% CI 1.65, 43.01) in analyses controlling for sex and Māori ethnic identity. In contrast, there was no evidence that schizotypy predicted active suicidal ideation (OR = 2.28, 95% CI 0.47, 11.16) or suicide-related behaviour (OR = 1.37, 95% CI 0.31, 6.09).
Discussion: Study findings suggest that schizotypy classification during early to mid teenage years predicts passive suicidal ideation up to two years later. In contrast, schizotypy did not predict more severe levels of suicidal ideation or behaviour over this period. Important study limitations include the rudimentary nature of the assessment of suicidality and the modest sample size.

T36. The discriminative value of the strauss and carpenter prognostic scale for prediction of clinical diagnosis in early onset psychosis

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Background: Diagnostic stability in early-onset first episode psychosis (EOP) –wherein psychotic symptoms present before 18 years of age-, is low due to differential diagnostic-related issues. Initial clinical presentation may be heterogeneous and unspecific, making it difficult to ascertain the diagnosis, with the most frequent change at this stage being to schizophrenia spectrum and to bipolar disorder (1). The Strauss and Carpenter Prognostic Scale (SCPS) is one of the most widely used questionnaires in outcome prediction research (2,3). The aim of the present study is to determine the discriminative value of the SCPS for predicting clinical diagnosis in subjects with a first episode of EOP.
Methods: A subsample of 77 EOP patients completed baseline assessments from the original CAFEPS sample (3). A total of 13 additional patients were included from an EOP inpatient psychiatry unit (4). Clinical diagnosis was determined at two years follow-up using the Spanish version of the K-SADS-PL. Premorbid adjustment and level of social and occupational functioning for the year prior to baseline assessment were determined using the SCPS. Binomial logistic regression analysis was used to predict clinical diagnoses (i.e. schizophrenia or bipolar disorder), based on premorbid adjustment and level of functioning at baseline (i.e. SCPS items). Backwards-stepwise regression analyses were conducted in order to further analyze the predictive value of SCPS items in clinical diagnosis.
Results: The logistic regression model was statistically significant ($\chi 2(20) = 60.834$, $P < 0.001$). The model explained 67.5% (Nagelkerke R2) of the variance in clinical diagnosis and correctly classified 85.6% of cases with SCPS 3A, 11B, 12 and 13 items significantly predicting diagnosis. Results of a forward stepwise regression model revealed that item 11B predicted a significant amount (14.9%) of the variance in clinical diagnosis, even when variance for all other variables in the final model was accounted for (final model summary included 5 items from SCPS –i.e. 3A, 5, 11B, 12 and13 - ($\chi 2(5) = 49.79$ $P < 0.001$)- and explained a total of 58.4% of the variance of clinical diagnosis.
Discussion: A model of 5 individual SCPS items at baseline was capable of predicting clinical diagnosis at 2 year follow up in patients with a first episode of EOP. These data demonstrate that individual SCPS items are capable of distinguishing clinical features in EOP, with potential clinical relevance to higher diagnostic accuracy at baseline. In particular, SCPS items assessing the average number of social relationships in the past year, longest period that any psychiatric symptoms persisted, presence of thought disorder, delusions, or hallucinations in the past year and presence of depression, hypomania or mania in the past year have predictive value for diagnosis of schizophrenia vs. bipolar disorder. Further research should focus on differentiating SCPS from other premorbid functioning scales in order to produce a more accurate predictive model aimed at increasing diagnostic precision at the time of the first presentation of psychotic symptoms in EOP.

T37. Baseline characteristics of children and adolescents with psychosis risk syndrome: a comparison study versus healthy controls

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Background: Last years, it has been a switch in the model to approximate the diagnosis and treatment of patients with schizophrenia spectrum disorders, focusing in the prevention and the early detection, to improve the outcome (McGorry, 2008). The concept of ultra-high risk of psychosis (Miller *et al*, 2002) or psychosis risk syndrome (PRS, Correll *et al*, 2010), have been worldwide spread. However, the application of this concept to children and adolescents is recent (for a review, Tor *et al*, submitted). Objectives: To compare the clinical and demographic characteristics and treatment of a sample of children and adolescents with PRS and healthy controls (HC).
Methods: A prospective longitudinal study in which help-seeking subjects who met PRS criteria were recruited from the Child and Adolescent Psychiatry and Psychology departments of Hospital Clinic and Hospital Sant Joan de Déu (Barcelona, Spain). Inclusion criteria: 1) Attenuated positive or negative symptoms in the previous 12 months; 2) Brief intermittent psychotic symptoms; 3) 1st or 2nd degree relative with schizophrenia or schizotypical disorder plus impairment of functioning; age:10-17 years. Exclusion criteria: IQ < 70 and a

diagnosis of neurodevelopmental disorder. The Semistructured Interview for Prodromal Syndromes and Scale of Prodromal Symptoms (SIPS/SOPS) were administered. A clinical scale battery (GAF, Young, Hamilton, LSP, SLES, etc.) was administered, including the diagnostic interview Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version (K-SADS-PL). A sample of age and gender matched HCs were also included. Exclusion criteria: 1st or 2nd degree familiar with a psychotic disorder; neurodevelopmental disorder r IQ < 70.The same assessment was performed in the HC sample.
Results: 82 PRS subjects (15.1 ± 1.8 years, range: 11-17 years; 41.7% males) and 37 HC (15.5 ± 1.5 years, range: 11-17 years; 35.1% males) were included. In the PRS sample, 78.9.5% met criterion 1 for inclusion. 46.5% had familiar history of psychotic disorder. PRS subjects had more divorced parents ($\chi2 = 13.295$, $P = 0.010$) and repeated more academic courses ($\chi2 = 12.587$, $P < 0.001$) than HC. No differences in drug use were observed, except for higher caffeine use in HC ($\chi2 = 10.670$, $P < 0.001$). All the SOPS, GAF, LSP, Hamilton and Young scores were significantly higher in PRS than in HC. Number of stressful life events and their subjective affectation were also higher in PRS subjects than in HC (t = -3,617, p«0.001; t = -4.187, $P < 0.001$).75.8% of PRS vs. none CC subjects ($\chi2 = 50.510$, $P < 0.001$) met DSM-IV criteria for a present diagnosis: mood disorder: 37.5%; OCD and other anxiety disorders: 15.7%; ADHD: 10.9%; ODD or conduct disorder: 6.3%, eating disorders: 1.6%. 58.2% of subjects met criteria for a second diagnosis. 94.7% of PRS subjects received some type of treatment vs 16.7% of HC (only psychological)($\chi2 = 65.215$, $P < 0.001$): 16.9% only psychological, 31% only pharmacological, 49.3% combined and 1.4% psychopedagogical. Regarding pharmacological treatment, 35.6% subjects took a selective serotonin reuptake inhibitor (SSRI) combined with an antipsychotic; 18.6% only antipsychotics; 13.6% only SSRI and the rest, different types of drug combinations. 67.8% of subjects took more than one drug at the same time.
Discussion: PRS subjects presented mainly attenuated positive symptoms (75% meeting a DSM-IV diagnosis), and almost half of them had family history of psychotic disorders. PRS subjects scored higher than HC in all the psychopathological scales, including stress scores. The majority of PRS subjects received some type of treatment, mainly a combination of psychological and pharmacological one, being SSRI altogether with antipsychotics the main prescribed medication.

T38. Transition to psychosis in children and adolescents at ultra high risk in Italian neuropsychiatry services: a follow-up study

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Background: Identifying subjects at risk of developing psychosis has been shown as one of the main strategies to improve outcome in psychosis. The ultra-high risk (UHR) criteria are the most widely used to diagnose individuals in a putative prodromal phase. They detect attenuated psychotic symptoms (APS), brief limited intermittent psychotic symptoms (BLIPS), genetic risk and deterioration syndrome (GRD). A fourth experimental criteria, the attenuated negative symptoms (NEG), is being studied (Fusar-Poli, 2007).
However, some aspects of the UHR approach, such as its feasibility and reliability in specific groups such as children and adolescents, is under investigated.
We describe here the follow up results of a feasibility study of the first Italian service for early diagnosis and treatment of UHR children and adolescents.
Methods: In the setting of the Neuropsychiatric unit of the Neurological National Institute C. Mondino, Pavia, Italy we used the Comprehensive Assessment of At Risk Mental State (CAARMS) to determine if help-seeking patients met one of the UHR criteria (including the experimental one "NEG") at baseline and we monitor the longitudinal outcome identifying subjects who had a transition to psychosis (DSM-IV diagnosis of any psychotic disorder).
Results: We present data from the 2 years follow-up of the feasibility study. 50 help seeking patients between 12 and 18 years old were included in our study (52% were male; mean age 15.6 y, 1.54 SD), 43 referred from the Neuropsychiatry ward, 5 from outpatient services, 2 from private practitioners. The socio-economic status was low in the majority of them (32/50; 64%). 22 of them met inclusion criteria for UHR (HR+: 4 GRD, 17 APS, 1 BLIPS), 9 of them met the NEG criteria only (HRNeg), 10 were already psychotic, and 9 were not at risk (HR-). 17 out of the 22 HR+ subjects also showed attenuated negative symptoms.
After an average follow-up of 685,82 days (292,53 SD) 6 subjects (19,35% of the total HR+ and HRNeg subgroup) developed psychosis (4 psychosis NOS, 1 schizoaffettive disorder, 1 delusional disorder). 5 of them where HR+ at baseline. 1 of them was at risk only for the experimental criteria of the negative symptoms (HRNeg). All of the patients that made a transition met the NEG inclusion criteria at baseline. None of the HR- subjects had a transition to psychosis. The mean transition time was of 280,16 days. The longest transition time was of 631 days in the subject that was at risk at baseline only for negative symptoms.
Discussion: Our results show a transition rate in adolescents lower than the one available in literature in groups of adults. This underlines the need of longer follow-up in children and adolescents. We also hypothesize that the presence of attenuated negative symptoms plays an important role in the evolution to psychosis in specific groups such as children and adolescents. Further research on bigger samples is required to better understand the role of attenuated negative symptoms as inclusion criteria in the UHR approach.

T39. Psychosocial characteristics of voice hearing in Norwegian adolescents: a population-based study

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Background: Young people that are troubled by hearing non-existent voices may be at risk for psychosis. Thus, understanding the demographic, environmental and psychological characteristics and/or risk factors for voice hearing has clinical implications. In the present study we examine the influence of central psychosocial variables on the tendency to being troubled by voices.
Methods: A population-based cohort of Norwegian adolescents attending secondary education aged 16-18 ($n = 10346$) completed a web-based questionnaire (the "ung@hordaland"-survey) on mental health including psychosocial background variables. Being troubled by voices was assessed by using an item from the extended Launay-Slade Hallucinations Scale: "I have been troubled by hearing voices in my head". Responses were given on 5-point scale. The adolescents were grouped into a not hearing voice and hearing voice group based on a score of 0-1 (0 = "certainly does not apply to me" and 1 = "possibly does not apply to me") or 3-4 (3 = "possibly applies to me" and 4 = "certainly applies to me"), respectively. Adolescents answering 2 = "unsure" were excluded from the group analysis. Previous findings have shown that 5,3% of the adolescents in this dataset are troubled by hearing voices (Kompus, Løberg, Posserud, Lundervold, 2015). 14 psychosocial variables from the web-based questionnaire were chosen based on previous studies, 7 of these were further derived by means of factor analyses to maximize validity.
Results: Levene's test revealed that all but one of the variables had unequal variances. Therefore, F-tests not assuming equal variance were used in order to test group differences. All differences were statistically significant due to the large sample size, so effect sizes were calculated (Partial Eta2). The following effect sizes emerged presented by decreasing effect size: Experience of self-value.047, Affective symptoms.035, Self-harm.028, Anxiety.027, Dysregulation of activation.027, Distractibility.021, Family alienation.019, Experience of trauma.018, Self-efficacy.014, Experience of bullying.010, Social functioning.006, Illicit drug use.004, School grades.004, and Days absent from school.002.
Discussion: Medium – to large effects sizes were seen in relation to experience of self-value and trauma, affective and anxiety symptoms, dysregulation of activation and self-harm, distractibility and family alienation, suggesting differences in relation to both markers of sub-optimal mental health and environmental risk-factors. Other variables, mainly related to school and social functioning did not differentiate the adolescents troubled by voices to the same extent. This could partly be explained by the inclusion route being via the adolescents' schools. Since these psychosocial variables are interrelated, more

sophisticated analysis is needed to further entangle the unique direct and indirect effects on voice hearing.

T40. Prevalence, clinical differences and impact of anxiety disorders on conversion to psychosis in youth at high risk of developing psychosis

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Background: Comorbid diagnoses of anxiety are found in subjects at high risk for psychosis, also called Psychosis Risk Syndrome Subjects (PRSS). Social phobia was identified as the most prevalent diagnosis in PRSS. However, little is known about the role of anxiety in the transition to psychosis. Some studies found that anxiety would predate the onset of a bipolar or psychotic disorder. Nevertheless, it is still a controversial issue. The aim of this study is to investigate the prevalence of anxiety disorders at baseline, and the association with any attenuated symptom and with later transition to psychosis
Methods: Prospective, naturalistic and multicentric study conducted in help-seeking child and adolescent population (age 10-17). Inclusion criteria: 1) Attenuated positive or negative symptoms in the previous 12 months; 2) Brief limited intermittent psychotic symptoms: 3) First or second degree relative with schizophrenia or schizotypical disorder plus impairment of functioning. Exclusion criteria: IQ < 70 and a diagnosis of neurodevelopmental disorder.
Psychopathology was assessed by The Semistructured Interview for Prodromal Syndromes and scale of Prodromal Symptoms (SIPS/SOPS) and the semi-structured interview Kiddie-Sads-PL. SPSS 19.0 package was used to analyze data performance
Results: A total of 89 PRSS (mean age 15,09 (±1,72); 58,4% females) were recruited.10 patients had been experienced a full-blown psychotic illness. The 50% of converters (mean age 15,3 (±1,75); 60% females) presented an anxiety disorder at baseline which met the DSM-IV-TR criteria (2 diagnosis of panic disorder, 1 social phobia, 2 general anxiety disorder, 3 obsessive-compulsive disorder (OCD), 1 phobia and 1 separation anxiety disorder). 20% of non converters (mean age 15,07 (±1,73); 58,2% females) were diagnosed with an anxiety disorder (1 diagnostic of panic disorder, 5 social phobia, 2 general anxiety disorder, 2 diagnosis of OCD, 3 diagnosis of phobia, 2 separation anxiety disorder, 2 non specific anxiety disorder, 1 agoraphobia).There were no age ($P = 0{,}693$) nor gender ($P = 0{,}915$) differences between converters and non-converters. The transition to psychosis was associated with high rates of anxiety disorders ($P = 0{,}037$). The diagnosis of anxiety was correlated to one attenuated negative symptom (N4 = emotional restriction ($P = 0{,}039$; $r = 0{,}227$). In patients with anxiety there was a trend to have more attenuated negative symptoms but this trend didn't show significance ($P = 0{,}069$; $r = 0{,}198$)
Discussion: High rates of anxiety have been observed in patients with schizophrenia, psychotic disorders and PRRS. Differences in psychopatology seem to be the most investigated issue. Most of the studies reported high rates of anxiety in patients with severe attenuated psychotic symptoms, more specifically with attenuated positive symptoms like suspiciouness. However, we found this association in attenuated negative symptoms and in patients who fulfilled the transition to psychosis. Although more longitudinal studies in high-risk population are needed to clarify controversial issues, treatment of anxiety would be a challenge to delay the onset and severity of psychosis.

T41. Adolescent trajectories of cognition and risk for psychosis

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Background: Impairments in multiple cognitive domains are apparent among youth who later develop schizophrenia, but it has been hypothesized that different impairments might follow distinct developmental courses from childhood into adolescence. The aim of the study was to examine developmental trajectories of cognitive growth during adolescence in youth at-risk for psychosis.
Methods: 104 participants were assessed at approximately 24-month intervals (time 1, aged 9-12 years; time 2, 11-14 years; and time 3, 13-17 years) on measures of scholastic achievement, memory, and executive function. Cognitive development between ages 9-17 years was compared between youth characterized by a triad of well-replicated developmental antecedents of schizophrenia (ASz, $N = 32$); youth with a least one affected relative with schizophrenia or schizoaffective disorder (FHx; $N = 29$); and typically developing youth (TD, $N = 45$).
Results: Longitudinal mixed models for repeated measures data indicated that, between the ages of 9-17 years, ASz and FHx groups (relative to TD youth) displayed static impairments on word reading, numerical operations, verbal working memory, visual memory and some aspects of executive functioning, but dynamically changing patterns of cognitive growth on spelling, verbal memory and verbal fluency subtests.
Discussion: The present study identified two important patterns of cognitive growth among youth at-risk for psychosis that have also been observed premorbidly among individuals with schizophrenia. The stable cognitive deficits observed in this study may represent more suitable targets for cognitive training interventions than dynamically changing patterns of cognitive growth that appear to reflect developmental plasticity and recuperation.

T42. The presence of comorbid mood disorder in psychosis risk syndrome in a child and adolescent sample has no influence in transition rates to psychosis

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Background: Psychosis Risk Syndrome (PRS) is characterized by the presence of several clinical indicators that reflect the patient vulnerability for developing a psychotic disorder. Accumulating research evidence has shown that the risk of transition to psychosis in subjects with clinical high risk (HR) criteria ranges from 18% at 6 months up to 32% by 3 years, although the percentages vary in the different studies. Moreover, 70-80% of the subjects with HR have lifetime comorbidity and 50-60% have a current comorbidity of axis I with depressive disorders being the most common.
The aim of this study is to describe and determine the prevalence of depressive disorders and their impact on psychosis transition in PRS subjects in a child and adolescent sample from a preliminary phase of a longitudinal multicenter study
Methods: Prospective longitudinal and multisite study, which evaluated the clinical, cognitive and neuroimaging results of patients with PRS compared with a control group. Inclusion criteria for PRS patients were: age between 10 and 17 years, one or more of the criteria for PRS, as assessed by the SIPS interview, no diagnosis of psychotic disorder, autism spectrum disorder, neurological disease and / or mental retardation. We evaluate the subjects with the Kiddie-Sacks Scale (K-SADS-PL), the Hamilton Depression Rating Scale (HDRS) and the Structural Interview for Prodromal Syndromes (SIPS). Clinical data were available from baseline and 12 month follow-up. Data analysis was performed by SPSS 20.0 statistic program.
Results: A total of 34 PRS subjects were included. At 12 months follow up, 10 PRS individuals had transitioned to psychosis (15.3 ± 1.75 years, range: 11.50-17.50 years; 60% females) and 24 PRS had non-transitioned (15.58 ± 1.76 years, range: 11.50-17.50 years; 62.5% females) being the rate of transition to psychosis 29%.The lifetime and baseline prevalence of mood disorder evaluated with K-SADS-PL in PRS non-transitioned was respectively 30% and 40% while in PRS transitioned was respectively 42% and 54%. We found no differences in HDRS scores between PRS non-transitioned and transitioned to psychosis ($P = 0.894$). We found positive correlations between HDRS scores and the SOPS items. In PRS transitioned subjects: P1 (Unusual Thought Content/Delusional Ideas)

($P = 0.006$; correlation 0.824), N2 (Avolition) ($P = 0.008$; correlation 0.81), D total ($P = 0.048$; correlation 0.67), D3 (Trouble With Focus and Attention) ($P = 0.05$; correlation 0.66), D4 (Personal Hygiene) ($P = 0.05$; correlation 0.66). In PRS non transitioned subjects: D4 (Personal Hygiene) ($P = 0.025$; correlation: 0.47), G3 (Motor Disturbances) ($P = 0.027$; correlation 0.45).
Discussion: Results show no significant differences in HDRS score between PRS transitioned and non-transitioned subjects. This confirms no effect of baseline or lifetime mood disorder comorbid diagnoses on transition to psychosis. However, we have found more correlations between SOPS items and HDRS score in PRS transitioned to psychosis (P1, N2, D3, D4 and D total) than in non-transitioned (D4 and G3), therefore depressive symptoms are likely to influence psychopathology and global functioning but do not affect the risk of transition to psychotic disorder.

T43. Neurodevelopmental disorders and their impact on initial treatment failure in early onset psychosis: a historical cohort study using electronic patient records

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Background: Neurodevelopmental disorders increase the risk of developing a psychotic disorder in childhood and are associated with poor clinical outcomes. However, little is known about the effect of neurodevelopmental co-morbidity on the response to antipsychotic medications. Using clinical data from a large electronic case register of child and adolescent mental health records, we sought to investigate whether initial treatment failure (iTF, defined as the initiation of a third trial of novel antipsychotic as a result of non-adherence, resistance and adverse effects to prior antipsychotic treatment) was associated with co-morbid autism spectrum disorders (ASD), attention-deficit hyperactivity disorders (ADHD) and intellectual disability (ID).
Methods: Data were obtained from a first episode psychosis cohort of 602 children (51% male), aged between 10 and 17, referred to inpatient and community based Child and Adolescent Mental Health services in South London, UK. Data for age, sex, ethnicity, adaptive function, co-morbid ICD-10 diagnoses at presentation and the number of unique antipsychotic medications prescribed in a 5 year observation period were extracted from electronic patient records using the Clinical Record Interactive Search system (CRIS). In this cohort study, we modelled the effect of co-morbid neurodevelopmental disorders on antipsychotic treatment failure over a 5-year period using Cox regression.
Results: Of the 602 children with first episode psychosis, 104 (17.3%) developed iTF within the follow up period. Of those children with iTF 9.6% ($n = 10$) had a persistently ineffective response to two consecutive trials different antipsychotics, 15.4% ($n = 16$) experienced persistently non tolerable adverse effects, 3% ($n = 3$) showed persistent non-adherence, and 78% ($n = 77$) showed a combination of these reasons. We identified a significant association between co-morbid ASD and developing iTF which persisted after controlling for potential confounders including socio-demographic factors, other co-morbid neurodevelopmental disorders (i.e ADHD, ID) and markers of disease severity (adjusted hazard ratio(aHR) 2.10; 95% CI 1.13–3.92; p = .02). We found Black ethnic group was positively associated with iTF (aHR 1.87: 95% CI 1.04–3.38; p = .04) whilst adaptive function (as measured by the CGAS) at first presentation was inversely associated (aHR 0.98; 0.96-99, $P = 0.02$); we found no significant effect of ADHD or ID on iTF.
Discussion: Children with psychosis and co-morbid ASD at first presentation are much less likely to have a straightforward response to antipsychotic medication. This suggests that psychosis within ASD may require different strategies in terms of treatment and clinical engagement than conventional approaches.

T44. Prediction of functional outcome in young patients with a recent-onset psychiatric disorder: beyond the traditional diagnostic classification system.

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Background: Poor functional outcome among patients with mental illness is not unique to psychotic disorders. Nevertheless, research on early predictors of functional outcome has primarily focused on individuals with an "at-risk mental state" (ARMS) for psychosis rather than across diagnostic groups in the early stages of psychiatric illness. We develop a multidimensional predictive model of functional outcome in young outpatients with the recent onset of psychiatric illness.
Methods: Prospective longitudinal study of consecutively screened non-psychotic outpatients (ages 17-35). Participants were interviewed with the Comprehensive Assessment of At Risk Mental States to assess ARMS status. Baseline demographic, clinical, neurocognitive, theory of mind, and neurological soft signs (NSS) measures were collected. The DRD1-rs4532 polymorphism was analyzed in a subgroup of participants. At 2-3 year follow-up, clinical and functioning data was collected. The Global Assessment of Functioning (GAF) scale was the primary outcome measure. A score higher or lower than 65 at follow-up defined the "Good" or "Poor" functional (PF) outcome subgroups, respectively. A binary logistic model was constructed to predict functional outcome in the entire sample using predictor variables generated within the following domains: demographic, clinical, ARMS, neurocognitive, theory of mind, NSS and functioning at baseline.
Results: 138 outpatients (53% male) participated at baseline then 116 agreed to clinical and functional follow-up assessment. 54.3% of patients experienced PF at follow-up. The final predictive model, with an accuracy of 79.7%, consisted of 3 variables: Attention, Avolition, and Motor-coordination; the addition of the DRD1-rs4532 polymorphism increased the accuracy to 81.9%. The model was independent of the ARMS status, the DSM diagnosis and psychotic conversion.
Discussion: Our results are the first to demonstrate that in a secondary mental health setting, a trans-diagnostic approach that takes into account specific neurocognitive, clinical, neurological, and genetic information, has the potential to identify those individuals with a common functional trajectory that is independent of diagnosis or ARMS status. Specific early therapeutic interventions that target modifiable risk factors and emphasize functional recovery in young psychiatric samples, independent of psychosis risk, is essential.

T45. Psychosis prediction in secondary mental health services. A broad, comprehensive approach to the "at risk mental state" syndrome.

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Background: Standardized criteria for detection of individuals "at risk mental state" (ARMS) for psychosis mainly rely on the expression of subsyndromal positive symptoms (SPS). SPS-based criteria may lack of specificity in detecting a real ARMS status when ARMS samples are characterized by high rates of comorbid psychiatric syndromes, such as those recruited in secondary mental health facilities.
Methods: 138 non-psychotic outpatients (aged 17-35) were recruited in secondary mental health services, with the aim of developing a predictive model of psychosis transition not relying on the SPS-based definition of psychosis risk and independent of psychiatric diagnoses.

Participants were interviewed with the Comprehensive Assessment of At Risk Mental States to assess ARMS status and followed up for up to 3 years (mean follow-up time, 2.3 years; SD = 0.9). Baseline demographic, clinical, cognitive, and Neurological Soft Signs (NSS) measures were collected. Cox regression was used to derive a risk index.
Results: The conversion rate to psychosis was 21% for the overall sample, 34% for ARMS+ and 9% for ARMS-. The final predictor model, with a positive predictive validity of 75% consisted of three variables: visuospatial/constructional deficits, sensory integration and theory of mind abnormalities, and it cut across the ARMS and DSM-IV categories.
Discussion: To the best of our knowledge this is the first study to develop a predictive model of psychosis transition not relying on the SPS-based definition of risk. The use of the proposed predictive algorithm may enable a more selective recruitment in secondary mental health settings, potentially reducing duration of untreated psychosis and improving prognostic outcomes.

T46. The BDNF VAL66MET genotype regulates prepulse inhibition of acoustic startle, an endophenotype of schizophrenia: sensitivity to glucocorticoid stress hormone

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Background: Reduced expression of Brain-Derived Neurotrophic Factor (BDNF) has been implicated in the pathophysiology of schizophrenia. The BDNF Val66Met polymorphism, which results in deficient activity-dependent secretion of BDNF, has been reported to mediate stress sensitization and clinical features of schizophrenia, although clinical studies have been inconsistent (Notaras *et al.*, Neuroscience and Biobehavioral Reviews 2015). Here we investigated whether chronic stress may be a factor that determines allele of risk within this disorder. The specific aim of the study was to investigate the effect of this polymorphism on Prepulse Inhibiton (PPI), a translational model of sensorimotor gating which is disrupted in schizophrenia.
Methods: We utilized BDNFVal66Met mice genetically modified to carry a humanized BDNF transcript expressing the Val66Met polymorphism (hBDNFVal66Met) and studied the long-term effect of chronic corticosterone (CORT) exposure in these animals as a model of history of stress. PPI was measured using automated startle chambers which delivered startle pulses and prepulse-pulse combinations and recorded the animals' startle responses. PPI was assessed at both 100msec and 30msec inter-stimulus intervals (ISI).
Results: Analysis of PPI at the commonly used 100msec ISI identified that, irrespective of CORT treatment, the hBDNFVal/Met genotype was associated with significantly reduced PPI. In contrast, PPI was not different in hBDNFMet/Met mice compared to the hBDNFVal/Val genotype. At the 30msec ISI, a significant genotype x CORT interaction reflected that CORT treatment selectively disrupted sensorimotor gating of hBDNFVal/Met heterozygote mice but not hBDNFVal/Val or hBDNFMet/Met mice. Analysis of startle reactivity revealed a significant hBDNFVal66Met genotype x CORT x sex interaction, reflecting that chronic CORT reduced startle reactivity of hBDNFVal/Val male mice by 51%. However, ANCOVA suggested that this was independent of the effect of CORT and hBDNFVal66Met genotype on PPI.
Discussion: We provide the first robust evidence of a distinct BDNF 'heterozygote disadvantage' phenotype using the sensorimotor gating endophenotype of schizophrenia, and that a history of stress hormone exposure interacts with BDNF Val66Met genotype. These results extend our previous observations of selective CORT effects on fear extinction in the hBDNFMet/Met genotype (Notaras, Hill, Gogos and van den Buuse, Molecular Psychiatry in press). Overall, our studies therefore show that effects of the BDNF Val66Met polymorphism vary by behavioural paradigm and, potentially, clinical symptom domain.

T47. ARC/ARG3.1 genetic disruption in mice causes dopamine system alterations and neurobehavioral phenotypes related to schizophrenia

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Background: Recent human genetic studies highlighted the post-synaptic Activity-regulated cytoskeleton-associated protein (Arc) complex as a convergence signal for several genes implicated in schizophrenia. However, the functional significance of Arc in schizophrenia-related neurobehavioral phenotypes and brain circuits is unknown.
Methods: We used genetically modified mice with targeted deletion of the Arc gene (Wang *et al.*, 2006). A comprehensive behavioral assessment for functions that have been studied in rodents as relevant to schizophrenia. In addition, using a combination of ex vivo molecular assessments, in vivo microdialysis and electrical stimulation coupled with in vivo two-photon imaging we investigated the effects of Arc genetic disruption on different aspects of dopaminergic system functions.
Results: We demonstrated that genetic disruption of Arc in mice produces deficits in sensorimotor gating, social, and cognitive abilities, as well as altered locomotor/amphetamine responses consistent with schizophrenia-related phenotypes. Furthermore, genetic disruption of Arc led to reduced frontal cortical dopamine release and mesocortical circuit activation concomitant with increased postsynaptic D2 expression in the striatum.
Discussion: These findings identify a previously unexpected role of Arc in the regulation of dopaminergic neurotransmission and show that genetic disruption of Arc can lead to a hypoactive mesocortical and upregulated mesostriatal D2 signaling with schizophrenia-related behavioral phenotypes. These results support the notion that Arc is a point of convergence for the pathophysiology of schizophrenia.

T48. Phase ii, double-blind, randomised, placebo-controlled study of adjunctive taurine in first-episode psychosis

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Background: Taurine is an inhibitory neuromodulatory amino-acid in the central nervous system. Taurine activates GABA- and glycine-insensitive chloride channel and inhibits the NMDA receptor. It also functions as a neuroprotective agent and has a role in neural development and neurogenesis. The aim of this study was to determine the efficacy of adjunctive taurine in improving symptomatology and cognition among patients with a DSM-IV first-episode psychotic disorder.
Methods: This was a randomised, double-blind, placebo-controlled trial (January 2007 and May 2009). Patients taking low dose antipsychotic medication were randomised to receive once-daily taurine 4 g or placebo for 12 weeks. One hundred and twenty one first-episode psychosis patients aged 18-25 years attending early intervention services in Melbourne, Australia consented to participate. The co-primary outcomes were: change in symptomatology (measured by the BPRS total) and change in cognition (measured by the MATRICS composite score) at 12 weeks. Secondary outcomes included tolerability and safety and additional clinical and functioning measures.
Results: Eighty six participants ($n = 47$ taurine; $n = 39$ placebo) were included in the final analysis. Taurine significantly improved symptomatology measured by the BPRS total score (95% CI 1.8-8.5; $P = 0.004$) and psychotic subscale (95% CI 0.1-1.5; $P = 0.026$) when compared to placebo. Additionally, improvements were observed in depression (CDSS; 95% CI 0.1-3.0; $P = .047$) and global functioning (GAF; 95% CI 0.3-8.8; $P = 0.04$) scores. There was no group difference in composite cognitive score (95% CI -1.7-1.0; $P = .582$). A significant group difference was found on one safety and tolerability item: Psychic item 2 (Asthenia/Lassitude/Increased Fatigability) of the UKU, with the taurine group showing a more favourable outcome ($P = 0.006$).

Discussion: While adjunctive taurine did not improve cognition, it appears to improve psychopathology in patients early in the course of a first-episode psychosis who are also receiving low-dose antipsychotic treatment. The use of taurine warrants further investigation in larger randomised studies, particularly early in the course of psychosis.

T49. The effect of virtual reality exposure therapy on social participation in people with a psychotic disorder: a multi-site randomized controlled trial

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Background: Many patients with a psychotic disorder live a life of limited participation in society, even if their psychotic symptoms have been treated successfully. An important factor in sustaining social isolation is that social situations reactivate experiences of social anxiety, ideas of reference and paranoid thoughts. The patient has learned to escape these situations, resulting in a short-term reduction in distress, which in turn strengthens the safety behavior and enhances avoidance. Exposure exercises may break this vicious circle. Virtual Reality Exposure Therapy (VRET) is an evidence based treatment for several anxiety disorders. It has the potential to be an affordable and accessible form of treatment to enhance social participation and wellbeing for patients with a psychotic disorder and social withdrawal.
Methods: The study design is a single blind randomized clinical trial with three-months follow-up. VRET is compared to treatment as usual (http://www.controlled-trials.com/ISRCTN12929657). The VRET.P treatment consists of sixteen treatment sessions of sixty minutes each, within an eight-week timeframe. Social participation is measured with Ecological Momentary Assessments (EMA), before and at end of treatment, and at three months follow-up. Primary outcome is objective and subjective social participation. Objective measures include the time spent in the company of other people and the type of people spent time with. Subjective social participation is measured as momentary paranoia, perceived social threat and event stress as experienced in situations with other people.
Results: We finished the inclusion period of the study. One hundred and sixteen participants were included in the study. Follow-up is completed in December 2015. We will be able to present the main results of the study in April 2016 on the conference. Preliminary case reports suggest that many patients are able to reduce their safety behavior and participate more fully in daily life after VRET.P treatment.
Discussion: VRET.P may be effective for improvement of social participation in patients with psychotic disorder.

T50. Correlation between functionality and symptom control in acute schizophrenia patients

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Background: The treatment goals for patients with schizophrenia include not only eliminating symptoms, but also maximizing quality of life and adaptive functionality.[1] PANSS (Positive and Negative Syndrome Scale) and PSP (Personal and Social Performance scale) were reliable tools for the evaluation of symptoms and functionality in the acute and stable stage of schizophrenia. In the previous studies, there was significant correlation between functionality and symptom in maintenance phase,[2,3] while few studies focused on the correlation in acute phase. We aimed to investigate the correlation between function and symptom, and explore the factors which are associated with functionality in acute phase of schizophrenia.
Methods: An 8-week, open-labelled, single-arm and multi-center study was conducted to evaluate the effects of flexible-dose paliperidone extended release (ER) tablets in treating acutely patients with schizophrenia in China. A total of 608 patients with schizophrenia were enrolled, and 602 subjects were included in the Full Analysis Set (FAS), and the PANSS total score of each patient was ≥ 70 at baseline. Subjects would be required to be hospitalized within the first 7 days after the study initiation. Follow-up visits were scheduled at Weeks 2, 4, and 8 (endpoint). PANSS, PSP, CGI-S (Clinical Global Impression - Severity Scale), treatment satisfaction, sleep quality and daytime drowsiness were assessed at every visit point. This is a post hoc analysis of the study, focused on the correlation between functionality and symptom management in acute schizophrenia patients, and the factors associated with functionality. Logistic regression analysis and Pearson correlation analysis were applied.
Results: There were 602 subjects (FAS) included in the analysis. PSP total scores increased and PANSS total scores decreased gradually during the study, PSP and PANSS total scores were negatively correlated at all visits ($P < 0.0001$).
In the 495 subjects with PANSS reduction $\geq 30\%$ at endpoint, the percentage of subjects with PSP change from baseline ≥ 10 increased gradually (from 39.19% at Week 1 to 92.12% at Week 8). In the 103 subjects with PANSS reduction $< 30\%$ at endpoint, most of them had PSP score change from baseline < 10 (from 81.55% at week 1 to 76.7% at week 8). In the subjects with PSP total scores change ≥ 10 at endpoint compared with baseline, the percentage of subjects with PANSS reduction $\geq 30\%$ increase gradually (from 38.3% at week 1 to 95% at week 2). In the 118 subjects with change in PSP total scores < 10 at endpoint compared with baseline, most of them have PANSS reduction $< 30\%$ (66.95% at endpoint). At week 1, subjects with PSP total score change ≥ 10 has higher possibility to get better symptom control in the endpoint, compare with those subjects with PSP total scores < 10 (OR = 2.85, 95%CI = 1.68-4.84). The association is more remarkable at endpoint (OR = 38.48, 95%CI = 21.84-67.49). The factors which influenced the changes of PSP total score at endpoint included disease duration, PANSS total scores at baseline and endpoint, all the PANSS subscale scores, treatment satisfaction, sleep quality and daytime drowsiness at endpoint.
Discussion: PSP total scores and PANSS total scores were significantly correlated in acute phase.
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T51. Associations of negative symptoms and psychosocial functioning in patients at risk for psychosis

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Background: Impairment of psychosocial functioning in patients with psychosis is common and related to various factors such as symptoms and neurocognition. Recent research suggests that these impairments precede the onset of frank psychosis and are already present in patients with an at risk mental state (ARMS) for psychosis. Furthermore, they seem to persist independent of later transition to psychosis and despite of preventive treatments. Identifying relevant factors that impact psychosocial functioning is crucial to a broader understanding of ARMS and the development of suitable intervention strategies. In patients with psychotic disorders, mainly negative symptoms seem to affect psychosocial functioning. Negative symptoms are also experienced by ARMS patients and have been repeatedly associated with impaired psychosocial functioning. However, recent research suggests that this may partly be due to an overlap of measures of negative symptoms and psychosocial functioning.
Aim of the present study was to assess the association between negative symptoms and psychosocial functioning, disentangling this conceptual overlap. Based on the few studies available so far, it was

hypothesized that negative symptoms predict poor psychosocial functioning in ARMS even after correction for confounding characteristics.
Methods: Data of 57 patients with ARMS for psychosis who participated in the early detection of psychosis (FEPSY) study[1] were analyzed. Measures of psychosocial functioning included the Global Assessment of Functioning (GAF) and occupational status. Negative symptoms were assessed by the Scale for the Assessment of Negative Symptoms (SANS), which includes both subscales that overlap with functioning measures (subscales with conceptual overlap; COS) and subscales that do not (conceptually distinct subscales; CDS). Hierarchical regression analyses were conducted to evaluate the distinct contribution of the different negative symptom subscales in predicting psychosocial functioning while controlling for education and neurocognition (composite score).
Results: Negative symptoms were significantly correlated with poorer psychosocial functioning. CDS contributed independently to psychosocial functioning. After controlling for education (ΔR2 = .122, p = .008) and neurocognition (ΔR2 = .229, p = .008), CDS (ΔR2 = .274, p = .030) and COS (ΔR2 = .475, p = .006) contributed independently to the prediction of psychosocial functioning. The complete model explained 40% of the variance (Adj. R2 = .400, p = .000).
Discussion: These results support the notion of negative symptoms directly affecting psychosocial functioning above the impact of neurocognition, confirming findings by previous studies. This effect seems to not only be due to construct similarities between negative symptoms and functioning, as negative symptom domains without conceptual overlap were also significant predictors of psychosocial functioning. This emphasizes the relevance and impact of negative symptoms in patients with ARMS. Thus, interventions targeting the reduction of negative symptoms could be the key to improving psychosocial functioning in these patients.
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T52. Evaluating the verbal episodic memory deficits in emerging psychosis using structural equation modeling

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Background: Neurocognitive deficits are a robust marker in patients with schizophrenic psychoses. Although many studies have focused on verbal memory in these patients, to the best of our knowledge, none have focused on the pattern of learning in at risk mental state (ARMS) for psychosis and first episode psychosis (FEP) patients so far. Previous studies on verbal episodic memory have shown that FEP patients consistently perform worse than ARMS and HC and ARMS perform intermediate to FEP and HC. The objective of this study was to model the learning curve of ARMS and FEP patients using latent growth curve modelling. An important advantage of this approach is that it allows disentangling initial recall, which is strongly determined by attentional processes, from the rate of learning (i.e. learning slope). Based on meta-analyses, we hypothesized that the sequence of performance on the CVLT will be the following: HC > ARMS > FEP and that the learning rate tends to be more impaired than initial recall in both ARMS and FEP patients.
Methods: The data analysed in this study were collected within the prospective Früherkennung von Psychosen (FePsy) study, which aims to improve the early detection of psychosis (1). Verbal episodic memory was assessed using the California Verbal Learning Test (CVLT), which is a widely used instrument to assess verbal learning strategies and processes. 99 FEP subjects were compared to 125 ARMS and 68 healthy controls (HC) using latent growth curve analysis which is a statistical technique used in the structural equation modeling (SEM) framework to estimate growth trajectories. Compared to classic regression models, SEM has the advantage of being able to take measurement error into account and to estimate unbiased relationships between latent (i.e. unobserved) variables. Within the growth curve analysis the proposed parameter initial recall corresponds to the intercept and the parameter learning rate to the slope of the growth curve. Both parameters refer to trials 1 to 5 of the CVLT.
Results: A comparison of three nested models with different shapes for the learning curve revealed that an approximately logarithmic growth curve (x2 = 50.937, df = 15, *P* = 0.000, AIC = 6413.414, CFI = 0.961, RMSEA = 0.091, TLI = 0.948, SRMR = 0.061) and a freely estimated growth curve (x2 = 33.827, df = 13, *P* = 0.001, AIC = 6398.494, CFI = 0.977, RMSEA = 0.074, TLI = 0.965, SRMR = 0.055) provided both good fit to the data. Hence, for ease of interpretation, the approximately logarithmic model was used for comparing initial recall and learning rate of ARMS and FEP patients. FEP showed significantly lower scores in initial recall (p = .013) and learning rate (*P* = 0.012) compared to ARMS and HC. Additionally, a trend wise significance for lower scores in learning rate was found for ARMS compared to HC (p = .070). When adjusting for sex FEP still showed significantly lower scores compared to ARMS and HC (initial recall: p = .015; learning rate: p = .010) whereas ARMS showed significantly lower scores than HC in learning rate (p = .048).
Discussion: This is the first study examining learning curves in ARMS, FEP and HC using structural equation modeling. In accordance with our hypothesis, results indicated a worse performance of FEP compared to ARMS and HC and a performance of ARMS intermediate to those two groups. Findings are in line with existing literature indicating that the verbal learning rate tends to be more impaired than attentional processes in both ARMS and FEP patients.
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T53. Gender differences in the symptomatology of patients at-risk for psychosis - results from the EU-GEI study

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Background: Gender differences in symptomatology have been widely reported among chronic schizophrenia patients and partly also in first episode patients. However, many studies conducted in this area so far show inconsistent results, ranging from a higher impairment in specific symptoms observed in men to no gender differences regarding symptom presentation.[1] The contradicting literature could be due to methodological inaccuracies or reflect the heterogeneity of the symptomatology. Furthermore, little is known about gender differences in patients with a so-called at-risk mental state (ARMS) for psychosis. The aim of this study was to test for potential gender differences in the baseline symptomatology of ARMS patients beyond possible effects of confounders (e.g. cannabis use).
Methods: The data analyzed in this study were collected within the multicenter European Gene-Environment Interactions (EU-GEI) study. Clinical symptoms were assessed in 342 ARMS patients (female, *n* = 151) using five observer-rated scales, namely, the expanded version of the Brief Psychiatric Rating Scale (BPRS), the Scale for the Assessment of Negative Symptoms (SANS), the Comprehensive Assessment of At-Risk Mental State (CAARMS), the Montgomery-Åsberg Depression Rating Scale (MADRS), and the Young Mania Rating Scale (YMRS).
Linear mixed effects models with a random intercept per center to account for clustering in the data were used to compare symptomatology at baseline between men and women. All *P*-values were fully corrected for multiple testing using the False Discovery Rate (FDR) procedure.
Results: There were no gender differences in demographic variables and psychiatric medication intake. However, men showed significantly higher rates of current cannabis use (*P* = 0.028) compared to women. With regard to symptomatology, when corrected for multiple testing, we found that ARMS men had significantly higher negative symptom scores (BPRS Negative Symptoms: *P* = 0.035, d = 0.418; SANS Affective Flattening: *P* = 0.035, d = 0.396; SANS Alogia: *P* = 0.035,

d = 0.499) than ARMS women. However, when *P*-values were additionally adjusted for current cannabis use, these differences were no longer significant (BPRS Negative Symptoms: $P = 0.475$; SANS Affective Flattening: $P = 0.475$; SANS Alogia: $P = 0.475$). No gender differences were found for other domains such as positive or affective symptoms.
Discussion: We did not find any gender differences in ARMS regarding symptom presentation at baseline. Unadjusted analyses indicated higher negative symptoms in men with medium effect sizes. However, a significantly higher proportion of cannabis consumers among male patients was observed. The gender differences in negative symptomatology disappeared when the data were corrected for cannabis use.
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T54. Beat victimization! A psychomotor resilience training with elements of kickboxing for individuals with a psychotic disorder: results of a feasibility study.

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Background: Individuals with a psychotic disorder are at an increased risk of becoming victim of a crime. Victimization can have a major impact on the lives of already vulnerable patients, and ultimately entails high costs for society (Choe, Teplin, & Abram, 2008). Research has revealed several factors (e.g. impaired social cognition, aggression regulation problems, assertiveness, self-stigma, self-esteem) to be associated with victimization in patients with a psychotic disorder. To address these risk factors, we developed a psychomotor resilience training with elements of kickboxing. In preparation of a multi-centre randomized controlled trial, we performed a feasibility study which aimed to (1) explore the willingness of patients to participate in an intervention including kickboxing, (2) evaluate the training protocol, 3) explore suitable outcome measures.
Methods: Twenty-four psychotic patients were recruited from the department of psychotic disorders of GGZ-Drenthe. Twenty weekly training sessions were provided by a psychomotor therapist and an expert by experience. Following every session the training protocol was evaluated by the trainers, psychologist and a martial arts expert. Victimization was determined with the crime victimization scale (IVM; Kamperman *et al.*, 2014). Social behavior was assessed by means of a Dutch Social Functioning Inventory (IOA; Dam-Baggen & Kraaimaat, 1999), aggression regulation was assessed with a Dutch Self-expression and Control scale (ZECV; van Elderen, Verkes, Arkesteijn, & Komproe, 1996). Differences pre- and post-intervention were determined by means of repeated measures analyses. After the intervention, participants were asked about subjective experiences with the training.
Results: Patients were willing to participate in the study; within six weeks 24 participants were recruited. At baseline, 58% of the participants reported that they had been victimized in the past five years. The training showed no effect on social behavior as measured with the IOA. Results reveal a marginal effect on control over internalization of aggression. After the intervention, participants had the idea that the training resulted in a decreased chance of victimization, more self-esteem, more empowerment, setting boundaries more easily and feeling safer outside.
Discussion: Patients were enthusiastic to participate in a study including an intervention with kickboxing techniques. Baseline results showed that victimization is a serious problem for these individuals. The IOA did not seem a suitable outcome measure to determine the effect on social behavior and will be replaced with another questionnaire in the RCT. The ZECV did seem a suitable outcome measure. Participants had the idea that the training had a positive effect on the risk factors of victimization. Following, we will test the efficacy of the training by means of a multicentre randomized controlled trial.

T55. Subjective experiences in psychosis early detection – factor structure of the Frankfurt complaint questionnaire

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Background: Patients suffering from schizophrenia are not only affected by positive symptoms but are also experiencing various disturbances, often already several years before the onset of frank psychosis1. Initially, these are often only subjectively experienced by patients themselves as deviations from their "normal" self, and were called basic symptoms. They can be assessed as a self-report with the Frankfurt Complaint Questionnaire (FCQ) which has been used in seven languages (German, English, French, Spanish, Italian, Japanese and Taiwanese). Although several studies have examined the factorial structure of the FCQ, results are still inconclusive. Besides the original four-factor-solution, one or two-factorial solutions have been suggested. Furthermore, all previous studies relied on exploratory factor analysis (EFA) and treated binary FCQ items as if they were continuous, which can severely bias the resulting factorial structure. The current study is the first to investigate the factorial structure of the FCQ using 1) confirmatory factor analysis (CFA), 2) categorical item methodology and 3) a combined sample of at-risk mental state (ARMS) for psychosis and first episode psychosis (FEP) patients.
Methods: The FCQ is a self-rating questionnaire whose items were derived from interviews with schizophrenia patients. It contains 98 items and has a yes/no answer scale. A sample of 96 ARMS and 73 FEP patients participating in the prospective FePsy (Früherkennung von Psychosen) study2 in Basel, Switzerland was used to explore the factorial structure of the FCQ. The following previously proposed factorial solutions were compared using CFA: 1) the 10-factorial solution by Süllwold *et al.*. 2) The EFA derived four-factorial solution of Süllwold *et al.* 3) the one factorial solution suggested by Yon et al.3, 4) the three factorial solution of Mass *et al.*, and 5) the 24 item short version of Cuesta *et al.*. All models were estimated using Bayesian methods. Models that were not too complex for the weighted least square estimator (WLSMV) (i.e. not more than 4 factors) were additionally estimated with WLSMV as it provides a larger variety of fit indices. Furthermore, we tested if any factors of the FCQ were able to predict transition to psychosis in our sample of ARMS patients using survival analysis.
Results: All tested models provided an acceptable fit to the data. The short version thereby seemed to fit best. Overall, the one factor solution proved to be the best fitting model. Predictive validities could not be found for any of the factors.
Discussion: The results of the present study suggest that the covariance between FCQ items is best explained by a single underlying latent factor. Our results using a sample of ARMS and FEP patients therefore seems to be in line with previous studies3. Compared to interviews assessing basic symptoms such as SPI-A or BSABS, predictive validities seem to be lower in this self-rating questionnaire. Therefore, future studies should compare the two methods of assessment item by item.
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T56. Plasma and serum brain derived neurotrophic factor levels and their association with neurocognition in at-risk mental state, first episode and chronic schizophrenia patients

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Background: Brain derived neurotrophic factor (BDNF) is known to be involved in numerous cognitive processes. Peripheral BDNF levels in plasma and serum are used as in-vivo correlates of cortical BDNF. Since cognitive deficits are recognized as core feature of psychotic disorders, preceding the onset of the illness (Pflueger, Gschwandtner, Stieglitz, & Riecher-Rössler, 2007), it is of utmost importance to investigate the relation between BDNF levels in emerging psychosis and their correlation with cognition to elucidate this matter. However, there are so far no studies investigating BDNF levels in individuals with an at-risk mental state (ARMS) for psychosis. The aims of the present study were hence the following: first to assess peripheral BDNF levels across different stages of potentially emerging psychosis, and second to investigate their association with cognitive performances.
Methods: Plasma and serum BDNF levels were measured and correlated with neuropsychological performance in ARMS ($n = 18$), first episode psychosis (FEP; $n = 6$), and chronic schizophrenia patients (CS; $n = 11$) within the project "Vulnerability and Resilience Factors of Schizophrenia" funded by the Swiss National Foundation. Neuropsychological domains assessed were intelligence, verbal memory, working memory, attention and executive function.
Results: Plasma ($P = .001$) and serum ($P < .001$) BDNF levels differed significantly between groups and were highest in CS, intermediate in FEP and lowest in ARMS. Across all groups, plasma BDNF and verbal learning and memory were negatively correlated ($r = -.361$; $P = .064$), while a positive correlation was found between plasma BDNF and executive functioning ($r = .356$; $P = .069$), with both correlations being at a trend level. A hierarchical step-wise multiple regression revealed that both BDNF parameters significantly predicted the outcome of the ToH task ($P = .023$; $R^2 = .433$).
Discussion: The low BDNF levels in ARMS compared to the other two groups were surprising, as based on the literature decreased levels with progression of the illness were expected. The low BDNF level in ARMS implies an important drop of this neurotrophin prior to the onset of the disorder. The associations of peripheral BDNF with neuropsychological performances preceding the onset of the disorder are so far inconsistent but could, if these findings are replicated, point towards a link of these variables. However, as this is the first study to investigate peripheral BDNF levels in ARMS and their correlation to neuropsychological performances, no firm conclusions can be drawn and more research is needed.

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T57. Long-term tolerability of aripiprazole once-monthly in patients with schizophrenia following treatment of an acute exacerbation

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Background: Aripiprazole once-monthly 400 mg (AOM 400) is a long-acting injectable antipsychotic, which is available for the treatment of schizophrenia. Aripiprazole exhibits partial agonism at the dopamine D2 receptor and serotonin 5-HT1A receptor and antagonism at the 5HT2A receptor. The efficacy of AOM 400 was demonstrated in adults experiencing an acute psychotic episode where significant improvements were shown in symptoms and functioning versus placebo in a double-blind, placebo-controlled 12-week study (NCT01663532, Kane *et al.* 2014). The present open-label safety extension study investigated the long-term tolerability of AOM 400 in patients with schizophrenia who initiated treatment following an acute episode.
Methods: This was a 26-week, multicenter, open-label, extension study (NCT01683058) in adult patients with schizophrenia who completed the lead-in study (NCT01663532) for the acute treatment of schizophrenia. Only patients completing the lead-in study with outpatient status were eligible for inclusion in the extension, and the last visit in the lead-in study served as the baseline visit for the extension. Patients from the placebo arm of the lead-in study received blinded oral aripiprazole 10-20 mg/day for 14 days after the first injection of AOM 400. To maintain blinding of the lead-in study, patients from the AOM 400 group of the lead-in received double-blind placebo tablets for the first 14 days. In the extension, patients received 6 injections with AOM 400 (dose reduction to 300 mg was permitted based on the investigator's judgment) every four weeks. Due to the open-label, single-treatment design, data from treated patients were summarized using descriptive statistics. No efficacy data were collected.
Results: Of the 74 patients who enrolled in the in the extension study, 46 had received AOM 400 and 28 had received placebo in the lead-in study. A total of 45 (60.8%) patients completed the 26-week extension, and of the 29 (39.2%) patients who discontinued the study, most were lost to follow-up ($n = 9$, 12.2%). Overall, 49/74 (66.2%) patients reported treatment-emergent adverse events (TEAEs) during the study, with the majority being mild to moderate in severity. TEAEs occurring in $\geq 5\%$ of patients were weight increased (29.7%, 22/74), akathisia (12.2%, 9/74), headache (8.1%, 6/74), weight decreased (8.1%, 6/74), and hyperlipidemia (5.4%, 4/74). The incidence of potentially clinically relevant weight gain ($\geq 7\%$ increase in body weight) at the last visit was 15.5% (11/71). Serious TEAEs and TEAEs resulting in discontinuation were reported by 6.8% (5/74) and 8.1% (6/74) of patients, respectively. The only serious TEAEs reported in $\geq 2\%$ of patients were depression and schizophrenia, each in 2.7% (2/74) of patients. There were no other clinically relevant findings regarding vital signs, injection site, laboratory values, or suicidality scales.
Discussion: Long-term treatment with AOM 400 following an acute exacerbation of schizophrenia was well tolerated with low rates of discontinuation due to adverse events or lack of efficacy. The instances of increased body weight and akathisia are consistent with the safety profile of AOM 400. For 8 of the 22 patients with TEAEs of increased weight in the extension study, the event began during the lead-in study. Note that drug-related, continuing TEAEs of the lead-in study were also counted in the extension study. Long-term treatment with AOM 400 was well tolerated in patients with schizophrenia whether treatment began during acute exacerbation of symptoms, or upon entering the extension study. No new safety signals were noted.

References:x

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T58. Results of an FDA device clearance trial for plasticity-based adaptive cognitive remediation (PACR)

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Background: Computerized cognitive remediation programs have consistently demonstrated benefit to cognitive function in people with schizophrenia in several single-site studies and a few multi-site studies. Much of this work was limited to specific interventions focused on auditory processing speed and accuracy. The current study

was designed to extend these studies with a comprehensive multimodal intervention (Plasticity-based Adaptive Cognitive Remediation, PACR) composed of auditory, visual, executive function, and social cognition exercises. A large multi-site trial was designed to assess the safety and efficacy of PACR for the treatment cognitive impairment in schizophrenia, and was of the size, methodological rigor, and duration required for regulatory clearance as a medical device by the US Food and Drug Administration (FDA).
Methods: 150 patients with DSM-IV-TR diagnosed schizophrenia from 11 sites across the United States were enrolled into the trial based upon the MATRICS guidelines for cognitive enhancement trials. Patients were stratified based upon baseline cognitive performance on the MATRICS Consensus Cognitive Battery (MCCB), and randomized to receive treatment with 130 one-hour sessions of PACR or a control condition of video games 4-5 times per week over the course of 6 months. PACR is a set of eleven computerized cognitive training exercises designed to improve the speed and accuracy of information processing and neuromodulatory function. Each module involves an adaptive procedure to ensure learning, stimulus sets designed to generalize to real-world function, and a "game" wrapper that encourages controlled engagement of neuromodulatory systems. Treatment response was measured with two co-primary outcome measures: the MCCB for cognition, and the University of California, San Diego Performance Based Skills Assessment (UPSA-2) to measure functional capacity. Each outcome measure was analyzed separately using a mixed effects longitudinal linear model with subject as a random effect and the following fixed effects: site, treatment (PACR and control), week (week 0, 13 and 26), and treatment by week interaction. The primary contrast of interest was PACR versus control at Week 26.
Results: There were no significant differences between groups on demographic or clinical factors at baseline. Patients were aged 43 +/-12 years of age, with MCCB composite scores of 29+/-13 and UPSA-2 scores of 87+/-15. Of the 75 patients randomized to each treatment group, 44 completed treatment with PACR while 58 completed treatment in the computer game condition ($P = .05$). Useful field of view, but not auditory time order judgment, used as positive controls for target engagement, demonstrated significant improvement with PACR compared to the control condition. Changes in MCCB and UPSA-2 were small, and did not differ significantly between treatment groups.
Discussion: In contrast to previous studies assessing the effect of plasticity-based computerized cognitive remediation limited to the auditory system and verbal learning, the current larger study of a more comprehensive program consisting of exercises targeting auditory, visual, executive function, and social cognition did not demonstrate significant improvement in cognitive performance measures. Possible explanations include lack of target engagement, negative interference between auditory and visual training, and overall program efficacy. Additional analyses will focus on demographic and clinical measures that distinguished responders from non-responders, the relationship between "treatment engagement" markers and treatment response, and the reasons for the increased drop-out rate in patients randomized to the PACR intervention.

T59. Long-term safety and durability of effect of aripiprazole lauroxil in a one year schizophrenia extension study

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Background: Aripiprazole lauroxil (AL; ARISTADA™, Alkermes, Inc.) a long-acting injectable (LAI) antipsychotic is approved for the treatment of schizophrenia. We report on efficacy and safety outcomes from a 1-year extension study of long-term treatment with AL.
Methods: This 1-year AL treatment extension study enrolled subjects ($n = 478$, safety population) from two sources: de novo subjects with chronic stable schizophrenia; and rollover subjects who had completed a double-blind, 12-week, placebo-controlled study. De novo subjects received monthly injections of AL 882 mg, and rollover (placebo or AL) subjects received monthly injection with either AL 441 mg or AL 882 mg depending on their assigned treatment in the preceding placebo-controlled study. Subjects who are first assigned to active AL also received daily oral aripiprazole (15 mg) for 3 weeks. The key primary and secondary objectives were to characterize the safety, and to evaluate the durability of therapeutic effect of AL during long-term treatment of subjects with stable schizophrenia.
Results: Of 478 (de novo [$n = 242$], rollover [$n = 236$]) enrolled subjects, 462 had evaluable post-baseline data. At baseline, the mean (SD) age was 39 (12) years, 58% were male, 64% were white, 19% were black, 17% were Asian, and the mean (SD) PANSS total score was 61 (14). High proportions of subjects received ≥ 9 (76%) or ≥ 13 injections (69%) of AL. Of the 110 and 368 patients enrolled in the 441 mg and 882 mg AL study arms, respectively, 32% of patients discontinued in each study arm. Drug-related adverse events were reported in 29 (26%) and 112 (30%) of subjects in the 441 and 882 mg AL arms. Treatment-emergent adverse events observed in $\geq 5\%$ of subjects were insomnia (8%), and increased weight (5%). Serious drug-related adverse events were reported only in the 882 mg arm [3 subjects ($< 1\%$)]. Overall incidence of Parkinsonism and akathisia based on the movement scale were 7% and 5%, respectively. The majority of patients (77%) gained ≤ 5 kg over 16 months, and, at any post-baseline visit, 88 subjects (18%) had a weight increase of $\geq 7\%$. Overall response ($\geq$30% decrease in PANSS total score from baseline to Day 365 or, CGI-I of 2 or 1) was achieved by 51% of subjects at endpoint. Overall, the mean (SD) change from baseline in PANSS total score at study endpoint was -8 (10) and in CGI-S was -0.4 (0.7). The mean (SD) reduction in PANSS total for the placebo to 441 mg AL subject group was -19 (15) and the placebo to 882 mg AL subjects was -12 (12).
Discussion: Treatment of subjects with schizophrenia for ≥ 1 year with AL demonstrated continued safety and additional therapeutic effect. As most safety extension studies have the limitation of selecting for responders, about half the study subjects were treated de novo. The low drop out/high retention of this study supports the high overall safety and tolerability of AL for patients with schizophrenia. Further, the low proportion with weight gain supports the beneficial metabolic profile of the treatment with AL LAI. This study supports continued reduction in symptoms with maintenance AL with over half of completers meeting response criteria.

T60. The importance of vulnerability factors in at-risk mental state of psychosis individuals

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Background: Stressors such as major life events or prevailing stress have been found to influence the onset and course of schizophrenic psychoses.[1] They are thought to exert their effects by interacting with preexisting vulnerability indicators, leading to vicious circles which in turn provoke frank psychoses.[2] Accordingly, the identification of indicators of heightened vulnerability for psychoses and relevant stressors may have important consequences to our understanding of the aetiology of these disorders. Various indicators of heightened vulnerability to psychosis and relevant stressors have been identified. However, it has scarcely been assessed prospectively to what extent these vulnerability factors are indeed more prevalent in individuals with an at-risk mental state (ARMS) for psychosis. Moreover, it remains largely unknown whether any of these contribute to the prediction of psychosis development in ARMS individuals.
Methods: In total, 28 healthy control subjects, 86 first-episode psychosis patients and 127 ARMS individuals were recruited as part of the prospective 'Früherkennung von Psychosen' (FePsy; English: early detection of psychosis) study.[3] The relative frequencies of 13 distinct vulnerability factors for psychoses were compared between healthy control subjects, psychoses patients, those individuals with an ARMS with subsequent transition to psychosis (ARMS-T; $n = 31$) and those without subsequent transition (ARMS-NT; $n = 55$). Survival analyses were conducted to determine associations between time to transition to psychosis and vulnerability factors in all 127 ARMS individuals.
Results: The vulnerability factors "difficulties during school education or vocational training" and "difficulties during employment" were more commonly present in ARMS and first-episode psychosis

individuals than in healthy controls. Moreover, ARMS and first-episode psychosis individuals more commonly reported "being single" and "having difficulties with intimate relationships". Finally, both aforementioned groups more frequently reported being burdened with specific stressful situations, including "being burdened with intense positive feelings towards others", "being burdened with noisy environments" and "problems with working under time pressure". However, there were no significant differences regarding these factors between ARMS-T and ARMS-NT. Subsequent survival analyses revealed no significant association between time to transition to psychosis and any of the included vulnerability factors.
Discussion: We confirm that a variety of vulnerability factors are frequently present in ARMS individuals and first-episode psychosis patients. However, these vulnerability factors do not appear to carry a predictive value for an onset of psychosis and may rather be linked to the presence of psychopathological symptoms in general. Future research should focus on vulnerability and protective factors in ARMS individuals in more detail and their interplay with genes to gain new insights into the pathogenetic mechanisms underlying the onset of clinical symptomatology and full-blown psychosis.

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T61. The influence of a muscarinic M1 receptor antagonist on brain choline levels in patients with a psychotic disorder and healthy controls.

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Background: Approximately 80% of patients with a psychotic disorder report cognitive impairments. These impairments are often present before the onset of psychosis and persist after other symptoms have been effectively treated and have a negative effect on functional outcome. Patients often experience these symptoms as the most disabling aspect of the disease. Research has shown that muscarinic cholinergic receptors play a major role in cognitive processes. A post-mortem study of chronic schizophrenia patients demonstrated a reduction of up to 75% in the number of muscarinic M1 receptors (Scarr *et al.*, 2009). With this study we aimed to investigate in-vivo whether there are differences in choline levels in the anterior cingulate cortex (ACC) and striatum between recent onset medication-free patients with a psychotic disorder and healthy controls subjects.
Methods: The two groups were matched for age, gender and IQ. Both the ACC and the striatum have a high density of M1 receptors. In addition, we investigated differences in cholinergic reactivity between the two groups using biperiden, a M1 receptor antagonist, as a pharmacological challenge. Baseline choline concentrations were obtained with 3Tesla Magnetic Resonance Spectroscopy (MRS, PRESS) for 9 patients (mean age 27 years, 7 males and 2 females) and 12 HCs (mean age 26 years, 8 males and 4 females) after administration of a placebo. To measure cholinergic reactivity (placebo – biperiden) we conducted a second measurement after oral administration of 4 mg biperiden. Order of the scans was counterbalanced.
Results: An independent samples t-test showed that the patients had higher baseline levels of free choline in the ACC compared to healthy controls ($P = 0.039$). Additionally, compared to the healthy control group, there was a trend for lower cholinergic reactivity in the patients ($P = 0.055$). No significant differences were found in the striatum.
Discussion: Higher baseline as well as reduced cholinergic reactivity in the ACC suggests diminished availability of M1 receptors in patients with a psychotic disorder in this brain area. These results are in line with post-mortem findings in patients with chronic schizophrenia. Possibly, reduced M1 availability is associated with cognitive impairments in psychotic patients.

T62. ALKS 3831 demonstrated equivalent antipsychotic efficacy while addressing weight gain: results from a phase 2, randomized, olanzapine-controlled study

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Background: ALKS 3831 is a combination of olanzapine (OLZ) and samidorphan, designed to address weight gain seen with OLZ treatment.
Methods: After 1 week of OLZ lead-in, subjects were randomized (1:1:1:1) to once daily OLZ+placebo or ALKS 3831 (OLZ+ 5, 10 or 20 mg samidorphan) for 12 weeks. All subjects then received ALKS 3831 during a 12-week extension phase.
Results: Change in PANSS total score (primary endpoint) with ALKS 3831 was equivalent to OLZ alone (LS-mean difference (SE):0.6 ± 0.9 (95% CI: -1.2, 2.5). ALKS 3831 treatment demonstrated significantly lower mean percent change in body weight from baseline in all study patients (FAS1, $n = 300$) vs. OLZ of 31% and, of 51% ($P < 0.05$) in the subset of subjects with observed weight gain during OLZ lead-in (FAS2, $n = 195$). Risk of $\geq 10\%$ weight gain with OLZ alone was significantly greater than with ALKS 3831 (2.7 times. 95% CI: 1.1, 6.7; $P = 0.02$) in FAS1 or in FAS2 (4.1 times. 95% CI: 1.4, 12.3; $P = 0.008$). Adverse events (frequency $\geq 5\%$) in ALKS 3831 subjects were somnolence, sedation and dizziness. Extension data demonstrated both PANSS scores and weight remained stable with ALKS 3831 treatment. Further increase in weight was blocked when subjects switched from OLZ to ALKS 3831.
Discussion: ALKS 3831 demonstrated efficacy equivalency to OLZ alone but also with consistent blockade of further OLZ-induced weight gain for up to 24 weeks. The safety profile of ALKS 3831 and OLZ were similar. These data suggest ALKS 3831 may be an important new treatment for schizophrenia.

T63. A phase 3 study to evaluate weight gain of ALKS 3831 compared to olanzapine in adults with schizophrenia

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Background: An earlier Phase 1 study of ALKS 3831 (a combination of olanzapine and samidorphan) versus olanzapine alone in healthy volunteers demonstrated less weight gain in the ALKS 3831 treatment arm after 3 weeks. A subsequent Phase 2 study demonstrated similar efficacy and safety between olanzapine and ALKS 3831 treatments and significantly less weight gain in patients treated with ALKS 3831 compared to olanzapine over a 12-week period in patients with schizophrenia. The planned 24-week study, which is a part of the ENLIGHTEN study program, is designed to confirm and further evaluate these findings.
Methods: The proposed study is a two-arm, double-blind, active comparator controlled, multi-center study (planned $N = 540$) slated to begin enrollment in 2016. Inclusion criteria include both genders between 18 and 55 years of age (inclusive), non-obese defined as a body mass index (BMI) of 18.0 to 30.0 kg/m2, a DSM-5 diagnosis of schizophrenia, who can be treated on an outpatient basis defined as: no hospitalizations for acute exacerbations of schizophrenia within 6 months before Visit 1, Positive and Negative Syndrome (PANSS) total score of 50 to 90 (inclusive) and, Clinical Global Impression of Severity (CGI-S) score of ≤ 4. Exclusion criteria include diagnosis of additional psychiatric conditions, use of prohibited or contraindicated drugs and abnormal lab results during screening. After up to a 4-week screening

period, subjects will be randomized 1:1 to either olanzapine or ALKS 3831 treatment for 24 weeks. Active ingredients in once-daily oral doses will include ALKS 3831 10/10 (10 mg olanzapine/10 mg samidorphan) or 20/10 (20 mg olanzapine/10 mg samidorphan) or olanzapine (10 or 20 mg). The samidorphan dose was selected based upon results of the Phase 2 study that demonstrated a 10 mg dose was optimal for robust efficacy and safety of ALKS 3831. Adjustment of the olanzapine dose will be allowed up to week 4, then stay fixed for the remaining 20 weeks. In addition to PANSS and CGI-S parameters, body weight, metabolic parameters (including fasting triglycerides, cholesterol, and glucose) and psychiatric symptoms will also be evaluated. Co-primary endpoints will be change in percent body weight and the proportion of subjects with ≥ 10% weight gain from baseline at Week 24. Other endpoints include the Impact of Weight on Quality of Life –Lite Questionnaire (IWQOL-Lite) total score and change from baseline in EuroQol-5D (EQ-5D). Movement disorders, pharmacokinetic, and pharmacodynamic parameters will also be measured.
Results: This is a new study.
Discussion: This is a new study.

T64. Safety, tolerability, and pharmacokinetics of single rising doses of BI 425809 given orally to healthy male volunteers: a partially randomised (within dose groups), single-blind, placebo-controlled, phase i study

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Background: BI 425809, a glycine transporter 1 (GlyT1) inhibitor, is a new chemical entity being developed for the treatment of cognitive impairment associated with schizophrenia (CIAS) and Alzheimer's disease. The objectives of this trial were to (1) examine safety and tolerability in healthy male volunteers (HV), (2) characterise the pharmacokinetic (PK) properties of BI 425809 after single dose, and (3) examine the relative bioavailability (BA) of tablet versus powder for reconstitution into oral solution (PfOS).
Methods: This trial consisted of a partially randomised (within dose group), placebo-controlled, single-blind, single rising dose (SRD) part, followed by a randomised, open-label, crossover BA part. In the SRD part, HV were randomised in a 3:1 ratio (drug:placebo) to nine dose groups of BI 425809 (0.5, 1, 2, 5, 10, 25, 50, 100, 150 mg). In the BA part, 25 mg of PfOS and tablet under fasted conditions were explored in a cross-over design. 83 HV (72 in SRD, 11 in BA) participated in the trial. The PK parameters, including Cmax and AUC, were characterised. Safety was evaluated with adverse event (AE) monitoring, clinical laboratory assessments, vital signs, ECG, physical examinations, ophthalmologic tests, and visual analogue scales (VASs) to assess psychedelic effects (B&L, Bowdle).
Results: In the SRD part, plasma PK profiles of BI 425809 were similar for all dose groups, characterised by a rapid absorption phase and at least a biphasic disposition phase. The gMean plasma values for Cmax, AUC0-tz, and AUC0-∞ ranged from 10.0-2970 nmol/L, 115-46,600 nmol·h/L, and 187- 48,500 nmol·h/L, respectively, from 0.5 to 150 mg. Linear regression analysis of the PK parameters Cmax, AUC0-tz, AUC0-∞, and Ae0-24 resulted in a slope of approximately 1, where a slope of 1 corresponds to perfect dose proportionality. Median tmax was observed within 1 h for all dose groups; the gMean t1/2 values ranged from 32.5 to 47.0 h and the gMean CL/F values ranged from 72.3 to 101 mL/min. The amount of BI 425809 excreted in urine increased with dose, but the gMean fractional renal excretion remained almost the same over all dose groups and was low (about 5%) across all doses. In the BA part, the median tmax in plasma was 0.875 h for 25 mg solution and 4 h for the 25 mg tablet under fasted condition. The adjusted gMean ratios for AUC0-tz and Cmax for tablet versus PfOS were 80.53% (90% CI: 74.00%, 87.64%) and 50.02% (90% CI: 45.15%, 55.412%), respectively. Over half of the subjects (56.6%) had at least one AE, and about a third of the subjects (39.8%) had an AE deemed by the investigator as treatment related. All AEs were of mild or moderate intensity except one severe AE (vomiting) in the highest dose group. No serious AEs were reported. There was a general trend towards dose dependency in intensity and frequency of AEs. Frequencies of subjects with AEs generally increased with dose, from 16.7% in the 0.5 mg group to 100.0% in the 150 mg group. The most frequent AE was headache, followed by fatigue, blurred vision, vertigo, dizziness, and somnolence. A dose-related response was observed on VAS of CNS effects. At high doses, several VAS scores showed relevant increases (e.g. for "feeling drowsy").
Discussion: BI 425809 showed dose-linear PK in all exposure parameters over the entire dose range. The bioavailability of BI 425809 was decreased when administered as a tablet compared with when administered as an oral solution. BI 425809 PfOS demonstrated dose-dependent increase in frequency and intensity of AEs, which were most commonly CNS-related.

T65. Safety of lurasidone in older adults with schizophrenia: a pooled analysis of short-term placebo-controlled studies

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Background: Older patients with schizophrenia may be more susceptible than younger patients to adverse events associated with antipsychotic treatment (eg, extrapyramidal symptoms [EPS], sedation, and metabolic syndrome; Jeste DV & Maglione JE. Schizophr Bull. 2013;39[5]:966-968). Lurasidone is an atypical antipsychotic agent that has demonstrated efficacy in the treatment of adult patients with schizophrenia. This pooled, post hoc analysis evaluated the safety profile of lurasidone in older adults with schizophrenia.
Methods: Individual patient data were pooled from 7 similarly designed, multiregional, randomized, double-blind, placebo-controlled, 6-week studies of fixed-dose, once-daily, oral lurasidone (18.5, 37, 74, 111, 148 mg/d) conducted in adult patients (age 18-75 years) with acute schizophrenia. This analysis examined safety assessments, including treatment-emergent adverse events, laboratory measures, and vital signs in older patients (≥55 years old) and younger patients (< 55 years old). Treatment group differences were summarized using descriptive statistics; changes from baseline to Week 6 were calculated using a last observation carried forward (LOCF) approach.
Results: This analysis included 243 patients who were ≥ 55 years old ($n = 168$ received lurasidone; $n = 75$ received placebo) and 1973 patients who were < 55 years old ($n = 1340$ received lurasidone; $n = 633$ received placebo). Mean age was 60.4 years and 59.7 years in older patients receiving lurasidone or placebo, respectively, and 37.6 years in younger patients (both treatment groups). The majority of patients were male in both the older (60%) and younger (72%) patient groups. The most common adverse events (in ≥ 5% of lurasidone-treated patients and at least twice the rate observed with patients receiving placebo) for lurasidone versus placebo were akathisia (10.1% vs 5.3%; number needed to harm [NNH] = 21) in older patients; and akathisia (13.3% vs 2.7%; NNH = 10), nausea (10.7% vs 5.5%; NNH = 20), somnolence (9.1% vs 3.8%; NNH = 19), and sedation (8.5% vs 3.6%; NNH = 21) in younger patients. In older patients, mean change in weight from baseline to Week 6 endpoint for lurasidone and placebo groups was -0.1 kg and -0.5 kg, respectively; median change from baseline was 0.0 mmol/L and -0.04 mmol/L, respectively, for total cholesterol; -0.07 mmol/L and-0.03 mmol/L, respectively, for triglycerides; and 0.17 mmol/L and -0.14 mmol/L, respectively, for glucose. In younger patients, mean change in weight from baseline to Week 6 endpoint for lurasidone and placebo groups was 0.5 kg and 0.0 kg, respectively; median change was -0.14 mmol/L and -0.18 mmol/L, respectively, for total cholesterol; -0.05 mmol/L and -0.08 mmol/L, respectively, for triglycerides; and 0.0 mg/dL and 0.06 mmol/L, respectively, for glucose.
Discussion: The safety profile of lurasidone was similar in older (≥55 years) and younger adult patients with schizophrenia. The most common adverse event observed with lurasidone in patients ≥ 55 years old was akathisia. In both older and younger patients, lurasidone was associated with minimal changes in weight, lipids, and glucose.
Sponsored by Sunovion Pharmaceuticals Inc.
ClinicalTrials.gov identifiers: NCT00044044; NCT00088634, NCT00549718, NCT00615433, NCT00711269, and NCT00790192. One study was completed prior to the requirement to register trials.

T66. Positive phase 3 clinical trial of ITI-007 for the treatment of schizophrenia: safety results from a randomized, double-blind, placebo-controlled trial

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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. Vital signs, 12-lead ECGs, clinical laboratory values, and adverse events were reported.
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 ($P = 0.022$). [Please see companion abstract/poster for more details on efficacy]. Consistent with previous studies, ITI-007 was safe and well-tolerated as evidenced by a motoric, metabolic, and cardiovascular profile similar to placebo, and no clinically significant changes in akathisia, extrapyramidal symptoms, prolactin, body weight, glucose, insulin, and lipids.
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 likely contributes to the favorable safety profile of ITI-007, with reduced risk for hyperprolactinemia, akathisia, extrapyramidal symptoms, and other motoric side effects. ITI-007 also lacks off-target pharmacological interactions that may contribute to cardiovascular and metabolic liability of other treatment options. As such, ITI-007 represents a novel approach to the treatment of schizophrenia.

T67. Yoga reduces the brain's amplitude of low-frequency fluctuations in patients with early psychosis

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Background: Physical exercise attracted increasing attention for improving neurocognitive functioning in patients with psychotic disorders. However, there has been limited understanding of the neural mechanism of these effects. This study aimed to investigate the effects of aerobic exercise and yoga on cerebral spontaneous functional fluctuations in patients with early psychosis.
Methods: A total of 140 female patients with early psychosis were recruited and 124 received the allocated intervention in a randomized controlled study of 12 weeks of yoga or aerobic exercise compared with a wait-list group. 91 participants were scanned at baseline, and 72 had completed the scans at 12 weeks. The amplitudes of low-frequency functional (ALFF) fluctuations were compared among three groups, and the correlation between ALFF, cognition and clinical symptoms were examined.
Results: The ALFF decreased in the precuneus for the yoga group, and increased in the occipital cortex for the wait-list control group. These changes were correlated to the improvements of symptoms and working memory measured in all the participants.
Discussion: It is the first study to investigate the effects of yoga and aerobic exercise on brain function in patients with early psychosis. The results help to understand the possible neurobiological underpinnings for the cognitive and clinical improvements from yoga and aerobic exercise, and shed light on the application of exercise in clinical practice as a safe and convenient add-on treatment for psychosis.

T68. Can resting-state patterns predict aberrant salience in early psychosis spectrum?

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Background: The theory of aberrant salience suggests that symptoms of psychosis arise from the incorrect assignment of salience to internal and external stimuli. Previous studies have shown that patients with recent onset psychosis (ROP) as well as patients with a clinical high risk for psychosis (CHR) exhibit aberrant salience. Fronto-striatal networks represent the neural basis of salience attribution and reward processing that is affected in psychosis and CHR patients.
The aim of this study was to use functional connectivity-based multivariate pattern analysis (MVPA) to classify good performance on a salience attribution task as measured by low implicit aberrant salience (low labS) and poor performance as measured by high implicit aberrant salience (high labS) in early psychosis spectrum (EPS) patients by applying a model generated in healthy controls (HCs).
Methods: HCs ($n = 30$), ROP ($n = 16$) and CHR ($n = 18$) patients underwent resting-state fMRI (RS-fMRI) and participated in the salience attribution test (SAT) outside the scanner as part of the PRONIA-study (Personalized Prognostic Tools for Early Psychosis Management). The two patient groups were combined into an EPS group ($n = 34$) because they showed no difference in SAT performance in previous studies. On the SAT, subjects had to perform a speeded response task while implicitly learning the relationship between cue-image categories and high or low reward contingency. labS was defined as the abnormal speeding of responses on task-irrelevant cue trials with a reward probability of 50%. Good SAT-performers (low labS) and poor SAT-performers (high labS) were identified via median split within each study group.
MVPA was used to classify good vs. poor SAT performers in HCs by applying a L1-regularized L2-loss support vector machine. The model derived from this classification was then applied to EPS data.
Results: The classifier was able to differentiate between good and poor SAT-performers in HCs with a balanced accuracy of 80.0% (sensitivity and specificity: 80.0%). The discriminative pattern included connections between orbitofrontal and striatal, orbitofrontal and insula, globus pallidus and parietal, and caudate and temporal regions. In contrast, applying this model to EPS data yielded a lower classification performance of 50.0% (sensitivity: 52.9%, specificity: 47.1%).
Discussion: The high classification performance of 80.0% balanced accuracy was driven by differences in RS connectivities underlying reward processing and salience attribution in good HC relative to poor HC SAT-performers.
The difficulties in applying the model to EPS patients could be due to altered brain functioning in EPS. Connectivities that were informative for the classification in HCs might be altered in EPS in such a way that they held no information for the classification of good vs. poor SAT-

performers. Another possible explanation could be the heterogeneity of the EPS group that contained CHR and ROP patients.
To the best of our knowledge, this is the first study using RS connectivities to predict aberrant salience in good vs. poor performance across HC and EPS individuals. The high classification accuracy when distinguishing good from poor performers based on RS data in HCs serves as a promising finding in the aberrant salience research domain and supports further investigations in EPS patients.

T69. The association between cognition and sub-domains of negative symptoms in schizophrenia

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Background: The relationship between negative symptoms and cognitive deficits in schizophrenia remains inconclusive and studies have presented conflicting results. Some studies found correlations (Addington *et al.*, 1991; Bozikas *et al.*, 2004) while some did not (Bagney *et al.*, 2015). Bagney *et al.* (2015) conclude that there is no relationship between negative symptoms and cognition, and that the positive results previously found could have resulted from overlapping of definitions of cognition and negative symptoms, or simply due to the instruments used. Therefore, it is worthy to re-examine this contentious relationship with refined measurement of both cognition and negative symptoms. To our best knowledge, no study has examined association of specific domains of negative symptoms (such as avolition, alogia, and blunted affect) with cognition in schizophrenia and thus, the present study aims to fill this gap.
Methods: Forty participants (23 female and 17 male) diagnosed with schizophrenia were recruited for this study. The diagnosis of schizophrenia was ascertained with the Structured Clinical Interview for DSM-IV (SCID). Brief Assessment of Cognition in Schizophrenia (BACS; Keefe *et al.*, 2004) was used to assess cognitive deficits as it is a reliable, comprehensive and widely used neuropsychological battery to evaluate cognition in schizophrenia. The 16-item Negative Symptom Assessment (NSA-16; Axelrod *et al.*, 1993) was used to assess the severity of negative symptoms as it outperforms the older scales such as the Positive and Negative Syndrome Scale (PANSS; Kay *et al.*, 1987), in terms of better content validity and relying less on behaviors when scoring (Garcia-Portilla *et al.*, 2015). Both the overall composite score and the five subscale scores of NSA-16 were used in the analysis.
Results: Participants had a mean age of 31.8 years (SD: 6.8; range: 20–49), and an average 13.8 years (SD: 2.9; range: 8.5–20) of education. Their mean age at illness onset was 22.8 years (SD: 6.5; range: 14–43 years), their mean duration of illness was 8.9 years (SD: 7.0; range: 1–24). Thirty-seven participants (92.5%) had never married, and 34 (85.0%) were Chinese, 6 (15.0%) were Malay or Indian.
The BACS Z-scores were calculated with the age and gender adjusted using the Singapore Norm (Eng *et al.*, 2013). The mean BACS composite Z-score was -1.66 (SD: 1.29; range -5.09–1.29) and mean overall composite NSA-16 score is 41.68 (SD: 8.49, range 25–66). The BACS composite Z-score had statistically significant negative associations with four domains of NSA, including communication dysfunction($r = -.42$, $p = .007$), dysfunction in sociality ($r = -.37$, $p = .019$), motivational dysfunction ($r = -.41$, $p = .009$), and reduced psychomotor activity ($r = -.36$, $p = .021$) and with the overall composite score ($r = -.53$, $p < .001$). A marginally significant association was also found for emotional/affective dysfunction ($r = -.293$, $p = .066$).
Discussion: Association between cognitive deficits and negative symptoms were found in this study – cognitive performance was worse as negative symptoms increased. Moreover, the association is rather general than specific to certain domains of negative symptoms, as almost all subscales of NSA-16 exhibited moderate correlations with BACS composite score. We surmise that the relationships amongst the different domains of negative symptoms and cognition may be more complex and inter-related; for example, both the cognitive impairments and motivational deficits may affect the communication which in turn affects the sociality, or the motivation may affect the cognitive performance as patients will not put their best efforts in the tasks. Further studies are needed to delineate the relationships between negative symptom sub-domains and cognition.

T70. Belief flexibility and delusions in psychosis: a systematic review

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Background: Belief flexibility (BF) refers to the cognitive ability to "reflect on one's own beliefs, change them in the light of reflection and evidence, as well as generate and consider alternatives" (Garety *et al.*, 2005, p. 374). As a measurable construct (Freeman *et al.*, 2004; Moritz *et al.*, 2006), BF is separable from delusional conviction and valid in its own right (So *et al.*, 2012; Moritz *et al.*, 2010). A negative reasoning bias in belief flexibility (i.e., belief inflexibility) has been found to be significantly associated with delusion severity (Garety *et al.*, 2005; Hurn *et al.*, 2002), dimensions of delusions (e.g., conviction; So *et al.*, 2012), and a poorer response to cognitive therapy for psychosis (Garety *et al.*, 1997). Interventions targeting reasoning biases including BF have resulted in a reduction in delusions (Balzan *et al.*, 2014; Ross *et al.*, 2009; So *et al.*, 2015). These studies have mainly adopted interview assessments (possibility of being mistaken, reaction to hypothetical contradiction, and generation of alternative explanations, Freeman *et al.*, 2004). In recent years, there is an increase in the variety of BF measures by using experimental tasks (Woodward & Moritz, 2006; Kaliuzhna *et al.*, 2012) and self-reports (van der Gaag *et al.*, 2013). However, little is known about how BF measured by these tools relate to delusions. In light of the development of different measures for belief flexibility and delusions in each study, we conducted a systematic review to collate existing data to further delineate the relationship between BF and delusions. We addressed the following questions: 1) whether belief flexibility is associated with overall psychopathology of psychosis or with delusions specifically, 2) how strong the relationship between belief flexibility and severity of delusions is, and 3) how strong the relationship between belief flexibility and dimensions of delusions is.
Methods: This systematic review follows the PRISMA guideline (Liberati *et al.*, 2009). A systematic search for English literature using PsycINFO (1806 - 2015, present), PsyARTICLES, PubMed and MEDLINE (1946 - present) was conducted in late August, 2015. Empirical studies that investigated the relationship between belief flexibility and delusions (severity and/or dimensions) in at least one clinical sample were included. Meta-analysis was conducted using Comprehensive Meta-Analysis, Version 3.3.070 (CMA; Borenstein *et al*, 2014). For binary measures of BF (e.g., possibility of being mistaken), effect size was computed from means and standard deviations. For ordinal and continuous measures of BF (e.g., bias against disconfirmatory evidence), correlation coefficients were used for effect size aggregation.
Results: Preliminary analysis included 7 studies, out of which 4 studies measured BF by using interview assessments and 3 studies using experimental tasks. Overall, the effect sizes of association between BF and delusional severity ranged from 0.168 to 1.020, and the effect sizes of association between BF and delusional conviction ranged from 0.516 to 1.461.
Discussion: We are currently gathering original data from 15 authors, and will finalise the analysis in January 2016. In the final version, we will report Hedge's g, its 95% confidence interval, and the associated z and *P* values.

T71. Longitudinal change in neurocognition and its relation to symptomatic and functional changes over 2 years in individuals at clinical high-risk for psychosis

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Background: Negative symptoms and functional disability represent the core of schizophrenia and both are associated with cognitive

impairments. We explored the course of cognitive change and its relation to symptomatic and functional changes in individuals at clinical high-risk (CHR) for psychosis to identify cognitive indicators of long-term course. Such attempts may offer insight into the pathological changes associated with the development of illness in the prodromal state.
Methods: Forty-seven CHR individuals completed neurocognitive, clinical, and functional assessments at baseline and 2-year follow-up; twenty-eight healthy controls were assessed for neurocognitive and functional measures at baseline and 2-year follow-up. The delta values of CHR individuals in neurocognitive, clinical, and functional domains were determined from differences between baseline and follow-up scores to estimate the degree of change.
Results: Although overall longitudinal cognitive performance of CHR individuals improved, the magnitude of improvement was not statistically different from that of normal controls at the group level. However, the individual data yielded two groups of CHR subjects showing opposite trajectories of cognitive change in semantic fluency (i.e., improvement or decline), which was significantly associated with changes in negative symptoms and functional measures. Moreover, the relationship between negative symptoms and functioning were more strengthened over time than baseline.
Discussion: Our findings show that semantic fluency seems to be a neurocognitive indicator reflecting clinical courses in CHR individuals. The longitudinal relationship of negative symptoms and functioning with semantic fluency may represent ongoing pathological processes in neural systems involving aberrant fronto-temporal interaction in the early phase of schizophrenia.

T72. Prospective memory remains impaired two years after onset of schizophrenia

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Background: Prospective memory (PM) impairments have been found in patients with schizophrenia and their unaffected siblings. Evidence suggesting illness association and familiality supports that PM impairment may be an endophenotypic marker of schizophrenia. One previous study reported that PM remains impaired one year after the onset of schizophrenia. However, the long-term trajectory of PM impairment in schizophrenia remains unclear. Further longitudinal studies are needed to delineate the trait-like property of PM impairments in schizophrenia.
Methods: We recruited 57 patients with first-episode DSM-IV schizophrenia from an early psychosis clinic, and 97 healthy controls in the neighbouring community. Patients were followed-up at four time-points for two years. Time- and event-based PM were assessed using a validated computer-based "dual-task" paradigm. Healthy controls were assessed at the baseline. We compared the 24-month trajectories of time- and event-based PM in patients with first-episode schizophrenia, using repeated measures ANOVA: Time Point (baseline, 6 month, 12 month, 24 month) x PM type (time-, event-based). We also compared the group differences in PM functions using univariate ANOVAs.
Results: All patients completed assessments at all time-points. At baseline, patients with first-episode schizophrenia exhibited impairments in time- ($F[1,152] = 42.59$, $P < 0.001$, corrected with Bonferroni adjustments) and event-based ($F[1,152] = 48.24$, $P < 0.001$, corrected with Bonferroni adjustments) PM, compared with controls. At 24 months, time-based ($F[1,152] = 6.62$, $P = 0.022$, corrected with Bonferroni adjustments) but not event-based ($F[1,152] = 1.45$, $P = 0.462$, corrected with Bonferroni adjustments) PM remained impaired in patients with first-episode schizophrenia. The Time Point main effect was significant ($F[3,54] = 13,12$, $P < 0.001$), suggesting that PM improved with time in patients with first-episode schizophrenia. The Time Point by PM type interaction showed a trend of significance ($F[3,168] = 2.46$, $P = 0.078$), suggesting that time-based PM impairment was stable, relative to event-based PM impairment.
Discussion: Our findings are generally consistent with previous results, and support that time-based PM remains impaired two years after the onset of schizophrenia. To our understanding, this study is one of the few longitudinal studies examining the trajectory of time- and event-based PM, using the longest follow-up duration and the largest sample of patients with first-episode schizophrenia. Our results add further evidence that supports PM impairments as possible endophenotypic marker of schizophrenia.

T73. Trajectories of social cognition in schizophrenia and schizophrenia spectrum disorders

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Background: Social cognition is considered as a main predictor of functional outcomes. New data has been published lately on dynamics of social and neurocognition during the course of schizophrenia. We would like to challenge the postulate that social cognition is stable phenomenon by evaluating social cognitive impairments in patients with first episode psychoses (FEP), chronic schizophrenia (CS) and schizophrenia-spectrum disorders (SSD).
Methods: In a cross-sectional study 71 patients with FEP, CS and SSD were assessed with a battery of clinical and social cognitive tests. Patients were assigned to four diagnostical groups: 1 - Schizoaffective disorder, 2 - Paranoid schizophrenia, 3 - Catatonic, Simple and Undifferentiated schizophrenia (mixed group with severe disorders), 4 - Schizotypal disorder. Three key social cognitive domains were assessed: Emotion perception, Theory of Mind and Attributional style. Mann-Whitney analysis was performed for paired group comparisons, Kruskal-Wallis analysis was used for multiple groups comparisons.
Results: Patients with schizoaffective disorder and schizotypal disorder showed better scores in Hinting task ($M = 18.9$ $SD = 1.3$ and $M = 18.3$ $SD = 1.8$ respectively) than patients with paranoid schizophrenia and severe forms ($M = 16.6$ $SD = 2,7$ and $M = 17.4$ $SD = 1.8$ respectively ($P = .003$). Patients with FEP showed better results in Hinting task (18.1 ± 2.4) versus CS patients (17.4 ± 2.0) ($P < .05$). No differences in emotion perception (Ekman-60 task) among FEP and CS patients were detected. Patients with schizoaffective disorder showed better scores in emotional processing comparing to all forms of schizophrenia and schizotypal disorder patients (groups 1 to 4: $M = 52.0 \pm 4.2$ vs. $= 46.6 \pm 9.8$, $M = 47.4 \pm 8.0$, $M = 47.0 \pm 5.2$, $P < .05$). No significant differences in attributional style were registered among all groups.
Discussion: Emotion perception and Theory of Mind domains show different level of impairment across FEP and CS patients and across different forms of schizophrenia and schizophrenia spectrum disorders. Emotion processing tends to be a more stable domain, Theory of Mind follows the progredient course of the disorder. Further longitudinal studies are needed to establish relations of social cognition domains to the course and severity of schizophrenia and schizophrenia spectrum disorders. Emotionality and capacity for empathy should be taken into account in future research.

T74. Theory of mind impairment as a vulnerability marker for schizophrenia and its relation with schizotypal traits: a family based study.

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Background: The term theory of mind (ToM) refers to the capacity to infer one's own and other persons' mental states (beliefs, intentions, desires, emotions) and is a well-studied component of social

cognition. There are consistent evidences that ToM capabilities are impaired in schizophrenia (SZ) (Sprong *et al.* 2007; Bora *et al.* 2009); however, whether it is a state dependent or trait remains controversial (de Achaval *et al.*, 2010; Janssen *et al.* 2003). To date, studies investigating social cognition in unaffected relatives of patients with schizophrenia have shown inconsistent results (Lavoie *et al.* 2013) and how the schizotypal traits could moderate social cognition abilities remains unclear (Irani *et al.* 2006, Montag *et al.* 2012).We explored ToM in SZ patients, first degree relatives and healthy subjects in order to test whether deficits in ToM may be a putative endophenotypic marker of schizophrenia. We also investigated the role of SZ liability (i.e. schizotypy) as modifier of ToM.
Methods: The sample consisted of 39 stable patients with a first episode of a schizophrenia-spectrum disorder (DSM-IV-TR), 82 healthy first degree relatives and 81 controls. ToM was assessed using the Hinting Task (HT, Corcoran *et al.* 1995) and schizotypy with the Schizotypal Personality Questionnaire-Brief (SPQ-B; Raine and Benishay 1995), which generates three dimensional scores: cognitive-perceptual, interpersonal and disorganisation. We tested the effect of gender, age, years of education, IQ and family history on HT performance for each group. Only age and gender showed to have an effect so they were added as covariables in the following analyses.
Results: Comparison of HT performance between probands, first degree relatives and control groups (ANOVA test, adjusted for age, gender) showed a significant effect of group on HT total score ($F = 9.34$ $P < 0.001$). Post-hoc tests specified that patients performed significantly worse than relatives ($P < 0.001$) and controls ($P < 0.001$). High scores on SPQ-IP ($F = 5.437$, $P = 0.023$) and SPQ-CP ($F = 5.144$, $P = 0.026$) were related to worse ToM, in relatives but not in patients or controls.
Discussion: In our sample, ToM deficits are present in patients and not in relatives or controls. However, the observed influence of high levels of schizotypal traits suggests the link between ToM and schizophrenia liability, raising the possibility that ToM deficits could be candidate endophenotypes for schizophrenia.
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T75. Uncovering the computational processes underlying motivational deficits in early schizophrenia

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Background: Motivational deficits are a prevalent and persistent feature of schizophrenia, representing key determinants of outcome. Despite the known burden of this domain of psychopathology, the underlying mechanisms contributing to its clinical expression remain uncharacterized. Patients can theoretically manifest clinical amotivation resulting from impairments in a range of reward processes, including their valuation of outcomes, their ability to learn relationships between actions and outcomes, or their calculation of the effort required to obtain valued outcomes. In the present study, we employed multiple objective neuroscience-driven paradigms to elucidate the computational processes that might underlie motivational deficits in people with schizophrenia.
Methods: Fifty-eight stable outpatients with schizophrenia and 58 individually matched healthy control subjects completed a battery of reward processing tests. Each test was designed to evaluate a specific reward-related computational process. Briefly, participants completed an effort-based decision making task to evaluate effort cost computations, and reward learning was assessed using a probabilistic reinforcement learning task. Hedonic experience was evaluated using an emotion evocation task coupled with in-the-moment responses, as well as a measure of global reward valuation. To minimize potential confounds in the assessment of negative symptoms, we included only patients who were relatively young and had a recent-onset of illness to minimize potential disease chronicity effects, were receiving atypical antipsychotic monotherapy, were not experiencing prominent medication-related extrapyramidal side effects, and did not meet criteria for an Axis I disorder apart from schizophrenia (e.g., substance dependence, obsessive-compulsive disorder).
Results: At the time of assessment, the mean age of the participants was 26 years, and patients' mean duration of illness was less than 5 years. Patients with schizophrenia demonstrated impairments in the effort-based decision making and reward learning paradigms, but showed no difference in their valuation of reward compared to controls. Effort cost computations were not correlated to patients' overall reward learning capacity or with measures tapping into patients' ability to rapidly and rationally utilize feedback information to guide choice. Moreover, deficits in the computation of effort costs remained in a subsample of patients with adequate reward learning capacity. Patients' effort cost computations were significantly correlated with clinical measures of motivational deficits and functional status, but not with other clinical variables such as depressive symptoms.
Discussion: Our study examined several potential reward-related mechanisms that could undermine goal-directed behaviour in schizophrenia; results point toward a fundamental impairment in the computation of effort costs or in the integration of this signal with subsequent processes. These impairments cannot be accounted for by other concurrent reward processes such as patients' ability to use feedback to guide decisions or in their valuation of rewards. Such computational abnormalities contribute to the clinical manifestation of apathy and impact real-world community functioning. Targeting these computational impairments may represent a novel strategy for therapeutic discovery, and one that is more tractable than focusing on the broad non-specific construct of negative symptoms. Performance-based measures of effort and motivation may aid in this process, and serve as viable endpoints in clinical trials as these are more closely linked to underlying deficits.

T76. Encenicline increases the matrics consensus cognitive battery neurocognitive composite score in patients with schizophrenia

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Background: People with schizophrenia suffer from broad and significant cognitive impairment and perform ~1 to 1.5 standard deviations below normal controls. This degree of impairment is analogous to 15 IQ points. Encenicline is an alpha7 nicotinic acetylcholine receptor agonist and may improve cognition in people with schizophrenia. Subjects with schizophrenia from the US in the encenicline Phase 2B study were assessed with the MATRICS Consensus Cognitive Battery (MCCB), a 10-test battery assessing seven domains of cognition. As social cognition is distinct from neurocognition, the MCCB scoring software was updated in 2015 to support a new MCCB Neurocognitive Composite Score, calculated without the social cognition domain (MSCEIT). The new software made possible a new post hoc analysis.
Methods: Subjects with schizophrenia on a stable dose of atypical antipsychotics were randomized to receive encenicline 0.27 or 0.9 mg, or placebo, once daily for 12 weeks. Qualified raters assessed subjects with the MCCB at baseline, Day 44, and Day 84. To mirror the population of the ongoing Phase 3 studies, subjects aged < 50 years were included in this post hoc MCCB Neurocognitive Composite Score analysis ($N = 104$).
Results: Encenicline 0.27 and 0.9 mg were statistically superior to placebo at Day 84 as measured by the MCCB Neurocognitive Composite Score ($P = 0.038$ and $P = 0.024$, respectively). Effect sizes of the 0.27 and 0.9 mg groups were 0.55 and 0.57, respectively (number needed to treat ~4). There were no significant clinical or laboratory safety/tolerability findings.
Discussion: Re-analysis of the encenicline Phase 2B data using the recently published MCCB Neurocognitive Composite Score supports further development of encenicline for treatment of cognitive impairment in schizophrenia. Confirmatory Phase 3 studies are currently ongoing.

T77. The goals for better work outcome in Japanese patients with schizophrenia: cut-off performances on measures of functional outcomes

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Background: Work outcome has an important implication for financial independence and better quality of life in patients with schizophrenia. Our previous study reports that the cognitive domains of learning and emotional management, and everyday/social functioning domains of independence and vocational functioning, were potential predictors for number of hours worked (Sumiyoshi *et al.*, 2015). The aim of the current study was to provide cut-off points and cut-off performance scores on measures of these domains and on functional capacity to better predict work status.
Methods: Forty-five Japanese patients with schizophrenia were evaluated. Cognitive functioning and social functioning were assessed by the Japanese versions of the MATRICS Cognitive Consensus Battery (MCCB) and the Social Functioning Scale Individuals' version modified for the MATRICS-PASS (Modified SFS for PASS). Functional capacity was assessed with the UCSD Performance-based Skills Assessment-Brief (UPSA-B). The total work hours for the most recent 3 months was dichotomized into either "better- or poorer-work" status by means of a median split (i.e. above and below the medians of the patients group). It was used as the dependent variables for the Receiver Operating Characteristic (ROC) curve analysis. Independent variables were a cognitive domain score consisting of Learning and Social Cognition (Emotional management task) in the MCCB, a social functioning domain score consisting of Independence and Vocational functioning in the Modified SFS, and the UPSA Total score. The area under the curve (AUC) was estimated as the index of sensitivity. The optimal cut-offs were determined in a manner to maximize the sum of sensitivity and specificity (Youden, 1950). Cut-off performance percentages on the measures were calculated by dividing cut-off points by the maximum score of each domain score and multiplying by 100.
Results: ROC analyses showed that the AUCs were 0.71(95% CI: 0.55-0.87) for Learning/Emotional management, 0.78 (95% CI: 0.64-0.93) for the Independence/Vocational functioning, and 0.47 (0.30-0.65) for the UPSA total score. These results suggest that the former two scores elicit relatively good sensitivity to work status. The optimal cut-off points were estimated as 153.4 for the Learning/Emotional management, 53.5 for the Independence/Vocational functioning, and 81.6 for the UPSA-B total score, corresponding to 76.7%, 60.8%, 81.6% cut-off performance, respectively.
Discussion: The cut-off performance of 60-70% in the Learning/Emotional management score and the Independence/Vocational functioning score is found to be an indicator of better vs. poor work status. In contrast to our finding, performance on the UPSA-B has been reported to elicit good sensitivity in prediction of work status (Mausbach *et al*, 2011). Further studies should investigate the contribution of this measure to the prediction for work outcome in patients with schizophrenia.

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T78. Impact of the featural/configural processing of faces to the feeling of familiarity in schizophrenia

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Background: Familiarity processing is a crucial aspect of recognition that provides the subjective experience of having already perceived a stimulus, regardless of the context in which it was previously encountered (Song *et al.*, J. Neurosci, 2011). Familiarity disorders have been described in schizophrenia. A recent study showed a reduced familiarity threshold for faces in patients with schizophrenia compared to controls, suggesting a hyper-familiarity in patients (Horn *et al.*, J. Psychiat. Res., 2015). Yet, configural face processing seems to be impaired in schizophrenia, whereas featural face processing is preserved (Joshua *et al.*, Schizophr. Res., 2009). It has then been suggested that the feeling of familiarity is based on predominant featural face processing in schizophrenia, in comparison to controls who analyze both configural and featural information. Face inversion paradigms selectively alter the configural face processing (Yin, J. Exp. Psychol., 1969). Assuming that face familiarity abnormalities in schizophrenia are related to a deficit of global information processing, the objective of this study was to show a smaller face inversion effect on the feeling of familiarity in patients compared to controls.
Methods: 15 patients with schizophrenia (DSM-IV criteria) and 15 controls, matched to the patients for gender and age, were recruited in the study. Stimuli were individually tailored for each participant and consisted of black and white images constructed from 3 photographs of familiar faces and 3 photographs of unfamiliar gender-matched faces. Familiar faces were those of people personally known by the participants. Stimuli were morphs of familiar and non familiar faces, including different levels of familiarity (from 5 to 95%, increments of 10%). Two inverted conditions were created: a classical face inversion (90° rotation of the whole face) and a Thatcher illusion face inversion (eyes and mouth orientations preserved). The 90 morphed images generated for each participant were presented individually, upright, inverted or with the Thatcher illusion, in a randomized order. Participants were asked to press a button each time they felt familiar with the face that was presented. After the completion of the task, participants were asked to specify the identity of the persons they considered to be familiar. First, the percentage of familiarity detection was calculated for each of the 10 levels of familiarity, for each participant. Then, a familiarity threshold was estimated from the psychometric function that estimated the percentage of familiarity detection according to the familiarity levels in the morph.
Results: Results showed a significant effect of the familiarity level on the percentage of familiarity detection, in both groups. Moreover, inverted conditions (classical and Thatcher) led to a lower performance compared to the upright condition, in both groups. Patients showed a significantly lower familiarity threshold compared to controls in the upright condition. Surprisingly face inversion effect was significantly higher in patients than controls. Nevertheless, the Thatcher illusion significantly increased the performances in comparison to classical inversion, in the patients group only.
Discussion: Our results confirm the hyper-familiarity observed in schizophrenia patients, for upright faces (Horn *et al.*, J. Psychiatry Res., 2015). Nevertheless, face inversion leads to a hypo-familiarity in both groups. Both configural and featural information appear necessary to process face familiarity in schizophrenia patients. Nevertheless, restoring the featural information only (Thatcher illusion), partially improves the judgment in schizophrenia patient.

T79. Modeling difficulties in abstract thinking in psychosis; the importance of socio-developmental background

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Background: Immigrants with psychosis show more difficulties in abstract thinking on the Positive and Negative Syndrome Scale (PANSS) compared to the majority population. In schizophrenia difficulties in abstract thinking are associated with neurocognition and insight into illness. These associations are presented as universal, implying that cognitive processes are fundamentally similar across countries and cultures. However, some research suggests that cognition is a dynamic interplay between biology, socioeconomic background and cultural values. In this study we aimed to assess if differences in socio-developmental background influence abstract thinking in patients with psychotic disorders, even in cases where all participants are educated within the same school system.
Methods: Participants ($n = 174$) were recruited from in and outpatient units in Oslo. Inclusion criteria were 17–65 years, IQ > 70, fluent in a Scandinavian language, full primary education in Norway and a DSM-IV diagnosis of psychotic or bipolar disorder. First- or second generation immigrants ($N = 58$) were matched (1:2) with participants from the majority group by age (25, range 17–52), gender (45% female) and diagnosis (53% schizophrenia-spectrum, 35% bipolar disorder, 12% other psychosis). All participants completed a neurocognitive assessment and were interviewed with the PANSS. HDI for country of birth at year of birth was applied to all participants. This is a composite index measuring average achievement of a country based on three basic dimensions of human development; life expectancy, adult literacy and standard of living. Structural equation modelling was used to assess the model that best could explain variance found in abstract thinking.
Results: The model included a combination of the single indicators of PANSS item N5 abstract thinking and HDI, as well as latent variables assessed by principal component analysis for clinical factor (PANSS positive, negative and excited factor; items conceptual disorganization and poor attention) and neurocognitive factor (category fluency, category switching, digit span, and matrix reasoning). Both clinical and cognitive factor had a direct effect on abstract thinking (X2 difference = 32.081, df 8, $p < .001$). HDI did not however mediate this effect (X2 difference = 25.528, df 2, $p < .001$). The model with best fit ($x2 = 96.591$, df 33, $p < .001$) confirmed a significant indirect effect of socio-cultural background on abstract thinking through neurocognition, but not through clinical symptoms.
Discussion: Our findings suggest that the increased difficulties in abstract thinking previously found in immigrants with psychosis compared to a reference group is partially a consequence of differences in neurocognition and not psychosis pathology per se. Neurocognition however was influenced by participant's socio-developmental background. This may explain some of the variance found in neurocognition in patients with psychosis. The HDI is here considered a more objective rating than typical categorization into immigrant groups and also encases in part socio-developmental history strengthening our findings. A limitation of this method, however, is that it does not reflect on cultural aspects such as beliefs, values, and traditions, nor take into account the effect of different socio-economic status in ethnic minorities within nations. In conclusion, this study found that socio-developmental background influences difficulty in abstract thinking in psychosis by indirect effect through neurocognition suggesting that it be included as an important control variable in future studies of neurocognition in psychosis.

T80. Is cumulative life time depression positively linked to better cognition in schizophrenia?

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Background: It has consistently been shown in major depression (MD) that cumulative life time depression is negatively correlated with cognitive function. Conversely, in schizophrenia (SZ) life time depression has been related to more severe acute psychotic symptoms, but better cognitive functions (Chiappelli *et al.* 2014). In the current study we examined the influence of cumulative life time depression on episodic memory across patients with MD, SZ and healthy controls (HC).
Methods: Approximately 500 patients with SCID-confirmed diagnosis of major depression, schizophrenia, or schizoaffective disorder (SA) as well as an equal number of matched healthy controls were extensively phenotyped. The OPCRIT was used to operationalize cumulative life time depression: a score consisting of all items linked to depressive symptoms (e.g. duration of lifetime experienced depressive mood, dysphoria, sleep problems) was built. BDI and HAMD was integrated for state depression. To control for acute depressed symptomatology only remitted patients were included (HAMD < 8). During the fMRI task either a neutral face (encoding condition) or a scrambled picture (baseline) was presented. Participants were instructed to memorize the faces for later recognition as well as to indicate their sex via button press. In the subsequent recognition phase familiar faces from the fMRI task and non-familiar faces were presented side by side; participants had to select the familiar face by button press. The groups' neural responsivity in prefrontal areas and hippocampal formation were compared by a 3 x 2 ANOVA using a full factorial design with group (MD vs. SZ/SA vs. HC) and condition (baseline vs. encoding) as factors. The role of cumulative life time depression across the different groups is examined.
Results: We hypothesize both patient subgroups to exhibit decreased activity in lateral prefrontal regions and the hippocampal formation in contrast to HC. We further hypothesized that cumulative life time depression is positively linked to brain activity in these areas in SZ and negatively linked to MD, respectively.
Discussion: Schizophrenia and affective disorders overlap in several symptoms and cognitive deficits, however there appear to be distinct patterns in how longitudinal experience of depression is related to cognition in these disorders.

T81. Development of a platform agnostic software engine to facilitate widespread adoption of cognitive remediation therapy in schizophrenia

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Background: Studies have shown significant disruption in cognition in those with schizophrenia; with a strong relationship to poor long-term outcomes. Many studies have focused on developing tools to not only quantify the level of deficit but to also improve function. This is called cognitive remediation therapy (CRT). The systems powering CRT are generally a set of neuroscience tools operationalized into a specific technology framework with a variety of commercial and public domain offerings. While there are many choices there has been limited success in widespread adoption in schizophrenia specifically. There are many possible explanations for the limited adoption but we posit a major cause has been lack of an open solution that is technology agnostic and platform independent. With the dramatic change in technology over the last 10 years, researchers, clinicians, and patients have new expectations about how technology fits into their lives and specifically their health. Many CRT platforms do not take these expectations into account and instead rely on old technologies or passe trends. In order to gain widespread acceptance, a new methodology is required. Our solution, called Project Plasticity, is a new platform that hybridizes traditional neuroscience tasks with a popular video game engine and a cloud computing backend.

Methods: Our system is based on a series of well-defined cognitive tasks built on top of a custom, fully extensible framework. Tasks are written in either C# or JavaScript and utilize our framework in addition to the lower-level framework provided by the Unity game engine. The Unity engine is a leading video game development platform which provides task developers with robust 2d and 3d tools capable of being run on all modern platforms including desktop, mobile, WebGL, AR, and VR. Our framework sits between unity and the task implementations and provides core, common services (adaptive difficulty, response timing and verification, etc). Our framework also provides a pluggable cloud-based backend that is robust, resilient, and secure; capable of supporting any of the common core cloud providers. It scales elastically based on user demand and is able to allow focused management of data processing streams. Finally, the system encourages openness and transparency at every level so that patients, clinicians, and researchers can clearly document task operation and outcomes using consistent methods.
Results: The system is currently in the 6th round of iterative development. Multiple tasks have been developed alongside the core underlying services. Tasks have been tested under Android, Windows, and Mac but also have the capacity to run on iOS and a web browser under webgl. Tasks are configurable with respect to task parameters (number of trials and task complexity). During task administration, performance data are collected and stored in a cloud-hosted backend.
Discussion: Cognitive remediation is an important and relevant area with the potential to facilitate significant change in long-term outcomes. While neuroscience is moving forward rapidly, the technological implementations available to support widespread adoption are lacking. Due to the explosion of mobile devices, the cloud, and alternative platforms, new, exciting tools have become available to developers. It is now time to use these tools to build a next-generation platform that will enable improved access for patients, clinicians, and researchers. The goal being to evoke widespread change in an otherwise difficult to treat illness.

T82. The effect and mechanisms of implementation intention in improving prospective memory performance in schizophrenia spectrum disorders

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Background: Prospective memory (PM) refers to remembering to do something at a future time. Implementation intention is an encoding strategy in the form of "if I encounter X then I will do Y". It can be used to improve people's PM performance. Individuals with schizophrenia spectrum disorders are characterized by PM impairments. Three studies were conducted to examine the effect and mechanisms of implementation intention on PM in schizophrenia spectrum disorders. Methods: In the first study, we conducted a meta-analysis of the effect of implementation intention on PM in healthy participants. In the second study, we applied implementation intention to the schizophrenia spectrum including participants with schizotypal personality features (SPD) and schizophrenia patients to examine its improving effect on PM performance and the underlying mechanisms. In the third study, we explored the neural mechanisms of implementation intention on PM in healthy participants.
Results: In the first study, results showed that implementation intention can significantly improve PM performance in both young ($d = 0.445$) and older adults ($d = 0.680$). In the second study, results showed that implementation intention could help SPD participants and schizophrenia patients to improve their PM performance. However, they showed different mechanisms. SPD allocated significantly more cognitive resources to the PM task in the implementation intention condition. While for schizophrenia patients, implementation intention reduced their reliance on cognitive resources to perform the PM task and helped them to accomplish PM task more automatically. In the third study, results suggested that implementation intention affected the processes of intention maintenance and execution stages. At the intention maintenance stage, individuals with implementation intention showed stronger brain activation in the areas of temporal cortex including superior and middle temporal gyrus, anterior cingulated gyrus, insula and putamen. Implementation intention may enhance the processes of cue monitoring and intention representation. It is probably a controlled process. At the intention execution stage, individuals with implementation intention showed less activation in medial frontal gyrus, cuneus, anterior and posterior cingulated gyri. It is probably an automatic process.
Discussion: Implementation intention can help people with their PM performance. It may be a complicated process involving both automatic and controlled processing.

T83. Pupil dilation response to imagined emotional future events: relations to high and low levels of apathy in a non-clinical sample

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Background: Apathy is commonly defined as a quantitative reduction in goal-directed behavior (Levy & Dubois, 2006) and is a core negative symptom in schizophrenia. Apathy may partly result from a diminished capacity to foresee the rewarding value of a future pleasurable activity. Previously, it was shown that the pupil dilation response, a sympathetic nervous system marker, reflects levels of emotional arousal and interest (Bradly *et al.*, 2008), indicating that pupil reactivity could serve as a psychophysiological marker of sensitivity to future reward. We therefore investigated whether pupil responsivity related to valence of future positive, negative and neutral events. We furthermore investigated whether apathy was specifically predictive of the pupil response during envisioning future pleasurable activities.
Methods: Forty-seven healthy participants (Mean age: 22.5, $SD = 2$; 33 female) were included in the present study. Apathy was assessed using the Dutch version of the apathy evaluation scale (AES) and ranged from 18 to 43 ($M = 29.17$; $SD = 6.45$). All participants generated emotionally loaded self-relevant possible future events (30 positive, 30 negative, and 30 neutral items), which were rated on relevance and vividness of imaginary. During pupil dilation measurements (using the Research EyeLink-1000 system), these events were presented in a pseudorandomized order with the instruction to envision the occurrence of these future events. Informed consent was obtained from all participants.
Results: Participants with high levels of apathy (median-split based) demonstrated a lower maximum amplitude during affective forecasting of positive and negative events than low apathy individuals ($F1, 45 = 4.62$, $P = .04$), but no interaction of group and valence was observed ($F1, 45 = .63$, $P = .43$). No effects of valence, apathy, or interaction of valence and apathy was observed on the area under the curve estimation of total pupil responses.
Discussion: To our knowledge, this is the first study investigating the relation between apathy and the pupil dilation response during affective forecasting. Our findings suggest that pupil dilation response reflects levels of apathy to a certain extent and may be used as a complementary method to assess dimensions of apathy. Given the noradrenergic underpinnings of the pupil dilation response, and the relevance of noradrenaline and dopamine for motivated behavior, future studies using this approach could help unravel the neural basis of apathy.

T84. One year durability of the computer-assisted cognitive remediation therapy: neurocognition, self-esteem, quality of life and use of psychiatric emergency services

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Background: The cognitive impairment may be related with difficulty in managing medications or pharmacotherapy adherence in

schizophrenia. Medication non-compliance has an important impact on emergency rooms visits or hospitalization and consequently on health care expenditure.
The aim of the current study is to investigate the durability effectiveness of CACR on neurocognitive, quality of life and self-esteem outcomes and to examine their relationship with the use of psychiatric emergency services.
Methods: Sixty-seven participants were recruited from schizophrenia outpatients of the Department of Mental Health of Consorci Sanitari de Terrassa (NCT01598220). Thirty-eight were randomized to cognitive remediation therapy and twenty-nine to active control condition. For the follow-up study a total of 33 participants were enrolled in the study, 20 to the CACR condition group and 13 to the active control condition group. Sixteen subjects dropped out. All participants completed a comprehensive battery of neuropsychological tests and the Heinrichs–Carpenter Quality of Life Scale and the Rosenberg Self-esteem Scale. The use of emergency services and hospitalization were collected retrospectively at three assessment points: baseline (for the previous 12 month period; hereafter Time 0-T0), 12 month post-therapy (Time 1-T1), 24 month post-therapy (Time2-T2) and 36 month post-therapy (Time3-T3). The effect of CACR therapy on cognitive performance, quality of life and self-esteem measures was analyzed with two way mixed (time x group) analysis of variance (ANOVA) with treatment groups as the between-subjects factor (with two levels: therapy or active control group), and the three evaluations (baseline T1, post-treatment T2 and 12-month follow-up after intervention T3) as within-subject factors.
Chi-square test were used according to the nature of the variables studied emergency rooms and hospitalization.
Results: The neurocognition, quality of life and self-esteem differed in the CACR and active control groups. Then, contrasts were also performed comparing cognitive performance and sub-scales of QoL and self-esteem at the three assessment moments (baseline, post-treatment and 12-month follow-up after intervention) across CACR and active control groups. These contrasts revealed significant interactions when comparing these two groups' scores to baseline compared to 12-month follow-up after intervention. The results showed a significant group x time interaction in cognitive domains as well as in QoL and self-esteem. Within-subject contrasts showed a clear durability of improvements on the therapy group in several neurocognitive variables and in QoL and self-esteem measures. The chi-square test indicated relationship between experimental groups and emergency rooms and hospitalization on T1, T2 and T3. The results showed a higher use of emergency services and hospitalization in T1, T2 and T3 in control group.
Discussion: Results of the current study show that improvements on neurocognition, quality of life, and self-esteem that occur after a CACR are sustained after 12-months post-therapy. Moreover, CACR group shows a lower use of the emergency services and hospitalizations after 12-months post-therapy.

T85. Neurocognition in help-seeking individuals at risk of psychosis and bipolar disorder: outcome after 24 months

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Background: An important aim in schizophrenia research is to optimize the prediction of psychosis and to ameliorate strategies for early intervention. The objectives of this study were to explore neurocognitive performance in individuals at risk of schizophrenic and affective psychosis and to optimize the predictions through a combination of neurocognitive and psychopathological variables.
Methods: Information on clinical outcomes after 24 months was available from 97 subjects who had completed an extensive assessment at baseline. Subjects at risk of psychosis converting to schizophrenia (CHR+) were compared with subjects without conversion (CHR-) or who developed bipolar disorder (BIP). Logistic regression analyses and Receiver-Operating Characteristic curves were established to determine which baseline measure best predicts a transition to schizophrenia.
Results: The model that combined neurocognitive and psychopathological variables was the best for predicting clinical outcomes, presenting a specificity of 91.9%, sensitivity of 80.0%, and an overall positive predictive value of 88.5%. The area under the curve was 0.93 (SE 0.02, $P = 0.000$). The IQ and the neurocognitive domains of learning/memory and fluency significantly discriminated CHR+and CHR-. However, BIP and CHR- individuals could not be discriminated based on their neurocognitive data.
Discussion: Our results confirm previous evidence suggesting moderate premorbid cognitive deficits in schizophrenia. Individuals converting to bipolar disorder exhibited premorbid performance within the lower mean. Overall, clinical symptoms appeared to be a more sensitive predictor than cognitive performance. Nevertheless, both might serve as complementary predictors when assessing one's risk for psychosis.

T86. Smoking in pregnancy, adolescent mental health and cognitive performance in young adult offspring in a Finnish cohort sample

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Background: The association between prenatal exposure to tobacco and adult cognition is debated, including if there are differences according to sex. The effect of mental health problems associated with cognition, namely inattention and hyperactivity and psychosis risk, on the association between prenatal exposure to tobacco and adult offspring cognition also remains to be explored.
Methods: Participants were 471 individuals drawn from the Northern Finland 1986 Birth Cohort (NFBC 1986), matched by prenatal exposure to tobacco and socioeconomic factors and with rigorous exclusion criteria. Cognitive performance in adulthood was assessed with a range of tests and their association with exposure to smoking in pregnancy was measured by sex using linear regression controlling for potential confounders and followed by interaction analysis to examine associations with mental health where appropriate.
Results: There were no associations between prenatal exposure to tobacco and cognitive scores in females and associations with only vocabulary (-0.357 standard deviations, $P = 0.020$) and matrix reasoning (-0.293 standard deviations, $P = 0.037$) in males. There was evidence of mediation by inattention and hyperactivity in the association between prenatal exposure to tobacco and matrix reasoning score in males. Prenatal exposure to tobacco was associated with poorer matrix reasoning scores in males not at risk for psychosis but not in males at risk for psychosis (P value for interaction $= 0.017$).
Discussion: While associations between prenatal exposure to tobacco and cognition were limited, observed findings with measures of general intelligence in males add support to efforts aimed to eliminate smoking in pregnancy.

T87. Cognitive profiles in first episode schizophrenia spectrum disorders

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Background: Schizophrenia (SCH) is a disorder with variable phenotypic expression, variable patterns of course, complex etiology, and with the majority of affected population having a severe deteriorating course. The last decades have been marked by a significant interest in identifying clinical, neurocognitive, and other factors that can influence functional outcome in SCH. Abnormalities in cognitive

functions are a key component of SCH. Cognitive deficit in SCH appears heterogeneous with large intra-individual variability in test performance, that complicates the interpretation of cognitive test results. One of the causes of this hetereogenity is the assumption that cognitive domains in SCH are independent or only weakly correlated. The study of the interrelationships among domains is needed to better understand the patterns of intra- and inter – individual neuropsychological performance and clinical features. Taxonomic approaches may contribute to clarify cognitive heterogeneity. To our knowledge studies using taxonomic approaches in SCH are limited. The aim of this study is to identify in a first episode schizophrenia spectrum (FES) population if the decrease in the level of cognitive functions measured with the aid of a neuropsychological battery is random, independent or possible to be explained by profiles.
Methods: We recruited a study group (SZ) of 30 FES patients, who meet ICD-10 criteria, and a control group of 30 healthy volunteers (HC) matched for age, sex, and education. All participants completed a neuropsychological assessment which contained five basic domains: Speed of Processing, Attention/Vigilance, Working Memory, Verbal Learning and Memory, Visual Learning and Memory, and Executive Functions. For SZ psychotic symptoms were assessed based on the assessment of the PANSS scale. The dose of antipsychotic medication was converted to chlorpromazine equivalents to evaluate the effect of medication on cognitive functions. The raw scores for each test were converted to z-scores. To compose the cognitive domains, the average of the subtests´ z-scores was calculated. The SZ and HC global score of neurocognitive performance was compared using ANCOVA. Cluster analysis identified subgroups that were homogeneous and separated. Pearson correlations were calculated among the domain composites separately for SZ and HC. To compare the identified clusters with clinical and demographic variables one-way ANOVA and chi-squared test were used.
Results: In comparison to HC, the results of cognitive performance in SZ were significantly lower at most of the administered tests. Within the SZ, and within the HC group it was possible to distinguish several subgroups with different cognitive profile based on the cognitive performance. However, SZ group presented higher correlations between domains compare to HC group. For SZ group, the performance measured in the majority of these tests was not directly affected by the antipsychotic medication dose when converted to chlorpromazine equivalents.
Discussion: There are two main preliminary findings in this study. The first finding is that a hierarchical model may characterize cognitive test performance. The second finding is, that correlations among cognitive variables in SZ group are relatively higher than in HC groups. This can suggest that the latent structure of cognitive performance in FES is more unitary than has often been assumed. In order to confirm, and generalize these findings, we are currently running a longitudinal study in a bigger sample, and comparing FES with chronic states.
This study was supported by research grant from GAČR (16-13093 S), and the project "National Institute of Mental Health (NIMH-CZ)" and the European Regional Development Fund (ED2.1.00/03.0078).

T88. The value of novelty in schizophrenia

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Background: Influential models of schizophrenia suggest that delusions could arise as a consequence of a deficit in the balance between the value attributed to old and novel stimuli. These models suggest that patients experience incoming stimuli as excessively novel and motivating, with a consequent elaboration of the importance of this novelty into delusional belief. However, whether schizophrenia patients exhibit excessive preference for novelty and whether this interferes with adaptive behaviour has not yet been formally tested. Here, we employed a three-armed bandit task to investigate this hypothesis.
Methods: Twenty schizophrenia patients and twenty-four healthy controls were first familiarised with a group of images and then asked to choose between familiar and unfamiliar images associated with different monetary reward probabilities. By fitting a reinforcement-learning model we were able to estimate the values attributed to familiar and unfamiliar images when first presented in the task.
Results: In line with our hypothesis, we found increased preference for newly introduced images (irrespective of whether these were familiar or unfamiliar) in patients compared to healthy controls. In addition, we found a correlation between value assigned to novel images and task performance, suggesting that excessive novelty value may interfere with optimal learning in patients.
Discussion: Our findings provide the first experimental evidence of excessive novelty preference in schizophrenia and thus provide empirical support for those models emphasising such dysfunction in the disorder. Given the emerging evidence linking novelty value to dopamine levels, future studies should focus on establishing a link between dopamine dysfunction, novelty value and motivational dysregulation in patients.

T89. Perceptual metacognitive accuracy and grey matter volume in first-episode psychosis

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Background: Metacognition, or thinking about thinking, is a higher-order thought process that allows humans to inspect their own cognitive products for accuracy. Decision making processes are often dependent upon these assessments and attributing the appropriate level of confidence to one's cognitive processes may lead to better real-world decision making based on the information at hand. Better metacognitive accuracy has been associated with greater Grey Matter Volume (GMV) in the Pre Frontal Cortex (PFC) and the precuneus. Both Metacognitive deficits and GMV deficits in these and other anatomical regions have also been observed in schizophrenia By conducting research in first-episode psychosis, many of the confounding variables of exposure to neuroleptic medication and psychological treatments may be avoided. The present study set-out to investigate whether deficits in metacognitive accuracy are present in the early stage of schizophrenia, and whether these processing deficits are associated with GMV deficits in the PFC.
Methods: 40 first-episode psychosis (FEP) participants were recruited from Early Intervention in Psychosis Services in Sussex, UK and matched with 20 healthy control participants for age, gender and years of education. Metacognitive accuracy was measured using a visual perceptual task (Fleming *et al.* 2010) and a meta-d' calculation was employed to assess perceptual metacognitive accuracy for both FEP and control participants. Structural scans were also collected and a voxel-based morphometry (VBM) investigation was conducted to assess for GMV differences, and association between metacognitive accuracy and GMV.
Results: A significant difference was found between control and FEP participants ($P = .038$) with FEP participants demonstrating significantly worse perceptual metacognitive accuracy. The VBM analysis suggested structural deficits in the FEP sample compared to control participants in the frontal gyrus. No relationship was found however, between metacognitive accuracy and GMV in the PFC and no interaction effect was found between group and metacognitive accuracy.
Discussion: The present study suggests that perceptual metacognitive accuracy deficits are already present in FEP. An inability to discriminate between accurate and inaccurate decisions may account for the poorer psychosocial outcomes observed in schizophrenia. The GMV deficits in the frontal gyrus may also account for higher-order thought processing deficits also reported in schizophrenia. The lack of a relationship between metacognitive accuracy and GMV precludes a linear relationship being drawn between these findings however experimental design differences between the present study and known work may account for the disparities found. Understanding more about the relationship between GMV deterioration and cognitive processing may offer greater insight into the relationship to functional decline in schizophrenia. Cognitive deficits in schizophrenia may be better accounted for by functional connectivity in white-matter.

T90. Visual versus auditory cognitive training for people with schizophrenia

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Background: Cognitive impairments are important determinants of functional outcome in schizophrenia, which are inadequately treated by antipsychotic medication. Neuroplasticity based computerized cognitive trainings have been emerging for the last two decades and are an attempt to help patients with their cognitive impairments and global functioning. The aim of this study was to perform a computerized cognitive training to improve attention, concentration, learning, clinical symptoms and quality of life in patients. We were interested in testing the differential efficacy between a specific visual versus auditory computerized cognitive training and explore the biological markers that may be involved in these neuroplasticity based training processes.
Methods: We conducted a 40 hours computerized, adaptable, perception specific, cognitive training program in patients with schizophrenia. Patients came for 1 hour, daily, and performed a visual or auditory training, for about 2 months. Visual and auditory exercises were chosen to be the equivalent of one another and targeted cognitive domains such as divided attention, working memory and social cognition. Clinical, cognitive, emotional and biomarker data were collected before the training, half way through, and after the training, to assess progress in several aspects of their functioning and biology.
Results: Forty-two patients were enrolled in the training. Visual and auditory trainings showed improvements in the specific cognitive and emotional areas trained. Improvements of 35% and 43% were observed in divided attention for the visual and the auditory training respectively; 54% and 55% in memory; and 56% and 63% in social cognition. Visual and auditory cognitive trainings showed a transfer of skills in other cognitive domains of attention ($P < 0.001$), emotional decision making ($P < 0.05$), and emotion recognition ($P < 0.01$). The visual training was generally associated with higher improvement in these cognitive domains, and in the domains of working memory, spatial learning and reasoning and problem solving, whereas the auditory cognitive training was associated with milder improvements or sometimes a decrease in performance. Interestingly, both trainings improved clinical symptoms of schizophrenia ($P < 0.01$), and there was a correlation between the improvement observed in attention and memory and improvement of positive symptoms.
Discussion: Overall, the visual cognitive training appears to be highly efficacious in remediating cognitive impairments in schizophrenia. Further investigation is needed to understand why auditory training was not as efficacious. One hypothesis raised is that auditory hallucinations may generally prevent patients to focus on auditory stimuli as compared to visual ones. It was very encouraging to observe improvement in clinical symptoms with the training, which may help patients to reintegrate a more functional social and working life.

T91. Reduced susceptibility to the sound-induced flash fusion illusion in schizophrenia

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Background: Schizophrenia (SZ) is characterised by the presence of abnormal complex sensory perceptual experiences. The illness has previously been conceptualised as a disorder of the normal connectivity and integration within the brain, suggesting that abnormal sensory experiences could arise as a consequence of dysfunctional multisensory integration (MSI). MSI has primarily been studied in SZ using complex perceptual stimuli, but it remains unclear whether a dysfunction of MSI exists at an elementary perceptual level. The sound-induced flash illusion offers a framework in which to study abnormal integration using simple stimuli, whereby overall task performance, response bias, and true perceptual differences can be disentangled.
Methods: We used the sound-induced flash illusion paradigm in a sample of individuals with SZ ($n = 40$) and matched controls ($n = 22$). A fission illusion occurs when one visual flash, accompanied by two brief auditory beeps, is erroneously perceived as two flashes. Conversely, a fusion illusion occurs when two flashes, accompanied by a single beep, are misperceived as one. Signal detection theory (SDT) analyses were performed in order to characterise patients' and controls' sensitivity in distinguishing 1 and 2 flashes under varying auditory conditions.
Results: Patients and controls did not differ in their susceptibility to the fission illusion. In contrast, patients experienced significantly fewer fusion illusions. SDT analyses confirmed that this was due to a difference in sensitivity rather than response bias. Susceptibility to the fusion illusion was furthermore negatively correlated with illness duration in patients. Finally, susceptibility to both illusions correlated positively in patients with SZ, but was unrelated in healthy controls.
Discussion: Patients with schizophrenia demonstrate a specific deficit in audio-visual integration that is associated with greater perceptual demand, suggesting a more limited capacity for integration relative to healthy control subjects. The dysfunction is likely exacerbated as the illness progresses and the integrative mechanisms of the brain deteriorate further, highlighting the importance of addressing multisensory deficits at an early stage of the illness. Our findings lend support for the notion that separate mechanisms underlie normal perception of the fission and fusion illusions, whereas abnormal perception of both illusions in SZ is driven by a single dysfunction of MSI.

T92. The effect of childhood trauma on cognitive function in a sample of Chinese patients with schizophrenia

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Background: Childhood trauma is a major public health problem which has existed in human society for a long period of time. Recent studies showed that exposure to childhood trauma has adverse effects on cognitive. A few limitations of the existing studies were existed in this area. We designed a study including 162 Chinese patients with schizophrenia, using two standardized, validated instruments to assess the history of childhood trauma and cognitive function, to evaluate the effect of all types of childhood trauma on a variety of cognitive functions in Chinese patients with schizophrenia.
Methods: All participants were inpatients or outpatients from two psychiatric hospitals, Beijing Anding Hospital and Beijing Daxing Psychiatric Hospital in Beijing, China. One hundred sixty-two patients were assessed with the Childhood Trauma Questionnaire-Short Form (CTQ-SF) and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Clinical data were also collected. Associations between specific types of trauma, demographic variables and cognitive function were examined. Statistical analyses were conducted using the Statistical Package of Social Sciences (SPSS, version 16.0). All statistical differences were considered significant when $P < 0.05$ in both directions.
Results: Using the cut-off criteria, 26.5% (41/162), 21.2% (35/162), 35.8% (59/162), 55.8% (92/162), and 66.5% (109/162) of the sample reported EA, PA, SA, EN, and PN, respectively. Patients from urban area in the sample had significantly higher language, and RBANS total scores compared to patients from rural area (t = 2.800-2.864, $P < 0.01$). Patients with atypical antipsychotics in the sample had significantly higher delayed memory, and RBANS total scores compared to patients with typical antipsychotics (t = 2.515-3.938, $P < 0.01$). Significant positive correlations existed between years of education years and RBANS subscale except for immediate memory, and visuospatial construction(r = -0.212-0.489, $P < 0.05$). Similarly, significant positive correlations were observed between family income and immediate attention (r = -0.276, $P < 0.05$). However, duration of illness were negatively correlated with Language, delayed memory, and RBANS total score (r = -0.203-0.252, $P < 0.05$). Times of recurrence, and admission were negatively correlated with delayed memory. Significant negative correlations existed between physical abuse, sexual

abuse with language score (r = -0.190--0.216, $P < 0.05$). Similarly, physical neglect were negatively correlated with attention, delayed memory and RBANS total score (r = -0.167--0.206). Multiple linear regression analyses indicated that significant negative correlations existed between childhood physical neglect and story memory, attention, coding, list recognition, story recall ($P < 0.001$ for all). Similarly, multiple linear regression analyses indicated that sexual abuse was negatively correlated with language ($P < 0.001$), and physical abuse was negatively correlated with picture naming ($P < 0.001$).
Discussion: Using standard, quantitative instruments for both childhood trauma and cognitive function, we carefully assessed 162 Chinese patients with schizophrenia. We believe this is among the first to analyze all types of childhood trauma on a variety of cognitive functions using standardized instruments. Our findings indicate that specific forms of trauma contributed to different cognitive function in this sample. The results of this study lend weight to this proposition by finding neuropsychological differences between those patients with schizophrenia and who report childhood trauma and those who do not report such trauma.

T93. Counterfactual reasoning deficits are related with acute negative symptoms in schizophrenia

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Background: Counterfactual Thinking (CFT) is a mental process about spontaneous alternatives to past outcomes usually evoked as in a "if only" type of response. Used in response to real world experiences, counterfactual reasoning depends on mental models of alternative possibilities represented in the form of mental simulations. Previous research has found a global CFT impairment in schizophrenia, which might be the expression of a general cognitive impairment. In the present study we have further explored CFT performance of these patients and its relationship with socio-demographic characteristics, clinical symptoms and level of functioning.
Methods: The ability to generate counterfactual thoughts in front of a hypothetical scenario with a negative outcome was assessed in 40 patients diagnosed with schizophrenia (DSM-IV-TR criteria) and 40 healthy controls. Participants were matched by gender, age and educational level. We further explored whether any socio-demographic characteristic, clinical variables or level of functioning was related to performance in the experiment using the Positive and Negative Symptoms Scale (PANSS), the Clinical Global Impression-Schizophrenia Scale (CGI-SCH) and the Global Assessment of Functioning scale (GAF). Differences between groups was assessed using the Student's-t parametrical test and the U-Mann Whitney non-parametrical test for continuous variables, and the □2 or p-Fisher tests for categorical variables. In multivariate analyses, binary, ordinal or linear regression models were used depending on whether the dependent variable was considered categorical, ordinal or continuous, respectively. Statistical analysis was performed using the statistical package SPSS Version 18.0.
Results: Replicating previous research, results revealed schizophrenia patients to generate fewer number counterfactual thoughts compared to healthy controls in front of a hypothetical social scenario. Furthermore, CFT statistically significantly correlated with civil status among schizophrenia patients, where single participants had more probabilities of generating less counterfactual thoughts. In addition, high scores in negative symptoms on the PANSS scale were also found to be a predictor of a lessened capacity to generate CFT.
Discussion: Schizophrenia patients present difficulties activating alternatives that could help them face reality transforming a negative outcome into a positive through conditional reasoning. In addition, this impairment is related to acute negative symptomatology, which is not surprising if we take into account these sphere of symptoms include decreased context-dependent emotions and goal-directed activities. The relationship between negative symptoms and deficits in cognition has been well documented, and is known to persist irrespective of age and course of the disease. Taking in account the significant ecological impact of CFT deficits in functional outcome, we suggest that these deficiencies could be considered as potential targets for future treatments of schizophrenia.

T94. Initial psychometric evaluation of social cognitive measures in Singapore

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Background: Social cognition is an emerging area in schizophrenia research. Impaired social cognition in schizophrenia may be a primary mechanism through which patients exhibit poor functioning. Converging evidence indicate that social cognitive processes contribute to a variety of real world outcomes including social competence, quality of life and community functioning in schizophrenia. Social cognition shows promise as a treatment target and significant mediator that influences functional outcome in schizophrenia. While pharmacological agents have yet to demonstrate efficacy in improving social cognition, targeted interventions and remediation efforts improved social adjustment, social functioning and social skills. At present, there is a dearth of research that examines psychometric properties of social cognitive measures, thus limiting accurate and valid measurement of the construct and its related treatment response. The current study seeks to evaluate psychometric properties of 10 social cognitive measures based on results of a RAND panel (Pinkham *et al.*, 2013) in Singapore.
Methods: 46 participants with schizophrenia completed 10 measures of social cognition across 5 domains: Ambiguous Intentions Hostility Questionnaire (AIHQ), Internal, Personal and Situational Attributions Questionnaire (IPSAQ), Bell-Lysaker Emotion Recognition Test (BLERT), Penn Emotion Recognition Test (ER-40), Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT), Profile of Nonverbal Sensitivity (Mini-PONS), Relationship Across Domains (RAD), The Awareness of Social Inference Task-Revised (TASIT-R), Hinting Task and the Empathic Accuracy Task. Participants completed two study visits, held between 4-6 weeks apart. These tasks were evaluated on i) internal consistency, ii) test-retest reliability and iii) utility as a repeated measure as indexed by evaluating practice effect or floor and/or ceiling effect. Data regarding task practicality (mean administration time in minutes) and tolerability (participants' rating on their experience after completing the task) was also collected.
Results: Internal consistency as indexed by Cronbach's α was adequate (0.56-0.92) except for one branch of the MSCEIT. Adequate test-retest reliability was demonstrated on most tests (Pearson's r 0.54-0.84), except the AIHQ and one outcome score for the IPSAQ and two for the TASIT. There was little evidence of practice effects across tasks. With exception of the RAD, where 16% performed below chance level, there was little evidence that indicate floor or ceiling effects. Administration time ranged from 3.76 to 51.78 minutes. Tolerability ratings ranged from 4.78 to 5.45; with 1 representing extremely unpleasant and 7 representing extremely pleasant.
Discussion: Most tasks possess relevant psychometric properties. Nevertheless, continued research is necessary. Further assessment of psychometric properties in larger sample sizes, and test discriminability would be carried out. A brief battery that leverages on the psychometric assessment of each subtest would be formulated. A widely applicable and validated social cognition battery is likely to advance our understanding of social cognitive impairments in schizophrenia and facilitate ongoing remediation efforts and research.

T95. Perceptual inferences in schizophrenia: a preliminary study in healthy participants

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Background: Bayesian inference is a powerful tool that can explain a variety of cognitive processes, including multisensory integration, visual illusions and motor control. Could it also explain pathological symptoms such as hallucinations and delusions? In a recent paper, Jardri and Denève proposed that positive symptoms in schizophrenia could be generated by an imbalance between excitation and

inhibition in brain networks, which leads to circular inference, an aberrant form of inference where bottom up messages are counted more than once (Jardri and Denève, 2013). Such an impairment would lead to a system that "expects what it senses" and thus, overweights even weak sensory evidence. Their hypothesis was then validated by a probabilistic reasoning task (in prep.). Here, we intend to validate, with a pilot study in healthy subjects, a paradigm that could allow for experimentally testing the respective impacts of sensory evidence, prior, and of their combination on perception in schizophrenia and ultimately validating the circular inference framework in the domain of visual perception.
Methods: Necker Cube is an ambiguous figure, known to induce oscillations between 2 mutually exclusive percepts (perceptual bistability). Such figures were continuously presented to 50 healthy participants during 15 consecutive runs. We manipulated sensory evidence by adding shades to the stimuli (3 last runs) and prior expectations by giving different instructions to 3 different groups (15–15 – 20 participants), concerning the presence of an implicit preference. The cue systematically contradicted the instructions. Participants' responses were discretely and pseudo-regularly collected (Mamassian and Goutcher, 2005). Moreover, their eye-movements were continuously recorded using an eyetracker and their psychotic tendencies were measured using the PDI and the LSHS scale.
Results: In the absence of any cue or instruction, the 2 interpretations of the cube were found not to be equiprobable, thus confirming the existence of an implicit prior ($P < 0.001$). Manipulation of this prior had significant opposite effect ($P = 0.009$), either by exacerbating or cancelling the intrinsic bias of the system. The effect of sensory evidence was even stronger ($P < 0.001$), and induced a significant bias corresponding to the direction of the cue, regardless of whether it was congruent or not with the implicit prior. This effect was so strong that it overcame the impact of the instructions and determined the perceptual pattern when sensory evidence adjunction and prior manipulation were combined. Moreover, we found no significant effect of the eye-movements on our results. Finally, we were not able to find significant correlations between bistability (relative predominance, mean phase duration) and the measured psychotic tendencies, mainly because of the small sample and the small range of the answers. Theoretically, we found that the behavior could be well fitted by Bayesian models ("simple" Bayes, model with Markovian statistics) with low statistical dependencies between successive time steps.
Discussion: The above findings will be used as a reference, in order to study patients with psychotic symptoms and test our initial claim that psychosis is the result of over-counted sensory evidence. Some preliminary results from patients will also be presented.

T96. Towards a core dysfunctional timing network in schizophrenia: a meta-analysis

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Background: A focus on temporal processing offers a window into understanding the schizophrenia cognitive profile.
Timing and other cognitive domains are interrelated and share neuroanatomical basis. Increasing levels of cognitive control become them interlinked. Common brain regions engaged in timing and cognitive difficulty are abnormal in schizophrenia. We hypothesize that a dysfunctional temporal/ cognitive change network underlies the mechanism underlying deficient cognition in schizophrenia. The main goal of this study was to identify any brain structure activated both by increases of difficulty while executing a cognitive task and during time perception tasks in schizophrenia patients.
Methods: A search at PubMed and Web of Science was carried out between January 2012 and December 2014 to identify fMRI studies reporting brain activation patterns associated with changes in cognitive control published. Keywords were (fMRI) AND (attention OR working memory OR executive functions OR controlled processes) AND (schizophrenia). Exclusion criteria were studies 1) from which peak coordinates or statistical parametric maps could not be retrieved; 2) limiting their analyses to specific regions of interest; 3) using different thresholds in different regions of the brain; 4) using techniques other than fMRI; 5) that do not specify at least two levels of difficulty of the cognitive task or do not include some contrast between them; 6) considering a resting state or baseline as a lower level of difficulty; 7) using Independent Component Analysis; 8) case reports, qualitative studies, reviews and meta-analyses.
We conducted a Signed Differential Mapping (SDM) meta-analysis of functional neuroimaging studies in schizophrenia patients assessing the brain response to increasing levels of cognitive difficulty. We applied a multi-source pre-processing of the data in order to obtain more accurate and exhaustive recreations of the statistical tridimensional maps of the comparisons between patients and controls for the difficult vs. easy contrast. Next, findings were compared with those from an Activation Likelihood Activate (ALE) meta-analysis on neuroimaging studies exploring time perception in schizophrenia (3). The aim of this comparison was to detect brain regions activated or deactivated by both cognitive difficulty and time perception tasks.
Results: The search identified 1134 citations. Subsequent application of inclusion criteria reduced this number to 43 studies, with a total of 954 schizophrenia patients and 999 healthy volunteers. Patients showed significantly hypoactivation in bilateral inferior frontal and superior occipital gyri, right supplementary motor area, left inferior parietal gyri, left cuneus and red nucleus. They also showed significantly hyperactivation or failure of deactivation in right postcentral and fusiform gyri ($P < 0{,}005$). Findings are globally consistent with the above-mentioned ALE meta-analysis. Both agree in the statistically significant activation of certain brain regions: right frontal areas (mainly BA 6), parietal regions and basal ganglia. Schizophrenia patients showed, relative to healthy controls, significantly lower activation of these areas primarily in the right hemisphere during both time perception and cognitive control tasks.
Discussion: Our findings support the hypothesized activation of dysfunctional timing network by an increase in the difficulty of non-temporal cognitive tasks in schizophrenia.
Timing dysfunction may be at the root of cognitive deficits observed in these patients. Thus, a deficit in timing might be considered a trait marker of schizophrenia cognitive profile.

T97. Does schizophrenia impair the ability to sustain attention? Investigation of the proactive and reactive modes of control by exploring the underpinning oscillatory activity.

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Background: The inability to achieve and maintain the focus of cognitive activity on a given stimulation source or task, i.e. to sustain attention, is considered as a core cognitive deficit of schizophrenia, recognized as a probable causal explanation of multiple impairments observed in these patients (Green, 1996). Nevertheless, experimental results in this topic are not consistent highlighting either alteration or preservation, depending notably on the experimental approach (i.e. inhibiting ongoing behavior versus responding to infrequent targets) (for a review, see Hoonakker *et al*, in preparation). Furthermore, most studies cited in support of this view assessed overall performance rather than time on task effects related to sustaining attention per se (Demeter *et al*, 2013). The aim of our study is to address this controversial issue and to investigate, by exploring the underpinning oscillatory activity, the proactive and reactive modes of control underlying sustained attention ability. Indeed, the Dual Mechanisms of Cognitive Control Theory, proposes that cognitive control operates via two distinct modes: the proactive mode which relies on the anticipation of critical events and the reactive mode (stimulus-related and response-related) which is engaged after their occurrence (Braver, 2012). If this framework has yet proved to be very helpful to understand sustained attention ability in healthy subjects (Staub *et al*, 2014), it becomes even more relevant for schizophrenia in the sense that proactive control and associated fronto-parietal dysfunction may represent a robust marker of schizophrenia (Lesh *et al*, 2013).
Methods: Twenty four patients (9 females; mean age: 40.9 years; years of education: 12.3) and 24 age-, gender- and education-matched healthy controls participated in this within-subject experiment. Two tasks (30- min each) differing only in response mode were used. One of the tasks was the sustained attention to response task (SART;

Robertson *et al.*, 1997), a Go/No-Go task in which digits ranging from "1" to "9" were presented in a random order. Subjects were instructed to respond for each digit and inhibit response for the rare digit 3. In the second task, subjects were instructed to respond only to the rare digit 3. For performance and electrophysiological data analysis, the two tasks were divided into three 10- minute periods.
Results: Our first results which at this time only concern the Go/No-Go task, revealed that patients show reduced performance overall (slower speed of responses and greater attentional fluctuations), but no greater time on task performance decline. Electrophysiological findings showed that the amplitude of the pre-stimulus slow-wave, a marker of proactive control, remained stable with time on task in both groups. However, schizophrenia-related specificities exist notably in the recruitment of stimulus-related reactive control over the course of the task: the amplitude of the P3 (component related to resource allocation) decreases over time and the difference in N2 amplitude between Go and No-Go trials (related to conflict monitoring) is only evidenced during the first period of the task.
Discussion: These initial results suggest, in line with a recent study (Sanz *et al.*, 2012), spared sustained attention ability in schizophrenia even in an extended version of a Go/No-Go sustained attention task. On the electrophysiological level, we demonstrate for the first time that patients utilized reactive control processes decreasingly with time on task. However, contrary to our expectations, they were also able to maintain proactive control over the course of the task.

T98. Orthographic processing and lexical access in patients with schizophrenia: analysis of the N170 component

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Background: Reading has been proposed among the cognitive functions affected in schizophrenia. Evidence comes from standardized tests of passage (GORT, WJTA) or single-word reading (WRAT), for which patients exhibit lower scores than comparison subjects (Martinez *et al.*, 2013; Revheim *et al.*, 2006, 2014). As skillful readers are characterized by the speed and effortlessness with which they recognize written words, the degree of automaticity of word recognition processes seems to be the best indicator of reading level. The present study aimed to investigate the automatization of word recognition processes in patients with schizophrenia. We focused on the first step of word processing, i.e., the orthographic processing by exploring the coding of sublexical representations and the access to lexical representations.
Methods: The orthographic sublexical coding was explored by manipulating mean bigram frequency in words (dependencies among letters in word-forms) while the lexical access was explored by manipulating lexical frequency. A group of patients with schizophrenia and a control group carried out a lexical decision task (i.e., is the presented stimulus a word or not?). Reaction times and the early N170 neuronal evoked response were registered to measure the degree of automatization of word recognition processes.
Results: Behavioral results indicated a significant interaction between bigram frequency and lexical frequency. An inhibitory effect of bigram frequency appeared with high frequency words whereas a facilitatory effect of bigram frequency appeared with low frequency words. No effect interacted with the group. Electrophysiological results indicated a significant effect of bigram frequency and a significant effect of lexical frequency on N170 amplitudes. Larger N170 amplitudes were observed for low frequency than for high frequency words; larger N170 amplitudes were observed for low bigram frequency than for high bigram frequency words. Most importantly, no effect interacted with the group.
Discussion: Behavioral and electrophysiological data showed that patients with schizophrenia, as comparison subjects, were sensitive to orthographic sublexical and lexical information in the course of lexical access. First, patients showed an unimpaired perceptual coding of orthographic properties within the first 200 ms of word perception, suggesting preserved abilities to encode letter position in letter strings and orthographic regularities throughout exposure to print. Second, the results indicated that the activation of lexical representations occurs at an early stage of word processing, suggesting preserved abilities to rapidly map the visual features of a word to its mental representation.

T99. Effects of transcranial direct current stimulation (TDCS) on cognition, brain connectivity and symptoms in schizophrenia

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Background: Schizophrenia (SZ) is characterized by persistent cognitive deficits. TDCS has been reported to be effective in reducing hallucinations and other symptoms in schizophrenia and proposed to have potential beneficial cognitive effects in healthy controls and schizophrenics (SZ). The current research was a double-blind sham-controlled study to investigate the effects of tDCS on cognition, cigarette smoking, and symptoms in SZ. Recent research using fMRI imaging has shown abnormalities in resting state brain connectivity networks (ICN) in schizophasia compared to controls, in the fronto-parietal control network (FPN), default mode (DN) and other brain circuits, and some studies suggest that tDCS can alter these ICN in non-psychotic controls. We also present data from a preliminary open study of active tDCS which investigated tDCS effects on resting state brain connectivity circuits (ICN) in SZ.
Methods: 36 outpatients, with SZ or schizoaffective disorder (SA) participated in double-blind study of 5 sessions of active or sham tDCS (active- tDCS for 20 min, 2 ma). 29 SZ provided valuable data on cognitive effects. Evaluations included MATRICS battery (baseline and 1 day after 5th sessions), VIGIL CPT (session 2), PANSS, and auditory hallucinations scale (Haddock). 4 SZ patients participated in a preliminary open study of active tDCS using the same design, where resting state fMRI (R-fMRI) with 3 Tesla scanner was utilized to investigate changes in ICN between baseline and 5 session of tDCS.
Results: One day after the 5th tDCS session active tDCS SZ showed significant improvements, compared to sham, in MATRICS battery COMPOSITE scores ($P = .009$), MATRICS DOMAIN scores on WORKING MEMORY ($P = .002$), and ATTENTION-VIGILANCE ($P = .02$), as well as T cores on CPT (P T = .028) and Letter-Number Span ($P = .009$). Some of the other MATRICS Battery Domain scores also showed trends for improvement with tDCS. The other cognitive tests, which were evaluated directly after the tDCS session, did not show significant improvement of active vs sham tDCS, although there was a trend for reaction time to improve on VIGIL CPT with tDCS. There were no significant effects of tDCS on PANSS scores or auditory hallucinations. Preliminary R-fMRI data showed 5 sessions of tDCS showed changes in key areas of both executive and default mode networks suggesting an increase in FC strength/coherence for both networks
Discussion: The positive effects of tDCS on cognitive scores on MATRICS battery suggest that tDCS may be an especially useful modality for improving cognition in SZ, but this findings needs to be confirmed and replicated in additional investigations. The beneficial effects of tDCS on improving cognition may be related to changes in connectivity in specific brain ICN networks since some of these ICN have been previously shown to be abnormal in SZ and bipolar patients compared to controls.

T100. Age-specific abnormalities in working memory in early onset psychosis

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Background: Working memory (WM) is often conceptualized as storage buffers that retain information briefly, rehearsal processes that refresh the buffers, and executive processes that manipulate the contents of the buffers.
The prefrontal cortex (PFC) is a brain region featured with working memory function. The exact mechanism of how working memory

operates within the PFC circuitry is unknown, but persistent neuronal firing recorded from prefrontal neurons during a working memory task is proposed to be the neural correlate of this mnemonic encoding.
In our study we can see the difference between WM in patients who have suffered a First Episodic Psychotic (PEP) and controls taking in account the age onset psychosis.
Methods: We included a group of 80 adolescents with a first episode of psychosis compared to a group of controls.
Results: We found an interaction between age (<16 years and ≥ 16 years) and group (psychosis vs controls) in working memory ($P=0.04$). There were no difference in control group between those who are younger (<16 years) and older (≥ 16 years) (12.2 ± 2.3 vs 12.2 ± 2.3; $P=0.1$) in WM. However, we found a significative difference performance in WM between those patients with age younger and older.
Discussion: WM represents one's ability to maintain and manipulate information simultaneously in a short period of time and correlates with other higher order cognitions, such as executive function and fluid intelligence. The patients who have suffered a PEP with 16 or more years have worse WM abilities This area is nuclear for patients with psychosis so it will be able to investigate this kind of therapy to improve cognitive abilities, restore daily functioning and reduce psychotic symptoms.

T101. The relation of schizotypy and cognition with theory of mind in first-degree relatives of patients with diagnosis of schizophrenia

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Background: Many of studies have reported that patients with schizophrenia have Theory of Mind (ToM) deficits. Also, investigations in first degree relatives of schizophrenia patients have reported that ToM deficits may be a candidate of endophenotype for schizophrenia. The aim of this study was to assess the ToM abilities and its relations with neurocognition and schizotypal traits in patients with schizophrenia and their first degree relatives.
Methods: 25 patients with schizophrenia, their unaffected 25 first degree relatives and 30 healthy controls included. To asses ToM, we have used Dokuz Eylül Theory of Mind Index (DEToMI) and to assess neurocognition, we have used Neuropsychological Test Battery for all participants. Patients were assessed with Positive and Negative Syndrome Scale (PANSS) to measure clinical situation. First degree relatives and controls were assessed with Structured Interview for Schizotypy-Revised (SIS-R) to evaluate schizotypal traits. All participants were assessed with Hamilton Depression Rating Scales to measure depressive symptoms.
Results: In first-degree relatives, "faux pas" task scores were found lower than controls and neurocognitive functions were found worser than controls but not in all neurocognitive tests. In relatives, we have found only one strong correlation about ToM task and neurocognitive tests relations. Schizoytpal traits were higher than controls for some subscales. "Faux pas" and "suspiciousness" were correlated with middle power in relatives. In patients, all ToM task scores were lower than controls and many of neurocognitive tests scores were found lower than controls. Weak and middle correlations were found between ToM and neurocognitive measures.
Discussion: In our study, we have found ToM deficits in patient with schizophrenia and their first degree relatives. But, grade of ToM deficits of relatives were among the patients and controls. We found similar results for neurocognitive functions. There are relations between ToM and neurocognitive functions but we have found that degree of relations were substantially weak and middle. Also, in relatives, schizotypal traits were higher and one subscale of Tom and SIS-R were correlated with a middle power. Our results means, ToM has relations with neurocognitive function and schizotypal traits but the grade of this relations are little-middle. This study suggests that ToM may be a candidate of endophenotype for schizophrenia.

T102. Social cognition impairment profiles in treatment-resistant schizophrenia

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Background: The literature on social cognition profiles of patients with schizophrenia is sparse. Social cognition is linked to functional outcome and has become an important treatment objective. Social cognition remediation programs have generated considerable interest as these methods are far less costly than pharmacologic treatment and are likely to be safer. A growing consensus suggests that these interventions produce modest gains for patients with schizophrenia, however, very few of the studies completed to date have had sufficient statistical power to generate firm conclusions. The aims of the study were to assess the social cognition profiles of inpatients and outpatients with treatment-resistant and chronic schizophrenia, and to characterize the demographic and clinical illness features associated with social cognitive functioning.
Methods: Stable schizophrenia inpatients and outpatients ($n=63$) who fulfilled the DSM-IV-TR criteria for schizophrenia or schizoaffective disorder were tested with the Penn Emotion Recognition Test (ER-40), Facial Emotion Identification Task, Facial Emotion Discrimination Task, Dynamic Social Cognition Battery (assessing verbal, non-verbal, facial recognition, Theory of Mind), and the MSCEIT from the MATRICS Consensus Cognitive Battery (MCCB). Cross-sectional characteristics for patients were compared using t-tests and analysis of variance for continuous, and chi-square test for categorical variables. Correlation and multiple linear regression analyses were performed between social cognition measures and demographic variables (gender, age, education), course of illness (duration of illness, number of hospitalizations, comorbid substance abuse, and comorbid anxiety), and current symptoms (PANSS). Due to the small number of patients relative to the large number of independent variables, analyses were conducted unadjusted and adjusted for age and education only. The level of statistical significance was set at $P<0.05$.
Results: Social cognition impairments were marked in patients within all emotion recognition tasks and within the MCCB-MSCEIT domain. 75.12% patients had clinically significant impairment (>1.5 SD below normal mean) in non-verbal emotion recognition, facial emotion identification and social cognition as measured by the MCCB-MSCEIT ($P=0.042$). The global neurocognitive score as measured by the MCCB composite score correlated positively with social cognitive impairment ($r=0.536$, $P=0.023$). Higher age was associated with greater social cognition deficits compared to age-adjusted norms.
Discussion: A large proportion of patients with schizophrenia exhibited significant social cognitive impairments in emotion identification and recognition, and theory of mind, associated with clinically significant severity. These pervasive deficits support a strong emphasis on the need for effective treatment interventions for patients with social cognition impairments.

T103. Metabolic syndrome, abdominal obesity and hyperuricemia in schizophrenia: results from the FACE-SZ cohort

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Background: Abdominal obesity was suggested to be a better predictor than Metabolic Syndrome (MetS) for cardiovascular

mortality, however is has not been extensively studied in schizophrenia. Hyperuricemia (HU) was also suggested to be both an independent risk factor for greater somatic comorbidity and a global metabolic stress maker in patients with schizophrenia.
The aim of this study was to estimate the prevalence of MetS, abdominal obesity and HU, to examine the association between metabolic parameters with HU in a cohort of French patients with schizophrenia or schizo-affective disorder (SZ), and to estimate the prevalence rates of treatment of cardio-vascular risk factors.
Methods: 240 SZ patients (age = 31.4 years, male gender 74.3%) were systematically included. Metabolic syndrome was defined according to the International Diabetes Federation and HU if serum uric acid level was above 360 µmol/L.
Results: MetS, abdominal obesity and HU were found respectively in 24.2%, 21.3% and 19.6% of patients. In terms of risk factors, multiple logistic regression showed that after taking into account the potential confounders, the risk for HU was higher in males (OR = 5.9, IC95[1.7-21.4]) and with subjects with high waist circumference (OR = 3.1, IC95 [1.1-8.3]) or hypertriglyceridemia (OR = 4.9, IC95[1.9-13]). No association with hypertension, low HDL cholesterol or high fasting glucose was observed. Only 10% of patients with hypertension received a specific treatment, 18% for high fasting glucose and 8% for dyslipidemia.
Discussion: The prevalence of MetS, abdominal obesity and hyperuricemia is elevated in French patients with schizophrenia, all of which are considerably under-diagnosed and undertreated. HU is strongly associated with abdominal obesity but not with psychiatric symptomatology.

T104. Somatic diseases increase the risk of early re-hospitalization among 6,987 incident patients with schizophrenia

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Background: Prior somatic diseases are associated with an increased incidence of schizophrenia, but the extent to which somatic diseases are related to subsequent re-hospitalization after a first-time diagnosis with schizophrenia is unknown. To increase awareness about the importance of somatic diseases among patients with schizophrenia, the current study investigated whether prior somatic diseases predicted subsequent psychiatric re-hospitalization among people with incident schizophrenia.
Methods: Using Danish nationwide register data, we conducted a cohort-study among all individuals born in Denmark after 1977, and with a first-time schizophrenia diagnosis between January 1, 1996 and December 31, 2012, and followed until December 31, 2013. All prior somatic diseases diagnosed within the secondary healthcare system were identified, and we adjusted for important covariates (age, gender, year of diagnosis, in- or outpatient at first-time schizophrenia diagnosis, education, use of antipsychotics within the year prior to first-time diagnosis, parental psychiatric contacts and highest educational level, and psychiatric diagnoses prior to first-time schizophrenia diagnosis). We performed multivariable Cox proportional hazards regression analysis and report hazard rate ratios (HRR) of the association between prior somatic disease(s) and risk of (re)-hospitalization after one, two and five years.
Results: Of 6,987 individuals with incident schizophrenia, a total of 6,563 (94.0%) have had a hospital contact with a somatic disease prior to the schizophrenia diagnosis. Any somatic disease predicted a 1.32 (95%-CI: 1.06-1.65) fold higher re-hospitalization risk during the first five years of follow-up. We found a significant dose-response relationship between the number of prior somatic diseases and re-hospitalization risk ($P < 0.05$). In particular, infectious diseases (HRR = 1.15; 95%-CI = 1.04; 1.28), cardiovascular diseases (HRR = 1.33; 95%-CI = 1.09; 1.62), musculoskeletal diseases (HRR = 1.13; 95%-CI = 1.1.03; 1.25), epilepsy (HRR = 1.23; 95%-CI = 1.05; 1.44), and brain injury (HRR = 1.11; 95%-CI = 1.01; 1.21) significantly increased re-hospitalization risks.
Discussion: The current study identifies specific pre-existing somatic diseases as candidate predictors for the early illness course following first diagnosis of schizophrenia. In particular, cardiovascular diseases increased the risk of hospitalizations. Notably, well established risk factors for schizophrenia did not materially attenuate predictive effects of prior somatic diseases. Future studies should investigate if better treatment of somatic diseases may have an impact on the early treatment course of schizophrenia.

T105. Body weight and clinical outcomes in first episode psychosis patients: a 1-year follow-up study.

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Background: Patients with schizophrenia have increased risk of obesity, high morbidity for cardiovascular disorders and reduced life expectancy as compared to the general population (Saha *et al.* 2007; De Hert *et al.* 2011), which at least in part has been attributed to weight gain and dyslipidemic effects of antipsychotic drugs (Allison *et al.* 1999). There is, however, some evidence of a positive correlation between weight gain and clinical response to antipsychotic drug treatment (Meltzer *et al.* 2003; Hermes *et al.* 2011), possibly due to increased cholesterol favoring myelin development and neuron protection (Ferno *et al.* 2005 and 2006). In order to minimize the influence of environmental factors and poor treatment response that typically increases along the disease course, the current study focused on patients with first episode psychosis (FEP). We, thus, examined whether weight at inclusion and weight gain during antipsychotic drug treatment is associated with symptomatic remission and global functioning at 12-month follow-up in FEP. We hypothesized that there might be a positive correlation between weight gain and clinical outcome in FEP patients.
Methods: A total of 122 FEP patients were included from the ongoing naturalistic longitudinal TOP-study (Oslo, Norway). Inclusion criteria were (1) age 18 to 65 years and (2) a first episode of non-affective psychosis according to DSM-IV.
The mean age of the patients was 28.52 (SD: 7.60), and 43 (35%) were women. Median duration of untreated psychosis (DUP) was 40 weeks (range: 1–572). Ninety-nine patients (81%) were using antipsychotics at baseline. Weight was assessed with baseline BMI (i.e. body weight (kg) divided by the square of height (m)). Weight gain (kg) was measured as the difference between baseline weight and weight at 12 months. Antipsychotic use was dichotomized into yes/no variables. Symptomatic remission was measured with PANSS (Kay *et al.* 1987) using the criteria outlined by Andreasen *et al* 2005, and overall functioning with GAF split version (Guy *et al* 1976). Regression models were used to assess how BMI at baseline and weight gain during the first 12 months correlates with clinical remission and global functioning (GAF-F). Based on previous literature, relevant covariates such as age, gender, ethnicity and DUP were included in the analyses.
Results: Among the 122 FEP patients eligible for analysis, preliminary analyses of GAF-F using linear regression models did not show a significant association with baseline BMI ($P = 0.65$) or weight gain ($P = 0.47$), neither did logistic regression models for remission and baseline BMI ($P = 0.39$) or weight gain ($P = 0.83$). Multiple covariates including DUP, age, gender and ethnicity were used in all analyses.
Discussion: Previous literature has suggested a possible link between weight gain and favorable clinical response to antipsychotic treatment. Our preliminary analyses, however, does not support an association between BMI at baseline or weight gain during 12 months of follow-up and global functioning or symptomatic remission. This is in agreement with some studies on weight gain and clinical response (Hummer *et al.* 1995), but incongruent with others (Meltzer *et al.* 2003). Possible reasons for this might be differences in the subjects' age, prior antipsychotic exposure, study duration and outcome measures. Advanced models adjusted for multiple confounders will be performed to examine the associations in greater details.

T106. Prolactin concentrations in antipsychotic-naïve patients with schizophrenia and related disorders: a meta-analysis

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Background: The use of dopaminergic antipsychotics is associated with hyperprolactinaemia. However, some studies have found increased prolactin concentrations in patients with nonaffective psychosis (NAP) when they are antipsychotic-naïve (Song *et al*, 2014; Albayrak *et al*, 2014; Garcia-Rizo *et al*, 2012), while other studies have failed to replicate an increase.
Methods: We conducted a systematic review and meta-analysis of studies of prolactin in antipsychotic-naïve, newly diagnosed patients with NAP. Males and females were considered separately. We identified articles by searching Pubmed, PsycInfo, Web of Science, and reviewing reference lists of identified studies. We also conducted meta-regression of potential moderating variables.
Results: Seven studies of males ($N = 141$ patients, $N = 191$ controls) and five studies of females ($N = 67$ patients and $N = 116$ controls) met criteria for inclusion. The mean effect size for males was 1.02 (95% CI, 0.77, 1.26; $P < 0.001$) and 0.43 for females (95% CI 0.11, 0.76; $P < 0.02$). Meta-regression analyses for age, smoking, body mass index and cortisol were not significant. Funnel plots did not suggest the presence of a publication bias.
Discussion: Our meta-analyses found significantly increased prolactin levels in both male and female antipsychotic-naïve patients with NAP. The effect size was much larger for males than females. The small number of studies and limited matching for potentially confounding variables were limitations of the individual studies. These results have clinical implications, as prolonged hyperprolactinemia may lead to sexual dysfunction and osteoporosis, and first-generation and some second-generation antipsychotics can cause hyperprolactinemia.

T107. Lipid profile in schizophrenia: Tunisian study about 78 patients with schizophrenia and 68 controls

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Background: Cardiovascular diseases are common co morbidities of schizophrenia and constitute the main factors of high mortality in this pathology. Cardiovascular damages are favored by some risk factors, of which one of the most important is dyslipidemia. In this context, a study of lipid profile in schizophrenia is interesting.
The aims of this study were to estimate the prevalence of dyslipidemia among patients with schizophrenia, compare it with healthy controls and study its correlations with sociodemographic, clinical, and therapeutic characteristics.
Methods: It was a cross-sectional, comparative and analytical study conducted between April 2013 and March 2014 on 78 patients with schizophrenia and 68 healthy subjects who benefited from the dosage of four serum lipid parameters: total cholesterol (TC), High Density Lipoprotein Cholesterol (HDL-c), Low Density Lipoprotein Cholesterol (LDL-c) and triglycerides (TG). For associations with the sociodemographic and clinical settings, we used an information sheet and the following psychometric scales: PANSS (Positive And Negative Syndrome Scale), CGI (Clinical Global Impression), GAF (Global Assessment of Functioning) and Calgary scale for depression.
Results: Patients showed significantly higher levels of TC and LDL-c than controls with respectively ($t = 2.83$, $P = 0.008$) and ($t = 9.35$, $p < 0.001$). They also had a significantly higher cardiovascular index (CRI = TC / HDL-c); ($t = 2.23$, $P = 0.033$).
The rate of patients with hypercholesterolemia (TC ≥ 5mmol/l) was significantly higher than that of healthy controls (Relative Risk = 2.96; $P = 0.002$); likewise, the rate of patients with a hyper LDL-c (LDL-C ≥ 3 mmol / L) was significantly higher than that of healthy controls (Relative Risk = 18.79; $p < 0.001$). For the patients, LDL-c levels were significantly higher for patients aged 35 or over, the CRI was on average higher than 4 for men indicating a high cardiovascular risk and lower than 4 for women.
Patients with alcohol use showed significantly higher TC levels ($t = 1.6$; $P = 0.038$) and higher CRI ($t = 1.94$; $P = 0.015$), they had significantly lower LDL-c levels ($t = -2.91$; $P = 0.002$) and HDL-c levels ($t = -2.45$; $P = 0.044$). Patients with cannabis use showed lower TG levels ($t = -2.02$; $P = 0.049$).
Concerning clinical associations, The comparison of different patient groups according to the type of schizophrenia found that the paranoid type was associated with values of the CRI significantly lower compared to other patients ($t = 1.98$; $P = 0.05$). There was a positive correlation between the scores of Calgary scale of depression and of TG plasma concentrations ($r = 0.39$; $p < 0.001$).
Concerning therapeutic associations, there was a negative correlation between TG plasma concentrations and antipsychotic doses in chlorpromazine equivalent ($r = -0.3$; $P = 0.008$).
Discussion: The relatively small number of both populations, the small number of patients treated by atypical antipsychotics and the lack of evaluation of nutritional statute should be noted.
The vast majority of the literature confirms that lipid disturbances were more frequent in patients with schizophrenia and that these disturbances concern all lipid parameters. Reviewing the studies focusing on lipid profile in schizophrenia, lipid disturbances appear to be more common for older patients and for men, as it is the case in our study. Smoking and alcohol consumption appear to disrupt all lipid parameters.
Concerning clinical associations, most studies are consistent with our work. In fact, paranoid type of schizophrenia and the positive symptoms appear to be associated with less dyslipidemia while depressive symptoms worsen lipid parameters.

T108. Blood metabolite signature of the development of metabolic syndrome in first-episode psychosis

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Background: Psychosis patients are a high-risk group for type 2 diabetes (T2D). The co-morbidity is hypothesized to be related to both treatment side-effects and to metabolic changes occurring during the psychosis. However, the molecular mechanisms of this co-morbidity are not known currently. Metabolomic profiling could potentially enable the early personalized assessment of the T2D-risk and the selection of the lowest-risk antipsychotic treatment. In this study, we investigated aberrations in blood metabolite levels in first-episode psychosis patients at early stages of the antipsychotic treatment, and followed-up the development of the patients to associate the observed aberrations with clinical outcomes.
Methods: First-time psychosis patients ($N = 36$; among whom 18 with schizophrenia) were followed up for one year with data collected at baseline, two months and one year. Blood metabolites were analysed with two mass spectrometry-based platforms with broad analytical coverage of polar metabolites and molecular lipids (two-dimensional gas chromatography coupled with time-of-flight mass spectrometry, GC × GC-TOFMS, 363 metabolites; and ultra-high performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry, UHPLC-QTOFMS, 318 lipids; respectively). The observed metabolomic variables were clustered with a Bayesian nonparametric model to identify coherent compound groups. The molecular cluster profiles were analysed for differences between the case and control groups, for temporal changes during the follow-up, and for effects of antipsychotic medication (olanzapine, $N = 11$; risperidone, $N = 9$). Further, the profiles of metabolically healthy subjects at baseline ($N = 10$) were analysed for associations to follow-up changes in clinical markers of metabolic syndrome. Uncertainty arising from measurement noise, subject heterogeneity and low sample size were accounted for by using probabilistic modelling, non-parametric statistical methods and resampling techniques.
Results: Case subjects had lower levels of fatty acids and higher levels of polyunsaturated triacylglycerols at baseline. Saturated and

monounsaturated triacylglycerols at baseline were associated with a follow-up change in body mass. Among the subjects who were metabolically normal at baseline, the levels of carboxylic acids and phenols were inversely associated with follow-up changes in body mass and waist circumference, while saturated and monounsaturated triacylglycerols as well as lysophosphatidylcholines were inversely associated with changes in the insulin level. Olanzapine treatment increased the phosphatidylcholine levels, and risperidone treatment decreased the levels of saturated and monounsaturated triacylglecerols, carboxylic acids and high-density lipoprotein (HDL), when compared to other treatments.
Discussion: We identified a blood metabolite signature with disrupted levels of triacylglycerols, phosphatidylcholines and fatty acids in first-episode psychosis. Some of the changes were associated with follow-up changes in clinical indicators of metabolic syndrome, suggesting that metabolomic profiling could be a potential tool for identifying psychosis patients at the highest risk of developing a metabolic syndrome and T2D. The metabolite groups with altered blood levels in the first-episode psychosis patients of this study have been earlier reported to be associated with the development of T2D in non-psychotic individuals, suggesting that different mechanisms disrupting the molecular metabolic pathways lead to similar outcome with respect to the metabolic disease.

T109. Schizophrenia and metabolic syndrome: follow-up study

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Background: Metabolic syndrome (MetS) plays a major role in the decreased survival rate of schizophrenia patients. The high prevalence of MetS in the schizophrenia population is associated with the use of antipsychotic drugs, genetic factors, the psychotic process itself and lifestyle. In a previous study conducted between 2004-2007, we found that the prevalence of MetS in schizophrenia patients was higher from the general population only within the 20–29 age group. The overall 10 year risk of coronary heart disease (CHD) was calculated as 5.9% which was higher in patients with MetS compared to those without. The aim of the present study was to assess whether a change in the MetS prevalance has occurred in the initial patient population through time, and to determine the related prognostic factors for MetS, including sociodemographic and clinical characteristics, severity of psychopathology, antipsychotic treatment, physical activity and dietary habits. In addition, we aimed to compare the current CHD prevalence with the previously estimated 10-year risk.
Methods: The study was conducted at Hacettepe University Faculty of Medicine, Department of Psychiatry, Ankara, Turkey. The same 319 patients with schizophrenia or schizoaffective disorder who had been included in the initial study were tried to be reached for reevaluation. Physical measurements and laboratory tests indicative of metabolic parameters were performed. Patients were evaluated with the Positive and Negative Syndrome Scale (PANSS), UKU Side Effect Rating Scale (UKU), International Physical Activity Questionnaire (IPAQ), 24 Hour Dietary Recall Method and Nutrition Information Systems Package Program (BEBIS, version 6.1). Difference between the groups were analysed with the chi square and Mann Whitney U tests. The Univariate Variance Analysis and Kruskal Wallis tests were used when comparing two or more independent groups. The significance of the change in MetS prevalances was investigated with the McNemar test.
Results: One hundred and forty nine patients were evaluated, 19 patients refused to participate in the study, 18 patients were determined to be deceased, and remaining 133 patients could not be reached. According to the ATPIII, ATPIIIA, and IDF criteria, MetS prevalences increased from 34.2% to 44.3%, 37% to 53%, 41.7% to 55.7% respectively, through a mean follow up period of 8 years. Shorter period of psychiatric institutionalization, higher UKU total score, higher daily consumption of sugar, cholesterol, and polyunsaturated fatty acids (PUFA) were found in patients with MetS. Higher daily consumption of sugar and PUFA were determined among patients who developed MetS during follow-up. Overall mortality ratio was calculated as 9.67%. Coronary heart disease related mortality ratio was 33.3% and increased up to 72.2% when unknown causes of death was included to this ratio. Due to the high percentage of patients lost to follow up, a direct comparison of the current CHD prevalence with the previously estimated 10-year risk could not be made.
Discussion: Metabolic Syndrome prevalance was found to be increased among schizophrenia patients through time. Our study implies no association between the increase in MetS prevalance and sociodemographic/clinical characteristics, severity of psychopathology, and antipsychotic therapy. It seems that causal factors such as nutritional status, unrelated to clinical features and psychiatric treatment, play a role in this increased prevalance of MetS. The majority of deaths in schizophrenia patients was found to be due to CHDs.

T110. Clinical features of schizophrenia patients with violent behaviours: the need to consider distinct subtypes

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Background: Violent behaviour has important social relevance for the political, criminal justice, and health care systems. Evidence has accumulated that people with schizophrenia are associated with a greater risk of violence compared with the general population. Nevertheless, patients with schizophrenia do not constitute a homogeneous population and distinct phenotypes of schizophrenia patients (SP) with violent behaviour have been identified. However, little is known about the clinical features that are associated with these forms of behaviour. Different authors have suggested that at least two distinct pathways could lead to violent behaviour in schizophrenia: one associated with premorbid conditions, including antisocial conduct and another associated with the acute psychopathology of schizophrenia.
Besides, some authors have indicated that patients suffering from delusional misidentification syndromes (DMS) present an increased risk for violent behaviours with medical and legal consequences. DMS are group of phenomena whereby patients misidentify familiar persons, objects, or themselves and believe that they have been replaced or transformed. The problem is that DMS are descriptive and do not denote well-defined mental disorders, and so there are no formal guidelines for delineating the standards of assessment of these syndromes. Accordingly, we proposed to systematically test familiarity disorders in SP.
Methods: In this study, our goal was twofold: first, we aimed at identifying the clinical features that are associated with violent behaviour in SP, and more especially determining if some of these clinical features are more specifically associated with a particular form of violent behaviour; second, we focused on the prevalence of familiarity disorders and compared the profiles of patients with and without history of familiarity disorders.
24 incarcerated individuals who meet the diagnostic criteria of schizophrenia have been recruited. Psychotic symptoms, substance-use disorders and antisocial personality disorder have been assessed using the Positive and Negative Symptom Scale (PANSS) and the Mini International Neuropsychiatric Interview (MINI). The MacArthur Community Violence Interview and the Baratt Impulsivity Scale have been used to assess and characterize aggressive behaviour and impulsivity. Delusional misidentification syndromes have been explored on the basis of the psychiatrist interview.
Results: In our sample, 67% of patients presented substance use disorders, 71% presented or had presented a familiarity disorder and 74% have committed a severe physic assault (homicide or homicide tentative). In the group of patients who have committed a severe physic assault, we found a lower prevalence of antisocial personality disorder (33% versus 50% in the group without history of severe physic assault), but a higher prevalence of familiarity disorder (82% versus 50%). The comparison of patients with and without history of familiarity disorders revealed that more patients with history of familiarity disorders have committed severe physic assault. Moreover, these patients showed a higher PANSS score.
Discussion: These preliminary results confirm the heterogeneity of aggressive behaviour in SP, with in particular a profile of patients that present more psychotic symptoms, a familiarity disorder and who are at risk for severe violent behaviour such as homicides. The recruitment

need to be continued to confirm these data. A better understanding of the causal mechanisms involved in violent behaviour in SP is necessary to improve the assessment of the risk of violence by psychotic individuals and to contribute to an improvement in the therapeutic care of those patients.

T111. Reliability and validity of low scores on the positive and negative syndrome scale (PANSS) and the influence of prior information

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Background: Advances in the treatment of schizophrenia spectrum disorders have led to improved prognoses, but have also given rise to the question what exactly should be considered remission in the context of these disorders. The Remission in Schizophrenia Working Group recommended that for symptomatic remission, a patient has to maintain scores of mild (a score of 3 on the PANSS) or less on all of the following items: Delusions (P1), Unusual Thought Content (G9), Hallucinatory Behavior (P3), Conceptual Disorganization (P2), Mannerisms / posturing (G5), Blunted Affect (N1), Social Withdrawal (N4) and Lack of Spontaneity (N6). It was tested whether the PANSS could adequately detect patients in remission who may be so symptom-free that they can be considered to function at the same level as "healthy controls" and whether prior information regarding the patient's diagnosis may influence scoring of the PANSS.
Methods: This study included three groups of participants: four interviewees, two PANSS interviewers and 25 additional PANSS raters. The CAPE was administered to ensure none of the interviewees would be commonly considered "ultra high risk". Interviewers and raters were either told that he / she would score a PANSS interview with someone (condition A), and once after being told via email that he/she would conduct and score a PANSS interview with someone considered at ultra high risk for developing a psychotic disorder (condition B). Data were analyzed on the subscale level, secondly the data were analyzed on an item level and finally for exploratory purposes the in individual ratings were examined. To test whether prior information influenced the PANSS ratings paired samples t-tests were performed.
Results: Our sample of healthy controls received a significantly lower score on all scales when compared to the results from the validation study conducted by Kay *et al.* (1987). We examined the individual ratings and compared them with the remission criteria. The results showed that one healthy interviewee did not meet these criteria as rated by four PANSS raters. However ten other raters did rate this participant as being in remission. Furthermore all other individual ratings met the remission criteria. As for the two experimental conditions, no significant differences were found between the condition in which the raters had prior information and the condition in which they did not have this information.
Discussion: Informing interviewers and/or raters that persons are at risk of psychosis does not significantly influence their scoring. On average, raters did not rate participants as suffering from a psychotic disorder. In addition, the healthy subjects differed significantly on the PANSS total and subscale scores from reference scores of schizophrenia patients. These results should allay most concerns regarding the use of the PANSS to detect a state of remission defined by the Schizophrenia Working Group. The single rating where one interviewee did not meet the criteria for remission should likely be considered measurement error.

T112. Demographic, clinical, functional and cognitive profiles of individuals presenting with at-risk mental state (ARMS) for psychosis to arms screening program in Hong Kong

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Background: An increasing number of specialized early intervention programs using standardized clinical criteria in identifying individuals with at-risk mental state (ARMS) for psychosis have been established worldwide in the two decades. Literature has indicated that approximately one-third of ARMS subjects will develop full-threshold psychotic disorder over 3 years. Thus far, the majority of clinical services and research on ARMS were conducted in western countries. Data on baseline profiles and clinical trajectories of ARMS subjects in Chinese population are lacking.
Methods: Ninety-eight individuals aged 15-40 years who fulfilled the clinical criteria for ARMS by Comprehensive Assessment of At Risk Mental State (CAARMS) were recruited from a pilot screening program in Hong Kong between 2014-2015. Subjects will be followed up for 2 years. This report focuses on the findings of baseline assessments encompassing socio-demographic, clinical, functional and cognitive profiles.
Results: The sample had a mean age of 20.9 years. The majority were single (91.8%) and full-time students (61.2%), and 43% were male. Of the 98 subjects, 81, 5, 3 and 9 were categorized as attenuated psychotic symptom, brief-limited intermittent psychosis, vulnerability, and mixed groups (attenuated psychosis and vulnerability), respectively. Approximately 45% had psychiatric co-morbidity with depressive disorder (26.5%) being the most common diagnosis, and 12 subjects (12.2%) had history of attempted suicide. Most subjects exhibited poor role (GF: Role Scale score < 7; 71.4%) and social functioning (GF: Social Scale score < 7; 65.3%). The sample displayed significantly poorer cognitive functions than matched healthy controls ($n = 32$) in terms of working memory ($P < 0.001$), processing speed ($P < 0.001$), sustained attention ($P < 0.01$), verbal fluency ($P < 0.001$), and verbal ($P < 0.01$) and visual memory ($P < 0.05$) domains.
Discussion: Our findings concur with the literature that ARMS subjects display a high rate of psychiatric co-morbidity, poor social and role functioning, and significant cognitive impairment. Data on 2-year follow-up assessments, which are currently underway, will help clarify the longitudinal outcome of ARMS and prediction of psychosis transition.

T113. Early psychosis patients' and relatives' attachment style: association with clinical and functional presentation

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Background: Research in both clinical and early psychosis samples is increasingly indicating that the patients' attachment style impacts on psychosis symptom expression and functional adaptation. However, to our knowledge, the role of the relatives' attachment style has not been previously examined. This is of relevance given the critical role of the family environment on the patients' level of severity and long-term outcome. This study examined whether attachment styles of both early psychosis patients and their unaffected relatives were associated with patients' clinical and functional presentation.
Methods: A total of 31 (20 At-Risk Mental State and 11 First Episode Psychosis) patients in the early stages of psychosis and their respective relatives participated in the study. Relatives were those who had most contact and/or the most significant relationship with the patient. Both patients and relatives completed the Psychosis Attachment Measure. In addition, patients were administered the Positive and Negative Syndromes Scale and two complementary measures of social functioning, one based on the clinicians' perspective (the Global Functioning—Social Scale) and another based on the patients' perspective (the short version of the Social Functioning Scale). The analyses examined the associations of patient and relative attachment dimensions (anxiety and avoidance) with patient symptom dimensions (positive, negative and general psychopathology) and social functioning.
Results: Correlational analyses indicated that patients' attachment anxiety was positively associated with general psychopathology, whereas no associations were found between attachment avoidance and symptom dimensions. Self-reported social functioning was positively associated with patients' attachment anxiety and negatively associated with patients' attachment avoidance. Relatives' attachment

anxiety was inversely related to patients' negative symptoms. No significant associations were found with relatives' attachment avoidance. Notably, all significant associations were of medium effect size.
Discussion: The preliminary results suggest the relevance of considering the role of the relatives' attachment style, given that attachment style of both patients and relatives may affect the expression of symptoms/functioning in the early stages of psychosis. Future studies may consider investigating how patients' and relatives' attachment styles interact with other components of the family environment (such as relatives' expressed emotion and illness attributions) in affecting the course of early psychosis. It may be useful to examine patients' and relatives' attachment style in the context of psychological formulation and treatment planning of early psychosis patients.

T114. Affective symptoms in first episode psychosis: a dimensional approach

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Background: The affective dimension in first episode psychosis (FEP) has received relatively little attention compared to the focus on psychotic features. This may be in part because the current classification of endogenous psychoses is based on the Kraepelinian neat schizophrenic/affective dichotomy, despite the fact that this model does not fit to Schneider's "cases-in-between" - who present both prominent mood and psychotic symptoms, thus raising the likelihood of a continuum between schizophrenia and bipolar affective disorder.
Our aims were to investigate the prevalence and significance of affective symptoms in FEP and their relationship with current categorical diagnostic classification.
Methods: An affective assessment including Calgary Depression Scale for Schizophrenia (CDSS) and Young Mania Rating Scale (YMRS) on 144 FEP patients at their first contact with psychiatric services in South London, UK, was performed as part of the Genetics and Psychosis (GAP) study.
A principal component analysis of CDSS and YMRS was carried out and composite scores of each dimension were obtained using Anderson-Rubin method. Patients were grouped in affective psychosis (AP) and non affective psychosis (NAP) on the basis of their Operational Criteria Checklist for Psychotic Illness (OPCRIT) diagnosis, and the ability of affective dimensions to discriminate this diagnostic dichotomy was tested after analysis of variance.
Results: The occurrence of depressive symptoms was found to be common in both affective (CDSS scores: $M = 5.5$, $SD = 5.6$) and non affective (CDSS scores: $M = 4.7$, $SD = 5$) psychosis; $t(141) = 0.8$, $P = 0.4$. Manic symptoms were found to be present in both affective (YMRS scores: $M = 5.8$, $SD = 5.1$) and non affective (YMRS scores: $M = 5.7$, $SD = 5.7$) psychosis; $t(141) = 0.1$, $P = 0.36$.
A three component-model was the best solution found to describe the spectrum of affectivity in FEP, which shared three core of symptoms, namely depression, activation, and mania. The group of non affective psychosis showed higher scores on the 'activation' dimension [$F(1,138) = 4.19$, $P = .043$; Bonferroni corrected] than the group of affective psychosis. The other affective dimensions didn't show any significant difference between the groups.
Discussion: Our findings challenge the clear-cut dichotomy concept of schizophrenia versus mood disorders. We showed that affective symptoms overlap in the two groups which, theoretically, have to be mutually excluded – i.e. paradoxically, we found higher level of activation in the so-called non-affective psychosis.
Thus, dimensionality is a good basis to depict the affective spectrum of psychosis, cutting across multiple traditional diagnostic categories. In the long run, dimensional approaches to psychosis, reflecting the continuous symptom distribution, may be perhaps useful to investigate more biologically defined phenotypes.

T115. A multidimensional examination of delusionality and insight in body dysmorphic disorder versus psychotic disorders

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Background: Body dysmorphic disorder (BDD) is characterised by (i) an excessive preoccupation with an imagined defect in appearance, as well as (ii) repetitive behaviours and/or mental acts that occur in response to the preoccupation. Yet little is known about the nature of these overvalued ideas, as well as whether and how they differ from delusional beliefs typically encountered in psychosis. This study therefore aimed to perform a multidimensional examination of delusionality and insight in BDD relative to schizophrenia (SCZ) and schizoaffective disorder (SZA).
Methods: Participants were 27 BDD participants, 20 SCZ/SZA participants and 42 non-clinical controls (NC). Standard clinical and demographic information was collected. These participants also completed the Brown Assessment of Beliefs Scale (BABS) in relation to a principal preoccupation regarding body shape/weight in BDD (or general body dissatisfaction in NC) or a predominant delusion in SCZ/SZA. The Peters Delusions Inventory (PDI) was employed to assess a range of unusual beliefs and mental experiences.
Results: For total BABS, BDD ($M = 16.4$, $SD = 6.4$) and SCZ/SZA ($M = 15.0$, $SD = 5.0$) participants scored significantly higher than NC participants ($M = 9.3$, $SD = 5.1$). This pattern of significance was replicated for individual BABS items, except for Perception of Others' Views (BDD = SCZ/SZA = NC) and Reference (BDD > SCZ/SZA = NC). On the PDI, there were significant group differences on the number of questions endorsed (SCZ/SZA > BDD > NC), with the BDD and SCZ/SZA groups also differing significantly from the NC group on dimensions of Distress and Preoccupation, but not Conviction.
Discussion: These findings suggest that appearance-related concerns in BDD may not merely represent overvalued ideas, but in fact, bear a strong semblance to delusions often seen in psychosis. Such an inference conveys key nosological and therapeutic implications.

T116. Auditory verbal hallucinations in bipolar disorder (BD) and major depressive disorder (MDD): a systematic review

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Background: Auditory verbal hallucinations (AVHs) are not uncommon in bipolar disorder (BD) and major depressive disorder (MDD), but there has been scant research in the area. The current paper aims to draw together and provide a critical overview of existing studies of AVHs in BD and MDD.
Methods: A systematic review was undertaken using the search terms 'hallucinations' or 'hearing voices' in conjunction with 'bipolar disorder', 'mania' or 'manic-depressive' or 'major depressive disorder' or 'depression' or 'affective disorders' or 'mood disorder'. After applying a pre-defined set of inclusion criteria, 14 eligible peer-reviewed publications were accepted for further analysis.
Results: Prevalence rates of AVHs in BD (11.3-62.8%) and MDD (5.4-40.6%) varied. When psychotic features were examined, persecutory and grandiose delusions were especially common in BD (though the latter did not necessarily occur in conjunction with AVHs). A single known neuroimaging study has suggested increased fronto-temporal connectivity relating to AVHs in BD.
Discussion: AVHs remains a central but largely understudied symptom in BD and MDD. Methodological challenges relating to fluctuations in mood states and limited use of validated instruments, coupled with post-episode recall bias, pose as specific barriers to the collection of meaningful phenomenological information. Future research examining its phenomenology and clinical/neural correlates could bring about positive clinical implications as well as adapted therapeutic applications.

T117. Domains of psychosis in schizophrenia spectrum disorders

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Background: Psychotic disorders are defined by five domains of psychopathology: delusion, hallucination, disorganized speech, abnormal psychomotor behavior, and negative symptoms. Abnormalities in two of the five domains of psychosis are sufficient for the diagnosis of schizophrenia spectrum disorders. We hypothesized that schizophrenia spectrum disorder patients with abnormalities in no more than two domains differ in illness severity and functional impairment from patients with abnormalities in three or more domains of psychosis.
Methods: Chronic patients with schizophrenia spectrum disorders (104 schizophrenia and 59 schizoaffective disorder patients) were assessed with SCID-IV-TR, HAMD, YMRS, and PANSS. 63 patients were diagnosed with abnormalities in only two domains, the remaining 100 patients were diagnosed with abnormalities in three or more domains. The two groups were matched for age, gender, and race.
Results: Patients with abnormalities in three or more domains of psychosis had a greater number of psychiatric hospitalizations ($P < 0.05$), higher PANSS positive and total scores ($P < 0.01$ and $P < 0.05$), and lower general functioning as measured by the GAF scale ($P = 0.06$). Patients with abnormalities in no more than 2 domains of psychosis were more often diagnosed with anxiety disorders ($P < 0.05$) and less often with substance use disorders ($P < 0.05$).
Discussion: The polythetic definition of schizophrenia spectrum disorders leads to varying degrees of illness severity. We found that patients with less severe psychosis had higher rates of anxiety disorders and were less likely to be diagnosed with substance use disorders. This provides evidence that the number of psychotic symptoms can explain some of the heterogeneity of schizophrenia spectrum disorders.

T118. Low vitamin d associated with negative and depressive symptoms in psychotic disorders, but not with pro-inflammatory immune markers

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Background: In cohorts of patients with psychotic disorders the prevalence of vitamin D deficiency is high. Low levels of circulating 25-hydroxy vitamin D (S-25 OHD) are found to be related to severity of symptoms, but there is no designated symptom profile linked to low S-25OHD. Our first aim was to test if low S-25OHD was associated with increased positive or negative symptoms measured by the Positive and Negative Symptom Scale for schizophrenia (PANSS) and if low S-25OHD was associated with more severe depression measured by the Calgary Depression Scale for Schizophrenia (CDSS). Secondly, as vitamin D is perceived as a regulator of the immune system, we hypothesized that the associations between S-25OHD and symptomatology were partly mediated by pro- inflammatory immune markers found to be associated with increased psychotic and depressive symptoms.
Methods: Participants ($N = 358$) with a medical history of one or more psychotic episodes were recruited consecutively from in- and outpatient psychiatric units from a catchment areas based health care system. A five factor model from the PANSS was used to evaluate positive and negative symptoms. We performed multivariate regression models for each of the outcome variables to evaluate the effect of S-25OHD on the outcomes i.e. positive symptom factor, negative symptom factor, depressive symptoms and suicidal ideations (dichotomized from item 8 on CDSS). Variables with significant bivariate correlations with both the outcome variable and S-25OHD were entered hierarchical in blocks as possible confounders in the models. For the second research aim we investigated the correlations between S- 25OHD and the pro- inflammatory markers sTNF- R1, IL- 1Ra and OPG in a subsample with available immune analyses ($N = 232$).
Results: Low S-25OHD was significantly associated with negative symptoms (adjusted $R2 = 0.113$, $F(6,357) = 8.58$, $P < 0.001$). This was not influenced by gender, years of education, diagnose or ethnic background. Low S-25OHD was also significantly associated with depression (adjusted $R2 = 0.045$, $F(4,357) = 5.233$, $P < 0.001$), and this was not influenced by gender, season of the year or thyroxine levels. Low S-25OHD was bivariate correlated with suicidal ideations and this association was mediated by depression. The association between S-25OHD and positive symptoms was not significant after controlling for confounding variables. The bivariate correlations between S-25OHD and sTNF-R1, IL-Ra and OPG were not significant (Spearman's rho; $r = 0.095$, $P = 0.15$, $r = -0.029$, $P = 0.66$ and $r = 0.086$, $P = 0.19$ respectively), and we therefore did not continue further multivariate analyses.
Discussion: The significant association between low S-25OHD and higher negative symptom score is of great clinical relevance since negative symptoms are considered to have high impact on the patients' impaired quality of life and possible treatment strategies are in demand. Many patients with a primary psychotic disorder also suffer from co-morbid depressions that influence on life quality and have potential to increase self-harming actions; and we found a significant association between low S-25OHD and higher scores on the depression scale, including severe depression with suicidal ideations. The associations between low S-25OHD and both negative and depressive symptoms could go both ways, possible with self-amplifying effects, and randomized controlled trials should be performed to sort out the causality. Other biological mechanisms, like vitamin D's neuroprotective properties against oxidative stress or neurotrophic properties in the developing brain emerge as more important pathways than inflammatory pathways in the associations between vitamin D and symptomatology.

T119. Effect of stressful life events on schizotypal symptoms in siblings of patients with first-episode psychosis and healthy controls.

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Background: A recent review suggested a role of stressful life events (LEs) in the etiology of psychosis (Beards *et al.*, 2013). However, this conclusion was based on a few studies only, some of them of poor quality. Furthermore, very few studies have examined the quality and context of the LE, such as being dependent versus independent from the illness, the valence of the LEs or the emotional impact (i.e., positive (desirable) and negative (undesirable) events). The proposed analyses will investigate the association between frequency, valence and type of LEs and positive schizotypy in siblings of patients with first-episode psychosis and healthy controls.
Methods: Participants were siblings of patients with first-episode psychosis ($n = 1057$) and healthy controls ($n = 590$). This research was part of a longitudinal observational study called the 'Genetic Risk and Outcome of Psychosis Project' (GROUP) in the Netherlands. Recent life events were assessed with the Interview for Recent Life Events (Paykel, 1997). Participants reported the frequency, valence (negative or positive) and type (dependent and independent) of LE. Positive Schizotypy was assessed with the Structured Interview for Schizotypy-Revised (SIS-R; Kendler *et al.* 1989; Vollema & Ormel, 2000; Vollema & Postma, 2002).
Results: The frequency of LEs was associated with positive schizotypy in the siblings (B 0.02, 95% CI 0.01-0.024, $P < 0.001$) and in the healthy controls (B 0.016, CI 0.01-0.02, $P < 0.001$). A significant relationship was found between negative LEs and positive schizotypy in the siblings (B 0.03, 95% CI 0.02-0.03, $P < 0.001$) and healthy controls (B 0.03, 95% CI 0.02-0.04, $P < 0.001$), but not with positive LEs. When we grouped LEs according to dependent and independent events, there was a

marginally stronger association between independent LEs and positive schizotypy in the siblings (B 0.05, 95% CI 0.02-0.07, $P < 0.001$), compared to the control subjects (B 0.03, 95% CI 0.01-0.06, $P < 0.05$).
Discussion: This paper in a large sample of subjects confirmed a clear association between exposure to LEs and positive schizotypy. This was particularly true for negative LEs. When we specifically focus on independent LEs, the association was stronger in siblings compared to healthy controls, tentatively suggesting an interplay between genetic vulnerability and sensitivity to stressful environments in the etiology of positive schizotypy.

References:

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T120. Positive and negative schizotypy prediction of prodromal symptoms and schizophrenia-spectrum personality disorder traits: a 3-year prospective study

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Background: Schizotypy, a multidimensional personality organization, is a helpful construct for investigating the development of schizophrenia-spectrum psychopathology.
There is ample evidence supporting the validity of the positive and negative schizotypy dimensions; however, longitudinal investigations are needed. This study examined the prospective associations of positive and negative schizotypy with interview measures of prodromal symptoms and schizophrenia-spectrum personality disorder (PD) traits.
Methods: Data were derived from an ongoing longitudinal project examining risk for psychosis. At the first assessment, 547 nonclinical Spanish young adults completed the Wisconsin Schizotypy Scales. At the third assessment, approximately 3 years later, a selected subset of these participants ($n = 103$), oversampled for high schizotypy, were interviewed for prodromal symptoms (Comprehensive Assessment of At-Risk Mental States) and schizophrenia-spectrum PDs (Structured Clinical Interview for DSM-IV Axis II Disorders).
Results: Positive schizotypy predicted positive, behavioral, and general psychopathology symptoms. Negative schizotypy predicted emotional disturbance and schizoid PD traits. In addition, both dimensions predicted motor/physical symptoms as well as paranoid and schizotypal PD traits.
Discussion: Positive and negative schizotypy showed meaningful distinctive and overlapping prospective associations with prodromal symptoms and schizophrenia-spectrum PD traits, providing evidence of the predictive validity of these dimensions. The findings underscore the notion that schizotypy provides a valid framework for identifying risk for psychosis and the study of etiological mechanisms and trajectories of risk and resilience that should inform prophylactic interventions.

T121. Age at first-contact and 9-month outcome in patients with first-episode schizophrenia spectrum disorders

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Background: Over the last years, the interest about the study of early and late onsets of patients with schizophrenia has substantially increased, till to consider Age Of Onset (AOO) a surrogate measure of illness severity. Nevertheless, research findings on the role of AOO on clinical and functional outcomes in patients with schizophrenia and related psychosis are far to be consistent and more insight in this issue, through large sample follow-up studies of patients experiencing their first schizophrenic episode, is needed.
The aims of this study are to examine the influence of age of first contact (used as a proxy of AOO) with mental health services on the 9-month outcome (e.g. course of illness, number of hospitalization days and level of psychopathology, etc), in a large cohort of patients with first-episode schizophrenia spectrum disorders.
Methods: This study was conducted in 110 Community Mental Health Centres (CMHCs) in Northern Italy, delivering care to approximately 10 million inhabitants. The sample ($N = 346$ patients with first-episode psychosis, males 59.8%) was stratified into 3 groups according to the age at first service contact: Group 1 (15-24 years), Group 2 (25-34 years), Group 3 (35-54 years). A set of standardized measures (PANSS, PSYRATS, GAF, HAM-D) was administered at both baseline (i.e., after clinical stabilization and before treatment initiation) and 9-month follow up.
Results: At 9-month follow-up, younger patients were more likely to be hospitalized and, among those hospitalized, older patient had longer hospital stays. Age of first contact did not predict a specific type of course (continuous, episodic and mixed) at the 9-month follow-up. However, a higher proportion experiencing large improvements in negative and general symptoms was observed in younger patients. More than one third of the youngest patients exhibited a significant reduction in general and negative symptomatology at 9 months as compared to the oldest group.
Discussion: Age of onset was the main factor that predicted improvements in negative and positive symptoms. Further research in this area is needed.

T122. Temperament in individuals with psychotic disorders before and after the onset of illness

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Background: The Temperament and Character Inventory (TCI) is used to measure novelty seeking (NS), harm avoidance (HA), reward dependence (RD), and persistence (P). There are not many longitudinal studies of temperament in psychoses. We were able to study the stability of temperament in individuals with psychotic disorders (with onset of illness before and after first follow-up) and in non-psychotic controls.
Methods: As part of the 31-year follow-up survey of the prospective population based Northern Finland 1966 Birth Cohort, the TCI was filled by a large sample of individuals. A subsample of psychotic individuals, with the onset of illness before ($n = 16$) or after ($n = 15$) the 31-year follow-up, and non-psychotic controls ($n = 117$) filled in these scales again at the age of 43. We also studied the association between temperaments traits and psychotic symptoms (measured with Positive and Negative Syndrome Scale, PANSS) and attitudes to medication (Drug Attitude Inventory, DAI).
Results: The 31-year and 43-year temperament scores correlated strongly among controls (Pearson's r: NS 0.68, HA 0.60, RD 0.56, P 0.54), whereas correlations among psychotic individuals with the onset of psychosis before first follow-up were weaker (NS 0.38, HA 0.50, RD 0.17, P 0.53). Individuals who had their onset of psychosis after the first follow-up had a significant ($P = 0.02$) increase in HA from age 31 to 43-years when compared to controls. High HA before the onset of illness (at age of 31 years) associated significantly with a lower likelihood of remission and with more negative, disorganization and total symptoms in the PANSS. High NS before illness associated with a higher likelihood of remission according to the PANSS. At the age of 43 years, high HA score correlated positively with the total PANSS score, especially among those with earlier onset of psychosis ($r = 0.86$), but also among those with onset before the age of 31 years ($r = 0.44$). Other temperament dimensions were quite independent from the psychotic symptoms. In cross-sectional analyses at age 43-year, high RD associated with better attitude to medication ($P = 0.012$).
Discussion: Temperament was stable among controls, and more unstable in psychoses. In psychoses, increase in harm avoidance associated with getting ill, and it had a very strong positive association

with the amount and severity of symptoms. Premorbid harm avoidance and novelty seeking may also predict the clinical outcome in schizophrenia. Interestingly, also drug attitudes related to temperament. When studying the temperament in psychoses, the duration of illness and symptom severity should be taken into account.

T123. Neighbourhood characteristics and the rate of identification of young people at ultra-high risk for psychosis and risk of transition

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Background: There is a higher incidence of psychotic disorders in more socially deprived neighbourhoods and a higher risk in migrants living in neighbourhoods of low ethnic density. Yet it is unclear at what stage these neighbourhood environmental factors may exert an influence on the risk for psychosis. This study aimed first to determine if the rate of identification of individuals who were at ultra-high risk for psychosis (UHR) was associated with the level of social deprivation in the neighbourhood of residence. Second, it was aimed to determine if the rate of identification of UHR individuals who were migrants was associated with the proportion of migrants in the neighbourhood of residence (i.e. ethnic density). Finally, it was aimed to determine if the level of social deprivation or migrant status was associated with an increased risk of transition to psychosis.
Methods: UHR individuals at the Personal Assessment and Crisis Evaluation (PACE) service in Melbourne were included. Social deprivation as assessed according to postal code area of residence was obtained from census data and Cox regression analysis was used to calculate hazard ratios. Rate ratios were calculated to determine if there was a higher rate of identification of UHR individuals according to neighbourhood characteristics.
Results: A total of 219 UHR individuals were included and 9% of UHR individuals were first generation migrants and 41.9% were second generation migrants. There was a trend for UHR individuals to reside in relatively more deprived areas and there was no association between the rate of identification of UHR migrants and neighbourhood ethnic density. Over a median follow-up time of 4.8 years, 32 individuals (14.6%) were known to have transitioned to a psychotic disorder. The level of social deprivation was not associated with the risk of transition ($P = 0.83$). Similarly, first or second generation migrants did not have an increased risk of transition to psychosis ($P = 0.84$).
Discussion: There was a trend for individuals identified as being ultra-high risk for psychosis to live in more deprived neighbourhoods and this has implications for where services for these individuals should be located. Despite being established risk factors for psychotic disorders, social deprivation and migrant status did not increase the risk of transition to psychosis.

T124. A population-based longitudinal study of maternal prenatal depression and risks of psychosis and depression in adult offspring: role of childhood serum Interleukin 6

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Background: Maternal prenatal depression is associated with an increased risk of psychiatric disorders in offspring but precise mechanism for this association is unclear. We examined whether maternal depression during pre and postnatal period are associated with risks of psychosis and depression in adult offspring. We also examined whether these associations are influenced by serum interleukin 6 (IL-6) levels, an inflammatory cytokine, in childhood.
Methods: Main analysis of the association between maternal prenatal depression and psychiatric risk in offspring was based on 4198 participants from the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort. Depression was measured in mothers at 32 weeks pregnancy and 8 weeks postpartum and in fathers at 32 weeks pregnancy using the Edinburgh Postnatal Depression Scale (EPDS). In offsrping, serum IL-6 levels were measured at age 9 years using enzyme-linked immunosorbent assay. Psychotic experiences (PE) and psychotic disorder were assessed using the face-to-face, semi-structured Psychosis-Like Symptom Interview (PLIKSi) at age 18 years. Diagnosis of depression according to International Classification of Diseases, 10th Revision, (ICD-10) criteria was obtained by the computerized version of the Clinical Interview Schedule-Revised (CIS-R) at age 18 years. Logistic regression analysis was used to calculate the odds ratios (ORs) for PE, psychotic disorder and depression at 18 years for each SD (five points) increase in EPDS score at 32 weeks pregnancy (mothers and fathers separately) and 8 weeks postpartum (mothers). Linear regression examined the association between parental depression around pregnancy and serum IL-6 levels in childhood. Moderating effect of IL-6 on the association between maternal prenatal depression and risks of psychosis and depression in offspring was examined.
Results: At age 18 years out of 4198 participants 203 were assessed to have definite PE (4.8%), 68 met criteria for psychotic disorder (1.6%), and 317 met criteria for depression (7.8%). Maternal prenatal depression was associated with risks of psychotic disorder (adjusted OR, 1.46; 95% CI, 1.02-2.09) and depression (adjusted OR, 1.20; 95% CI, 1.02-1.42) in offspring at 18 years after controlling for potential confounders including postnatal depression. Maternal prenatal depression was associated with serum IL-6 levels in childhood at age 9 years (adjusted regression coefficient, 0.09; SE, 0.04; $P = 0.03$). Childhood IL-6 levels moderated the association between maternal prenatal depression and offspring psychosis and depression. There was significant association between maternal prenatal depression and risks of PE, psychotic disorder and depression in offspring at 18 years in the group with high (but not low) IL-6 levels at 9 years (OR = 1.37, 95% CI, 1.06-1.77; OR = 1.88, 95% CI, 1.23-2.87; and OR = 1.35, 95% CI, 1.09-1.68, respectively). Maternal postnatal depression or father's depression during pregnancy were not associated with IL-6 or psychiatric risk in offspring.
Discussion: Maternal depression in pregnancy contributes to risks of psychosis and depression in adult offspring. Maternal depression in pregnancy is associated with levels of the inflammatory cytokine IL-6 in childhood. Childhood IL-6 moderates the association between maternal depression in pregnancy and risks of psychosis and depression in adult offspring.

T125. Childhood traumas in young adults with clinical and familial risk for psychosis - the Northern Finland 1986 birth cohort

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Background: Childhood trauma increases the risk for psychotic disorder and prodromal symptoms according to previous studies. However, childhood trauma in subjects with familial risk for psychosis is less studied. We aimed to replicate the previous findings of the connection between childhood trauma and prodromal symptoms for psychosis in a birth cohort sample. In addition, we studied the childhood trauma in young adult offspring of parent with history of psychosis.
Methods: A field study for a subsample of the general population-based Northern Finland 1986 Birth Cohort (NFBC 1986) was conducted in 2007-2010 when the participants were 21-24 years old. The subsample is called the Oulu Brain and Mind Study. According to the Structured Interview for Prodromal Syndromes (SIPS) and Finnish Hospital Discharge Register (FHDR) and other register data four groups were created: psychosis ($N = 30$), Clinical Risk CR ($N = 47$) and Familial Risk FR ($N = 61$) of psychosis and controls ($N = 74$). CR presented prodromal syndromes for psychosis. FR group consisted of the offspring (cohort members) of parents with history of hospital-treated psychosis or A-type personality disorder. Subjects who had

psychosis or prodromal symptoms according to SIPS were excluded from FR group and included in the psychosis and CR groups.
The Trauma and Distress Scale (TADS) – self report questionnaire (Patterson *et al.*, 2002) was used to measure five types of traumatic childhood and adolescence experiences: emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect. The TADS questionnaire was originally used in the European Prediction of Psychosis Study (EPOS).
Results: Young participants with psychosis had statistically significantly increased risk having had experienced emotional abuse ($P < 0.05$), physical abuse ($P < 0.05$) and sexual abuse ($P < 0.01$) in childhood compared to controls when adjusted with gender, family SES and family type. Subjects with CR had increased risk for emotional abuse ($P < 0.01$), physical abuse ($P < 0.05$) and emotional neglect ($P < 0.01$) compared to controls. Subjects with FR did not have increased risk for any of the five trauma types compared to controls.
Discussion: Childhood traumas were connected to psychoses and prodromal syndromes for psychosis. These findings are in general in line with previous studies. Interestingly, parental psychosis did not increase the risk for childhood trauma in this study. This was a new finding.
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T126. Tobacco smoking and risk of first episode psychosis: a case-control study in Sao Paulo, Brazil

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Background: There is growing evidence suggesting that there may be a causal link between tobacco smoking and risk of first episode psychosis (FEP). A recent systematic review estimated a mean Odds Ratio of 3.2 for risk of FEP among smokers, compared to non-smokers. However, confounding by cannabis use and publication bias may explain, at least partially, that association. We examined whether the association between tobacco smoking and risk of FEP might be confounded by other exposures.
Methods: A population-based case-control study was carried out in Sao Paulo, Brazil. First episode psychosis cases from a specified catchment area of about 1.2 million inhabitants, aged between 18 and 64 years were individually matched by sex, age range, and neighbourhood to healthy controls (ratio 1:2). Information on history of tobacco smoking was obtained through direct interviews. For cases, number of years of tobacco smoking were counted only prior to the onset of first psychotic symptom. We used conditional logistic regression to estimate the magnitude of the association between history of cigarette smoking and risk of FEP, controlling for years of education, household income per capita, having a partner, and history of cannabis use.
Results: 191 FEP cases and 375 healthy controls, individually matched by sex, age group and neighbourhood (ratio 1:2), were included (52.8% females). 33.3% of cases and 25.4% of controls had a history of tobacco smoking. In the bivariate analysis, history of tobacco smoking (prior to first psychotic symptom among cases) was associated with risk of FEP (OR: 1.49 [95%CI: 1.02-2.17]; $P = 0.04$]. The association decreased after controlling for cannabis use (OR: 1.31 [95%CI: 0.88-1.95]; $P = 0.19$) and almost disappeared when controlling for years of education, income per capita and having a partner (OR: 1.00 [95%CI: 0.64-1.58]; $P = 0.99$).
Discussion: In the present study, the association between tobacco smoking and risk of FEP was completely explained by confounding exposures, supporting the possibility that previous studies described a spurious association.

T127. The influence of polygenic risk scores on the association between infections and schizophrenia

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Background: Several studies have suggested an important role of infections in the etiology of schizophrenia; however, shared genetic liability towards infections and schizophrenia could influence the association. We therefore investigated the possible effect of polygenic risk scores (PRS) for schizophrenia on the association between infections and the risk of schizophrenia.
Methods: We conducted a nested case-control study on a Danish population-based sample born after 1981 comprising of 1,692 cases diagnosed with schizophrenia between 1994-2008 and 1,724 matched controls. All individuals were linked utilizing nationwide population-based registers with virtually complete registration of all hospital contacts for infections. PRS were calculated using discovery effect size estimates weights from a separate meta-analysis (34,600 cases and 45,968 control individuals).
Results: A prior hospital contact with infection had occurred in 41% of the individuals with schizophrenia and increased the incidence rate ratio (IRR) of schizophrenia by 1.43 (95%CI = 1.22-1.67). Adding PRS, which was robustly associated with schizophrenia (by an IRR of 1.46 (95%CI = 1.34-1.60) per standard deviation of the score), did not alter the association with infections and the increased risk of schizophrenia remained (IRR = 1.41; 95%CI = 1.20-1.66). Furthermore, there were no interaction between PRS and infections on the risk of developing schizophrenia ($P = 0.554$). Neither did PRS affect the risk of acquiring infections among patients with schizophrenia (OR = 1.00; 95%CI = 0.89-1.12) nor among controls (OR: 1.09; 95%CI: 0.96-1.24).
Discussion: PRS and a history of infections have independent effects on the schizophrenia risk and the common genetic risk measured by PRS did not account for the association with infection in this sample.

T128. Inadequate cancer diagnostics among persons with severe mental illness: a population-based cohort study

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Background: Persons with severe mental illness (SMI) including schizophrenia, schizoaffective- and bipolar disorder, have a 15-20 year reduction in life expectancy compared to the general population; partly caused by a diagnostic delay of physical diseases. For cancer, a late diagnosis may lead to a more extended level of disease and hence more severe disease, which may explain the increased cancer

mortality seen in persons with SMI. Delayed or missing diagnosis of a cancer illness may explain why persons with SMI have a similar cancer incidence as the general population concurrently with the increased cancer mortality. However, conflicting results exist and there is a lack of knowledge to which extent more extended level of cancer contributes to the reduced life expectancy in persons with SMI. We aimed to compare cancer incidence rates for all cancer sites stratified on level of extent of disease and subsequent mortality rates among persons with SMI with the general population.
Methods: We used nationwide, population-based registers as data sources. A cohort including all persons born between year 1900-2001 and living in Denmark during follow up was followed for incident cancer between 1978 and 2011 and for mortality between 1978 and 2012. SMI was considered as a time varying exposure and persons with and without SMI with no prior cancer diagnosis was followed in two sub cohorts. Incidence rate ratios (IRR) and mortality rate ratios (MRR) were calculated with survival analysis (Poisson regression). All cancer sites were included except Non Melanoma Skin Cancer. The severity of cancer was given by subdivision of cancer into extent of disease, which indicates degree of spread; localized, regional, metastasized or unknown. All estimates for IRR and MRR are adjusted for age, calendar time and gender.
Results: Incidence
Our preliminary results show that 5,464 persons with SMI and 703,813 persons without SMI developed incident cancer during follow up.
Incidence of cancer diagnosis (IRR) in persons with SMI compared to those without, by extent of disease;
Localized cancer: 0.91 (95% CI: 0.87-0.95)
Cancer with regional spread: 1.03 (95% CI: 0.98-1.09)
Metastasized cancer: 1.13 (95% CI: 1.06-1.20)
Unknown extent of disease: 1.14 (95% CI: 1.08-1.21)
Mortality
Our preliminary results show that 4,262 persons with SMI and 524,962 persons without SMI died after being diagnosed with cancer.
Mortality rates (MRR) in persons with SMI compared to those without, stratified by extent of disease;
Localized cancer: 1.87 (95% CI: 1.77-1.98)
Cancer with regional spread: 1.40 (95% CI: 1.32-1.50)
Metastasized cancer: 1.82 (95% CI: 1.71-1.93)
Unknown extent of disease: 1.86 (95% CI: 1.75-1.98)
Discussion: Persons with SMI are less often diagnosed with localized and more often diagnosed with the most severe extent of cancer compared to the general population, which may indicate that the diagnostic process is systematic different among persons with SMI. Whether this difference is due to delay by patients, general practitioners or specialists cannot be disentangled by these data.
Persons with SMI have higher mortality following a cancer diagnosis on all levels of extent of disease compared to persons without SMI. This higher mortality may indicate that persons with SMI do not have the same access to or receive a lower level of cancer treatment due to lower compliance, tolerance or response to the given treatment compared to persons without SMI.
The results indicate a diagnostic delay in the cancer diagnosis among persons with SMI. This delay, together with unequal access to cancer treatment and a high level of multi morbidity, contributes to the increased mortality after a cancer diagnosis and hence the considerable reduced life expectancy.

T129. Pathway from perinatal circumstances to mortality at midlife in psychoses: a 45-year follow-up study of the Northern Finland birth cohort 1966

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Background: Excess mortality in schizophrenia has been reported widely, but less is known about other psychoses and perinatal circumstances as predictors of mortality. The aim of the study is to examine mortality and causes of death in schizophrenia and other psychosis compared to individuals without psychosis and whether perinatal circumstances predict mortality.
Methods: Among the individuals of the Northern Finland Birth Cohort 1966 ($n = 10\,933$), mortality and causes of death were followed until 31.12.2011 by national registers. Overall, 203 individuals had schizophrenia and 178 other psychoses until 31.12.2011. Mother's antenatal depression, wantedness of pregnancy, mother's age at birth, smoking during pregnancy, parity, paternal socio-economic status and family type at birth were considered as predictors of mortality.
Results: Overall, 11.8% of individuals with schizophrenia, 12.9% with other psychosis and 3.2% without psychosis had died. Individuals with schizophrenia (HR 3.60; 95% CI 2.38-5.45) and other psychoses (HR 4.05; 2.65-6.17) had elevated risk for mortality compared to individuals without psychoses after adjustment for gender. Overall, 43.5% of individuals with other psychoses had died of natural causes compared to 38.6% without psychoses ($P = 0.018$) and 20.8% with schizophrenia ($P = 0.015$). The causes of death did not differ between individuals with schizophrenia and without psychoses ($P = 0.154$). In individuals with psychoses, those whose father belonged to socio-economic class of farmers (V), had lower risk for mortality (HR 0.19; 0.05-0.82) than individuals, whose father belonged to high socio-economic class (I-II) after adjustment for gender and parental psychoses. In individuals without psychoses, mother's antenatal depression (HR 1.33; 1.00-1.77), smoking during pregnancy (HR 1.34; 1.02-1.77) and father's low socio-economic status (III-IV, HR 2.25; 1.26-4.00, V, 1.87; 1.00-3.48) predicted higher mortality after adjustments for gender and parental psychoses (and paternal socio-economic status).
Discussion: Individuals with psychosis, especially other psychoses, had excess mortality compared to individuals without psychosis. Individuals with other psychoses had relatively more natural causes of death than individuals with schizophrenia and without psychosis. Perinatal circumstances seem to be more important predictors of mortality in individuals without psychoses than with psychoses. It is important to pay attention to somatic morbidity in individuals with other psychoses in order to prevent their higher mortality.

T130. Joint effects of prenatal exposure to infection and peripubertal adversity in schizophrenia

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Background: Prenatal exposure to infection and early life adversity has both been linked with schizophrenia with rather modest effect sizes, and none of these factors seem sufficient to cause the disorder. However, evidence is accumulating to consider these factors as pieces in a multi-factorial causal path network.
Methods: We conducted a prospective cohort study on Danish register data, following 979,701 persons from their 15th birthday until onset of schizophrenia, emigration from Denmark, death or December 31, 2013, whichever came first 9.656 individuals developed schizophrenia within the 8.84 million person years of follow-up. We estimated the independent and joint effects of prenatal exposure to infection and peripubertal adversity.
Results: We found a significantly increased risk of schizophrenia among females exposed to infection *in utero*, significantly higher compared to males. Males on the contrary had a higher risk of schizophrenia after exposure to both insults, with interaction between infection and peripubertal adversity increasing the risk. Correlations between adversities throughout early life however, made it difficult to disentangle exposure into different periods.
Discussion: This study showed a significantly higher risk of schizophrenia among females after prenatal exposure to infection compared to males. It also showed that infection and adversity might combine synergistically to increase the risk of schizophrenia in males.
Strong correlation between exposures however, made these difficult to disentangle.

T131. Cannabis use and adherence to antipsychotics: a systematic review and meta-analysis

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Background: Antipsychotic medications play an essential role in the treatment of psychosis, but their effectiveness is often hindered by poor adherence. Previous reviews suggested that substance abuse may increase the risk of non-adherence to antipsychotics, resulting in negative outcomes in patients with psychosis. Cannabis is the most prevalent illicit drug in patients with psychosis, but the magnitude of its effect on non-adherence to antipsychotics has not been estimated as yet.
Methods: A meta-analytic method was adopted. Studies were identified through a systematic database search following the MOOSE guidelines. Studies were identified through a systematic database search. Adopting random-effects models, pooled odds ratios (OR) for risk of non-adherence to antipsychotic medications were calculated comparing: cannabis-users at baseline (CU) vs non-users at baseline (NU); NU vs continued cannabis users at follow-up (CCU); NU vs former users at follow-up (FU); FU vs CCU. Additionally, sub-group analysis, meta-regression and sensitivity analyses were performed.
Results: Fifteen observational studies ($n = 3678$) were included. Of these, 11 provided enough data for the estimation of a pooled effect-size. At baseline, increased risk of non-adherence was observed for CU as compared to NU (OR = 2.46, $n = 3055$). At follow up, increased risk was observed for continued users (CCU) as compared to NU (OR = 5.79, $n = 175$) and FU (OR = 5.5, $n = 192$), while there was no difference between FU and NU (OR = 1.12, $n = 187$). Sub-group analysis, meta-regression and sensitivity analyses did not detect significant effects of possible confounding variables.
Discussion: Cannabis use increases the risk of non-adherence and may represent a potential target for intervention to improve medication adherence in those with psychosis, for instance by an early switch to depot medication for cannabis users.

T132. Is hyper-theory-of-mind specifically and independently associated to psychotic experiences in preadolescence?

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Background: Longitudinal studies have found associations between psychotic experiences (PE) in childhood or adolescence and later psychotic spectrum disorder. However, only a small proportion of individuals with PE develop psychotic disorder and some develop other psychiatric outcomes, while the majority of individuals with PE stay below the clinical threshold. Thus, it is unclear if the presence of PE constitutes a specific risk marker of psychosis liability or a common risk marker of psychopathology and increased severity of psychopathology. This raises the question of whether it is possible to identify other markers of psychosis liability among individuals with PE, which may enable clinicians and researchers to identify those individuals with substantially higher risk of transition from PE to clinical psychotic disorder. Patients prone to psychosis, and schizophrenia in particular, show certain cognitive deficits that may trigger the onset or maintenance of PE. Deficits in Theory-of-Mind (ToM) abilities are among the most well-established, but these are prominent across different diagnostic categories. This suggests that ToM alterations are not specific to schizophrenia. Rather, while general alterations in ToM may be a vulnerability marker for psychosis and other psychopathology, more specific types of alterations may have a mediating role in the development of specific symptoms. We have previously found a stronger association between PE and the exaggerated type of ToM (HyperToM) than between PE and an overall low ToM. The aim of the current study was to explore the cross-sectional and longitudinal associates of PE with a particular focus on the specificity of HyperToM as correlate of PE as opposed to correlate of any mental disorder
Methods: We assessed 1630 children from the Copenhagen Child Cohort 2000 with psychopathological interviews and assessments of PE and of HyperToM at the age of 11-12 years. DSM-IV Mental disorders were diagnosed by clinical ratings based on standardized parent-, teacher- and self-reported psychopathology. Regression analyses were performed to test the correlates of PE and of any mental disorder.
Results: Univariate analyses showed familial psychiatric liability; parental mental illness during early child development; change in family composition; regulatory problems in infancy; onset of puberty; low family income; being involved in bullying; having a concurrent mental disorder, and HyperToM to be associated with PE. However, when examined in a single multivariate regression analysis to estimate their adjusted effects, only low family income, having a concurrent mental disorder, being involved in bullying, and HyperToM (OR = 1.81 95% CI 1.2-2.8, $P = 0.007$) remained significantly associated with PE. Further analyses of the specificity of these correlates with regard to outcome revealed that HyperToM was the only variable specifically associated with PE without concurrent mental disorder (OR = 1.71 95% CI 1.0-2.8, $P = 0.034$). Looking at the most prevalent concurrent diagnoses, HyperToM was not associated with neither neurodevelopmental disorders, anxiety nor depression. Finally, HyperToM did not share any of the investigated precursors with PE.
Discussion: The findings suggest that whereas a wide range of family and child variables are associated with PE and psychopathology in general, HyperToM is independently and specifically associated with PE. Thus HyperToM may have a specific role in the risk trajectories of PE, and may be useful in delineating differential pathways to psychopathological outcomes.

T133. Using home-recruitment to increase participation and representativeness of research among individuals with psychosis

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Background: The participation rates in epidemiologic cohort studies have declined in recent decades. Missing data is a serious problem especially in population based research reducing sample size and statistical power. We aimed to evaluate the effect of intensive home-recruitment on participation rate and non-response bias in a follow-up study on psychosis.
Methods: In the Northern Finland Birth Cohort 1966, baseline (1999-2001) and follow-up (2008-2010) studies were conducted for individuals with psychosis. The studies consisted of magnetic resonance imaging (MRI) of brain, cognitive testing, and psychiatric assessments. Altogether 81 out of 91 baseline participants were eligible and invited to participate in the follow-up study. In order to increase participation in the follow-up, those who were about to drop out were offered to be interviewed at home and chauffeured to the Oulu University Hospital for the MRI scan and cognitive testing. Positive and Negative Syndrome Scale (PANSS), Social and Occupational Functioning Assessment Scale (SOFAS), cognitive performance (selected measures from the California Verbal Learning Test (CVLT) and Visual Object Learning Test (VOLT)), and dose years of antipsychotic medication by the time of the follow-up study were compared between the home-recruited and standard protocol participants and the non-participants. Effect sizes (g) were calculated to compare the means.
Results: Altogether 18 (33%) of the follow-up participants ($n = 54$) were interviewed at home. Of the participants with schizophrenia 14 (35%), and with other psychoses 4 (29%), were interviewed at home. Compared to the standard protocol participants, the home-recruited participants had more total, negative, disorganization and excitement symptoms (total 63.1 vs. 43.4, g 0.95, P 0.013; negative 18.5 vs. 11.7, g

0.89, P 0.022; disorganization 21.5 vs. 15.3, g 0.81, P 0.008; excitement 13.3 vs. 10.2, g 0.91, P 0.023), lower functioning (SOFAS score 40 vs. 57, g -1.02, P 0.001) and cognitive performance (e.g. CVLT, total recall in trials 1-5 39 vs. 52, g -0.98, P 0.002; VOLT 55 vs. 61, g -0.73, P 0.039), and non-significantly higher use of antipsychotics measured at the time of the follow-up study (dose years 71.4 vs. 37.2, g 0.67, P 0.080). Compared to the non-participants, the results were similar but slightly smaller.
Discussion: In previous studies, those with more severe mental illness have been shown to cumulate into non-participants. By using home-recruitment we were able to increase the participation rate and to avoid problems of non-response bias: without home-recruitment the participants would have been less severely ill than the non-participants. In population-based studies for individuals with psychosis, effective recruitment may need special efforts.

T134. Exploring risk factors in early and late onset schizophrenia

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Background: This study reviews key risk factors in patients diagnosed with schizophrenia in order to identify trends according to age of onset by comparing presentations prior to 26 years(youth onset), between 26 and 40 years(middle adult age group), and after 40 years of age (Late onset schizophrenia or LOS).
Methods: The early psychosis program at St Vincent's Hospital Melbourne treats patients presenting in the early stages of psychosis between 16 and 65 years of age. A database was developed to capture key risk factors in all patients with an eventual diagnosis of schizophrenia ($n = 225$) and a file review of these cases was undertaken. These results were compared with results obtained from direct interview of current patients. Risk factor profiles were compared for patients with an onset prior to 26 years ($n = 104$), between 26 and 40 years ($n = 81$), and after 40 years of age ($n = 40$).
Results: The peak age of onset in the study sample was in the youth group especially between 17 and 22 years, with median age of 27. The proportion of males is greatest in the youth cohort (72.1%) and steadily decreases with age. The male and female prevalence rates approximate each other in later life.
Older age of onset was found to be associated with several graded trends in risk factors. This includes a reduction in the rates of a positive family history for schizophrenia as well as other mental illnesses. With age there was also a reduction in the rates of both recent and lifetime substance use. With an increased age of onset we noted trends towards greater levels of educational completion and better early psychosocial functioning. A higher proportion of first generation migrants and increased frequency of comorbid physical health problems was also reported with increased age of onset.
Of these trends, the older age groups had a statistically significant difference in family history of schizophrenia specifically, educational completion and some substance use on Chi-square testing ($P < 0.01$) compared to the youth age group. Weak trends were also suggested between older age of onset and risk factors occurring proximal to the onset of psychosis; including social isolation around time of onset, unemployment and unstable accommodation in the two years prior to onset.
Discussion: Distinct trends are noticeable with age. LOS patients have characteristic differences in their background risk factors compared to youth and middle adult groups, including less hereditary influence and greater female preponderance. Risk factors closer to the onset of psychosis appear to play a larger role in LOS, possibly as precipitants or markers in the development of disease. Substance use is a much greater issue among youth and middle adult groups, while physical health problems are considerably more prevalent among older patients.
Identifying the roles and mechanisms of specific risk factors in these distinct age-onset groups can enhance our understanding of possible aetiological mechanisms and facilitate tailoring of clinical management and service development to the needs of each specific age group.

T135. Estimation of incidence rate of first episode psychosis in a Brazilian large catchment area

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Background: The psychotic disorders, as schizophrenia, figure as a public health problem with important social and psychological impact to both patients and their relatives. This is an effort to estimate the incidence of first episode psychosis (FEP), during a period of three years, in a large catchment area in Brazil, a low/middle-income country. It results from our membership in the international consortium "European Network of National Networks Studying Schizophrenia Gene-Environment Interactions" (EU-GEI; http://www.eu-gei.eu/). Here, we describe an update of the incidence study currently in course in the region of Ribeirão Preto city, São Paulo State, Brazil, with a population at risk of 2,824,377 in three years.
Methods: FEP patients aged between 16 and 64 years old, seeking a mental health treatment for the first time in the defined catchment area from 1st April 2012 to 31st March 2015, were included in the study. The leakage study, as the final phase for the incidence estimation, covered, so far, 85% of the population at risk and is expected to finish in two months. The psychiatric diagnosis was made by trained research professionals according to the DSM-IV criteria and based on face-to-face interviews, medical records and information obtained with mental health professionals. Ethical consent was obtained from participants and from the coordinators of the department of health of the catchment area.
Results: Four hundred and thirty six FEP patients (56% males) were identified until now. Male FEP patients (mean = 30.47, SD = 11.90 years old) were significantly younger ($t = 3.39$, $df = 432$, $P = 0.001$) than female ones (mean = 34.20, SD = 11.84). The diagnoses of non-affective and affective psychosis correspond respectively to 51% and 49% ($\square 2 = 0.083$, $df = 1$, $P = 0.774$). The period between the beginning of the psychotic symptoms and the first contact with a mental health service ranged from 0 to 1292 weeks (median = 13.4 weeks). The incidence estimate of FEP with data collected at this moment is 15.5/100,000 inhabitants.
Discussion: Based on current data available, the incidence of first episode psychosis in Ribeirão Preto catchment area is similar to the observed in São Paulo city, which is characterized as one of the largest economic centers in the country. Further examination of incidence rates by population size of each municipality may contribute to better understand the relationship between urbanicity and incidence of FEP in this setting.

T136. Resilience in schizophrenia: a comparative study between a remote island and an urban area in Japan

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Background: Resilience, the "relative resistance to psychosocially adverse experiences", is influenced by various factors, but has rarely been investigated in patients with schizophrenia. Moreover, possible differences between residential areas have never been explored to our knowledge. Therefore, the aim of this study was to compare the resilience levels between patients with schizophrenia who were living on a rural island and an urban area in Tokyo, Japan, and to identify the factors associated with resilience in those patients.
Methods: This cross-sectional study was conducted for outpatients with schizophrenia or schizoaffective disorder (ICD-10) who live in

Ohshima Island, a small island located 120 km away from the center of Tokyo, Japan, and sex- and age- matched patients in an urban area in Tokyo. Assessment scales included the Resilience Scale (RS), EuroQol and Positive and Negative Syndrome Scale. Levels of salivary alpha-amylase (SAA) and plasma brain-derived neurotrophic factor (BDNF) were also examined, together with multiple demographic variables. Values of interest were compared using independent t-test or chi-squared test. Multiple linear regression analysis was performed to identify factors that were associated with RS total scores in the whole sample ($N = 80$); the following factors were included as independent variables: location of residence (Ohshima Island or urban area), sex, age (< 50 years or ≥ 50), duration of illness, EQ-5D VAS score, use of social resources, history of low birth weight (< 2500 g), GAF score, PANSS total score and biomarkers (i.e. SAA and plasma BDNF levels). A P-value of < 0.05 was considered statistically significant (two-tailed).
Results: Eighty subjects were included (40 each in two areas). No significant difference was found in the RS scores between the two groups (mean ± S.D., 103.9 ± 26.1 in Ohshima Island versus 109.4 ± 22.3 in the urban area, $P = 0.32$). There were significant differences in some of the characteristics between the two groups: higher BMI score, more siblings, less frequency of low birth weight, fewer previous hospitalizations, more frequent use of anticholinergic drugs, less use of social resources and lower plasma BDNF level on Ohshima Island as compared with the urban Tokyo sample. The linear regression analysis revealed that a longer duration of illness and a higher EQ-5D VAS score were significantly associated with a greater RS total score ($P = 0.037$ and $P = 0.016$, respectively) whereas biological data or the other factors including illness severity did not exhibit any significant relationships with resilience levels.
Discussion: Patients with schizophrenia living on a remote island and in urban area showed comparable degrees of resilience despite the difference in geographical location. Although resilience levels are known to be influenced by various environmental factors, those factors in the two groups, both of which are parts of Tokyo Metropolitan City, may have no essential differences. Moreover, even if the surrounding environment and cultural background are different, a similarity in illness severity and social functioning in the two groups may be a basis for similar resilience levels. On the other hand, a significant correlation was found between a longer duration of illness and greater resilience levels, which is a novel finding to the best of our knowledge. Illness duration and subjective quality of life may be more pertinent than urbanicity of residential area in determining resilience levels. Namely, greater resilience among people with a longer duration of illness may represent their successful psychological coping and adaptation.

T137. Socio demographic and clinical characteristics in first episode psychosis

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Background: In this study the relation between socio-demographic variables, alcohol and substance use, the environmental factors such as traumatic life events and psychotic symptoms in the first episode psychosis patients were examined.
Methods: The study sample consisted of 60 First Episode Psychosis patients and 60 healthy control subjects. Psychosocial risk factors were assessed using Social Environment Measurement Tool, Life Events Scale, Tobacco Alcohol Use Scale and Substance/Marijuana Use Scale. In addition to the clinical evaluation of the patient group PANSS, the Young Mania Symptoms Scale and Insight Scale were used for detecting psychiatric symptoms.
Results: We found statistically significant differences regarding the last year life events, birth season, obsessive compulsive symptoms, familial liability of schizophrenia and psychosis in 1st degree relatives, and attempted suicide in patients with first psychotic episode compared to healthy controls.
Discussion: Family liability and substance use were significant risk factors related to psychotic symptoms in patients with first episode psychosis.

T138. Schizophrenia-spectrum disorders and violent reoffending: a national cohort study of convicted prisoners

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Background: There are more than 10 million currently imprisoned, of which around 4% have schizophrenia-spectrum disorders according to systematic reviews. In the US and UK, over one-third of released prisoners are reconvicted for a new crime within 2 years. Evidence on whether schizophrenia-spectrum disorders increase the risk of reoffending is inconsistent. With large numbers of individuals with psychotic disorders in jails and prisons, clarification of this association is important to inform mental health services in criminal justice and on release from custody.
Methods: We undertook a longitudinal cohort study of 47 326 prisoners who have been imprisoned since January 1, 2000 and released before December 31, 2009 in Sweden. Data on diagnosed psychiatric disorders were obtained from both inpatient and out-patient registers. Socio-demographic and criminological factors were obtained from other population-based registers. Hazard ratios (HRs) for violent reoffending were calculated by Cox regression.
Results: 1237 (3%) of the men 130 (4%) of women had schizophrenia-spectrum disorders. A significantly increased hazard was also found for male prisoners with schizophrenia-spectrum disorders after adjustment for socio-demographic and criminological factors (adjusted HR = 1·20 (1·09-1·33), but not in the women (HR = 0·74 [0·45-1·20]). Comorbid substance use disorders increased these hazards (Adjusted HR in the men = 2·68 [2·41-2·98]).
Discussion: Contrary to expert opinion and previous research, we found that schizophrenia-spectrum disorders are independent risk factors for violent reoffending in male prisoners. National violence prevention strategies should consider the role of prison psychiatry.

T139. Predicting clinical outcomes in psychotic disorders using electronic case registers and natural language processing

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Background: It is not possible to reliably predict clinical outcomes in psychotic disorders. Existing research studies are based on relatively modest sample sizes and may not be representative of everyday clinical practice. Clinical information is widely recorded in the form of electronic health records (EHRs). The majority of useful data are stored in unstructured free text entries. However, the large volume of free text means that it is not feasible to manually read through records to identify data of interest. Automated information extraction methods such as natural language processing (NLP) offer the opportunity to quickly extract and analyse large volumes of meaningful data from free text EHRs. I present a summary of three studies using this approach to investigate clinical outcomes in people with schizophrenia.
Methods: Dataset: South London and Maudsley NHS Trust (SLaM) Biomedical Research Centre (BRC) Case Register comprising anonymised EHRs of over 250,000 people. NLP development: The software package TextHunter was used. All sentences containing keywords relevant to the constructs investigated were extracted using a support vector machine learning (SVM) approach. Predictor variables: presentation to high-risk clinical services, cannabis use (NLP-derived) and negative symptoms (NLP-derived). Outcomes: number of days spent in hospital, frequency of hospital admission and antipsychotic treatment failure. Covariates: age, gender, ethnicity, marital status and diagnosis. Statistical analysis: multivariable logistic, negative binomial, linear regression and mediation analysis using STATA.
Results: (i) Clinical outcomes of FEP in high-risk services ($n = 2{,}943$): 164 patients with FEP (5.6%) presented to OASIS, a clinical service in South London for young people with an at-risk-mental-state (ARMS) for psychosis. Presentation to the high-risk service was associated with 17 fewer days spent in hospital (95% CI -33.7, -0.3) and a lower frequency of admission (incidence rate ratio: 0.49, 0.39-0.61) in the 24 months following referral, as compared to patients who presented to conventional services. (ii) Cannabis and treatment failure in FEP ($n = 2{,}026$): Cannabis use was present in 46.3% of people with FEP. It

was associated with increased frequency of hospital admission (incidence rate ratio 1.50, 1.25-1.80) and greater number of days spent in hospital (B coefficient 35.1 days, 12.1-58.1). An increase in the number of unique antipsychotics prescribed to cannabis users mediated an increased frequency of hospital admission (natural indirect effect: 1.11, 1.04-1.17; total effect: 1.41, 1.22-1.64) and greater number of days spent in hospital (NIE: 16.1, 6.7-25.5; TE: 19.9, 2.5-37.3). (iii) Negative symptoms and clinical outcomes in chronic schizophrenia ($n = 7,678$): 55.7% of people with schizophrenia had at least one negative symptom documented. Negative symptoms were associated with increased likelihood of hospital admission (odds ratio 1.24, 95% CI 1.10-1.39), re-admission (1.58, 1.28-1.95) and length of stay (B coefficient 20.5, 7.6-33.5).
Discussion: It was possible to use EHR data extracted using NLP to investigate associations with clinical outcomes of psychosis in large sample sizes which would otherwise have been unfeasible to investigate using direct patient recruitment. These findings are important for mental healthcare services as they suggest that early detection of psychosis in high-risk services may be associated with better outcomes, and that greater attention should be given to cannabis use and negative symptoms in people with established psychotic disorders. The NLP tools developed in these studies also have the potential to support real-time clinical decision making at an individual patient level.

T140. A comparative study on the prevalence rate and treatment of agitation among Chinese newly hospitalized schizophrenics between psychiatric hospitals and general hospitals

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Background: Agitation is frequently reported with newly hospitalized patients suffering from schizophrenia, and may result in substantial adverse outcomes for themselves, others, and property. This study was designed to investigate the prevalence rate and treatment of agitation among newly hospitalized schizophrenics between psychiatric hospitals and general hospitals.
Methods: We conducted a non-interventional, multicenter, observational study in 10 psychiatric hospitals and 4 general hospitals. Information about agitation and treatment of all enrolled patients were investigated including general demographic data, disease characteristics, Clinical Global Impression-Severity (CGI-S), Positive and Negative Syndrome Scale–Excited Component (PANSS-EC), Modified Overt Aggression Scale (MOAS) and prescription.
Results: 1.Of 1512 patients enrolled in the study, 1400(92.6%) were eligible; the prevalence of agitation among psychiatric hospitals was significantly higher than that of general hospitals (64.30% vs. 52.8%, P□0.01□. 2. The general hospitals had higher proportion of oral medication□P□0.05□, whereas the psychiatric hospitals had higher proportion of intramuscular medication□P□0.01□and a combination of oral medication with intramuscular medication□P□0.01□. Oral medication most frequently prescribed was olanzapine□32.24%□, subsequently were risperidone□30.25%□, subsequently were clozapine□12.90%□; intramuscular medication most frequently prescribed was haloperidol□35.40%□, subsequently were ziprasidone□9.61%□, subsequently were benzodiazepines□4.69%□. The general hospitals had more than double use frequency of clozapine than the psychiatric hospitals□P□0.01□. With respect to ziprasidone intramuscular,12.5%□82□of patients from psychiatric hospital had ziprasidone intramuscular, while none of the patients from psychiatric hospital did. No statistical difference were found in oral risperidone□P□0.05□and haloperidol intramuscular□P□0.05□between the psychiatric hospitals and general hospitals.
Discussion: Our study indicated that, in China, the prevalence of agitation among psychiatric hospitals was significantly higher than that of general hospitals (64.30% vs. 52.8%, P□0.01□. In addition, patients in the psychiatric hospitals experienced a significantly older age, longer illness duration, more numbers of hospitalizations and higher CGI score, higher proportion of history of aggressive behaviors and involuntary admission than the general hospitals. These findings suggest that the psychiatric hospital group were more likely to be in more complex situations, higher risk of uncooperativeness and refractory schizophrenia, which may contributing to the different treatment. For the agitation sample, the psychiatric hospitals were more inclined to use intramuscular medication in managing this condition with schizophrenia, mainly haloperidol and ziprasidone. While no one used ziprasidone intramuscular in general hospital, considering the high price, uneven availability and deficient clinical practice play a role. As to clozapine, the use frequency in psychiatric hospitals and general hospitals was 9.8% and 23.4% respectively. Over the last decade, there was a falling trend in using frequency of clozapine in China. Since its unique advantages in psychiatric illness, it is significant to avoid the low utilization of clozapine and improve the rational use in the indication.

T141. The Gothenburg research and investigation on psychosis - grip: outcomes from a standardized clinical protocol for psychotic patients

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Background: Patients with schizophrenia-spectrum disorders often have other mental and physical health problems. This complexity poses challenges for clinicians to make correct judgements regarding diagnosis and treatment. A standardized clinical protocol was developed in order to improve diagnostics and provide the most adequate support for patients who are referred to the Department of Psychotic Disorders at Sahlgrenska University Hospital in Gothenburg, Sweden. The Department of Psychotic Disorders serves roughly 3000 patients. The standardized protocol consists of a somatic examination that includes health blood tests, a spinal tap, magnetic resonance imaging, and a neurological examination. Further, the protocol includes structured and semi-structured interviews with patients and family members that cover family and patient history, substance habits, and psychiatric symptoms. Moreover, screening instruments for general psychiatric symptoms, psychosis symptoms, and neuropsychiatric symptoms are used. Finally, neuropsychological, physical, and social functioning is also evaluated. All patients who are referred to the Department are offered an investigation according to the clinical protocol and can decline if they wish. The patients who agree to take part in the clinical investigation are also asked to participate in a research project (GRIP) attached to the clinical investigation. If they choose to give written informed consent, all data collected with the standardized clinical protocol can be coded and used for research purposes. The only difference between the patients who participate in GRIP and those who do not is that the blood and liquor from research subjects is stored for future use (including genetic analyses). All patients receive regular and structured follow-ups. One major aim of the GRIP study is to improve diagnostics by grouping subjects regarding symptom profiles, i.e. subgroups with similar phenotypes. It is possible to combine structured clinical information with genetics, neuroimaging, and liquor analyses to this end. The aim of the present study is to describe the group of research participants regarding the variables included in the clinical protocol.
Methods: The GRIP study has been approved by the Swedish Ethics Committee. The study design is naturalistic. The study is built into the ordinary clinical practice. All subjects who give written consent are included regardless of working diagnosis. No interventions are suggested. The instruments used to collect data include the PANSS and M.I.N.I. for psychosis and general psychiatric symptoms, the RAADS-R, ASSQ, and BAARS-IV for neuropsychiatric symptoms, the RAND36 for general health, the AUDIT and DUDIT for alcohol and substance habits, the WAIS-IV, TMT, and Tower of London for neuropsychological functioning.
Results: To date, 45 patients have been asked to participate in GRIP, 38 have given written informed consent, and three have withdrawn their consent. Of the 35 participants, 13 were women and 22 were men. The mean age was 36.5 years (SD = 10.3). Eighteen participants have agreed to a spinal tap whereas eight have declined. We are in the process of analyzing the first results from the GRIP study and will present clinically relevant results from spinal taps, MRI, and health blood samples. We will also describe the symptom profiles of the

participants together with background data and information regarding neuropsychological, physical, and social functioning.
Discussion: Our preliminary data will be discussed. We hope that the collection of a broad range of data will provide clinicians with significant information that will improve diagnostics and thereby benefit the patients. We are still in the process of fine tuning the clinical protocol and would highly value input that might help us to improve the protocol.

T142. Exploring the effect of COMT and BDNF polymorphisms on association between psychotic experiences and depression-suicidal ideation in a six-year follow-up of general population based sample

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Background: Individuals reporting psychotic experiences (PEs) are at increased risk of developing not only psychotic disorder but also depression and anxiety. PE has been also highlighted as a valuable clinical marker of risk for suicidal behaviour. There have been few studies to date, however, to assess psychotic experiences as a predictor of depression and suicidality over time. Furthermore, association between PEs and depression and suicide may be moderated by genotype including single-nucleotide polymorphisms of COMT and BDNF.
Methods: The TürkSch study (Izmir Mental Health Survey for Gene-Environment Interaction in Psychoses) is a prospective-longitudinal study consisting of several data collection stages to screen and follow up mental health outcomes in a general population sample. At baseline (T1, 2008), 4011 individuals aged 15–64 years were assessed on depression, suicidal ideation and extended psychosis phenotype using CIDI 2.1 and SCID-I. At follow-up (T2-on average 60 months later, 2014) participants (n: 2185) were interviewed for presence of any major depressive episode and suicidal ideation/attempt. Alleles rs4680 (COMTval158met) and rs6265 (BDNFval66met) were genotyped in a sub-sample (n: 262). Analyses excluded respondents with any psychotic disorder at T1 and T2 and based on outcomes of individuals with subclinical expression of PEs.
Results: Individuals with psychotic experiences at T1 were more than 2 and 2.5 times (adjusted OR: 2.3; 95% CI: 1.7-3.1 and OR: 2.7; 95% CI: 1.9-3.7 respectively) likely to experience at least one depressive episode or any suicidal ideation in the six-year follow-up (T2). While the rate of any depressive episode at T2 6.7% (n: 109) in the non-PE group (n: 1616), the same rate at T2 was 14.8% (n: 77) in the any PE group of T1 (n: 521). Suicidal ideation at T2 was reported by 6.1% (n: 99) of non-PE individuals at T1 while 16.3% (n: 85) of the respondents with any PE at T1 reported suicidal ideation at T2. Associations between PEs at T1 and depression and suicidal ideation at T2 were neither moderated by COMT nor BDNF polymorphisms.
Discussion: This is the first prospective general population study to examine moderator effects of COMT and BDNF on associations between PEs and depression and suicidal ideation. There was no evidence of an effect of COMT or BDNF polymorphisms. PEs are important but under-recognized marker of risk for depression and suicidal ideation.

T143. Evidence for neighbourhood effects on sub-clinical psychotic experiences: preliminary results from the south east London community health study

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Background: Psychotic-like experiences (PLEs) are discernible phenomena in community populations, that display evidence of aetiological and temporal continuity with psychosis per se. Risk factors for PLEs based on current evidence include male gender, age, non-White ethnicity, unemployment and lower socioeconomic status, and urbanicity, defined as exposure to urban residential environments over life. Associations with city living might exist because urban environments tend to be more deprived than rural areas. This is consistent with the psychosis literature- patterning of psychosis by area may in part be explained by local differences in deprivation, cohesion, and ethnic composition. No studies thus far have assessed these effects for PLEs in general population samples. One study, by Oher and others, evaluated the spatial distribution of psychotic symptoms in people with established psychotic disorder. However, the relevance of neighbourhood characteristics in influencing risk of psychotic symptoms in those without psychosis is unknown. This study uses a representative household survey located in South East London to assess the association between neighbourhood deprivation and psychotic-like experiences in the general population.
Methods: The South East London Community Health Survey (2008-2010) is a representative health survey of the residential population of two large inner-city boroughs in South East London, Lambeth and Southwark. The sample consisted of 1698 individuals, residing in 1075 households, collected through random sampling of a postcode address file for South London, who were then interviewed by trained researchers. For this analysis, the Psychosis Screening Questionnaire was used to assess the presence of different non-affective psychotic experiences (strange experiences, paranoia, hallucinations, and thought disorder). Information on neighbourhood deprivation was derived from the Index of Multiple Deprivations (IMD, 2011) dataset, which contains scores for deprivation for each small area of England and Wales based on census information. Latent variable analysis was done in STATA 14 using the item response theory command, accounting for the survey design. Univariate associations between the latent psychotic experience variable and neighbourhood deprivation indices were estimated using the mixed command.
Results: A ten-point increase in neighbourhood deprivation was associated with a small increase on the psychotic experiences latent variable (effect size:0.0048, 95%CI:0.0005,0.009), which remained after adjusting for age and gender(effect size:0.0047,95%CI:0.0005,0.009), but was rendered only marginally significant on adjustment for unemployment(0.0042,95%CI:0.00003,0.008).
Discussion: Psychotic experiences was associated with neighbourhood deprivation in this analysis of survey data, after accounting for age and gender. Remaining variability was explained in large part by individual unemployment, but there remained some weak statistical evidence for contextual effects. Further work should address this question in larger samples.

T144. Determinants of outcome in first-episode psychosis: re-admissions to psychiatric inpatient care

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Background: The content and organisation of mental health services have been changing seeking an optimal balance of services between community- and hospital-based psychiatric inpatient care. Attention has also increasingly been directed towards patients with chronically disabling conditions and the importance of long-term outcomes and functional abilities. A large body of research has been dedicated to uncovering the correlates of readmission and identification of risk factors for treatment planning, preparation of discharge and mental health policy planning.
Methods: We carried out a retrospective cohort follow-up study of 490 patients who presented with a first episode of affective and non-affective psychosis in east London between 1996 and 2000. Data were collected using standardized instruments from medical records in 53 primary and secondary care Trusts in England. Symptoms of mental illness were coded using the OPCRIT system. A full 10 year follow-up was achieved for 82% ($n = 350$) of the sample still alive and living in England. The follow-up period was divided into 6 month time windows resulting in a maximum of 7,000 observations for statistical analyses.
Results: Approximately one third of the sample ($n = 102$, 29.1%) were not re-admitted to psychiatric inpatient care after first presentation. A further 124 (35.4%) were re-hospitalized 1 to 3 times during follow-up and the remainder of the sample was more frequently re-admitted. A

small proportion of patients (41, 11.7%) were classified as revolving door patients with 11+ re-admissions during the follow-up. Factors characteristic for this group were: young age at first presentation, being male, black ethnicity, living in the borough of Hackney, UK born, single marital status, not owning the property where they lived in, parental discord before the age of 15, and a family history of criminal behavior. Surprisingly none of the clinical characteristics at baseline discriminated the groups. The eight risk factors were added up and the distribution was significantly different in the revolving-door patients. With regard to psychopathology during the follow-up, the most discriminating factor in this group was continuous abuse of drugs (pre-and post-onset of illness).
Discussion: Our findings suggest a dose relationship between vulnerabilities and severity of symptomatology with subsequent re-hospitalization. They further highlight the relevance of area effects on the occurrence of stressors which, in combination with continuous use of drugs, may lead to an early onset of psychotic illness. Further drug use and non-compliance may lead to re-emergence of psychotic symptoms with subsequent re-admissions.

T145. Does a syndemic or ethnicity explain disparities in psychosis in the UK?

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Background: Incidence studies in Europe have shown that certain ethnic groups have greater risk of all psychoses. In the UK the risk appears highest among African-Caribbeans. However, many migrant groups live in socio-economically deprived areas, some with unusual characteristics. Because incidence studies in the UK have been carried out in these same areas for the purpose of demonstrating ethnic and racial disparities, this questions whether there is a true association with ethnicity across the general population of the UK or whether there are specific area effects.
Methods: We carried out a cross-sectional survey of men 18 - 34 years using random location sampling to obtain representative samples of all UK men ($n = 1,999$), black and minority ethnic men ($n = 991$), and all men residing in the London borough of Hackney ($n = 760$). We compared self-rated measures of physical health, future physical health risks, sexual health, substance dependence, violence/ criminality, and psychiatric morbidity using standardized instruments. Psychotic-like-experiences were measured using the Psychosis Screening Questionnaire (PSQ). Confirmatory factor analysis was performed to assess evidence for a syndemic explanation of observed ethnic disparities.
Results: Compared to white men in the UK, young black and Asian men generally reported better current physical health and fewer risks for future health, with few disparities in sexual health, violence/ criminality, psychiatric morbidity. Disparities were not fully explained by socio-demographic differences. There were no disparities in psychotic-like-experiences observed across the UK. In contrast, black and Asian men in Hackney showed significantly worse sexual health, substance dependence, violence/ criminality, and psychiatric morbidity. A syndemic model of the joint effects of these factors confirmed significant interactions for black and Asian men living in Hackney.
Discussion: If psychotic-like-experiences at the population level reflect the risk for incidence cases of psychosis, these findings cast doubt on the notion of increased risk of psychosis in ethnic minority groups, specifically African-Caribbeans. They also suggest that socio-demographic factors are not sufficient to explain previous observations of disparity. The study found a syndemic consisting of psychiatric morbidity (specifically psychotic-like-experiences and symptoms of anxiety), poor sexual health, substance dependence and violence/ criminality with a positive biological interaction that exacerbates the negative health effects of each condition operating on black and Asian men in Hackney. Syndemic effects in the same areas in which incidence studies have demonstrated ethic and racial disparities in psychosis may be the true underlying explanation of these disparities.

T146. Academic performance in children of mothers with schizophrenia and other severe mental illness, and risk for the development of psychosis: a population-based study

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Background: Neurocognitive impairments are present in a significant proportion of individuals with schizophrenia and often precede the onset of overt psychotic symptoms. Such impairments are also detectable in the first-degree relatives of individuals with schizophrenia. Academic performance is generally considered evidence for neurocognitive ability. However, the associations between academic performance, subsequent schizophrenia and familial risk for psychosis are unclear. Using data from a large population-based cohort, we examined academic performance in Year 7 of children of mothers diagnosed with schizophrenia or other serious mental illness.
Methods: The sample consists of a subset of children from a large population-based cohort in Western Australia: 3,169 children of mothers with serious mental illness, including schizophrenia, bipolar disorder, unipolar major depression, delusional disorder or other psychoses (ICD-9 codes 295-298), and 88,353 children of comparison mothers without psychiatric morbidity. Academic performance was indexed on the Western Australian Numeracy and Literacy Assessment, a mandatory state-wide test, administered in Year 7 (approximately at age 12, representing readiness for secondary school). We examined below-benchmark performance (i.e. lower than the minimally acceptable standard) in the domains of spelling, numeracy, reading, writing, or in any of these domain. Demographics, maternal obstetric data and other parental information were obtained from linked databases and used as adjustments analyses.
Results: Overall, a higher proportion of children of mothers with serious mental illness performed below-benchmark (43.1%) than the reference group (30.3%; children of mothers with no known psychiatric disorder). Children of mothers with schizophrenia performed most poorly. After adjusting for covariates, children of mothers with serious mental illness were more likely than the reference group to perform below-benchmark across all academic domains except reading. Children of mothers with schizophrenia were more likely than the reference group to perform below-benchmark in any of the academic domains (OR = 1.38; 95%CI for OR = 1.07-1.79).
The development of psychotic disorder in offspring was significantly associated with prior below-benchmark performance in spelling (HR = 1.20; 95%CI for HR = 1.03-1.41), even when maternal psychiatric status was entered as an additional covariate (HR = 1.19; 95%CI for HR = 1.01-1.39). When offspring were stratified by maternal psychiatric status, spelling remained a significant predictor of the development of psychosis in children of mothers with serious mental illness (HR = 1.86; 95% CI for HR = 1.25, 2.77), but not in children of mothers with no know psychiatric disorder (HR = 1.09; 95%CI for HR = 0.91-1.30).
Discussion: Our data confirm that children of mothers with a serious mental illness are at increased risk to perform below the acceptable standard on academic achievement tests at age 12. After adjustment, only spelling was below-benchmark for children of mothers with schizophrenia, placing these children at disadvantage in literacy as they make the transition to secondary school. Poor spelling performance at age 12 was also a predictor of the later development of psychotic disorder in children of mothers with severe mental illness. This suggest that some cognitive deficits may already be evident at an early developmental stage in children at familial risk for mental illness, particularly those who go on to develop psychosis themselves.

T147. Higher complexity of EEG signal as a state marker in first episode psychosis compared to individuals with at risk mental state for psychosis and healthy controls.

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Background: Psychosis disrupts the stability and self-regulation of brain systems. Non-linear analyses such as complexity estimators applied to electroencephalography (EEG) are particularly relevant to study chaotic neural activity during psychosis (Fernandez *et al.* 2013). Various studies in schizophrenia have shown that complexity estimators vary across stages of the disease. Importantly, several studies have shown increased complexity estimators in first episode psychosis (FEP) compared to healthy controls, thus indicating a higher level of chaotic activity in early psychosis (Fernandez *et al.* 2013). However, it is still unknown if increased complexity is a state marker of FEP or a trait marker of the risk of psychosis. In order to address this issue, we studied the complexity of EEG signal in patients with FEP, compared to individuals with at risk mental state for psychosis (ARMS) and healthy controls (HC).
Methods: Patients and HC were recruited within the Basel FePsy Study for the early detection of psychosis (Riecher-Rössler *et al.* 2009). We included 47 patients with FEP, 67 with ARMS and 29 HC using the FEPSY study criteria, based on the Basel Screening Instrument for Psychosis (BSIP) (Riecher-Rössler *et al.* 2008). Symptoms of psychosis were assessed by BPRS and SANS. All the participants underwent a 19 channels resting state EEG recording at their inclusion in the study. After EEG pre-processing, the complexity of EEG signal was estimated with the Lempel Ziv Complexity (LZC). The LZC is a non-parametric measure in a one-dimensional signal, which counts the number of distinct substrings and the rate of their recurrence before computing it in a Z-score. The LZC was compared with an ANOVA with the group as between factor and the electrode location as within factor.
Results: The analysis showed a main effect of group, indicating that LZC was similar in ARMS and HC but was higher in FEP. The analysis also showed a main effect of electrode location on LZC but no interaction between electrode and group on LZC. Correlation analysis revealed a significant correlation between LZC and age.
Discussion: To our knowledge, this is the first study measuring EEG complexity in people with ARMS in comparison with FEP and HC. We showed a similar EEG complexity in people with ARMS and HC, but an increased EEG complexity in FEP patients. This result can possibly be interpreted as a higher level of neural chaotic activity in FEP patients. There was no gradation of LZC across HC, ARMS and FEP, which could eliminate this measure as a risk marker for psychosis. Since only FEP patients elicit an increased LZC, such a pattern could rather be considered as a state marker, specific for psychosis in comparison with ARMS and HC.

T148. Mismatch negativity (MMN) in psychosis following traumatic brain injury (PFTBI)

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Background: Patients who develop psychotic symptoms following a traumatic brain injury (PFTBI) are relatively rare (i.e., ~10%). Circuitry implicated in the neurogenesis of psychotic symptoms overlaps with circuitry typically affected by traumatic brain injury (TBI), however the neurobiological precursors and/or processes in the development of PFTBI remain unknown. Auditory mismatch negativity (MMN) is an event-related potential that indexes the preattentive detection of changes in the acoustic environment. Although impoverished MMN has been shown across a range of disorders, MMN deficiency has recently been described as a "break-through biomarker" in the prediction of disease risk/symptom onset. We sought to determine whether PFTBI patients demonstrate impoverished MMN akin to patients with schizophrenia as further evidence for the MMN biomarker for psychosis. We expected that MMN amplitude would be significantly reduced in both psychotic cohorts relative to TBI patients without psychosis and non-clinical controls.
Methods: Duration (100ms vs 50ms standard) and frequency (1050 Hz vs 950 Hz standard) MMN was measured at frontal sites where the difference waveform was maximal (F3, FZ, F4) in: nine PFTBI patients, nine TBI patients without psychosis, 17 schizophrenia patients without TBI, and 17 nonclinical controls.
Results: PFTBI and schizophrenia patients demonstrated significantly reduced amplitudes to both duration and frequency MMN at all three electrode sites relative to nonclinical controls as expected. However, TBI patients demonstrated statistically comparable amplitudes to both the psychotic cohorts and to the nonclinical controls (with the exception of frequency amplitude at F3 where TBI amplitudes were significantly larger than in schizophrenia).
Discussion: This is the first empirical event-related potential study in dually-diagnosed PFTBI. In support of a biomarker for psychosis, impoverished MMN to both duration and frequency deviants is apparent in PFTBI, akin to schizophrenia. Although MMN amplitude in TBI patients without psychosis was not significantly different from psychotic patients on the majority of contrasts, we note that peak amplitude was largely variable in TBI, with the mean looking more like nonclinical controls. Future work should determine the variability of MMN amplitude in TBI according to injury profile/lesion location, and follow TBI patients with reduced MMN amplitude to determine risk for transition to psychosis.

T149. C9ORF72 Repeat expansions that cause frontotemporal dementia are detectable among patients with psychosis.

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Background: A pathologic hexanucleotide repeat expansion in the regulatory region of C9orf72 causes frontotemporal dementia (FTD) or amyotrophic lateral sclerosis (ALS). In addition to features of dementia, behavioral abnormalities can be present among mutation carriers. It is uncertain whether a proportion of individuals clinically diagnosed with psychoses bear pathologic C9orf72 expansions in the absence of dementia.
Methods: We screened for C9orf72 repeat expansions among individuals diagnosed with functional psychoses such as schizophrenia (SZ)/schizoaffective disorder (SZA), and described the clinical features of individuals with the mutation.
Results: Pathogenic C9orf72 repeat expansions were detected in two pairs of related individuals following a survey of 740 participants in a psychiatric genetic research study. The mutation carriers included two siblings with schizophrenia, another unrelated individual with schizoaffective disorder and her non-psychotic mother. All the mutation-bearing patients with SZ/SZA had severe, florid illness, but did not provide a history suggestive of dementia or ALS.
Discussion: In conclusion, a small proportion of patients with SZ/SZA could bear C9orf72 repeat expansions. The patients showed atypical psychotic features without the typical cognitive features of dementia.

T150. Neurotrophin signaling in first episode psychosis: relation to response to antipsychotics after 1 year of follow-up

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Background: Previous studies have shown a pro/anti-inflammatory imbalance in patients with a first episode of psychosis (PEP), which continues 12 months after. Research in this area is increasingly focused on finding biomarkers that help us understand the pathophysiological mechanisms underlying the disease.
The aim of this study is to evaluate changes in the expression of neurotrophins BDNF and NGF and their receptors in peripheral blood to identify any potential correlation with levels of inflammation, clinical symptoms over time and response to antipsychotic treatment.
Methods: The study included 94 patients with a PEP and 80 healthy subjects. Blood samples and clinical data were taken both at baseline and 12 months later. The expression of BDNF, NGF and their receptors TrkB (functional and truncated) and TrkA was measured in peripheral mononuclear cells. The pro/anti-inflammatory parameters evaluated were NFkB, COX-2, iNOS, PPARgamma and 15d-PG12. Patients' functionality was measured by the GAF scale.
Results: Expression of the functional isoform (FL) of the BDNF receptor increases 1 year after diagnosis, whereas the truncated form (T) (inactive) descends. The ratio of both forms FL/T increases during follow-up only in the group of non-affective psychosis, suggesting different mechanisms underlying different subgroups of patients with PEP. Expression of NGF receptor, TrkA, increased in patients during follow. After adjustment for confounding variables basal levels of proinflammatory variables were significantly associated with the ratio FL/T, suggesting that increased inflammation would be associated with a higher ratio. Besides, the FL/T ratio could have a predictive role of the functionality of patient after 1 year, depending on whether the patient is treated with antipsychotic treatment or not.
Discussion: Inflammatory processes, neurotrophins pathways and functional status of the patient appear to be related which has important translational relevance. In particular, the level of expression of TrkB receptor isoforms (FL and T) should be considered before starting antipsychotic treatment in patients with a PEP.

T151. Minor neurological signs and clinical course in first-episode psychosis: a ten-year follow-up study

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Background: Minor neurological signs are already present not only at the time of first episode but even during prodromal phase in high-risk individuals and in healthy relatives of patients. They have therefore been proposed as a potential vulnerability biomarker for psychotic disorders. Here, we have investigated whether neurological signs at onset predict clinical course over the first ten years of illness.
Methods: Subjects were recruited as part of a large epidemiological study (AESOP; Aetiology and Ethnicity in Schizophrenia and other Psychosis) carried out in South London (UK). The presence and the severity of neurological signs was assessed in patients with first episode psychosis ($n = 234$) and in healthy controls ($n = 172$) with the Neurological Evaluation Scale (NES). After 10 years, we evaluated illness course using an amended version of the WHO Life Chart. Illness course was defined as episodic (one or more period of remission of at least 6 months, and no episode of psychosis lasting 6 months or more) or continuous (no period of remission lasting 6 months or longer). Premorbid IQ was assessed using the National Adult Reading Test (NART). In a subgroup of 55 patients neurological signs were also re-evaluated.
Results: At baseline, individuals with psychosis showed significant higher mean scores than healthy controls in primary ($P < 0.001$), motor coordination ($P < 0.001$), motor sequencing ($P = 0.005$) and total signs ($P < 0.001$) compared with controls (t-test). The ANCOVA analysis showed that continuous patients had significantly higher scores than episodic patients for primary signs, motor coordination and total signs ($P = 0.025$, $P = 0.001$ and $P = 0.001$ respectively). In contrast, controls had significantly lower scores than both continuous and episodic patients for motor coordination ($P < 0.001$) and total signs ($P = 0.025$ and $P < 0.001$). Even when covarying for age and NART IQ, the differences remained significant. Repeated measure analysis carried out on subjects with two neurological evaluations did not show any significant change in neurological scores over time.
Discussion: To our knowledge few studies have investigated the long-term predictive clinical significance of neurological signs at illness onset. This study provides further supports to the hypothesis that primary and motor dysfunction may characterize a subgroup of individuals more likely to have a non-remitting illness course. This is also consistent with previous evidence suggesting that an impairment of fine motor coordination and motor development can predict schizophrenia-spectrum disorders.

T152. Psychosis-risk is associated with increased cerebral blood flow in the striatum: results of an arterial spin labeling MR-study

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Background: Research on clinical high risk (CHR) states for psychosis indicates increased presynaptic striatal dopamine synthesis in CHR individuals as compared to controls. An increase in metabolic rate might also affect cerebral blood flow (CBF) in the respective regions. Here, we examined (1) if CBF in striatum differ between patients with and without CHR, and (2) if similar CBF changes are found in full-blown psychosis when compared with controls.
Methods: Samples: For the first aim, a total of 35 patients of the Bern Early Recognition and Intervention Centre were included. A CHR state was alternatively defined by ultra-high risk (UHR) or basic symptom (BS) criteria and met by 23 patients (CHR). UHR criteria were assessed by the Structured Interview for Psychosis-Risk Syndromes, BS criteria by the Schizophrenia Proneness Instrument. The clinical controls (CC, $n = 12$) did not fulfill CHR criteria or suffered from psychosis. Global level of psychosocial functioning was estimated using the Social and Occupational Functioning Assessment Scale (SOFAS). CHR and CC did not differ in age, sex or social functioning.
For the second aim, patients with an ICD-10 diagnosis of schizophrenia or schizoaffective disorder (SZ, $n = 32$) and healthy controls (HC, $n = 31$), matched for sex and age, were included. All patients reported medication-resistant positive symptoms at the time of scanning. Symptom severity in SZ was assessed with the Positive and Negative Syndrome Scale (mean total score = 76.6 ± 17.4).
Data Analysis: MRI was conducted on a 3 T MRI system. Participants were told to rest in the scanner and to stay awake with eyes closed. A pseudo-continuous arterial spin labeling (ASL) technique was used to measure CBF. ASL data analyses were performed with the aslm toolbox with MATLAB R2012a and SPM8. Data were z-transformed [z = (voxel CBF—global GM CBF) / SD] and corrected for gray matter (GM) volume. Because of inter-scanner variability, no direct comparison between the first (CHR, CC) and second (SZ, HC) samples was calculated. First, CHR were compared to CC with 2-sample t-tests, in a whole-brain, voxel-wise analysis. For the region of interest (ROI) analysis (ROI striatum = caudate & putamen, wfu-pickatlas), CBF values were extracted for left and right striatum, separately. Finally, SZ were

compared to HC in 2-sample t-tests with small volume correction for the ROI, i.e., the striatum.
Results: In the whole-brain voxel-wise analysis, CBF was significantly increased in CHR in the left putamen, the left insula and the lentiform nucleus, and significantly decreased in the right inferior frontal gyrus and the right middle temporal gyrus as compared to CC ($P < 0.001$, uncorrected). The ROI analysis revealed significantly increased CBF in CHR in the left striatum.
In comparison to HC, SZ demonstrated a significantly increased striatal CBF, predominantly in the caudate head and body (family-wise error corrected).
Discussion: This is the first study to demonstrate increased metabolic and neuronal activity within the striatum in a CHR sample. In both CHR and SZ, CBF in putamen and/or caudate was significantly increased as compared to the respective controls. Our results indicate that alterations of CBF in striatum might be a useful biomarker reflecting dopaminergic abnormalities that precede the onset of frank psychosis and positive symptoms, respectively. However, follow-ups of CHR patients and larger samples are required to examine prognostic accuracy of these alterations and potential associations with CHR symptoms, in particular with cognitive-perceptive BS and attenuated psychotic symptoms.

T153. Visual habituation is impaired in unaffected siblings of subjects affected by schizophrenia: a pattern-reversal VEP study

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Background: Sensory perception, including early phases of visual processing, are impaired in Schizophrenia. Relatives of subjects affected by Schizophrenia (SCZ), despite the absence of the characteristic clinical picture of illness, show similar perceptual deficits, including those of visual modalities. Also measures of sensory gating (or sensory habituation), considered as a protective mechanism against over-stimulation, results altered in relatives of SCZ. Impairment of habituation phenomena from visual paradigms, however, has not been yet demonstrated in relatives of SCZ. Recently, our group proposed that visual habituation, a reduction of the visual evoked response to sequential presentation of spatially structured stimuli measured with a Pattern-Reversal Visual Evoked Potential (PR-VEP) paradigm, is impaired in Schizophrenia. The aim of the present study was to measure the evoked responses of visual habituation PR-VEP paradigm in SCZ, their unaffected siblings (US) and healthy volunteers (HV), in order to investigate the hypothesis that US show abnormalities in visual habituation with an intermediate behaviour respect to SCZ and HV.
Methods: Twenty-four SCZ, with a clinical and pharmacological stable condition, were selected from an outpatient program, along with their twenty-eight US. Twenty HV were recruited as control group, comparable to SCZ and US for gender, age and education level. EEG signal was continuously recorded from a midline occipital electrode. Monocularly full-field black-and-white checkerboard pattern subtending 15′ of arc was presented, reversing in contrast at 3.1 reversal/s with 100% contrast for 800 consecutive trials. The EEG recording was divided in eight blocks of 100 consecutive trials. The peak latencies of N75, P100 and N145 components as well as the N75-P100 and P100-N145 peak-to-peak amplitudes for each block were measured. As a measure of habituation we used the slope of the linear regression line of the N75-P100 and P100-N145 peak-to-peak amplitudes.
Results: N75-P100 and P100-N145 amplitudes of the eight-block PR-VEP grand-average were different between the three groups; SCZ had significantly lower values than HV whereas US showed intermediate values between SCZ and HV. Repeated measure ANOVA models showed that the N75-P100 and P100-N145 amplitudes for the whole sample decreased between first and eighth block. Moreover, the "block × group" interaction effects resulted also significant: over the eight blocks, US amplitudes had middle values between those of HV, that showed a physiological reduction during the visual paradigm presentation, and those of SCZ, that did not present a reduction in PR-VEP amplitudes. The slope measures confirmed the halfway position of US between the normal values of HV and those of SCZ that revealed a lack of visual habituation. We didn't find significant differences between the three groups in the N75, P100 and N145 latencies in the average response to the 800 stimuli and between the 8 blocks.
Discussion: According to our hypothesis, visual habituation was abnormal in US showing intermediate neurophysiological indices between SCZ and HV. Our data contribute to extend the evidence of deficit in early sensory processing in Schizophrenia spectrum, proposing visual habituation as a potential novel endophenotype of Schizophrenia. Moreover, current findings suggests that visual habituation in Schizophrenia should be investigated more systematically in order to reveal new mechanisms that may have a role in the pathophysiology of Schizophrenia.

T154. The effects of −TAK-063 on cognition in a multiple dose, phase 1 study in healthy Japanese subjects and subjects with schizophrenia are consistent with its somnolent effects

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Background: TAK-063 selectively inhibits phosphodiesterase 10 A (PDE10A), which hydrolyzes both cyclic adenosine monophosphate and cyclic guanosine monophosphate. PDE10A is predominantly expressed in medium spiny neurons (MSNs) in the striatum, and PDE10A inhibition may modulate, indirectly or directly, the effects of glutamatergic and dopaminergic signaling. TAK-063 has demonstrated potential pro-cognitive effects in a variety of rodent models of attention, working memory, visual memory, and executive function. We have previously reported the pharmacokinetics and safety/tolerability of TAK-063 in a multiple rising dose study in healthy Japanese subjects (HJS) and subjects with schizophrenia (SS) in which subjects received either TAK-063 or placebo once daily for 7 days (TAK-063_104). In this study, TAK-063 was safe and well tolerated, and somnolence was the most common adverse event. Here, we report the effects of TAK-063 on cognition and postural sway as measured by the Cognitive Drug Research (CDR) computerized cognitive battery.
Methods: Healthy Japanese subjects ($n = 30$) and stable schizophrenia subjects who were washed out of their antipsychotic medications ($n = 47$) were enrolled in cohorts of 10 subjects each and randomized to either TAK-063 or placebo (8:2). The doses in HJS were 3, 10, and 20 mg; the dose levels in SS were 3, 10, 20, 30, and 100 mg. Safety and PK assessments were recorded throughout. Each subject completed 2 training sessions of the CDR test battery on Day-1, with additional assessments on Days 1, 2, 4, 6, and 7 prior to dosing and 2 and 6 hours after dosing. Data were analyzed as change from baseline (Day 1, predose). Mixed-model for repeated measurements analyses of covariance were utilized for analysis with baseline as covariate and dose and visit as fixed factors. Subjects nested within dose were fitted as a random factor. Visit was fitted as a repeated factor. The root mean square error was used to compute effect sizes (Cohen's d) for change from baseline difference to placebo scores. Each subject group was analyzed separately. The baseline predosing scores of the volunteers and patients were also contrasted using t-tests.
Results: With the exception of cognitive reaction time, deficits in various cognitive domains were observed in SS compared to HJS at Baseline. These deficits were mostly of medium to large effect sizes (0.5 to 0.8). In general, in both groups, TAK-063 caused impairments in measures of attention, working memory, and verbal and nonverbal episodic memory that were generally dose dependent and with medium to large effect sizes. In both groups, TAK-063 did not have an effect on speed of processing (cognitive reaction time). A large effect was noted in power of attention in HJS at 10 mg, with little impairment at 3 and 30 mg. Slight improvements in working memory in SS were observed at 3 and 10 mg, with dose-dependent impairments at higher doses. In HJS, but not SS, improvements in speed of memory were observed at all dose levels. Postural sway was increased with 10, 30, and 100 mg in SS with small to medium effect sizes, and by 10 mg in HS with a medium to large effect size.

Discussion: Preclinical studies in rodent models suggest that TAK-063 has potential pro-cognitive effects. In clinical studies of TAK-063, the most common adverse event has been dose dependent somnolence. The observed changes in cognitive measures in this study in both HJS and SS are generally consistent with somnolent-like adverse effects of TAK-063 during 7 days of dosing, though the results of this study are limited by the study design and small sample size. It is unknown whether any accommodation to the somnolent effects of TAK-063 would occur with longer dosing or would result in improvements in cognition.

T155. TAK-063 increases gamma synchrony in subjects with schizophrenia

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Background: TAK-063 selectively inhibits phosphodiesterase 10 A (PDE10A) and is in clinical development for the treatment of schizophrenia. Differences in electroencephalographic [EEG]; auditory mismatch negativity [MMN]; and eye-blink prepulse inhibition [PPI] deficits have been reported in schizophrenia patients indicative of impairments in gating, pre-attentional information processing, and neural synchrony, the latter evidenced by reductions in gamma power. In preclinical studies, TAK-063 has been shown to reverse the effects of ketamine on gamma EEG in rats and monkeys and normalize impairments in PPI in rats. We have previously reported the pharmacokinetics and safety/tolerability of TAK-063 in a double-blind, placebo-controlled, multiple rising dose study in healthy Japanese subjects and subjects with schizophrenia (TAK-063_104). Additional objectives of this study were to explore the effects on neurophysiological biomarkers in subjects with schizophrenia and are reported here.
Methods: Schizophrenia patients ($n = 47$) who were off-medication were dosed once daily with 3, 10, 20, 30, and 100 mg TAK-063 or placebo for 7 days. For these analyses, 43 completers were included: 9 randomized to placebo and 34 randomized to TAK-063.
A battery of neurophysiological measures was conducted at predose and at 4 h postdose on Day 1 and 4 h postdose on Day 7 using standard methods. The battery consisted of resting EEG, EEG with high-frequency auditory stimuli (30, 40, and 50 Hz) and auditory MMN with duration deviants and PPI (60 msec prepulse). MMN-processing consisted in the negative peak between 100-240 ms for deviant-standard responses and PPI-ratios were taken from peak-values in rectified blink-EMGs. Multi-electrode EEG recordings were reviewed to reject extracerebral artifacts. Digital filtering techniques were utilized and denoised data were transformed using the Fast Fourier method to obtain the following bands: delta (0–3.5 Hz), theta (4–7.5 Hz), alpha (8–12), beta (13–25 Hz), global gamma (30–50 Hz), and high gamma (40–50 Hz) and quantified in 5 regions as frontal, central, parietal, occipital, and temporal. Baseline-adjusted data were averaged in groups in order to compare each dose with placebo, and either a mixed model for repeated measurements or ANCOVA models was used which included baseline as a covariate and treatment group as fixed factor. For the EEG parameters, brain region and treatment group by region were added to the model.
Results: At baseline, presumed deficits in gamma power during the 40 Hz stimulus were present. Four hours after dosing on Day 1, significant restoration of synchronized 40 Hz EEG was observed for the 20 mg and 100 mg doses in all 5 regions ($P < 0.05$); no improvement was observed on Day 7. On Days 1 and 7, increases in (eyes-closed) resting alpha were observed, especially at the 20 mg dose (globally) and more modestly at 10 and 100 mg (posteriorly) with coincident decreases in slow waves. Trends of improvement of moderate MMN deficits were observed in the peak analyses in the 10 and 20 mg dose groups. No improvement in PPI in any dose group was observed.
Discussion: The effects of TAK-063 on neurophysiological measures are indicative of pharmacological effects in the brain. Improvements in gamma power and increases in alpha and coincident reductions in slow waves may be indicative of improved sensory awareness and cognitive function. These results, however, are limited by the small sample size and limitations of the study design.

T156. The PDE-10 a inhibitor TAK-063 reverses ketamine-induced changes in FMRI bold signal

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Background: Ketamine is an NMDA antagonist that has been used in preclinical and clinical models of psychosis. At sub-anesthetic doses in humans, ketamine produces effects that are similar to the positive, negative, and cognitive symptoms of schizophrenia. Ketamine has also been shown to induce changes in Blood Oxygen Level Dependent (BOLD) magnetic resonance signal in areas of the brain that are involved in the pathogenesis of schizophrenia. Lamotrigine and risperidone have been shown to attenuate the effects of ketamine on BOLD signal. Here we report the effects of a novel phosphodiesterase 10 A (PDE10A) inhibitor, TAK-063, on ketamine induced BOLD signal changes in humans.
Methods: This was a randomized, investigator- and subject-blinded, placebo-controlled, 3-period, incomplete crossover, phase 1 study designed to evaluate the effect of TAK-063 on fMRI BOLD signal during resting state and during a working memory activation task. The study population included 27 eligible healthy male subjects aged 18–45 years. Subjects were randomized in equal ratios to 1 of 9 treatment sequences. Each subject received placebo or 2 of the 3 doses of TAK-063 (3, 10, 30 mg) five hours prior to initiating scanning. Midway through the scanning protocol, subjects were administered IV ketamine designed to achieve a steady plasma concentration based on weight. BOLD echo planar images were obtained during a 20- minute resting-state sequence using a 3 T Siemens Verio scanner (TR = 2 s, TE = 28ms, 40 slices, 3mm slice thickness). FMRI images were analyzed using SPM8 and Matlab. Percent signal change for resting state data was calculated between pre-ketamine and post-ketamine infusion based on a priori regions of interest using SPM's Anatomy Toolbox. Percent signal change for the working memory task was calculated for the task versus baseline in the post-ketamine condition using the same region of interest used for resting state. An ANOVA model was used to perform the analyses for BOLD signal changes.
Results: Consistent with previous reports, ketamine administration increased BOLD signal in most regions of interest. Compared to placebo, TAK-063 at doses of 3 and 30 mg decreased the ketamine-induced BOLD signal changes in left and right anterior and posterior cingulate cortex, striatum, and ventrolateral and dorsolateral prefrontal cortex; effect sizes were generally dose-dependent. In substantia nigra, there was a decrease in BOLD signal at all dose levels. In general, TAK-063 reversed the ketamine-induced increases in resting BOLD signal. However, the observed effects at 10 mg were reduced relative to the effects of other dose groups. Signal changes observed during the working memory task showed TAK-063 decreases in task-related activation in anterior and posterior cingulate cortex, striatum, substantia nigra, as well as other regions. Similar to the resting state, the effect sizes were generally less in the 10 mg than in the other dose groups.
Discussion: Overall, these study results are consistent with observed reversal of ketamine-induced changes in BOLD signal by risperidone. To date, PDE10A inhibitors have not demonstrated clinical efficacy in the treatment of schizophrenia and it is unknown if these data are predictive of potential antipsychotic activity. The reason for the non-linear dose response of TAK-063 is unknown, but this pattern was evident in the BOLD signal changes in both resting state and during the working memory task. Further analyses will be required to understand the contributions of changes in blood flow to the observations in BOLD signal and to determine the potential treatment efficacy of TAK- 063 in individuals with psychosis.

T157. Altered right anterior insula activity during anticipation of food and social rewards in schizophrenia: an FMRI study

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Background: Previous studies have suggested that schizophrenia demonstrated diminished ventral striatal (VS) and anterior insula (AI) activities in anticipation to potential monetary reward. However, it is still not quite clear about whether the VS and AI dysfunction would be affected by different types of reinforcements (i.e. food and social interaction). In the present study, we employed both Food incentive delay (FID) task and social incentive delay (SID) task to detect neural substrates of reward anticipation with regarding of both physical and social domain in schizophrenia.
Methods: Twenty-eight patients with schizophrenia (Sz) diagnosed by DSM-IV and 29 healthy controls (HC) with aged, gender, educational level matched were recruited and administrated to the FID and SID task in the scanner. In order to explore the group differences in activities across brain regions, we firstly performed two-sample T tests between Sz and HCs for the contrast of anticipation of positive/negative valenced food/social images versus neutral images, respectively. Multiple corrections were performed using Family-wise-error rate at $p < .05$. In order to further examine the group difference in neural activity within the priori regions of interest (ROI), two-way repeated measure ANOVAs were performed on the % BOLD signal change of the bilateral VS and the AI during anticipation phase with valence (positive, neutral, negative) as within-subject variable and group (HC vs. Sz) as between-subject variable for FID and SID, respectively. Pearson correlations were performed between regional BOLD signal change percentage during reward anticipation, Chapman physical and social anhedonia scales, and clinical symptom scales in schizophrenia.
Results: In the whole brain findings, we did not observed diminished VS and AI activities during food and social reward/punishment anticipation, although patients with Sz exhibited diminished brain activity in the right superior temporal gyrus (63 -42 18, BA 22) during anticipation of avoiding disgusting food images compared to healthy controls. In viewing of absence of the VS and right AI dysfunctions in Sz, we further performed the ROI analysis within these two priori ROIs. It was found patients with schizophrenia demonstrated no signicant difference in the right AI activity among the positive, negative and neutral condition during anticipation phase ($F(2,110) = 1.42$, $p = .246$) while HC exhibited stronger right AI activations in anticipation of positive and negative food images compared to neutral images (positive > neutral: $p = .001$; negative > neutral: $p < .001$), reflected by a significant group x valence interaction ($F(2,110) = 6.515$, $p = .002$). As for social interaction images, similar findings were observed, reflected by a significant group x valence interaction ($F(2,110) = 8.402$, $p < .001$). However, there was no signfiicant group difference in brain activation in the bilateral VS during anticipation of food and social reward/punishment. Moreover, the right AI activities during anticipation of positive and negative food images were inversely associated with physical anhedonia score in Sz (positive food: $r = -0.415$, $p = .028$; negative food: $r = -0.529$, $p = .004$). General symptom in schizophrenia, however, was observed positively correlated with the left VS activity during anticaption of negative social images.
Discussion: Our findings suggest that 1) the flat right AI response pattern might play an important role in understanding the nature of reward and punishment anticipation dysfunctionin schizophrenia; 2) this altered response pattern of the right AI in Sz may be independent of the reinforcement types.

T158. PET imaging evidence of altered dopaminergic modulation of reward responses in ventral striatum in familial risk to psychosis

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Background: Abnormalities in reward processing are a consistent finding in psychotic disorder and have been proposed to be linked to dysregulated mesolimbic dopamine (DA) neurotransmission. Chaotic firing of DA neurons in the striatum of the patients is thought to attribute salience to irrelevant stimuli instead of signaling potential rewards. Despite the circumstantial evidence in support of this notion, it has never been decisively corroborated using neuromolecular imaging. We applied this method in a sample of first-degree relatives of individuals with psychosis to investigate the putative DAergic basis of the reward dysfunction as a mechanism of familial risk for psychosis.
Methods: Using a single DA D2/3 receptor [18 F]fallypride positron emission tomography (PET) scan we explored the DAergic activity in the mesolimbic regions of 16 unaffected siblings of individuals with psychosis and 16 gender-, age- and IQ-matched controls under reward condition. In six 10- minute independent learning blocks monetary reinforcement was probabilistically delivered upon the selection of the correct stimulus, and withdrawn upon the choice of the incorrect one. The main outcome measure was the reward-related DA activity (defined as the magnitude of reward-induced [18 F]fallypride displacement) in reward versus control condition in the right and left hippocampus, amygdala, putamen, caudate nucleus (CN) and ventral striatum (VST). Secondary outcome was the behavioral performance defined as the amount of money earned in the reward task.
Results: The relatives did not differ from controls in performance on the task ($P = 0.91$, $t(31) = 0.11$, $\beta = 0.11$), nor was there an effect of group on magnitude of reward-related tracer displacement in all ROIs (all $P > 0.05$). The relatives showed significant reward-related DA release in all regions except for right putamen and left CN. Importantly, in right VST there was a significant group x tracer displacement interaction on performance ($P = 0.047$, $t(31) = -2.9$, $\beta = -118,26$), with controls demonstrating a significant association between reward-related tracer displacement and performance on the reward task ($P = 0.03$, $t(15) = 2.5$, $\beta = 114,72$), that was not present in the relatives ($P = 0.26$, $t(15) = -1.2$, $\beta = 44,26$).
Discussion: Unaffected first-degree siblings of patients with psychosis demonstrated reward-induced mesolimbic DA activation comparable to healthy controls. However, unlike in controls, higher task-induced DA release in the right VST of the relatives was not associated with better performance on the task, possibly indicating altered mechanism of DAergic modulation of reward processing in this group. This result converges with prior reports implicating aberrant neural VST activity in reward dysfunction in patients with psychosis, and provides initial evidence for a qualitative DAergic abnormality related to familial risk to psychosis.

T159. Neural correlates of the negative prior expectancy bias in schizophrenia: an FMRI multivariate analysis.

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Background: Impaired emotion perception is a well-established and stable deficit in schizophrenia, having a significant impact on functional outcome. Recent work has examined the basic processes underlying emotion perception impairment, finding that difficulties arise from overdependence on 'prior expectations'. Prior expectations direct attention to emotions that are congruent with what is expected; in schizophrenia, dependence on negative prior expectations is heightened, and results in attribution of threatening emotions to non-threatening or neutral expressions. However, the brain processes underlying this negative prior expectancy bias in schizophrenia have

not been examined. The present study aimed to investigate the effect of negative prior expectations (induced by cues) on dynamic, multisensory emotion perception in patients with schizophrenia and the brain networks associated with impaired perception of neutral expression.
Methods: Twenty patients with schizophrenia and 20 healthy controls completed the study. We used a functional Magnetic Resonance Imaging (fMRI) paradigm with emotional videos and manipulated prior expectations with congruent or incongruent preceding emotional cues.
Results: We found that when viewing neutral videos preceded by angry cues patients with schizophrenia had significantly lower accuracy compared to healthy controls, and recruited a brain network involving the temporoparietal junction and hippocampus.
Discussion: There is converging evidence that hyper-connectivity between the temporoparietal junction and hippocampus produces symptoms such as delusions and hallucinations. In schizophrenia the negative prior expectancy bias may be a result of aberrant connectivity between the temporoparietal junction and hippocampus, which may influence the formation of delusional beliefs and incorrectly perceiving threat in neutral expressions.

T160. Aberrant shift of neural activity during hand gesture performance in schizophrenia: less motor but more limbic activity

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Background: Schizophrenia is characterized by poor social interaction contributing to poor functional outcome. Particularly nonverbal communication is disturbed. Neural correlates of impaired gesture performance are currently unclear. We thus tested functional correlates of gesturing in schizophrenia patients and healthy controls.
Methods: In total, 22 patients and 25 controls matched for age, gender and education level participated. We used an event-related (instructed delay) paradigm to dissociate brain activation during planning and execution of familiar (e.g. use scissors) and novel (e.g. spread little finger outwards) gestures. Performance was assessed by video monitoring and analyzed by blinded raters according to diagnosis and clinical status.
Results: During planning and execution of both gesture subtypes both groups activated brain areas of the praxis network. However, patients had reduced dorsolateral prefrontal cortex (DLPFC) activity and increased inferior parietal lobe (IPL) activity. Performance accuracy was associated with DLPFC activity in controls and with IPL activity in patients. During planning only patients showed additional activity in temporal poles, amygdala and hippocampus associated with delusion severity. Furthermore patients demonstrated increased dorsomedial prefrontal cortex activity during planning of novel gestures.
Discussion: We demonstrated an aberrant pattern of brain activation during gesturing in schizophrenia. In fact, a differential neural association with performance accuracy (DLPFC vs. IPL activity) was discovered. Moreover, only in patients we detected limbic activity, linked to delusion severity. These findings may reflect impaired action planning and a limbic interference planning gestures in schizophrenia. Together these alterations may contribute to poor gesture performance in schizophrenia.

T161. The effect of aripiprazol versus risperidone on planning-related brain activation

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Background: Impaired function of a fronto-striatal-parietal brain network may be the source of both negative symptoms and neurocognitive problems in psychotic disorders. Whereas most antipsychotics have a poor effect on negative symptoms and may decrease prefrontal activation, the partial dopamine D2-receptor agonist aripiprazole is hypothesized to improve negative symptoms. This study investigated whether patients with a psychotic disorder would show larger increases in prefrontal activation and concurrent negative symptom improvement after treatment with aripiprazole compared to risperidone treatment.
Methods: In this pharmacological neuroimaging study, 24 patients were randomly assigned to either aripiprazole or risperidone. At baseline and after nine weeks treatment they underwent an interview and MRI session. Here we reports on arterial spin labeling findings during performance of a planning task, the Tower of London that activates the prefrontal cortex.
Results: Aripiprazole treatment resulted in decreased activation of the middle and superior frontal gyrus and occipital gyrus, while activation increased in these regions after risperidone treatment. Activation increased in the ventral ACC and posterior insula after aripiprazole treatment, while it decreased after risperidone. Both treatment groups had an increase in ventral insula activation, and a decrease in occipital cortex, precuneus and caudate head activation. Positive symptoms, general pathology and depressive symptoms improved in both groups, but negative symptoms did not.
Discussion: In conclusion, risperidone and aripiprazole had differential, albeit partly overlapping, effects on planning-related brain activation that may be explained by their specific effects on the dopamine and serotonin system. Prefrontal capacity of aripiprazole treated patients appeared to improve, while posterior brain regions show a similar response to both antipsychotics.

T162. Are emotion processing deficits in schizophrenia and major depression mood-related symptoms?

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Background: Social interaction determines our daily life. Automatic neuronal circuits like emotion processing are involved in these interpersonal contacts. Both schizophrenia (SZ) and major depression (MD) often come along with patient's impairment of social interaction. This symptom as well as impaired emotion processing is well described for both diagnoses. Just like further studies showing amygdala hyperactivity in MD bias the automatic judgment of facial expressions, in SZ facial emotion processing deficits are associated with temporal lobe abnormalities. Nevertheless only few studies compare those different groups of patients directly.
Methods: To date approximately 60 patients with SCID-I confirmed diagnoses of SZ or schizoaffective disorder (SA) as well as an equal number of both matched patients with mood disorders and matched healthy controls (HC) were included in this study. They were phenotyped by self-assessment questionnaires (e.g. BDI, NEO-FFI, childhood trauma questionnaire (CTQ)) just as assessment by trained psychologists (e.g. HAMD, SAPS/SANS). They also underwent functional magnetic resonance imaging using a 3-Tesla Siemens scanner. Via the affective priming paradigm sad, happy and neutral faces as well as a no-face stimulus were subliminally presented and masked by neutral faces (Dannlowski *et al.*, 2013). The participants were asked to evaluate the facial expression fast and intuitively by button-press.
Results: In our study we will have a closer look at the influence of clinical outcome, especially affective and negative symptoms as well as personal traits on specific activation patterns like amygdala hyperactivation or temporal lobe abnormalities. We hypothesize to find influencing factors independently of diagnosis themselves.
Discussion: The aim of this study is to show possible differences or similarities not just between SZ/SA and HC but also between SZ/SA and MD. Focusing on different clinical outcomes and personal traits between SZ/SA and mood disorder patients as well as HC will lead to a better understanding of shared neurobiological fundamentals and maybe risk-factors of impaired emotion processing.

T163. Neurobiology of insight in schizophrenia: findings from a systematic review

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Background: Insight in schizophrenia, clinically, defined as awareness into illness, symptoms and need for treatment has long been associated with cognition, adverse clinical and functional outcomes and other psychopathological symptoms. Impaired insight has been associated with medication non-adherence, increase in relapse, frequent hospitalizations and increased involuntary commitments. Clinically, insight is associated with severity of positive and negative symptoms, longer duration of untreated psychosis, violence towards self and others and mood symptoms. Functionally insight has been associated with psychosocial functioning, vocational functioning and quality of life. Insight is also closely tied to patient-reported outcomes in schizophrenia. Emerging literature in insight in schizophrenia points to a neurobiological basis with a multifactorial etiology linking problems with facets of cognition such as neurocognition, social cognition and metacognition. However, the biological basis of insight is still poorly understood. The aim of this systematic review was to (1) critically evaluate and summarize advances in the study of the biologic basis of insight in schizophrenia and (2) to identify gaps in this knowledge.
Methods: PubMed, CINAHL, PsycINFO and EMBASE databases were searched to identify articles relevant to the neurobiology of insight in schizophrenia that was published in the last 6 years. Articles were chosen if the focus of examination was neurobiological. Articles on insight in conditions other than schizophrenia or psychoses and which did not investigate the neurobiological underpinnings of insight were excluded from the review.
Results: Twenty-six articles that met the inclusion criteria were systematically reviewed. Of the twenty-six articles, twenty-three used neuroimaging technology and three focused on cellular abnormalities. These studies identify the prefrontal cortex, cingulate cortex and regions of the temporal and parietal lobe (precuneus, inferior parietal lobule) and hippocampus as the broad neural correlates of insight.
Discussion: There is a growing body of literature that attests to the neurobiological basis of insight in schizophrenia. Current evidence supports a neurobiological basis of insight in schizophrenia and identifies specific neural correlates for insight types and its dimensions. Further studies that examine the precise biological mechanisms of insight are needed in order to apply this knowledge to effective clinical intervention development.

T164. Stress and emotion processing in siblings of schizophrenia patients: preliminary results

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Background: Stress is an important risk factor for schizophrenia (Corcoran *et al.*, 2003). However, the underlying neurobiological mechanisms are currently unknown. Key brain areas involved in stress regulation are the hippocampus and amygdala. Altered function and structure of these limbic structures have consistently been reported in schizophrenia patients, as well as healthy siblings of schizophrenia patients, implying that problems in stress regulation and emotion perception and expression are related to the genetic vulnerability for schizophrenia (van Buuren *et al.*, 2011). To further substantiate this notion, we aimed to identify the role of the limbic system in stress integration in healthy male siblings of schizophrenia patients, who are at genetic risk but are not ill and do not take antipsychotic medication. To this end, the effects of acute psychosocial stress on emotion processing were examined in unaffected schizophrenia siblings and healthy controls.
Methods: Brain responses to positive, negative and neutral pictures from the International Affective Picture System (IAPS) were measured using functional MRI in male unaffected schizophrenia siblings and matched healthy controls (in both groups psychiatric disorders were excluded) after exposure to the stress or control condition of the validated Trier Social Stress Test (TSST). The four groups (sibling-stress, sibling-no-stress, control-stress, control-no-stress) did not differ in age, education, ethnicity or body mass index. Saliva samples and subjective stress measurements were obtained throughout the experiment. Regions of interest (ROIs) consisted of amygdala and hippocampus and were created using the AAL-atlas (Tzourio-Mazoyer *et al.*, 2002). Preprocessing and statistical analyses of the images were performed with SPM8. GLMs were performed to test for the effects of stress (stress, no-stress), group (siblings, control) and their interaction on brain activation.
Results: Successful stress induction was confirmed by increased subjective stress level (visual analogue scale; main effect of stress, $P = 0.006$) and cortisol levels (main effect of stress, $P = 0.029$) in both healthy controls and schizophrenia siblings. We found a significant stress and disease interaction effect bilaterally in hippocampus activity during positive picture presentation (left, $P = 0.034$; right, $P = 0.026$). No significant interaction was found in the amygdala.
Discussion: These preliminary results suggest that schizophrenia siblings display different stress-induced activation patterns in the hippocampus in response to affective stimuli compared to healthy controls. Despite the absence of any psychiatric symptoms, the genetic vulnerability to develop schizophrenia may therefore be associated with abnormalities in the neural circuitry of emotion processing and an altered central stress sensitivity.
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T165. Emotion regulation and insight in schizophrenia: an FMRI task study

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Background: Insight is impaired in the majority of individuals with schizophrenia. Impaired insight is one of the most common reasons for poor treatment adherence and has been associated with poorer outcome. The etiology of poor insight remains unknown. In addition, numerous studies have shown emotional dysregulation in schizophrenia. In this study, we investigated the association between insight and brain activation during the most investigated emotion regulation strategy, namely reappraisal. We hypothesized a positive association between insight and activation of prefrontal areas and the insula during reappraisal.
Methods: 30 schizophrenia patients and 15 healthy controls were included. Clinical insight was measured with the Schedule of Assessment of Insight – Expanded (SAI-E; Kemp & David, 1997) which consists of three subscales: (1) awareness of illness, (2) relabeling of symptoms and (3) need for treatment. Cognitive insight was measured with the Beck Cognitive Insight Scale (BCIS; Beck *et al.*, 2004) which consists of two subscales: self-reflectiveness and self-certainty. A BCIS composite index score was computed by subtracting the self-certainty score from the self-reflectiveness score. All individuals performed an emotion regulation task in an fMRI scanner, during which pictures from the International Affective Picture System were used to generate negative affect (Ochsner *et al.*, 2002). Three emotion regulation conditions were examined, in addition to a control condition in which individuals had to attend to negative pictures: (1) cognitive reappraisal to decrease negative emotions, (2) expressive suppression of negative emotions and (3) cognitive reappraisal to increase negative emotions. In this study, the cognitive reappraisal condition to decrease negative emotions was of our main interest. Main effect analyses were performed within the entire group while regression analyses with insight only included schizophrenia patients.

Results of regression analyses are reported with an height threshold of $P < 0.001$ (uncorrected) and extent threshold of $k \geq 20$ voxels.
Results: Main task effects were in line with other studies using this task (Van der Meer *et al.*, 2014). Furthermore, better clinical insight (SAI-E subtotal score) was associated with less activation in the right insula and left medial prefrontal cortex (mPFC) during reappraisal. In addition, higher scores on the SAI-E subscale Need for treatment were associated with less activation in the left inferior frontal gyrus (IFG) and bilateral middle frontal gyrus. With regard to cognitive insight, higher BCIS composite index scores were associated with less activation in the left precentral gyrus and the left supplementary motor area (SMA) during reappraisal. In addition, higher scores on the BCIS self-reflectiveness subscale were associated with more activation in the white matter of the right middle cingulate gyrus, while lower scores on the BCIS self-certainty subscale were associated with more activation in the left SMA and left precentral gyrus/postcentral gyrus.
Discussion: During reappraisal, impaired clinical insight was associated with more activation in the mPFC and insula, while impaired cognitive insight was associated with more activation in the left precentral gyrus and left SMA. Our results may suggest that patients with impaired insight need to call upon more neural resources to exert cognitive control (through activation of the mPFC) and execute emotion regulation (through activation of the precentral gyrus and SMA) to decrease negative effect. This is in line with earlier studies finding associations between impaired insight and abnormalities of areas involved in cognitive control in schizophrenia.

T166. The effect of mentalization-based treatment in patients with first episode schizophrenia – a FMRI study

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Background: The impairment of social cognition including mentalizing is one of the core features of the illness and has a clear impact on functional outcome.[1] Several brain regions, including the medial prefrontal cortex (mPFC), bilateral temporoparietal junction (TPJ) and precuneus have been consistently found to be activated in various mentalizing tasks. Most studies in schizophrenia report hypoactivation of the core mentalizing system and impaired mentalizing ability.[2] Different treatment strategies including both treatment with atypical antipsychotics and social cognitive training[3,4] can improve functional outcome in patients with schizophrenia.[5]
The aim of the study is to investigate the effect of a mentalization-based treatment program on the mentalizing network in the brain in patients with first episode schizophrenia.
Methods: 12 patients diagnosed with schizophrenia according to DSM-IV-TR criteria and treated with atypical antipsychotics participated in the study (6 males, mean age: 30.43, SD = 9.35 years, years of education 13.23, SD = 2.45). Patients were randomized to an add-on mentalization-based treatment group (MBT; $n = 6$) and a treatment as usual group receiving only atypical antipsychotics ($n = 6$; TAU). A modified treatment program for psychoses was used based on the mentalization-based therapy developed by Bateman and Fonagy for borderline personality disorder.[6] Before and after the treatment fMRI analyses (fixed effects analyses) were carried out (3 Tesla, 5 blocks on /off, 36 s, TR = 3.62, SPM) using the n-back task.
Results: Preliminary results show single analyses due to the small sample size. Comparing the fMRI scans before and after treatment, increases in the activation patterns were found in first episode patients treated with MBT. In patients with TAU a reduction in the activation patterns was demonstrated (mean changes in the activation clusters in the MBT group was 5.53, SD 12.79, in the TAU group -5.80, SD 6.91).
Discussion: Mentalization-based treatment is a promising approach in the treatment of schizophrenia and can have an impact on social networks in the brain. Further studies are needed for a better understanding of social cognition and the related neural mechanism in schizophrenia.
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T167. Fronto-subcortical functional connectivity in patients with schizophrenia and bipolar disorder during a verbal fluency task.

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Background: The question of a continuum or a dichotomy between schizophrenia and bipolar disorder is not clearly elucidated. Therefore, the aim of the present study was to explore the functional connectivity (FC) in the language production network in response to a verbal fluency task in patients with schizophrenia (SZ), patients with bipolar disorder (BD), and healthy controls (HC) in order to identify specific FC patterns in these two pathologies. We specifically hypothesized that FC would be reduced in SZ compared to BD and to HC.
Methods: Forty nine participants: 15 SZ, 14 BD, and 20 HC were included in the study. Functional Magnetic Resonance Images (MRI-3 T) were acquired. The experimental paradigm consisted in mentally generating verbs in French, the native language of all participants, alternated with periods of silence considered as reference task. Maps of the Blood Oxygen Level Dependent (BOLD) signal contrast (Verbs minus silence) were generated in each participant in the MNI (Montreal Neurological Institute) space in order to obtain then a mean map in whole population considered as the language production network. Thus, FC was calculated in the following activated paired-seed regions: the left fronto-lateral cluster (LFLC) and the left subcortical cluster (LSCC); the medio-frontal cluster (MFC) and the LSCC; and the LFLC and the MFC.
Results: First, SZ presented a significant reduced FC compared to HC within two paired-seed regions (MFC – LSCC and LFLC – LSCC) while BD were not significantly different from HC. Second, SZ compared to BD exhibited a reduced FC within one paired-seed region (MFC – LSCC). No differences were highlighted between the LFLC and the MFC among the three populations.
Discussion: Our results support the hypothesis of a specific medio-prefronto-striato-thalamic functional dysconnectivity implicated in the pathophysiology of schizophrenia. This reduced fronto-subcortical FC could be a functional brain biomarker of schizophrenia.

T168. Brain PDE10A occupancy measured by PET after oral administration of TAK-063, a newly developed PDE10A inhibitor, in human volunteers

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Background: Phosphodiesterase 10A (PDE10A) is selectively expressed in the striatal regions in the brain and may play a role in modulating dopaminergic and glutamatergic second messenger pathways. PDE10A inhibitors may be useful in treating psychiatric and neurodegenerative diseases such as schizophrenia and Huntington disease. TAK-063 is a potent and selective inhibitor of PDE10A. Recently, PDE10A occupancy by TAK-063 was successfully measured with [11C]T-773, a selective PDE10A inhibitor, in nonhuman primates. In this study, PDE10A occupancy of TAK-063 was estimated using[11C] T-773 after a single oral dose of TAK-063 in human subjects.
Methods: Twelve healthy male subjects were enrolled. After intravenous bolus injection of [11C]T-773, dynamic PET scans were performed using high-resolution research tomograph (Siemens) at baseline and postdose timepoints. After baseline PET, all 12 subjects had one PET measurement approximately 3 h after a single oral dose of TAK-063 (3-1000 mg) and 8 had a second PET measurement approximately 23 h postdose. Arterial blood samples were taken continuously with an automated blood sampling system during the first 10 min and then manually thereafter. Metabolite analysis of the radioligand was performed with radio high-performance liquid

chromatography to evaluate the fraction of the parent compound. Venous plasma samples were taken during PET to measure plasma concentrations of TAK-063 and its metabolite M-I. After the reconstruction of the PET images, time activity curves were generated for the putamen and cerebellum delineated on the MRI/PET coregistered images. PET data were analyzed with 2-tissue compartment models using metabolite-corrected arterial input function. Total distribution volume (VT) was calculated for the brain regions. The specific binding part (VS) of VT was calculated as the VT of the putamen minus the VT of the cerebellum. PDE10A occupancy was calculated as the percent change of the VS between the baseline and postdose PET scans. The relationships between PDE10A occupancy and TAK-063 plasma concentrations were fitted including a hyperbolic function: occupancy (%) = plasma level /(Kd+plasma level) × 100, where Kd is the plasma concentration of TAK-063 that achieves 50% occupancy of PDE10A in putamen.
Results: After a single administration of 3 to 1000 mg of TAK-063, PDE10A occupancy in putamen was 2.8% to 72.1% at 3 h postdose. Occupancy in putamen increased in a dose- and plasma concentration-dependent manner. At 23 h postdose, PDE10A occupancy in putamen was 0% to 42.8% following administration of 3- to 100- mg doses of TAK-063. For 3 h postdose data, Kd was estimated to be 64.7 ng/mL for TAK-063, 23- h postdose data were similar to those estimated from 3- h data.
Discussion: TAK-063 showed PDE10A occupancy in areas of the brain in which PDE10A is highly expressed (putamen) in a plasma concentration-dependent manner in human brain in vivo. These results may be useful for dose selection in future clinical trials of TAK-063.

T169. Choosing with others in mind: neural mechanisms of social mindfulness in health and psychosis.

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Background: Psychosis is characterized by problems in social functioning, including social decision making. Social Mindfulness (SoMi), the ability to 'mind other people's interest' and to recognize their wishes is important for smooth social interactions and could be affected in psychosis. The new SoMi paradigm requires choosing one item out of two similar categories (red and green apples) presented in a ratio 2-2 and 3-1. In the 3-1 ratio, the choice can have implications for the second player: When choosing the single item (the 'unmindful choice'), there will be no choice left. Choosing one of the identical items is considered socially mindful. Unmindful choices activate caudate, insula and medial prefrontal cortex (mPFC)[1], key areas that have been linked to aberrant social processing in psychosis. We investigated the neural responses to the task in patients with early psychosis and patients at ultra-high risk (UHR) for psychosis to see whether any SoMi problems exist before the full-blown illness. We hypothesized that both patients and UHR show different neural activation from controls, especially in the unmindful choices.
Methods: Twenty patients with diagnosis of psychosis (16-21years), 17 UHR patients (16-31) and 47 healthy controls (16-31) performed the SoMi task in an MRI scanner. Positive and negative symptoms were measured with the CAPE, the GPTS and the PANSS. The groups were compared in choice pattern and associated brain activation. Whole brain and region of interest (ROI) analyses were conducted.
Results: Patients and UHR did not differ in symptom severity. Patients made more unmindful choices, whereas UHR and controls made more mindful choices. However, patients' choices only differed significantly from controls, not from UHR. Symptom severity did not correlate with the choice pattern.
Whole brain analysis showed that patients activated the mPFC less than the other groups, when making mindful choices. When choosing unmindfully, controls activated the mPFC more than the other groups. Caudate activation was significantly higher in controls compared to the two patient groups, when making mindful choices. For unmindful choices patients activated the caudate significantly more than the other groups.
Caudate activation for mindful choices was confirmed by ROI analysis and UHR showed least caudate activation when choosing unmindfully. mPFC was only significantly activated by controls when making unmindful choices. ROI analysis also revealed that patients recruited the ACC less than the other groups during mindful and unmindful choices. Insula was activated by all groups when making unmindful choices.
Discussion: Behaviorally, UHR resembled healthy controls, making more mindful than unmindful decisions. Differences in neural activation did not depend on symptom severity nor medication. Choosing unmindfully, controls activated mPFC more than both the patient and UHR group, possibly suggesting that controls engaged more in mentalizing activity; the fact that this finding extended to the UHR group suggests that it is part of the vulnerability to psychosis. In contrast, ACC activation was reduced in patients but not in the UHR group, possibly indicative of compensatory mechanisms. The UHR group further showed a distinct pattern of caudate activation, indicating that this region might be affected by psychosis differently than in the prodromal phase. In conclusion, SoMi seems to be still intact in the prodromal phase. This phase is especially important for interventions that aim to prevent a further decline in social functioning associated with full-blown psychosis.

T170. Neural correlates of reward processing in healthy siblings of patients with schizophrenia

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Background: Deficits in motivational behavior and psychotic symptoms often observed in schizophrenia (SZ) may be driven by dysfunctional reward processing (RP). RP can be divided in two different stages; reward anticipation and reward consumption. Aberrant processing during reward anticipation seems to be related to SZ. Studies in patients with SZ have found less activation in the ventral striatum (VS) during anticipation of reward, but these findings do not provide information on effect of the genetic load on reward processing. Therefore, this study investigated RP in healthy first-degree relatives of SZ patients.
Methods: The sample consisted of 94 healthy siblings of SZ patients and 57 healthy controls. Participants completed a classic RP task, the Monetary Incentive Delay task, during functional magnetic resonance imaging (fMRI).
Results: As expected, there were no behavioral differences between groups. In contrast to our expectations, we found no differences in any of the anticipatory reward related brain areas (region of interest analyses). Whole-brain analyses did reveal group differences during both reward anticipation and reward consumption; during reward anticipation siblings showed less deactivation in the insula, posterior cingulate cortex (PCC) and medial frontal gyrus (MFG) than controls. During reward consumption siblings showed less deactivation in the PCC and the right MFG compared to controls and activation in contrast to deactivation in controls in the precuneus and the left MFG. Exclusively in siblings, MFG activity correlated positively with subclinical negative symptoms.
Discussion: These regions are typically associated with the default mode network (DMN), which normally shows decreases in activation during task-related cognitive processes. Thus, in contrast to prior literature in patients with SZ, the results do not point to altered brain activity in classical RP brain areas, such as the VS. However, the weaker deactivation found outside the reward-related network in siblings could indicate reduced task-related suppression (i.e. hyperactivation) of the DMN. The presence of DMN hyperactivation during reward anticipation and reward consumption might indicate that siblings of patients with SZ have a higher baseline level of DMN activation and possible abnormal network functioning.

T171. Prevalence of metabolic syndrome in patients with schizophrenia in Korea: a multicenter nationwide cross-sectional study

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Background: It is well known that patients with schizophrenia have a reduced life expectancy. Especially, cardiovascular disease is one of the most important causes of mortality. This increased prevalence of diabetes and hypertension and increased mortality may be partially due to metabolic syndrome. The prevalence of metabolic syndrome (MetS) in patients with schizophrenia is 2-4 times higher than healthy control. The prevalence of MetS in patients with schizophrenia varies from 20% to 40% across the studies because of using different definition of MetS and confounding factors.
To overcome these limitations, we designed the nation-wide study with limited exclusion criteria for investigation about the prevalence of MetS in Korea, and the relation between psychiatric medication and the prevalence of MetS.
Methods: This study is multi-center, cross-sectional, and observational study for patients diagnosed with schizophrenia or schizoaffective disorder according to DSM-IV TR criteria. Sixteen hospitals - three mental hospitals and thirteen university affiliated general hospitals – enrolled patients aged 18 to 65 years prescribed any antipsychotic medication for treatment of schizophrenia or schizoaffective disorder between Aug 2011 and Aug 2013. Among 892 patients consented to participate the study, we excluded 47 patients of them due to lack of information such as age, gender, blood pressure (BP), waist circumference, or blood laboratory results. The index date of each patient was defined as the date of blood sampling. Doses of major antipsychotics were converted to olanzapine equivalent dose.
The metabolic syndrome was diagnosed with the definitions by the modified National Cholesterol Education Program's Adult Treatment Panel III (ATP III-A) for Korean (3 or more of the following 5 criteria: waist circumference $\geq$ 85 cm in women, $\geq$ 90 in men, fasting blood glucose $\geq$ 100 mg/dL or specific treatment for hyperglycemia, serum triglyceride (TG) $\geq$ 150 mg/dL or specific treatment for the lipid abnormality, HDL $<$ 40 mg/dL in men, $<$ 50 mg/dL in women or specific treatment for the lipid abnormality, and arterial blood pressure ($\geq$ 130/85) or specific treatment for hypertension.
Results: The number of participants in final analysis was 845. The mean age was 40.2 ±11.2 years (min:18, max:65) and number of male patients was 419 (49.6%). 379 patients (monotherapy group) took only one antipsychotic medication during one year before index date
Prevalence of metabolic syndrome of all patients was 36.5% ($N = 308$). The prevalence of metabolic syndrome was significantly higher in male patients than in female patients (male 40.8%; female 32.2%, X2 = 6.83, $P = 0.009$) and significantly correlated with age (odds ratio: 1.02, 95% CI: 1.01 - 1.04, $P = 0.0003$) and duration of illness (odds ratio: 1.03 95% CI: 1.01-1.04,$P = 0.0013$).
The prevalence of metabolic syndrome across major antipsychotics were quetiapine (18.8%), aripiprazole (22.0%), amisulpride (33.3%), paliperidone (33.3%), olanzapine (34.0%), risperidone (35%), haloperidol (39.4%), and clozapine (44.7%)
Discussion: This study showed that the prevalence of the metabolic syndrome in patients with schizophrenia or schizoaffective disorder was 36.5% and higher in male patients than in female patients (40.8% vs. 32.2%, respectively). In addition, we found that the prevalence of MetS increased significantly with increasing age and duration of illness. It was lowest among quietiapine(18.8%) and aripirazole (22.0%) and highest among haloperidol (39.4%) and clozapine (44.7%).
The limitation of this study is that we were not able to obtain total dosage of antipsychotics prescribed more than one year before the index date.

T172. Metabolic risk factors in first episodes of psychosis: findings from the PEPS study

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Background: Patients with psychotic disorders often suffer from excessive medical co-morbidities and mortality when compared to the general population. Available data on antipsychotic-induced metabolic risks are often constrained by potential confounding effects due to prior antipsychotic treatment
Methods: In this study, we assessed the baseline prevalence of metabolic abnormalities and changes following treatment with commonly-used antipsychotic drugs during two years in a cohort of 335 first episodes of psychosis (FEP) patients from the PEPs Study and 253 healthy controls.
Results: At baseline, the FEP group presented statistically significant ($P < 0.05$) higher mean levels of total cholesterol, prolactin and diastolic arterial pressure and lower HDL cholesterol and TSH than the healthy control group. After the two years of follow-up, the FEP group showed higher mean levels of glucose, glycated hemoglobin, triglycerides, and lower HDL cholesterol, together with higher body mass index and waist circumference. The majority of FEP patients received a second generation antipsychotic (96.3%), orally (95%), and in adjusted doses according to the products specifications (87.2%).
Discussion: Our findings suggest the existence of an incremented baseline prevalence rate of individual metabolic risk factors in FEP and that worsen during the first two years of treatment.

T173. Studying cortical thinning in schizophrenia with ultra high-field MRI

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Background: Patients diagnosed with schizophrenia show structural brain abnormalities such as ventricular enlargement and cortical (gray matter) thinning.[1,2,3] Disease-related cortical thinning is primarily seen in frontal and temporal areas and to a lesser extent in the parietal lobe. This cortical thinning could be due to a different size, density, or arrangement of neurons, neuroglia and nerve fibers.[4] However, it is yet unknown which of the six cortical layers are affected and to what extent they are affected.
Magnetic resonance imaging (MRI) sequences can be made sensitive to different tissue properties and contents. Recently, an ultra high-field MRI (7 T) sequence sensitive to myelin within gray matter was developed.[5] As certain layers contain more myelin than others, the usage of this sequence makes it possible to (in part) distinguish between different layers in the human neocortex. Laminar information could give important insight in the underlying pathogenic and pathophysiological processes and thus may provide further support for existing hypotheses and open up new avenues of research.

Methods: Twenty patients with schizophrenia (DSM IV diagnoses schizophrenia, schizophreniform, schizoaffective; male and female) and 20 healthy controls (male and female) who all previously participated in the TOPFIT study[6] are scanned (after obtaining written informed consent) on a 7 T MRI scanner (Philips, Best, NL), with various image contrasts. Sequences that are run include three 0.5 mm isotropic myelin-sensitive T1-weighted, one 0.8 mm isotropic myelin-sensitive T1-weighted, one 0.8 mm isotropic regular T1-weighted, and one 0.5 mm isotropic T2* scan. Data will be processed with the use of an in-house developed software pipeline,[7] in which average cortical profiles per brain area are calculated. Average cortical profiles are compared between sequences.
Results: Patients and healthy controls are currently being included.
Discussion: At the time of writing, 12 patients and 12 controls have been included. This data not only allow us to study the role of the different cortical layers in schizophrenia in high detail but — in combination with 3 T scans previously acquired in the TOPFIT study — allow us to study to what extent this layer information is in part present at 3 T.

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T174. Neuroanatomical markers of autistic traits in first episode psychosis

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Background: Psychotic disorders and those on the autism spectrum share phenotypic similarities and have been reported to co-occur at elevated rates. On the neuroanatomical level, overlapping and distinct areas of association have been reported. The current study adopted a voxel-based morphometry (VBM) approach to identify neuroanatomical markers of autistic traits in first episode psychosis (FEP).
Methods: 31 FEP individuals (25M;6 F, mean age 25 years; SD = 5) were recruited from the Birmingham and Solihull Mental Health NHS Foundation Trust in Birmingham, UK. They underwent magnetic resonance imaging at the Birmingham University Imaging Centre and completed the Autism-Spectrum Quotient for the assessment of autistic traits (AQ; Baron-Cohen *et al.*, 2001).
Images were analysed using the VBM8 toolbox in SPM8. Grey and white matter volumes were examined controlling for gender and age. Spatial extent threshold was determined by 10,000 Monte Carlo simulations conducted using 3dClustSim (AFNI), which yielded a cluster extent of 763 voxels for grey matter and 720 voxels for white matter at an exploratory voxel-wise threshold of $P < 0.01$. Cluster size threshold was corrected for non-stationarity (Hayasaka *et al.*, 2004) with the VBM8 toolbox.
Results: Data of one male participant was excluded from analyses due to excessive movement. No significant association was found between grey matter volume (reduced or increased) and AQ score. Increased white matter volume in left postcentral/supramarginal gyrus and right middle temporal gyrus (temporo-occipital part) was associated with higher AQ scores. After applying more stringent correction (voxel-wise threshold $P < 0.002$ with a cluster extent of 295 voxels), only the cluster in the right middle temporal gyrus remained significant. No significant association was found between reduced white matter volume and higher AQ scores.
Discussion: The observed brain pattern highlights areas of increased white matter volume that in FEP may be associated with higher AQ scores. These findings are consistent with reports of altered fractional anisotropy in these areas and may be associated with the processing of socio-emotional information. This may inform targeted treatment in FEP individuals who present with co-occuring or co-morbid autistic traits.

T175. HPA axis function and grey matter volume reductions: imaging the diathesis-stress model in individuals at ultra high-risk of psychosis

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Background: The onset of psychosis is thought to involve interactions between environmental stressors and the brain, with cortisol as a putative mediator. We examined the relationship between the cortisol stress response and brain structure in subjects at Ultra High Risk (UHR) for psychosis and healthy controls.
Methods: Waking salivary cortisol was measured in 22 individuals at UHR for psychosis and 17 healthy controls. Grey matter volume was assessed using MRI at 3 T. The relationship between the stress response and grey matter volume was investigated using voxel-based analyses. Our predictions of the topography of cortisol action as a structural brain modulator were informed by measures of brain glucocorticoid and mineral corticoid receptor distribution obtained from the multimodal neuroanatomical and genetic Allen Brain Atlas.
Results: Across all subjects, reduced responsivity of the HPA axis was correlated with smaller grey matter volumes in frontal, parietal, and temporal cortex and in the hippocampus. This relationship was particularly marked in the UHR subjects in the right prefrontal, left parahippocampal/fusiform and parietal cortices. Relative to healthy controls the UHR subgroup that subsequently developed psychosis showed a significant blunting of HPA stress response, observed at trend level also in the whole UHR sample.
Discussion: Altered responses to stress in people at high risk of psychosis are related to reductions in grey matter volume in areas implicated in the vulnerability to psychotic disorders. These areas may represent the neural components of a stress vulnerability model.

T176. Individual prediction of long-term outcome in adolescents at ultra-high risk for psychosis from baseline MRI brain scans

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Background: Previous studies of individuals at ultra-high risk (UHR) for psychosis have focused primarily on the identification of biomarkers to predict which individuals will transition to psychosis. However, the majority of individuals will prove to be resilient and go on to experience remission of their symptoms and function well. The aim of this study was to investigate the possibility of using structural MRI measures collected at baseline in UHR adolescents to quantitatively predict their long-term clinical outcome and level of functioning.
Methods: We included 64 UHR individuals (12-18 years old at recruitment). At six-year follow-up, we determined resilience for 43 UHR individuals. Baseline MRI brain scans were processed using FreeSurfer, resulting in a total of 311 measures of subcortical volumes and cortical thickness, surface area, volume and gyrification. Support Vector Regression models were trained to predict long-term

functional and clinical outcome from different selections of these baseline MRI measures on a continuous scale, instead of the more typical binary classification.
Results: Six-year follow-up level of functioning as well as negative and disorganization symptoms could be predicted at the individual level with correlations up to 0.42 for baseline subcortical volumes and long-term level of functioning.
Discussion: We showed that structural magnetic resonance brain images can be used to quantitatively predict long-term functional and clinical outcome in UHR individuals, suggesting that there may be scope for predicting outcome at the individual level. Moreover, we recommend classifying individual outcome on a continuous scale, enabling the assessment of different functional and clinical scales separately without the need to set a threshold.

T177. Intrinsic connectivity of fronto-temporal networks in adolescents at ultrahigh risk for psychosis: comparison with first episode psychosis patients and controls

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Background: Fronto-temporal functional connectivity has been reported to be altered in adults with first-episode psychosis (FEP) and at ultra-high-risk for psychosis (UHR). Fronto-temporal cortices undergo important developmental changes during adolescence; however no study so far has assessed intrinsic connectivity of fronto-temporal networks in adolescents during the early stages of psychosis. Therefore, we aimed to assess intrinsic connectivity of the salience, auditory and language networks in adolescents at UHR, in relation to adolescents with a FEP and to healthy controls.
Methods: Thirty-four UHR individuals, thirty-four FEP patients and thirty-seven healthy controls (HC) aged 12-18, were recruited from the Hospital Clinic of Barcelona, Spain. Resting-state functional magnetic resonance imaging (fMRI) and a high-resolution T1 three-dimensional image were obtained on a 3 T Siemens Magnetom Trio Tim. Subjects were excluded on the basis of movement above 1.5mm translation and 1.5 degrees rotation in either x, y, or z axes, detected during realignment. Following preprocessing, which included corregistration of anatomical to functional data, normalisation into standard Montreal Neurological Institute space and smoothing with an 8 mm full width at half-maximum Gaussian kernel, scrubbing was applied using a framewise displacement threshold of 0.2 mm where bad points were linearly interpolated, in order to control for potential micromotion artifacts. Spatial independent component analysis (ICA) was then conducted employing the Group ICA fMRI Toolbox. Components depicting connectivity in frontal and temporal brain regions were visually inspected and networks underlying salience, language and auditory processing were determined. The salience network encompassed the bilateral insula, anterior cingulate, and superior temporal and inferior frontal gyri. The language network included the middle temporal, inferior frontal gyri and the superior medial frontal cortex, and the auditory network encompassed the superior temporal gyri, HeschI gyri, insula and right inferior frontal gyrus. ANOVA models were conducted for each network with SPM12, controlling for age.
Results: There were no between-group differences in gender ($\chi 2 = 0.269$, $P = 0.874$). There was, however, a trend towards an older age in FEP patients ($F = 2.86$, $P = 0.062$). An effect of group was detected for the language network ($F = 14.06$, $P = 0.009$) in a cluster encompassing the right inferior/middle frontal gyrus (MNI coordinates [45,39,–3]). Specifically, FEP patients exhibited decreased intrinsic connectivity in this region of the language network. A volume-of-interest approach was conducted so as to extract signal values for each individual within the cluster where group differences were observed. UHR subjects showed intermediate values of connectivity in this region between HC and FEP patients. Examination of grey matter volume within this cluster showed no differences between groups. No differences in intrinsic connectivity emerged for the salience or the auditory network.
Discussion: Our results suggest that functional dysconnectivity of language-related regions may be a marker of risk for psychosis, which may already be identified during adolescence. Disruption in functional connectivity in the language network may be detectable prior to the structural changes observed in these brain regions in adult samples.

T178. Hippocampal glutamate and hippocampal functional connectivity in schizophrenia

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Background: Impairments in episodic memory are amongst the most robust abnormalities in schizophrenia and have been linked to hippocampal dysfunction. Using MRS we previously reported an increase in hippocampal glutamate+glutamine (Glx) in unmediated patients with schizophrenia (SZ) (Kraguljac *et al.*, 2013). Because elevated Glx levels might result from GABA interneuron hypofunction and hippocampal interneurons generate oscillations in the gamma frequency ranges that are thought to synchronize brain activation, elevated Glx levels could affect hippocampal functional connectivity. To further characterize hippocampal abnormalities in unmedicated SZ and their relationships to elevated Glx, we measured resting state hippocampal functional connectivity (FC). Given prior findings that hippocampal FC is predictive of better memory performance in healthy controls (HC), we explore the relationship between hippocampal FC and memory function in SZ and HC. We hypothesized that, in SZ, the correlation between resting state hippocampal FC and hippocampal Glx would be abnormal in brain regions subserving memory function.
Methods: MRS spectra were acquired in left hippocampus (PRESS; TR/TE = 2000/80 ms) and analyzed using jMRUI. Resting state functional MRI scans were acquired during a 5-min gradient recalled EPI sequence. Using a seed-based approach and SPM 8, we examined the FC of the hippocampus, using anterior and posterior seeds. Memory performance was measured using the delayed memory score of the RBANS. Matched HC were scanned as well.
Results: Compared to HC, SZ showed abnormal FC patterns with both anterior and posterior hippocampal seeds. We identified a significant group interaction in the correlation between hippocampal FC and Glx levels: in SZ, but not in HC, hippocampal FC to posterior cingulate cortex (PCC) was significantly correlated with Glx levels. Replicating prior results (Ranganath *et al.*, 2005), in HC, we found a significant positive correlation between hippocampal FC to PCC and memory performance. In contrast, in SZ, there was a significant positive correlation between hippocampal to anterior cingulate cortex (ACC) FC and memory performance.
Discussion: In SZ, we identified a correlation between hippocampal FC to PCC and Glx but failed to identify the correlation between hippocampal FC to PCC and memory function seen in HC. Because PCC is a region pivotal for memory function, these data suggest that elevated Glx levels in SZ might have impaired the FC between the hippocampus and PCC in a way that affected its relationship with memory performance. SZ might rely on different neural network to subserve memory function. These findings serve as an important first step towards understanding how altered hippocampal glutamate function in SZ contribute to memory impairments and suggest way to leverage these findings towards the development of pharmacological interventions to improve memory function.

T179. Cognitive correlates of functional connectivity in schizophrenia: a resting-state FMRI study

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Background: Schizophrenia (SZ) is a severe psychiatric disorder with heterogeneous symptoms. In addition to positive and negative

symptoms, cognitive impairments – especially working memory deficits – are among the most prominent symptoms and they play a crucial role in patients with SZ. Neuroimaging studies showed multiple structural and functional brain abnormalities, e.g. for the dorsolateral prefrontal cortex (dlPFC), which is known to be an important region for working memory performance. Furthermore, functional integration between spatial discrete brain regions is known to be affected in SZ. Consequently, it has been postulated that structural and functional alterations, as well as changes in the connectivity of the dlPFC, may underlie deficits in working memory performance.
Methods: In the present study, functional connectivity (FC) of the dlPFC was investigated using resting-state fMRI. Via correlation analysis the association between dlPFC FC and individual working memory performance was analyzed.
25 patients with paranoid SZ and 28 matched healthy controls were tested. The study consisted of an fMRI sequence (EPI) during rest, while participants were instructed to lie still and look at a white fixation cross. FC of the dlPFC was computed with a seed-correlation-analysis (SCA) using a Matlab script in combination with NeuroElf. Additionally, cognitive functioning was assessed employing by the Matrics Consensus Cognitive Battery (MCCB).
Results: SZ patients showed deficits in all working memory domains. In direct comparison to healthy controls, the patient group displayed altered FC patterns between the dlPFC and other brain regions of the memory network, e.g. to parietal, frontal as well as limbic regions. Also, altered FC to the caudate nucleus in SZ patients was significantly correlated with verbal working memory performance and the total score of the MCCB working memory domain.
Discussion: The results are interpreted in consideration of the disconnectivity hypothesis in SZ. The assumption of a disconnetivity syndrome which may underlie cognitive deficits, e.g. working memory, in SZ is supported by findings of recent studies, which have also reported pathologic hypo – and hyperconnectivity in SZ patients during working memory tasks and rest. Thus, aberrant FC during rest might be an interesting integrative biomarker for cognitive symptoms in SZ.

T180. Relationship between abnormal gyrification and clinical variables in first-episode schizophrenia

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Background: The neurodevelopmental model of schizophrenia has been widely accepted in the literature. Brain gyrification is regarded as a potential marker of early neurodevelopment. However, previous neuroimaging studies of gyrification in schizophrenia have reported inconsistent results. In addition, it remains unclear whether aberrant gyrification in schizophrenia, if present, is associated with clinical symptoms or cognitive impairments.
Methods: T1-weighted structural magnetic resonance imaging (MRI) scans were obtained by 1.5- T scanner from 62 patients with first-episode schizophrenia and 57 age- and gender- matched healthy control subjects. MR images were preprocessed using FreeSurfer version5.3. The local gyrification index (LGI) of entire cortex was continuously assessed using the method by Schaer and colleagues (Schaer *et al.*, 2008). Clinical symptoms of the patients were rated with the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) at the time of scanning. Executive function was examined with the Wisconsin Card Sorting Test (WCST) in a subgroup of the patients ($n = 28$). A general linear model controlling for age and sex was used to estimate group differences and to conduct vertex-by-vertex whole brain LGI correlation analyses with clinical variables.
Results: Compared with the controls, the patients showed significantly higher LGI in the bilateral superior frontal, right inferior parietal, and bilateral occipital regions. The number of WCST categories archived in schizophrenia patients was negatively correlated with LGI of the anterior cingulate and rostral middle frontal regions in the right hemisphere. In addition, total SAPS scores were positively correlated with LGI in a cluster including the temporal pole, insula, and parahippocampal gyrus in the right hemisphere.
Discussion: Our findings of increased gyrification index suggesting brain hypergyria support early neurodevelopmental abnormality in schizophrenia. Our results also suggest that lower executive function and more severe positive symptoms in schizophrenia may partly be related to aberrant neurodevelopment especially in the right hemisphere.

T181. Information processing speed mediates the relationship between white matter and general intelligence in schizophrenia

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Background: Several authors have proposed that schizophrenia is the result of impaired connectivity between specific brain regions rather than differences in local brain activity. White matter abnormalities have been suggested as the anatomical substrate for this dysconnectivity hypothesis. Information processing speed has been proposed as a key cognitive resource by facilitating higher order cognition – such as general intelligence - by allowing multiple cognitive processes to be simultaneously available. However, there are a lack of established associations between general intelligence, processing speed and structural brain parameters in schizophrenia. In this study, 28 patients with schizophrenia underwent brain diffusion tensor MRI to investigate these relationships. We hypothesised that the relationship between white matter and general intelligence would be mediated by processing speed.
Methods: White matter water diffusion parameters were studied using Tract-based Spatial Statistics and computed within regions of interest (ROIs) defined using a standard atlas. Principal component analysis (PCA) was conducted on 46 white matter ROIs for fractional anisotropy (FA) and mean diffusivity (MD), in order to extract general factors of white matter microstructure.
Results: PCA was conducted on neurocognitive subtests to extract measures of general intelligence and processing speed. We found a positive correlation ($r = 0.75$, $p < 0.001$) between general intelligence and white matter FA that was partially and significantly mediated (60.66% CI: 0.13 to 0.74) by processing speed.
Discussion: These findings suggest a plausible model of structure-function relations in schizophrenia, where white matter structure may provide a neuroanatomical substrate for general intelligence, which is partly supported by speed of information processing within brain networks.

T182. White matter correlates of impaired gesture performance and recognition in schizophrenia

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Background: Schizophrenia is associated with defective nonverbal communication contributing to poor social skills. Previous studies have shown that schizophrenia patients are significantly impaired in gesture performance and recognition. However, brain structural correlates of impaired gesture performance are unknown. Therefore, we investigated the relationship between white matter abnormalities and impaired gesture performance and recognition in schizophrenia. We hypothesized that gesture deficits are related to reduced fractional anisotropy (FA) of the superior longitudinal fascicle, uncinate fascicle and the corpus callosum, which connect key regions of the cerebral praxis network.
Methods: In 43 patients with schizophrenia spectrum disorders, gesture performance was assessed by the comprehensive Test of Upper Limb Apraxia (TULIA) and gesture recognition by the Postural

Knowledge Task (PKT). Performance was video recorded and blindly rated for accuracy. Structural brain imaging was measured in all patients using a 3- T MR Scanner. White matter microstructure was correlated with TULIA and PKT scores using Tract-Based Spatial Statistics (TBSS) including age as a covariate.
Results: The TULIA total score correlated with white matter microstructure at $P < 0.05$ (corrected) in clusters of the frontal white matter in the anterior cingulum, corpus callosum, corona radiata as well as the uncinate fascicle. Thus, superior performance was associated with increased FA. The PKT total score was associated with white matter at $P < 0.05$ (corrected) in the same fibers and additionally in the superior longitudinal fascicle and internal capsule. Again, superior recognition accuracy was associated with increased FA.
Discussion: Aberrant white matter of commissural, association and projection fibers are associated with poor gesture performance and recognition in schizophrenia. Particularly, abnormalities of white matter microstructure in key fibers of the praxis network like the superior longitudinal fascicle, uncinate fascicle and the corpus callosum correlated with gesture performance. Conclusions for the pathogenesis of nonverbal communication can be drawn from these results, as they argue for a contribution of specific brain structural alterations for gesture deficits. In addition, implications for gesture trainings can be obtained in order to improve nonverbal communication in schizophrenia.

T183. Preventing psychosis: improving brain networks in ultra high risk patients by means of psychological interventions.

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Background: Contemporary psychological treatments have developed a more integrative mindset, enriching the field by combining knowledge from neuroscientific approaches with third wave cognitive behavioral therapies. Neuroscience has provided increasing evidence of the plasticity of the brain, and consequently a possibility to affect brain networks through specified training and psychotherapy.
Aberrant neurodevelopment can cause vulnerability to both psychosis and social cognitive deficits. The real-life value and clinical relevance of social cognition is indisputable. Social cognition may be the strongest predictor of functional outcome in schizophrenia, is regarded a promising early risk-indicator for schizophrenia and a high priority for preventive intervention development. However, treatment strategies remain marked by a lack of evidence and agreement on specific treatment methods and targets.
The aims of the present study are to explore potential change in brain connectivity as a result of a specialized psychological intervention (social cognitive training) in patients at ultra-high risk of psychosis. Furthermore, we aim to explore cross-sectional and longitudinal associations between the disrupted brain networks and social cognitive deficits. The question we wish to answer is whether social cognitive training can improve disrupted brain networks associated with social cognition in patients at ultra-high risk of psychosis.
Methods: The present study is affiliated an ongoing large randomized, controlled and blinded parallel-group superiority clinical trial, aiming to investigate whether cognitive remediation and social cognitive training can improve neuro-cognition and social cognition in patients at UHR for psychosis: the FOCUS trial. The trial is enrolling a total of 126 help-seeking patients aged 18-40 and matched healthy controls, with repeated examinations at baseline and at 6 and 12 months' follow-up. Patients are randomized to intensive manual based Cognitive Remediation and Social Cognitive training (SCIT) plus standard treatment or standard treatment. Primary outcome on brain connectivity will be assessed with microstructural measures such as fractional anisotropy (FA), using whole-brain voxelwise tract-based spatial statistics (TBSS), fiber-based analysis and network analyses. Outcomes on social cognitive function is assessed with SRS-2; HiSoC, CANTAB (ERT); TASIT and SCSQ. Psychosocial function is assessed with SOFAS, PSP and Cornblatt.
Results: Trial initiation was April 2014, and to date the FOCUS-trial has included 75 patients and is expected to complete inclusions in 2017.
Discussion: Even if clinical symptoms are hypothesized to be the result of structural brain deficits, the relationship between the structural networks and specific cognitive deficits remain poorly understood. Considering the complexity of social cognition, requiring a coordinated function of a widely distributed network of brain regions, it is a plausible hypothesis that social cognitive deficits may be related to disrupted connectivity between implicated regions. Neural correlates of social cognition are suggested as a promising intervention target, using biomarkers for monitoring treatment response. Including both social cognition and the specific biological markers of abnormal brain changes in patients at Ultra-High Risk for psychosis, will allow us to examine if psychological treatment could delay or even prevent some of the progressive brain changes linked to schizophrenia.

T184. Schizotypy and psychosis proneness effects in a working memory FMRI paradigm

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Background: Working memory deficits are among the best validated putative enodphenotypes for schizophrenia, and are known to be linked to lateral prefrontal activation differences in functional MRI studies. Recent brain structural studies have suggested that variation in levels of schizotypy, a phenotypical risk marker for schizophrenia, or psychosis proneness, might affect variation in brain structure in areas also affected by schizophrenia. We evaluated the effect of positive and negative schizotypy and positive vs. negative symptom dimensions in a non-clinical sample on a well-established Sternberg working memory test.
Methods: We studied a sample of $n = 59$ healthy control subjects with no psychiatric disorder or history thereof and no first-degree relative with a psychotic disorder. All subjects underwent functional MRI using an established Sternberg working memory task (Schlösser *et al.*, 2008). The task included two variations: a maintenance condition (in which three letters were just memorized) and manipulation (in which three letters have to be mentally rearrange according to their position in the alphabet). All subjects complete the SPQ-G (German version of the Schizotypal Personality Questionnaire; providing subscores for positive and negative schizotypy), and the CAPE (community assessment of psychic experiences, giving a positive and negative symptom scale). fMRI analyses were carried out with SPM8, taking into account the encoding vs. the maintenance stages of the task. For the purpose of this analysis, we focused on prefrontal activation differences.
Results: For negative schizotypy (SPQ-G), we found a negative correlation with left dorsolateral/ventrolateral prefrontal activation during the encoding stage, as well as left superior prefrontal cortex for the difference between manipulation and maintenance trials. We did, however, not find similar effects for the positive symptom dimensions of CAPE, which rather showed negative correlation in anterior parietal areas. However, for the CAPE negative symptom dimension, a weak effect in the left anterior lateral prefrontal cortex in the manipulation > maintenance comparison emerged. Most effects, however, did not survive correction for multiple comparisons.
Discussion: Our results provide first support for an effect of schizotypy and psychosis proneness in healthy, non-risk volunteers on prefrontal activation during a working memory task. They are thus compatible with the notion of a continuum among biological markers of schizophrenia, but remain unclear whether these relate to potential genetic effects of other sources of variation. Also, effects were weak overall, thus necessitating replication of findings.

T185. Brain structural correlates of schizotypy in healthy subjects: cortical thickness and folding

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Background: Schizotypal traits are a phenotype risk marker for schizophrenia and have been associated with brain structural variation in healthy subjects. In this study, we aimed to analyse high-resolution

structural 3 T data, correlating scores on the SPQ-G scales for positive and negative schizotypy with cortical thickness and cortical folding.
Methods: We analysed data from $n = 158$ healthy subjects (no psychiatric history, no first-degree relatives with psychotic disorders) from two university centers (Jena and Tübingen, Germany), who underwent scanning on 3 T Scanners (Siemens, Tim Trio systems, with almost identical T1-weighted MPRAGE sequences). Freesurfer software was used to extract cortical surfaces and calculate vertex-wise cortical thickness (and folding, resp.), which was then correlated with either positive schizotypy or negative schizotypy scores, resp. (derived from the SPQ-G, the German version of the Schizotypal Personality Questionnaire). In a subset of patients ($n = 102$; Jena), we also correlated scores form the CAPE (community assessment of psychic experiences), which provides scores for positive and negative symptom dimensions, reflecting psychosis proneness.
Results: We found a positive correlation for positive schizotypy and cortical thickness in the left precuneus / medial parietal cortex, and a negative correlation in the right lateral prefrontal cortex (both corrected). The CAPE positive dimension score correlated significantly (positively) with right middle frontal gyrus and left middle temporal gyrus. For cortical folding, we found a positive correlation with the CAPE positive symptoms dimension in the left inferior temporal cortex.
Discussion: Our findings corroborate the hypothesis of schizotypal traits modulating brain structural endophenotypes of schizophrenia. They suggest that even in healthy, non-clincal subjects, the degree of positive schizotypy is correlated with brain structural variation in areas relevant to the pathophysiology of schizophrenia. It unclear, however, whether this relation across a putative spectrum (including schizotypal personality disorder or other schizophrenia spectrum disorders, and schizophrenia itself) is linear or non-linear, and whether it is determined by genetic factors.

T186. Structural plasticity of whole brain networks following aerobic endurance training in multi-episode schizophrenia patients and healthy controls

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Background: It has been suggested that reduced connectivity between brain regions might represent a central pathophysiological process underlying the brain changes observed in patients with schizophrenia. Following this disconnectivity hypothesis, the reduced integration of brain networks might hamper cognitive processing and ultimately result in psychotic symptoms seen in schizophrenic patients. In the present study we tested the hypothesis that an exercise intervention could specifically target these alterations of brain network architecture and in this way alleviate clinical symptoms.
Methods: In the present study multi-episode schizophrenia patients ($n = 20$) and healthy control subjects ($n = 21$) underwent a 6-week exercise intervention consisting of aerobic endurance training followed by a 6-week period of aerobic exercise combined with a cognitive training battery. A control group of multi-episode schizophrenia patients ($n = 19$) took part in a 12-week intervention consisting of table soccer (known as "foosball" is the US) for the same amount of time. A clinical assessment, neuropsychological testing and neuroimaging were performed at baseline, after 6 and 12 weeks. Diffusion-tensor imaging (DTI) sequences were used to reconstruct white-matter fibre tracts and to derive structural connectivity networks across the whole brain. We used graph-analytical measures (clustering coefficient, minimal path length) to measure changes in whole brain network architecture following the training intervention.
Results: At baseline there were no significant differences between the three groups in any of the investigated graph-analytical measures (all $P < 0.05$). In the healthy individuals there was a significant increase in brain network integration following the intervention as indicated by reduced minimal path length ($P < 0.01$) but no change in the clustering coefficient. In patients with schizophrenia there was no significant change in minimal path length or the clustering coefficient following either the treatment or the control intervention. Post-hoc analysis of patients in the treatment group indicated higher increase in brain network integration as measured by the minimal path length was associated with stronger decrease in clinical symptoms as measured by the PANSS scale.
Discussion: Our results demonstrate the sensitivity of structural brain network architecture to the aerobic endurance training intervention in healthy individuals. In patients with schizophrenia improvements in clinical symptoms following aerobic exercise were associated with changes in network architecture. The reduced sensitivity of the patient sample to the intervention might result from the chronicity of their disorder as well as the previous antipsychotic medication.

T187. Subcortical shape differences in regions supporting working memory in high and low functioning schizophrenia

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Background: Schizophrenia is characterized by poor community functioning in multiple domains. Recent evidence suggests that targeting social cognition and neurocognition may lead to greater improvement in community functioning. To further investigate the relationship between functioning and neurocognition, our group recently utilized cluster analysis, to first classify schizophrenia subjects into groups of "high" and "how" levels of community functioning (HF-SCZ and LF-SCZ, respectively). When these subgroups were compared across six domains of neurocognition, we found they uniquely differed on verbal working memory. This evidence suggests that verbal working memory may be more proximal to elevated levels of community functioning, and may be a specific treatment target to enhance functioning. To further investigate the relationship between working memory and community functioning, we evaluated the morphology of subcortical structures that support working memory between HF-SCZ, LF-SCZ, and healthy controls (CON). The overarching goal of this project is to evaluate the structural integrity of critical nodes within the working memory circuit between HF-SCZ and LF-SCZ.
Methods: HF-SCZ ($n = 24$), LF-SCZ ($n = 18$), and CON ($n = 46$) underwent structural Magnetic Resonance Imaging (sMRI) in a 3 T Siemens Trio system. Two high-resolution 3D T1-weighted MPRAGE volumes optimized for gray-white contrast [TE = 3.16ms, TR = 2400ms, 1x1x1mm voxels] were collected. The MPRAGE scans were aligned with the first scan and averaged. In addition, subjects underwent two 3D T2-weighted scans using Siemen's SPACE sequence (a variant of a 3D turbo spin echo sequence) [TE = 455ms, TR = 3200ms, 1x1x1mm voxels, turbo factor = 139]. Subcortical surface features of the caudate and thalamus were derived through application of large-deformation high-dimensional brain mapping. This atlas-based transformation technique uses a template image of the structure, which is first aligned with the target regions in each subject via anatomical landmarks and is subsequently warped onto the target via diffeomorphic mapping of voxel intensities. Principal component analysis assessed localized shape differences. This analysis generated eigenvectors which are used to calculate individual shape scores that represent unique variation in the shape in the left and right hemispheres. For each structure, the first 10 eigenvectors per hemisphere were selected for further analysis, as these account for more than 80% of the total shape variance. Repeated-measures Analysis of Variance (rm-ANOVA) was used to evaluate between group differences.
Results: Compared to CON, HF-SCZ show greater inward deformation in the total thalamus ($F_{9,60} = 2.53$, $P < .05$), anterior thalamus ($F_{9,60} = 2.26$, $P < .05$), and outward deformation in the dorsomedial thalamus ($F_{9,60} = 3.65$, $P < .01$). LF-SCZ also show inward deformation relative to CON in total thalamus ($F_{9,54} = 2.34$, $P < .05$) and anterior thalamus ($F_{9,54} = 2.41$, $P < .05$), and greater outward deformation in the caudate ($F_{9,54} = 2.81$, $P < .01$). Compared to each other, HF-SCZ show greater inward mean deformity in the anterior thalamus ($F_{1,40} = 4,89$, $P < .05$) and LF-SCZ show greater inward deformation in the remaining dorsal regions ($F_{9,32} = 2.61$, $P < .05$).
Discussion: These results suggest differential patterns of shape deformation in HF-SCZ and LF-SCZ when compared to each other and healthy controls. Identifying critical neural mechanisms contributing to functional recovery will aid in focused development of potential

treatment targets to engage these sites. Future research could evaluate whether these subcortical shape patterns are predictive of treatment response or course of illness.

T188. Extracellular and brain tissue related abnormalities in subjects at clinical high risk for psychosis in Shanghai

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Background: White matter (WM) microstructural alterations, including axonal deterioration, demyelination, and neuroinflammation have been thought to be associated with schizophrenia. It is still unclear, however, whether signs of WM alterations as identified by diffusion MRI precede the onset of psychosis. With advanced diffusion imaging analyses we explored whether or not WM alterations are present in subjects at clinical high risk (CHR) for psychosis.
Methods: 50 CHR subjects (77% naïve to psychotropic medications) and 30 healthy controls were recruited as part of the Boston-Shanghai project (Seidman & Wang, PIs). Subjects met criteria for clinical high risk as defined by the Structured Interview for Prodromal Syndromes and Scale of Prodromal Syndromes. Images were acquired on a 3 T Siemens magnet. Analyses for each subject included a measure of fractional anisotropy (FA) derived from diffusion tensor imaging (DTI), as well as two measures from free-water imaging. The first measure is extra-cellular free-water (FW) which describes water diffusion in extracellular space and may be a putative measure of neuroinflammation. The second measure is free-water corrected fractional anisotropy (described as FAT), which eliminates free water and measures water diffusion within and surrounding tissue. The latter has been viewed as associated with more neurodegenerative processes (Pasternak *et al.*, 2012; Pasternak *et al.*, 2015). Group comparisons were made using voxel-wise tract-based spatial statistics (TBSS).
Results: We found widespread reductions of FA in CHR subjects. In contrast, the free-water analysis showed a limited extent of FAT decreases, but a prominent increase in FW over the entire brain. When averaging FAT over the voxels with significant group differences, mean FAT values in CHR subjects were significantly correlated with decreases in Global Assessment of Functioning (GAF) scores, whereas mean FW values were not correlated with GAF scores. In addition, we explored age effects on WM alterations by separating all subjects into adult ($\geq$21 years) and adolescent groups ($<$ 21 years). Whole-WM FAT values were significantly lower in adult CHR subjects than in adult HCs, whereas whole-WM FW values were significantly higher in adolescent CHR subjects than in adolescent HCs.
Discussion: These findings demonstrate WM microstructural alterations before the onset of psychosis. Similar studies conducted in first-episode and chronic cases suggest that increased FW may be attributed to neuroinflammation, whereas decreased FAT is more likely related to axonal degeneration. The current findings are consistent with the findings in first-episode and chronic patients and suggest that signs of neuroinflammation and neurodegeneration are observed even before the onset of psychosis, albeit to a lesser extent, than are observed in previous studies with psychotic subjects. The role of both neurodegenerative and inflammatory processes may thus be key to understanding the neurobiology and development of psychosis in those who are at high clinical risk for psychosis.

T189. The effects of genetic and environmental risk factors for schizophrenia on cortical thickness

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Background: It is now widely accepted that both genetic and environmental factors can increase the risk of Schizophrenia (SCZ) and Bipolar Disorder (BD). It is also well evidenced that there are differences in cortical thickness between SCZ or BD patients when compared to Healthy Controls (HC). It is however unknown whether environmental or genetic factors have a direct impact on cortical thickness in these populations, although there is some evidence that both factors impact upon global, frontal and temporal volume reductions. We have therefore investigated the effect of PolyGenic Risk Scores (PGRS) and environmental risks for SCZ on cortical thickness. We hypothesised that PGRSs and ERSs for SCZ will be related to cortical thinning globally and in the frontal and temporal lobes.
Methods: 98 structural MRI scans of the brain were acquired at 3 T for HC ($n = 41$), SCZ ($n = 37$) and BD ($n = 20$). Cortical reconstructions were generated using FreeSurfer (v5.3). PGRSs, based on the latest SCZ Working Group of the Psychiatric Genomics Consortium findings (PGC-SCZ, 2014), were available for 59 participants (HC = 31, SCZ = 24, BD = 4). Environmental data was only available for the patients ($n = 57$). For these environmental measures we followed the methodology of Stepniak *et al.* (2014). Environmental measures included; cannabis use, childhood life events (CLEQ), migration, urbanicity and obstetric complications. Each of these factors was scored as a 1 if present and 0 if not. An ERS was created where the number of risks for each individual was calculated to give a possible score from 0-5. ANCOVAs were used to determine if these environmental measures and PGRSs had an effect on global and lobar estimates of cortical thickness. Multiple comparisons were allowed for using FDR.
Results: There was a significant effect of PGRS on global cortical thickness in both the left ($F = 5.23$, $df = 1$, $P = 0.03$) and right ($F = 7.73$, $df = 1$, $P = 0.02$) hemisphere within the whole sample. Right ($r = -0.33$) and left ($r = -0.38$) global cortical thickness was negatively associated with increased polygene scores. This was not attributable to case/control status. When investigating environmental risk within the patient group there was a significant main effect of ERS ($F = 7.23$, $df = 1$, $P = 0.04$) on the right temporal lobe cortical thickness which remained after FDR correction. Each additional environmental risk factor had an effect on greater cortical thinning. Environmental effects remained significant even when controlling for PGRS at the 0.1 threshold.
Discussion: Increased PGRSs for SCZ is related to global cortical thinning in HC, SCZ and BD participants. Environmental risk is related to cortical thickness loss within the right temporal lobe in patients. Genetic and environmental risk factors for SCZ appear therefore to have effects that can be differentiated. This possibly provides a mechanistic means by which different risk factors may contribute to the onset and severity of SCZ and BD. Further studies are needed to determine if this finding can be replicated in a larger sample.

T190. Decreased EEG spectral entropy modulation associated with cognitive impairment in schizophrenia.

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Background: Functional disconnectivity may contribute to schizophrenia and may be assessed using electroencephalography (EEG). Spectral entropy (SE, quantifying global EEG spectral regularity) and median Frequency (MF, the frequency that divides the spectral power by a half) are useful measurements to assess connectivity using EEG. We have previously reported in a completely different sample deficits of modulation of SE and MF in schizophrenia during an odd-ball test related to clinical symptoms.
Methods: EEG was acquired in 44 schizophrenia patients (8 first-episodes) and 44 healthy controls during an odd-ball task. Cognitive data (BACS, WAIS and WCST) and PANSS scores were also collected. SE and MF values were assessed for each electrode at baseline (-300 to 0 ms previous to the stimuli) and response (150 to 450 ms after stimuli)

windows. SE and MF modulation were defined as the corresponding response minus baseline difference in these parameters. We assessed the significance of the differences in SE and MF between baseline and response separately in patients and controls. Moreover, SE and MF modulation values were compared between patients and controls, correcting for multiple comparisons. Finally, the relation between clinical and cognitive parameters and SE and MF modulation as well as the classificatory accuracy of these values were assessed.
Results: SE and MF values at baseline were significant larger in patients. There were significant SE and MF decreases from baseline to response windows in both groups. The SE and MF modulation values were significantly lower in patients at central electrodes (Fz and Cz). A similar pattern was observed in first-episode patients. In the patients, SE modulation at Fz was inversely correlated to verbal memory, motor speed, working memory, executive function, and positive symptoms. Furthermore, SE modulation at Cz was positive correlated with percentage of perseverative errors (WSCT test). Lineal discriminant analysis with a leave-one cross-validation classified correctly 63.6% of subjects.
Discussion: We replicated the deficit of EEG modulation (SE and MF) in schizophrenia patients in a completely different sample. The distribution of this modulation deficit was similar as it was in our previous report. In the present sample, that modulation deficit of the EEG was associated to an impaired cognitive performance.

T191. Hippocampal-striatal-midbrain connectivity during reward prediction in high-risk subjects for psychosis: correlations with abnormal belief formation and dopamine

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Background: Animal models propose that abnormal hippocampal activity drives striatal hyperdopaminergia in psychosis that may contribute to abnormal salience processing. Although previous multimodal imaging studies indicate alterations in the relation between hippocampal activity and striatal dopamine function in subjects at high-risk for psychosis during reward prediction, no study has yet explored the relation between hippocampal-striatal-midbrain connectivity and striatal dopamine function.
Methods: We applied dynamic causal modelling to fMRI data during reward prediction in 28 at-risk mental state (ARMS) subjects for psychosis and 32 healthy controls (HC). 18 F-DOPA PET scanning was used to measure striatal dopamine function in 14 ARMS subjects and 17 HCs. Effective connectivity parameters within the hippocampal-striatal-midbrain circuit were correlated with striatal dopamine function and abnormal belief formation.
Results: ARMS subjects revealed significantly increased connectivity from the ventral striatum to the midbrain compared with HCs ($t58 = -3.117$, $P = 0.003$), the degree of connectivity in ARMS subjects correlated positively with abnormal belief formation ($r = 0.488$, $P = 0.011$). The modulation of midbrain to ventral striatum connectivity induced by rewarding cues correlated negatively with baseline dopamine function in the limbic striatum in ARMS subjects ($r = -0.701$, $P = 0.008$) but not HCs ($r = -0.186$, $P = 0.491$).
Discussion: Ventral striatum to midbrain connectivity during reward prediction is altered in high-risk subjects for psychosis and related to positive symptomatology, suggesting a prognostic marker for emerging psychosis. According to recent animal models, alterations in VS to midbrain connectivity maybe due to abnormal GABA activity that precedes striatal hyperdopaminergia, providing a potential target for early treatment interventions.

T192. Contribution of oxytocin pathway genes to amygdala activity in schizophrenia, bipolar disorder and healthy controls

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Background: BACKGROUND Building on oxytocin's effect on social cognition, the hormone and neuropeptide has been proposed as pharmacological therapy for several psychiatric disorders, including schizophrenia. Several studies have shown that social cognition rely on distinct neural circuits from those involved in other cognitive processes and brain imaging studies propose medial prefrontal cortex, ventrolateral prefrontal cortex, amygdala, the inferior parietal lobe and the temporal cortex as contributing areas. In particular, amygdala dysfunction has been associated with altered emotion processing in schizophrenia in several studies. A neuropeptide that has been shown to modulate amygdala activity and social cognition is oxytocin, however, studies of oxytocin pathway genes and amygdala activity in patients with schizophrenia are lacking. Several genes may be involved in amygdala activation, however the oxytocin pathway genes have already been associated with core symptoms in schizophrenia reliant on this particular brain region, making them important candidates for investigation. The aim of this study is to explore whether oxytocin pathway genes contribute to amygdala reactivity using functional Magnetic Resonance Imaging (fMRI) and to see if this potential effect is enhanced in patients with scizophreniaspectrum (SZ) and bipolar disorder (BP) compared to healthy controls.
Methods: METHODS Participants ($n = 344$, including 90 SZ cases, 103 BP cases and 151 healthy controls) take part of the TOP study, a multicenter collaboration on psychosis research in South- Eastern Norway. They all underwent the same protocol at baseline, which include a clinical and physical examination by a physician, structural and functional MRI, extensive neuropsychological testing by a psychologist, collection of blood samples for somatic screening and DNA analyses. DNA was genotyped using the Affymetrix Human SNP Array 6.0 (Affymetrix Inc, Santa Clara, CA, USA). SNPs relevant in previous literature from genes producing the oxytocin receptor (OXTR) will be selected as candidate polymorphism for investigation. We will use data from a fMRI Amygdala Reactivity Task. In this task participants selected which of two stimuli (displayed at the bottom of the screen) matched a target stimulus (displayed at the top). The images displayed were either human faces expressing anger or fear (faces matching task) or geometrical shapes (the sensorimotor control task). Individual contrast images were created by subtracting "faces" from "figures". Then, the peak voxel in each hemisphere was defined as the voxel with most evidence of differential activation as measured by a t-test applied to the voxels within amygdala. The activations of these two voxels are carried forward as the phenotypes for the genetic association analysis. Statistical analyses will mostly be done using SPSS, and tools for genotype data (PLINK and custom made MatLab scripts). Task-induced amygdala activation is estimated using a specialized statistics package (SPM, FSL). Linear regression with an additive model with correction for sex, age and diagnosis will be used for comparisons of amygdala activation between individuals with different oxytocin gene polymorphisms in all three groups.
Results: To this date, all data have been collected, but the statistical analyses have not yet been performed. Results will be presented at the conference.
Discussion: To this date, all data have been collected, but the statistical analyses have not yet been performed. Results will be presented at the conference.

T193. Effects of muscarinic M1 receptor sequence variation on executive function in schizophrenia and healthy controls

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Background: Schizophrenia patients present with a range of debilitating cognitive impairments, with most patients performing one to two standard deviations below healthy controls on a range of neurocognitive measures. Considerable evidence has implicated that a dysfunctional muscarinic system contributes to the higher-order cognitive impairments prevalent amongst people with schizophrenia. Human and animal studies have documented that disruption to the regular functioning of the M1 muscarinic receptor subtype is associated with pronounced cognitive impairments, and that recently developed allosteric activators can improve cognitive performance through targeting this receptor. It is,

therefore, significant that people with schizophrenia who are heterozygous at the M1 receptor gene C267C (rs2067477) have been reported to retain executive function capacities: this is evidenced by enhanced performance on a single measure of executive function, the Wisconsin Card Sort Test (WCST), compared to patients who are homozygous. The current study sought to further explore the association between the M1 receptor gene sequence and executive functioning using the MATRICS consensus cognitive battery (MCCB) in both patients with schizophrenia and healthy controls.
Methods: Preliminary data was recorded from 97 patients diagnosed with schizophrenia or schizoaffective disorder and 136 healthy controls. Participants completed the Mazes task of the MCCB, with a small subset completing the WCST. This was apart of an ongoing investigation into the association between genetic variations and cognition in schizophrenia. Whole blood or saliva samples were collected from each participant for genotyping.
Results: After accounting for group differences in premorbid intelligence, no significant main effects of diagnostic group or genotype were found for the Mazes task or the WCST. Preliminary results suggest that the effect of genotype on WCST performance is the same for healthy controls as per patients and the pattern of results in the patient group is consistent with previous research showing a performance advantage for the heterozygous C/A group. A significant group by genotype interaction was reported for the Mazes task. Again, the results resonate with previous findings, with heterozygous patients (M = 18.6, SD = 6.2) out performing homozygous patients (M = 15.3, SD = 6.6) on the Mazes task. In contrast, the opposite genotype effect was observed amongst healthy controls.
Discussion: Our preliminary findings resonate with previous research that has suggested that variations in the M1 receptor gene sequence can influence executive function capacities in patients with schizophrenia. This has now been demonstrated across a number of executive function measures, and our data suggests the MCCB executive function measure is also a reliable indicator of this effect. However, it is evident that additional research in this area is required to explore how variations in the M1 receptor gene influence other aspects of cognition in both patients and control groups.

T194. A study of gene-gene interactions between genes on chromosome 22Q11 in schizophrenia in Korea

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Background: Schizophrenia is a complex genetic disorder. In the genesis of schizophrenia, gene-gene interaction is thought to play some role. Genes such as COMT, PRODH, and ZDHHC8 located on chromosome 22q11 might have been linked to schizophrenia. We examined the effects of gene-gene interactions residing within chromosome 22q11 in patients with schizophrenia in Korea.
Methods: The gene-gene interaction analysis was done with 227 unrelated patients with schizophrenia and 292 normal controls in Korea. COMT_rs4680, PRODH_1945, PRODH_1766, ZDHHC8_v25 and ZDHHC8_v26 were genotyped. In case-control study, logistic regression and multifactor dimensionality reduction model were applied to investigate the interactions between these genotypes.
Results: Logistic regression found interactions between COMT_rs4680 and ZDHHC8_v25 ($P = 0.0392$) in patients with schizophrenia in Korea. MDR could not find interactions between genes on chromosome 22q11 in schizophrenia.
Discussion: These results imply that gen-gene interactions between COMT and ZDHHC8 on chromosome 22q11 might be implicated in the genesis of schizophrenia in Korean populations.

T195. Gender-specific associations of the brain-derived neurotrophic factor VAL66MET polymorphism with neurocognitive functioning and clinical features in patients with schizophrenia

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Background: To explore associations of the brain-derived neurotrophic factor (BDNF) Val66Met polymorphism with cognitive functioning and psychopathology in patients with schizophrenia.
Methods: We included 133 subjects meeting the DSM-IV criteria for schizophrenia who were in the post-acute stage of the disease. BDNF Val66Met genotypes were identified via polymerase chain reaction. The computerized neurocognitive function battery, Positive and Negative Syndrome Scale (PANSS), Calgary Depression Scale for Schizophrenia (CDSS), Social and Occupational Functioning Scale (SOFAS), and the Subjective Well-Being Under Neuroleptic Treatment-Short Form (SWN-K) were administered. Gender-stratified sub-analysis was also conducted to identify gender-specific patterns in the findings.
Results: In male patients, no significant difference in any measure by BDNF genotype was evident. In female patients, scores on the CDSS and the total PANSS and all subscales were significantly higher in valine (Val) carriers. In addition, scores on the SOFAS and SWN-K were significantly lower in Val carriers. In terms of neurocognitive measures, female patients with the Val allele had significantly poorer reaction times and fewer correct responses on the Continuous Performance Test (CPT) and the Trail Making Test (parts A and B). After adjustment of PANSS total scores and log-transformed CDSS scores, CPT outcomes were significantly poorer in female patients with than in those without the Val allele.
Discussion: Gender-specific associations of the Val allele with poor neurocognitive function and more severe psychopathology were evident. Further studies are required to explore the mechanisms of these differences and the potential utility of the BDNF genotype as a predictor of outcome in patients with schizophrenia.

T196. Association between ZNF804A and the risk of schizophrenia and bipolar disorders across diagnostic boundaries

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Background: Zinc finger protein 804A (ZNF804A) has been reported as a candidate gene for both schizophrenia and bipolar disorder. However, few studies examined the effect of this gene on the vulnerability of the two disorders in the same study population. We investigated the genetic association between ZNF804A and schizophrenia, bipolar disorder, and psychotic symptoms in the Korean population.
Methods: A total of 582 patients with schizophrenia, 339 patients with bipolar I (BP-I) or bipolar II disorder (BP-II), and 502 healthy controls were recruited. Nineteen tag SNPs across the ZNF804A region and two additional SNPs (rs7597593 and rs1344706) showing significant associations with psychotic disorders in previous studies were genotyped. The association was evaluated by logistic regression analysis using additive, dominant, and recessive genetic models.
Results: BP-I showed a highest trend of association with ZNF804A. Nine SNPs revealed nominally significant association with BP-I under additive and dominant models (the lowest *P*-value of 0.006 at rs1366840). However, none of these associations remained significant

after correcting for multiple testing. For schizophrenia, four SNPs showed a nominally significant association with the lowest *P* value of 0.008 at rs17617468. BP-II showed a weaker trend of association with the lowest *P* value of 0.022 at rs10497662. In a post-hoc analysis, psychotic symptoms in three patients groups across diagnostic boundaries did not show an association trend with ZNF804A.
Discussion: We identified a possible role of ZNF804A in the common susceptibility of schizophrenia and bipolar disorders. However, no association trend was observed for psychotic symptoms. Further efforts are needed to identify a specific phenotype associated with this gene crossing the current diagnostic categories.

T197. Exome sequencing in patients with schizoprenia

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Background: The genetic architecture of schizophrenia is complex. The so far identified genetic risk factors include both common, low-penetrant variants and rare, high-penetrant variants. Using Exome Sequencing, an increasing number of potentially phenotype relevant high-penetrant variants are currently being identified among patients with schizophrenia. Due to the large number of mutations identified so far, it is difficult to distinguish between phenotype neutral and schizophrenia relevant mutations. Additional genetic evidence for each potential schizophrenia candidate gene is warranted.
Methods: In total, 150 patients with schizophrenia were subjected to Exome Sequencing. The patient cohort was enriched for an early age at onset and a poor prognosis. All individuals were of German descent according to self-reported ancestry.
We focused on providing additional evidence for previously reported schizophrenia candidate genes (genes reported to carry a de novo mutation in a patient with schizophrenia). So far, eight Exome Sequencing studies focusing on de novo mutations in patients with schizophrenia have been published. These studies report mutations in more than 750 different genes.
Results: On average, we identified two mutations per patient in genes that were previously reported to carry a de novo mutation. To further prioritize the potential schizophrenia candidate genes and to be able to distinguish between phenotype neutral and phenotype relevant mutations, we (i) will genotype all identified variants in 1,000 controls in order to exclude that the identified variants are common in the German population; (ii) perform set-based tests in the largest genome-wide association study of schizophrenia to date to test for an association between common variants in the candidate genes and schizophrenia; and (iii) focus on genes that are brain expressed. The most promising candidate genes will be re-sequenced in a large, independent patient-control cohort.

T198. Vitamin D treatment during pregnancy prevents schizophrenia-related phenotypes in a maternal immune activation animal model

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Background: We have established that maternal vitamin D deficiency is a risk-factor for schizophrenia in offspring. Maternal Immune Activation (MIA) induced by a variety of infectious agents is also a known epidemiological risk factor for these conditions. Vitamin D deficiency is alarmingly common in women of childbearing age. Given vitamin D is a well known regulator of immune function we have addressed the question of whether it could ameliorate behavioural phenotypes relevant to these psychiatric disorders in a well-described MIA animal model.
Methods: Gravid C57Bl6 mouse dams were treated with the viral mimic poly(I:C) (polyriboinosinic-polyribocytidilic acid), a synthetic analogue of double-stranded RNA at gestational day 9. Poly(I:C) induces a cytokine-associated viral-like acute phase response in both the placenta and foetal brain. MIA or vehicle exposed dams simultaneously received 400ng/kg 1,25 α (OH)2D3 (the active hormonal form of vitamin D) or corn oil vehicle. One cohort of offspring were tested as juveniles for behaviours relevant to psychiatric conditions such as amphetamine-induced locomotion, social interaction, fear conditioning, marble burying and behaviour in an elevated plus maze. Inflammatory cytokines were measured in both maternal blood and foetal brains 4 hrs after exposure to Poly(I:C).
Results: As previously shown, Poly(I:C) increased locomotor response to amphetamine, impaired social interaction and impaired acquisition of fear learning compared with vehicle treated dams ($P < 0.05$). Co-administration of vitamin D however completely abolished all these phenotypes whilst having no adverse effects on vehicle treated animals. In addition Poly(I:C) also severely impaired marble burying (an ethologically normal behaviour in rodents and possible measure general anxiety) compared to vehicle treated controls ($P < 0.05$). Co-administration of vitamin D again completely abolished this phenotype whilst having no adverse effects on vehicle treated animals. There was no effect of poly(I:C) on elevated plus maze behaviour.
Again as expected Poly(I:C) treatment induced a robust elevation in the inflammatory cytokines IL-6, IL-1β and TNFα both in maternal circulation and in foetal brain ($P < 0.0001$). To our surprise, Vitamin D co-administration had no effect on the production of these inflammatory cytokines in both the Dam and foetal brain ($P < 0.05$).
Discussion: This is the first study to show that vitamin D may be preventative in a widely used model of psychiatric disease. In particular the restoration of normal locomotor sensitivity to amphetamine by vitamin D indicates developmental dopamine systems are targeted by vitamin D. However the broad spectrum of behavioural phenotypes abolished by vitamin D indicates multiple pathways are targets for the therapeutic actions of vitamin D during brain development. Our findings suggest the neuroprotective mechanism/s invoked by vitamin D during brain development extend well beyond its role as an anti-inflammatory factor. We are now investigating whether maternal supplementation with cholecalciferol may be just as effective.

T199. IL-6 is a critical factor in the hippocampus-mediated neural circuit alteration underlying psychosis-associated phenotypes

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Background: Recent studies suggest that patients with psychosis were reported to have increased blood and CSF levels of immune-associated molecules, such as inflammatory cytokines including IL-6. Alteration in IL-6 have also been reported in post-mortem brains of patients with schizophrenia. Nonetheless, the role of IL-6 in the brain for psychosis-associated phenotypes remain to be explored. Recent human brain imaging studies suggest that hippocampus (HP) is a critical brain region involved in psychosis phenotypes. However, a key mediator in HP involved in psychosis phenotypes remains elusive. Thus, we hypothesize IL-6 may play an important role in the altered HP-mediated neural circuit for psychosis-associated phenotypes. To address this question, we used previously reported the cuprizone short-term exposure (CSE) mouse model that elicits specific elevation of IL-6 in astrocyte in the HP and behavioral endophenotypes associated with psychosis.
Methods: Young adult C57BL/6 J male mice were fed either a diet containing 0.2% cuprizone, the copper chelator, or a control diet consisting of standard mouse chow for one week. In order to examine the role of IL-6 for psychosis-associated phenotypes in the CSE mouse model, IL6 expression was specifically suppressed in the dorsal HP by AAV-mediated knockdown approaches, followed by neurochemical, histological and behavioral assays. In addition, ex vivo autoradiography for TSPO, a marker of activated microglia and astrocytes, was conducted using the clinically translatable [125I]iodo-DPA-713 radioligand.
Results: We found that one week short exposure to cuprizone produces psychosis-associated behavioral abnormalities without

robust demyelination. In addition to elevated IL-6 expression predominantly in hippocampal astrocytes, an increase in binding of TSPO was observed in the HP. CSE mice display a hyperlocomotor response to amphetamine and an increase in synaptic dopamine in the nucleus accumbens. The CSE mice also display a deficit in Y-maze spontaneous alternation and short term object recognition memory. Of note, knockdown of IL-6 in the dorsal HP ameliorated observed behavioral abnormalities in the CSE mice.
Discussion: IL-6 in the dorsal HP is a critical factor in the HP-mediated neural circuit alteration underlying psychosis-associated phenotypes observed in the CSE mice model. The CSE mouse model may be a useful tool to study molecular mechanisms underlying HP-mediated neural circuit alteration-associated psychotic behavioral phenotypes.

T200. Perinatal asphyxia and cesarean section changes the expression of novel schizophrenia risk genes in rat

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Background: Epidemiological studies suggest that obstetric complications, particularly those related to hypoxia in the offspring during labor and delivery, is a risk factor for the development of schizophrenia later in life. Impacts of perinatal asphyxia on postnatal life have been studied in a rodent model in which global hypoxia was imposed during the perinatal period (asphyxia model), and this model has been shown to manifest several abnormalities in adulthood that have relevance to schizophrenia. On the other hand, there is some evidence suggesting that cesarean section (C-section) itself is associated with schizophrenia. Therefore, we also examined the effects of C-section per se as one of potential exogenous insults. Besides, a strong genetic component is known to be involved in schizophrenia. Recently, novel schizophrenia loci, including CNNM2, CSMD1 and MMP16, have been reported by GWAS. Thus, we are intrigued to examine whether these novel schizophrenia risk genes would be altered in their expressions in our asphyxia-induced rat model as well as in the C-section rat model. However, little is known about whether these gene expressions are virtually involved in maturation of the central nervous system (CNS). Hence, we also analysed expressions of the genes in the course of neural and oligodendrocytic differentiation to confirm involvement of the novel schizophrenia risk genes in the maturation of the CNS.
Methods: We analysed expressions of schizophrenia risk genes by quantitative real-time PCR. These gene expressions were measured at three periods, neonatal, adolescence and adulthood. We analysed expression levels of these genes in rat brain tissues, such as prefrontal cortex (Pfc), the striatum (Str), and the hippocampus (Hip), which are suggested to be critically involved in schizophrenia. We also analysed expressions of the genes during neuronal and oligodendrocytic differentiation using human neuronal (SK-N-SH) cells and human oligodendrocytic (MO3.13) cells.
Results: We found that the expression of Cnnm2 was elevated in rodents specifically exposed to asphyxia, whereas C-section caused altered expression in other two genes, Csmd1 and Mmp16. Time course of such alteration varied; some lasted from the neonatal period to adulthood and other occurred only after birth. Cnnm2 expression was significantly downregulated in Pfc and Str via asphyxia. In asphyxia, long-lasting altered expression was observed in Pfc, while the alteration was limited to the neonatal period in Str. On the other hand, C-section upregulated Csmd1 expression (in Str and Hip) and Mmp16 expression (in Str). The altered level of Csmd1 expression was conserved until adulthood in Str, while its alteration was transient in Hip. The Mmp16 expression was upregulated remarkably but just after C-section in Str. We then confirmed the involvement of the genes in the CNS; CNNM2 and MMP16 expressions were upregulated in the differentiated neuronal cell line. In the maturated oligodendrocytic cell line, CNNM2 and MMP16 expressions were downregulated, while CSMD1 expression was upregulated.
Discussion: Long-lasting changes in gene expressions found are reminiscent of the persistent nature of the phenotype of schizophrenia. However, some alterations were observed only at the perinatal period. These alterations may affect neuro-manipulation such as neural differentiation and glial maturation early in life, and such an impact may lead to permanent CNS deficits. In addition, C-section may be related to the pathophysiology of schizophrenia via involvement of CSMD1 and MMP16. Further research elucidating the mechanisms of asphyxia and C-section for affecting CNS would help to understand the pathophysiology of schizophrenia.

T201. Overexpression of G-protein coupled receptor 85 (GPR85) in the rat hippocampus induces deficits in spatial short-term memory

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Background: The G-protein coupled receptor 85 (GPR85) is an orphan receptor expressed abundantly in the brain that is involved in regulating neural and synaptic plasticity and modulating diverse behaviors. In addition, human findings showed that genetic variants in GPR85 have been associated with risk for schizophrenia. Previous studies in transgenic mice overexpressing GPR85 demonstrated that these animals display reduced dendritic arborization and decreased hippocampal neurogenesis as well as impaired performance in tests of social behavior and cognition. Thus, we investigated whether an increased expression of GPR85 in the hippocampus by an adenoassociated virus (AAV) vector-driven approach may regulate memory function in the hippocampal-dependent object location test in rats.
Methods: Overexpression of GPR85 was obtained by the AAV vector designed and selected for its ability to increase GPR85 levels in vitro. Wistar rats received stereotactic intra-hippocampal injections of AAV9-hSyn-V5-GPR85 or AAV9-stuffer vectors and were tested in the object location task, 3 and 6 weeks later. AAV-mediated GPR85 overexpression in the hippocampus of rats was checked by immunohistochemistry.
Results: Overexpression of GPR85 restricted to the hippocampus resulted in impaired memory performance of rats in the object location task addressing spatial memory domain.
Discussion: This study shows that hippocampal overexpression of GPR85 in rats results in an impaired performance in the object location test. The effects on spatial memory observed in the present study corroborates previous findings from other studies and further support the idea that GPR85 inhibition may be a potential approach to improve cognition in schizophrenia and other psychiatric disorders.

T202. Age-dependent alterations in gabaergic signaling, mediators of inflammatory pathways and redox homoeostasis in frontal cortex of the MAM rat model

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Background: Schizophrenia is a neurodevelopmental disorder with risk factors of both genetic and epigenetic origins. In the methylazoxymethanol (MAM) rat model, embryos are exposed to a teratogen in utero during a critical period for the developing frontal cortex (E17). This manipulation results in a variety of behavioral and neurochemical differences in the offspring, which become evident only after puberty, thus mimicking the typical age of onset for schizophrenia. The present work sought to understand in greater depth the molecular alterations arising in young and aged animals.
Methods: Brains were harvested from naïve E17 MAM rats at 3, 6, and 12 months of age. Frontal cortex was split, with one half fixed for histology. From the other half, medial prefrontal cortex was collected for HPLC analysis of metabolic thiols. Plasma were collected for measurement of cytokines. Surrounding frontal cortex was frozen separately for RNA extraction and sequencing. A separate cohort of MAM rats was trained in a continuous trial-unique delayed nonmatching-to-location (CTUNL) working memory task. Tissue was

collected for RNA extraction after the rats had completed multiple testing sessions (16 months old).
Results: Initial RNAseq analysis in young MAM rats showed a large number of dysregulated transcripts that have been observed to be differentially expressed in post-mortem human brain, such as the GABAergic markers NPY and CCK. Parvalbumin (PV) was not reduced at the transcript level despite significant reduction in PV+ neurons measured by immunohistochemistry. Pathway analysis of genes in common between MAM rat and schizophrenia brain revealed several signaling pathways, inflammatory pathways and pathways suggestive of oxidative stress. The increased inflammatory signature in frontal cortex was not matched by changes in peripheral cytokines. Measurement of metabolites in the glutathione (GSH) synthesis pathway revealed age-dependent increases in multiple metabolites such as cystathionine and GSSG, with a resulting reduction in the GSH/GSSG ratio. Analysis of working memory showed no impairment in performance once the MAM had learned the task, but animals showed slower acquisition.
Discussion: The present dataset describes molecular and biochemical changes in the frontal cortex of the adult MAM rat arising from environmental manipulation of its developmental trajectory. Some features of schizophrenia pathology, such as a reduction in PV+ neurons, reduced GABergic trancripts and increased inflammatory transcripts, can be observed in the MAM rat. Alterations in glutathione metabolism, which grow in magnitude with age, suggest persisting oxidative stress in the medial prefrontal cortex. Working memory, as measured by CTUNL, was not overtly impaired, but the MAM rats showed a slower learning curve than control rats. Taken together, these data add to the picture of a neurodevelopmental model that may have utility in evaluating therapeutic efficacy of novel compounds that promote central anti-oxidant systems, reduce neuroinflammation, or increase interneuron function.

T203. Transgenerational transmission and modification of behavioral deficits induced by prenatal immune activation

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Background: Maternal exposure to infectious or inflammatory insults during pregnancy increases the offsprings' risk to develop neuropsychiatric disorders, including schizophrenia. It remains unknown, however, whether the increase in disease susceptibility induced by prenatal immune challenges could be transmitted across subsequent generations without any further immune exposures. The phenomenon of non-genetic transgenerational transmission of behavioral traits has attained increasing recognition in view of its potential importance in the etiology and treatment of multi-factorial disorders. The present study is the first to examine possible transgenerational effects using a well-established model of maternal viral-like immune activation in mice.
Methods: Pregnant mice (F0) were injected with the viral mimetic poly (I:C) (5 mg/kg, i.v.) or control solution in early pregnancy (gestation day 9). Upon reaching early adulthood, F1 offspring were either allocated to behavioral testing or breeding, the latter of which served to produce subsequent (F2 and F3) generations of poly(I:C)-exposed or control ancestors. Extensive behavioral testing was then carried out in all generations. In addition, we performed genome-wide transcriptional profiling to determine possible gene expression changes in the amygdala of F1 and F2 mice using next generation mRNA sequencing.
Results: Behavioral analyses in F1, F2 and F3 offspring revealed that deficits in social interaction and cued fear, both of which emerge in F1 poly(I:C) offspring, are also present in the F2 and F3 generation. F1 poly(I:C) offspring also showed increased sensitivity to the psychostimulant drug amphetamine. Interestingly, the F2 and F3 poly(I:C) generations displayed the opposite pattern, namely reduced amphetamine sensitivity. Behavioral despair emerged as a novel phenotype in the F2 and F3 poly(I:C) generation without being manifest in F1 offspring. Transcriptomic analyses revealed 2217 differentially expressed genes in F1 poly(I:C) offspring relative to F1 controls, and 4015 DEGs in F2 poly(I:C) offspring relative to F2 controls. A remarkable number of genes (1132) were differentially expressed in both generations. Many of these common genes are part of the dopamine- and cAMP-regulated phosphoprotein 32 kDa (DARPP-32) signalling pathway.
Discussion: Our findings demonstrate that behavioral deficits induced by prenatal infection can be transmitted and modified across subsequent generations. The transmission of common behavioral phenotypes across generations may be linked to abnormal DARPP-32 signaling, whereas transcriptional changes in generation-specific gene sets may underlie the emergence of generation-specific behavioral abnormalities such as sensorimotor gating (F1) and behavioral despair (F2 and F3). Future experiments will examine the possibility that the behavioral abnormalities and the differences in gene expression following prenatal immune activation are transmitted to subsequent generations via modifications in the epigenetic machinery.

T204. role of AMPA receptor deficiency in the onset of schizophrenia in an inducible genetic mouse model

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Background: Adolescence is characterized by important molecular and anatomical changes with relevance for the maturation of brain circuitry and cognitive function. This time period is of critical importance in the emergence of several neuropsychiatric disorders accompanied by cognitive impairment, such as affective disorders and schizophrenia. The molecular mechanisms underlying these changes at neuronal level during this specific developmental stage remains however poorly understood. GluA1-containing AMPA receptors, which are located predominantly on hippocampal neurons, are the primary molecular determinants of synaptic plasticity. We investigated here the consequences of the inducible deletion of GluA1 AMPA receptors in glutamatergic neurons during late adolescence.
Methods: We generated mutant mice with a tamoxifen-inducible deletion of GluA1 under the control of the CamKII promoter for temporally- and spatially-restricted gene manipulation. Analysis comprised a standard battery of behavioural tests for revealing schizophrenia-like abnormalities, as well as neurochemical and gene expression analysis for identifying possible changes in striatal dopamine and NMDA receptors
Results: GluA1 ablation during late adolescence induced cognitive impairments, but also marked hyperlocomotion and sensorimotor gating deficits. Unlike the global genetic deletion of GluA1, inducible GluA1 ablation during late adolescence resulted in normal sociability. Deletion of GluA1 induced redistribution of GluA2 subunits, suggesting AMPA receptor trafficking deficits. Mutant animals showed increased hippocampal NMDA receptor expression and no change in striatal dopamine concentration.
Discussion: Our data provide new insight into the role of deficient AMPA receptors specifically during late adolescence in inducing several cognitive and behavioural alterations with possible relevance for neuropsychiatric disorders.

T205. UBE3B expression in the prefrontal cortex during development and in schizophrenia

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Background: The prefrontal cortex, a major site of dysfunction in schizophrenia, undergoes extensive developmental changes during adolescence, including the remodeling and pruning of circuitry in neuronal networks that eventually lead to enhanced cognitive decision making ability in adulthood. Our previous work explores gene expression regulation in normal, postnatal human development; specifically at layer 3 pyramidal cells that furnish corticocortical connections in the prefrontal cortex. We identified genes that are both developmentally regulated and differentially expressed in schizophrenia. One of these genes is the ubiquitin ligase-encoding gene, UBE3B, a paralog to the widely studied UBE3A which has been previously correlated with autistic behaviors in mice. Alterations in the ubiquitination system are known to contribute to developmental neurological diseases such as Angelman Syndrome and other autism spectrum disorders. Our protein and gene expression analysis findings

suggest that UBE3B expression increases developmentally and is decreased in schizophrenic samples, and thereby could contribute to the developmental pathophysiology of schizophrenia by disturbing periadolescent synaptic refinement of prefrontal cortical circuitry.
Methods: Nissl-stained homogenous populations of pyramidal neurons were extracted from layer III of the prefrontal cortex via the Arcturus XT Laser Capture Microdissection protocol from a cohort of pre-adolescent ($n = 7$) and post adolescent ($n = 6$) control subjects. Total mRNA was then isolated and amplified using the Picopure mRNA Isolation Kit from Arcturus. Expression profiling experiments were conducted using the Affymetrix X3P microarray chip. The generated data were normalized with MAS5. Differentially expressed genes in pre- vs post-adolescent subjects were determined using ANOVA, and filtered with an FDR-corrected *P* value of 0.05 and a fold change of 1.5. A pathway analysis was performed with GeneGo software to determine the biological significance of the differentially expressed genes
UBE3B protein expression levels were verified using an immunohistochemistry staining protocol with an anti-ube3b polyclonal antibody made in rabbit and an anti-rabbit secondary made in goat. Tissue was fixed in 4% paraformaldehyde and cut at 20µm(developmental cohort) and 10 µM(disease cohort). Images were taken at 2.5x magnification to visualize staining. 500uM x 500uM columns were drawn to count Ube3B and Ube3b/Nissl co-localization staining through A9 prefrontal cortex layers I-VI.
Fold change microarray data were validated with qRT-PCR in an ongoing investigation of the genes of interest. Templates were generated from the LCM cohort cDNA and amplified using SYBR Green and normalized to GAPDH.
Results: UBE3B cellular density increases developmentally and is also seen to be decreased in adult subjects with schizophrenia (SZ). The percent of total ube3b-exressing cells, specifically pyramidal neurons, is also decreased in SZ. Genetically, we found UBE3B to be upregulated in the healthy post-adolescent cohort, and down-regulated in the adult SZ cohort versus the healthy adult control.
Discussion: We are particularly interested in UBE3B, a gene that was found to be upregulated during periadolescent development but downregulated in subjects with SZ. Because UBE3B is involved in ubiquitination, which has been strongly implicated in the regulation of synaptic plasticity, our findings raise the hypothesis that altered expression of UBE3B could contribute to the developmental pathophysiology of SZ by disturbing periadolescent synaptic refinement of prefrontal cortical circuitry.

T206. The dopaminergic response to acute stress in health and psychopathology: a systematic review

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Background: Previous work in animals has shown that dopamine (DA) in cortex and striatum plays an essential role in stress processing. We reviewed the evidence for the role of DA in the human acute stress response in both healthy individuals and those at increased risk for or diagnosed with a psychiatric disorder.
Methods: PUBMED was searched for studies published before January 8th 2015 using the following Boolean phrase: ("positron emission tomography" OR "PET" OR "single photon emission computed tomography" OR "SPECT" OR "single photon emission tomography" OR "SPET") AND ("dopamine") AND ("stress" OR "pain").
Results: All studies included (n studies = 25, n observations = 324) utilized DA D2/3 positron emission tomography and measured DAergic activity during an acute stress challenge. The evidence in healthy volunteers (HV) suggests that physiological, but not psychological, stress consistently increases striatal DA release. Instead, increased medial prefrontal cortex (mPFC) DAergic activity in HV was observed during psychological stress. Across brain regions, stress-related DAergic activity was correlated with the physiological and psychological intensity of the stressor. The magnitude of stress-induced DA release was dependent on rearing conditions, personality traits and genetic variations in several SNPs. In psychopathology, preliminary evidence was found for stress-related dorsal striatal DAergic hyperactivity in psychosis spectrum and a blunted response in chronic cannabis use and pain-related disorders, but results were inconsistent.
Discussion: Physiological stress-induced DAergic activity in striatum in HV may reflect somatosensory properties of the stressor and readiness for active fight-or-flight behavior. DAergic activity in HV in the ventral striatum and mPFC may be more related to expectations about the stressor and threat evaluation, respectively. Future studies with increased sample size in HV and psychopathology assessing the functional relevance of stress-induced DAergic activity, the association between cortical and subcortical DAergic activity and the direct comparison of different stressors are necessary to conclusively elucidate the role of the DA system in the stress response.

T207. No link between duration of prodromal and psychotic symptoms and brain structural volumes in emerging psychosis

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Background: The time period during which patients manifest psychotic or unspecific symptoms prior to treatment (duration of untreated psychosis, DUP and the duration of untreated illness, DUI) has been found to be moderately associated with poor clinical and social outcome, which may amongst others be due to "neurotoxicity" of untreated psychosis. Equivocal evidence exists of an association between DUP/DUI and structural brain abnormalities, such as reduced hippocampus (HV) (Bühlmann *et al.*, 2010), pituitary volume (PV) (Büschlen *et al.*, 2011) and grey matter volume (GMV) (Borgwardt *et al.*, 2007). The objective of this work was to examine if DUP and DUI are associated with grey matter volume abnormalities in HV, PV or GMV.
Methods: Using a region-of-interest (ROI) based approach, we present data of 39 patients from the Basel FePsy (Früherkennung von Psychosen) (Riecher-Rössler *et al.*, 2007) study for which information about DUP, DUI and HV, PV and GMV data could be obtained. 23 of the patients were identified as first-episode-psychosis patients (FEP), 16 as at-risk-mental-state (ARMS – T) patients, who later made the transition to frank psychosis.
Results: We found no significant association between DUP/DUI and HV, PV or GMV when corrected for sex, age and antipsychotics, though we found a statistical trend for a weak negative association between DUI and GMV in FEP.
Discussion: Our results do not support the hypothesis of a "toxic" effect of untreated psychosis on brain structure.

T208. Increased expression of alpha-2,8-sialyltransferase 8 (ST8SIA2) in superior temporal gyrus of elderly patients with schizophrenia

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Background: The role of posttranslational protein modifications (PTMs) in the pathophysiology of schizophrenia (SCZ) is a recent target of investigation in this devastating neuropsychiatric illness. One PTM, glycosylation, has come under study due to the role glycan adornment plays in modulating a wide variety of inter- and intracellular processes. Carbohydrate active enzymes (CAzymes), glycosyltransferases and glycosidases, comprise approximately 2% of the human genome and mediate this functionally important PTM.
Sialyltransferases (SiaTases) and sialidases respectively attach or cleave the 9-carbon α-keto sugar, N-acetylneuraminic acid (NeuAc or sialic acid) on a substrate molecule. NeuAc is commonly found at the terminus of glycan branches and is uniquely able to form extended homopolysaccharide chains. Polysialic acid (PSA) is synthesized by the addition of 8+ NeuAc units attached via an α-2,8-linkage hydrolyzed by ST8SIA2, ST8SIA4, or less efficiently by ST8SIA3. PSA and polysialylated proteins play important roles in the spatiotemporal

regulation of neurodevelopmental processes, and reduced PSA is a feature of SCZ pathophysiology. Specifically, reduced polysialylation of neural cell adhesion molecule (NCAM, PSA-NCAM), but not total NCAM expression, is evident in the hippocampus and dorsolateral prefrontal cortex (DLPFC) in SCZ.
Our lab recently investigated transcription of CAzymes in SCZ DLPFC and, contrary to our expectation, found increased mRNA of both SiaTases and sialidases. While reduced PSA-NCAM has been suggested to contribute to decreased neuroplasticity and reduced volume of SCZ superior temporal gyrus (STG), evidence supporting this hypotheses has not been reported. To elaborate on potential deficits of NeuAc in SCZ STG, we measured the protein expression of ST8SIA2, ST8SIA3, NEU1, and NEU2. We hypothesized that, consistent with increased transcription of these CAzymes, SiaTases and sialidase protein levels are increased in SCZ.
Methods: Samples of gray matter from the full cortical thickness of the left STG (Brodmann area 22) of 16 elderly SCZ and 14 comparison subjects were obtained from the Mount Sinai Medical Center brain collection. Prepared samples of total homogenate were loaded in 4-12% Bis-Tris gels and run using standard SDS-PAGE and semi-dry transfer methods. Membranes were then probed with antibodies against ST8SIA2, ST8SIA3, NEU1, NEU2, and valosin-containing protein (VCP) as a loading control. The relative abundance of proteins was determined by measuring the signal intensity of each target normalized to the signal intensity of VCP.
Results: Protein expression of ST8SIA2 is altered in schizophrenia.
ST8SIA2 demonstrates a 22% increase in expression relative to COMP subjects in SCZ ($t(28) = 2.75$, $P = 0.01$). ST8SIA3, NEU1, and NEU2 expression was not found different between diagnostic groups in STG.
Discussion: ST8SIA2 is the primary mediator of PSA-NCAM synthesis, and mutations of the ST8SIA2 gene have been correlated with increased SCZ susceptibility risk. These single nucleotide polymorphisms have recently been shown to functionally impair α-2,8-SiaTase activity in vitro, suggesting that deficient NeuAc hydrolysis may lead to upregulated transcription and translation of a mutated ST8SIA2 gene in SCZ STG, as we report here. While this may be an indication of cellular compensation in the disorder, it is noteworthy that 11 of the 16 SCZ subjects were on typical antipsychotics within 6 weeks of death and this finding may represent a medication effect rather than an inherent feature of SCZ pathophysiology. Further investigation of PSA, PSA-NCAM, and ST8SIA2 expression in SCZ STG of unmedicated patients in earlier stages of the disorder are warranted.

T209. Unravelling the role of schizophrenia risk genes in microglia: specific functions in the anti-inflammatory phenotype?

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Background: It is becoming more and more clear which genes are associated with schizophrenia. How these risk genes contribute to schizophrenia pathogenesis is still largely unknown. It has been shown that the expression of schizophrenia risk genes is not restricted to neurons but also enriched in immune cells. In addition, pathway analysis has revealed that the risk genes cluster not only in neuronal but also in immune pathways. Which specific immune cells and pathways are affected in schizophrenia is still unknown. The aim of the present study is to investigate the expression and function of schizophrenia risk genes in human microglia, the main population of immune cells in the brain.
Methods: From GWAS, CNV and linkage studies nineteen schizophrenia risk genes were selected for further analyses. The expression of these genes was assessed in primary human microglia isolated from post-mortem brain tissue and compared to the expression in total brain tissue. The regulation and function of microglia-enriched genes was studied in primary microglia as well as monocyte-derived macrophages in vitro.
Results: Expression of seven out of nineteen genes was enriched in microglia compared to whole brain tissue. Polarization of human primary microglia and human primary monocyte-derived macrophages with anti-inflammatory stimuli, particularly dexamethasone and TGF-β, but not pro-inflammatory stimuli, resulted in a significantly higher expression of most of the microglia enriched genes. Two of the schizophrenia risk genes were silenced in human primary monocyte-derived macrophages using small interference RNAs and the knock-down resulted in downregulation of seven out ten TGF-β target genes.
Discussion: Expression of part of the schizophrenia risk genes is enriched in microglia and further increased after stimulation with dexamethasone and TGF-β. Moreover, knock down of one of these genes resulted in downregulation of TGF-β response. These results suggest that schizophrenia risk genes may be involved in specific functions of alternatively activated microglia cells, such as controlling inflammation, tissue repair, or in the development of microglia and that dysregulation of these functions may be involved in schizophrenia pathogenesis.

T210. Effect of clozapine and haloperidol in the morphology and neurodevelopment of zebrafish embryo.

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Background: In recent years, alterations in cognitive, motor, socio–emotional and adaptive behaviour in children exposed in utero to antipsychotic drugs has been observed. FDA places Haloperidol and Clozapine in Pregnancy Categories C and B due to the lack of well-controlled safety studies. On the other hand, some data suggest antipsychotics might impact in the morphology of brain structure. In this regard, second generation antipsychotics (SGAs) show different neuroplastic effects when compared to first generation antipsychotics (FGAs). In particular, SGAs have been shown to mitigate gray matter volume reductions, common phenotype present in schizophrenic patients. This effect suggests SGAs could have a neuroplastic effect. Additional studies have reported a decrease in cortical thickness during treatment with SGA. It is not understood if these effects might be related to an effect in neurogenesis, neuronal apoptosis, or to a different reason altogether.
We aim to study the teratogenic potential and putative neuroplastic effect of haloperidol and clozapine during CNS development using zebrafish developing embryos.
Methods: Zebrafish embryos were obtained by mating adult fishes by standard procedures. All fish strains were maintained individually as inbred lines. Wild type, strain AB; Tg[Mü4127]; Tg[neurod:GFP]; Tg[Isl1:GFP]; Tg[Isl3:GFP] (also called Isl2b). All procedures used have been approved by the PRBB animal care facility and Users ethical committee, and followed national and European regulations.
Concentrations 0.1μM, 1μM, 10μM, 100μM and 1 mM were tested. Mortality and embryonic morphology were quantified during the assay at 3 different time-points (24, 48 and 72 hpf). In whole mount antibody staining embryos were incubated O/N at 4 °C with rabbit anti-GFP [1:500], mouse anti-DsRed [1:500], rabbit anti-phosphoHistone3 (pH3) [1:500], or mouse anti-HuC. TUNEL assay was also performed.
Results: Clozapine and Haloperidol were lethal at 100 μM concentration in zebrafish embryos. Teratogenic doses of both drugs were observed in the range of 0.,1 to-10 μM. No effect appeared on patterning, differentiation and apoptosis at 10 μM and below, with no significant differences when we compared average number of pH3-positive cells per hemisegment among control (DMSO1% = 10.75 ± 3.59), haloperidol (10.5 ± 3.51; $P = 0.9$) or clozapine (7.5 ± 3.1; $P = 0.2$). Neurogenesis was affected predominantly by clozapine at 10 to 100 μM concentration, and to a less extend by Haloperidol at same concentrations. Embryos exposed either drug do not exhibited significant variation in the number of differentiating neurons. 10μM Haloperidol treated embryos showed similar number of cells expressing neuroD per hemisegment (10μM = 12,16 ± 0,932) compared with controls (12,275 ± 0,941). However, exposure to clozapine reduced neurogenesis 9%. Moreover, a significant ($P < 0,05$) decrease in the number of neuroD-GFP+ cells was detected in embryos exposed to 100 μM for both drugs: reduction of 31,7% for clozapine and 16,8% for haloperidol.
Discussion: Teratogenic doses of both drugs are in the range of 0.1 to 10 μmicroM at which two phenotypes can be observed, one with

lordosys, and other characterized by pericardial edema. No effect appeared on patterning, differentiation and apoptosis at doses of 10 μM and below. Clozapine and Haloperidol impairs neurogenesys and are lethal at concentration of 100 μmicroM in zebrafish embrios.

T211. Prefrontal gray matter volume loss is associated with decreased working memory performance in adolescents with a first episode of psychosis

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Background: Cognitive maturation during adolescence is modulated by brain maturation. High-order cognitive processes [i.e. Sustained Attention (SA), Working Memory (WM) and Executive Function (EF)] have been associated with the prefrontal cortex. In typical development, frontal lobe gray matter (GM) volume typically peaks at 11-12 years whereas gains in WM are extended up to 15-19 years of age and EF performance improves up to mid-twenties (1). SA, a basic underlying cognitive process required to complete any activity is the first one to develop. Studies examining frontal cortical changes and cognitive performance in psychosis over time lend support for an altered development of higher brain cognitive functions [2] which parallel progressive GM loss over time [3,4]. However the direct relationship between these processes has not been assessed to date in early onset psychosis. We aimed to assess the relationship between changes in GM volume in the frontal lobe and SA, WM and EF performance in adolescents with a first episode of psychosis over 2years.
Methods: A subsample of 33 first-episode psychotic patients (mean age 15.82; range [11–17]) and 47 matched controls (mean age 15.26; range [13–17]) completed both baseline and longitudinal cognitive and neuroimaging assessments from the original CAFEPS sample (110 patients and 98 controls [5]). A structural MRI was obtained in five 1.5 T scanners. Lateral frontal lobe GM volumes were obtained using an automated method based on the Talairach´ atlas. Prefrontal cortex cognitive related abilities were assessed using subtests of SA (Digits Forwards WAIS-III, time to complete TMT-A, number of correct items from words and colors Stroop test, number of correct responses and average reaction time from the CPT); WM (Digits backwards and letter-number sequencing, WAIS-III) and EF (TMT(B-A), number of errors, number of perseverative errors and categories of the WCST, Stroop Interference score, total COWAT score)(z-scores). ANCOVA was used to examine differences between groups in longitudinal change in lateral frontal GM volumes using age, scanner site, ICV at baseline and interscan ICV change at 2 years as covariates of no interest. Partial correlation analyses were performed to determine the association between changes (2-year minus baseline) in frontal GM volumes and SA, WM and EF performance (composite score) within each group. In order to analyse the predictive value of changes in frontal GM over cognitive performance, backwards stepwise regression analyses were conducted.
Results: Patients showed significantly greater loss of GM volume in the frontal lobe [left ($F = 5{,}825$; $P = 0{,}018$); right ($F = 7{,}007$; $P = 0{,}010$)] than healthy controls at 2years follow up. Longitudinal change (decrease) GM volume was positively associated with decreased WM performance in patients [left ($r = 0{,}484$; $p = 0{,}009$); right ($r = 0{,}422$; $P = 0{,}025$)]. No association was found in healthy controls. Results of a backwards stepwise regression model revealed that change in frontal GM volume over time predicted a significant amount (left 19%; right 16%) of the variance of change in WM, even when variance for all other variables in the final model was accounted for. No association was found between longitudinal GM volume change and SA or EF in these groups.
Discussion: Adolescents with a first episode of psychosis presented a specific decrease in GM volume in the frontal lobe during the first two years after illness onset. Within patients but not controls, progressive loss of GM volume was associated with decreased WM function. Our results suggest that during adolescence, patients seem to follow an abnormal neurodevelopmental trajectory in which progressive reduction of frontal GM volume might contribute to the observed working memory dysfunction.

T212. Why is exotropia (one specific type of strabismus) a significant risk factor for schizophrenia?

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Background: Several recent studies have shown that children with strabismus (specifically exotropia) have a significantly increased risk of developing schizophrenia decades later (Toyota *et al.*, 2004; Schiffman *et al.*, 2006; Yoshitsugu *et al.*, 2006; Mohney *et al.*, 2008; Ndlovu *et al.*, 2011; increased risk 3 to 185fold, median ~70fold), suggesting an overlapping pathophysiology for both diseases or a role of exotropia as a risk factor for schizophrenia. The association of schizophrenia with exotropia but not esotropia suggests that the two relevant rectus muscles (medial and lateral) differ in their susceptibility to this process. We here identified which genes known to be associated with schizophrenia have abnormal expression patterns in strabismic medial rectus extraocular muscles. Given the link between exotropia and schizophrenia, we also tested the hypothesis that seasonality of birthdates may be similar between the two groups of patients.
Methods: Samples from strabismic lateral and medial rectus muscles were obtained during corrective surgeries; normal samples were obtained from deceased organ donors. Consistent gene expression differences of 2-fold or more on targeted or customized PCR arrays were compiled from paired comparisons ($n = 4$ per condition). We selected 86 molecules of particular interest based on known risk factors for schizophrenia. Birth months of 5,847 patients with either exotropia or esotropia were normalized to geographically matched birth records, analyzed with a chi-square test, and compared with published data from cohorts of patients with schizophrenia.
Results: Among 381 genes encoding signaling molecules, 22 were consistently and significantly dysregulated in strabismic medial rectus muscles. Almost half (10) of these were known biomarkers for schizophrenia (Schwarz *et al.*, 2010; Miller *et al.*, 2011), including cytokines, growth factors and their receptors, and downstream signaling pathways. NRG1, VEGFA were decreased, while CTGF, CXCR4, IL7, TNF, NTRK2, IL10RA, TNF and TNFR were increased. Birthdates of patients with exotropia showed a pronounced peak in summer months ($P = 0.001$, chi-square test), similar to the birth pattern of people with schizophrenia who have primary negative symptoms (Messias *et al.*, 2004).
Discussion: Our gene expression data indicate a molecular link between exotropia and schizophrenia. This suggests that the gene expression profile in the medial rectus muscle may be related to the risk of developing schizophrenia. We are currently exploring whether the dysregulation of schizophrenia-related molecules is specific to strabismic medial rectus muscles (exotropia) and absent in strabismic lateral rectus muscles (esotropia). We are also exploring whether infants with very early correction of their exotropia have a reduced incidence of schizophrenia, as has been hypothesized (Korn, 2004). Neurodevelopmental abnormalities may lead to both medial rectus extraocular muscle dysfunction and brain dysfunction, or exotropia, when it manifests early in life and compromises visual capacity, may increase the risk of the development of psychosis (Landgraf and Osterheider, 2013; Silverstein *et al.*, 2013). The new findings may aid in the development of methods to predict the risk of schizophrenia years prior to the appearance of psychotic symptoms, and conceivably aid in the prevention of some percentage of cases of schizophrenia.

T213. Very preterm born adults experience elevated levels of psychopathology that are associated with the volumes of corticostriatal white matter tracts

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Background: Very preterm birth has been associated with an increased risk of psychiatric disorder later in life. Higher rates of sub-clinical psychopathology might also be expected in preterm populations as a whole. Establishing the aetiological mechanisms underlying these sequelae is crucial in developing preventative strategies and treatments. The objective of this study is to evaluate psychopathology and its structural brain correlates in very preterm adults
Methods: We assessed psychopathology in a cohort of 127 adults who had been born very prematurely (VPT, < 33 weeks) and a group of 88 term-born controls aged 30 years, using the 'Comprehensive Assessment of At Risk Mental States' (CAARMS). Using Diffusion Magnetic Resonance Imaging (MRI) data we also studied possible structural alterations in corticostriatal tracts, due to their known involvement in a variety of neurodevelopmental and neuropsychiatric disorders.
Results: VPT participants had higher rates of psychopathology on two CAARMS symptom clusters: a 'Negative-Interpersonal' cluster (NI, $P = 0.018$), relating to symptoms of anhedonia, depression and anxiety and a 'Communication-Cognitive-Behavioural Disorganization' cluster (CCBD, $P = 0.013$), relating to symptoms of disorganized/odd behaviour, poverty of speech and cognitive and affective disturbance. The volume of five corticostriatal tracts (see below) was also significantly smaller in the VPT group (all $P < 0.05$). A number of negative correlations were found between the two CAARMS clusters and corticostriatal tract volumes (i.e. higher symptomatology = lower tract volume): NI cluster scores and Striatal Working Memory/Attention tract (r = -0.20, p = .045), Striatal Sensorimotor tract (r = -0.33, p = .004) and Striatal Default Mode Network tract (r = -0.30, p = .013); CCBD cluster scores and Striatal Frontal tract (r = -0.21, p = .038) and Striatum Limbic tract (r = -0.21, p = .033), after Benjamini-Hochberg FDR correction.
Discussion: These results demonstrate increased rates of psychopathology in a sample of adults aged 30 who survived VPT birth, which could be at least partly explained by volumetric alterations of selective cortiocostriatal tracts involving amongst the others, the limbic and frontal cortices and the default mode network, which are crucial for emotion/salience processing.

T214. Uncovering components of cognitive behavioural case management (CBCM) in UHR individuals: what is implemented and what is effective?

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Background: Converging evidence suggest that cognitive behavioural therapy (CBT) and cognitive behavioural case management (CBCM) may provide a safe and effective pre-emptive treatment option in people at ultra-high risk (UHR) for psychosis. However, given the broad nature of this treatment approach, it is not clear which CBCM strategies are implemented and which components should be routinely incorporated. The aim of the current study was to characterise the provided components and progression of a CBCM regimen and to analyse the relationship between these components and symptomatic and functional outcome.
Methods: As part of a larger trial comprising 304 UHR individuals (Neurapro-E study), participants were provided with a manualised intervention of CBT embedded within case management (CBCM). Participants received 6-20 CBCM sessions, depending on their need, for up to 12 months. CBCM components used were registered post-session by the clinician using a checklist. Clinical status and symptomatic/functional outcome was assessed at baseline and reassessed at 6, 9 and 12-months. Analytical methods (in progress) include descriptive analyses of the implemented CBCM components (cross sectional and over the course of the treatment period); multiple regression analysis, as well as survival analysis associating particular CBCM elements to symptomatic outcome and clinical status.
Results: CBCM data were available for 282 participants. Participants received on average 14 CBCM sessions. Over the treatment period, most prevalent implemented strategies were mental state and symptom monitoring (67%), assessment of symptoms (46%) and stress management (44%), with relapse prevention/termination (12%) and crisis management (13%) as least prevalent. Preliminary regression analyses suggest that a higher number of provided sessions, as well as CBCM component assessment of symptoms predicted higher total depression (MADRS) and general psychopathology scores (total BPRS score) at 12 months ($P < .01$).
Discussion: These preliminary results indicate that a prominent aspect of cognitive behavioural intervention for UHR patients is stress management, in line with stress-vulnerability models of psychosis onset, as well as monitoring symptom progression. The relationship between higher number of CBCM sessions and worse symptom scores at 12 month follow up was most likely driven by those patients with greater clinical need and worse symptom profile requiring a greater amount of clinical intervention.
Further analyses to be presented at the conference will address whether particular components of CBCM (e.g., treatment focused on positive symptoms) relate to particular aspects of clinical outcome (e.g., reduced transition rate, improved functional outcome, etc.).

T215. Individualized metacognitive therapy for delusions: effectiveness in a pragmatic controlled trial

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Background: Delusions constitute a hallmark symptom of psychotic disorders. Since extensive research has linked the emergence and maintenance of delusions to reasoning biases (i.e., specific distorted thinking styles), there has been an increased interest in the therapeutic efficacy of interventions that aim to improve such reasoning biases. Individualized metacognitive therapy (MCT+; free download in 10 languages at www.uke.de/mct_plus) is a short, structured and fully manualized treatment program for patients with psychosis that leans on the principles of cognitive-behavioral therapy but adopts a 'backdoor' approach: Through engaging exercises the patient is introduced to reasoning biases, before individual symptoms are addressed. Aim of the present study was to assess the effectiveness of MCT+ in the context of a pragmatic controlled trial.
Methods: The study was designed as a randomized, controlled, rater-blind trial. Participants were 92 patients with schizophrenia-spectrum disorders and current or past delusions. In order to ensure generalizability of results, exclusion criteria were restricted to mental retardation, major brain damage, and substance dependence. Patients were allocated to either MCT+ or a control intervention (computerized cognitive training), of which they received up to 12 twice-weekly sessions. All patients continued receiving their usual care (including therapy groups and medication) during the study. The primary outcome measures were PANSS item P1 (delusions) and PSYRATS delusions total score at 8 weeks. Results were calculated with ANCOVAs adjusting for baseline scores. Intention-to-treat (ITT) analyses included all patients who participated in at least one treatment session (MCT+ $n = 44$; control $n = 35$); missing data were estimated using multiple imputation. Per protocol analyses (PP) included all patients for whom follow-up data were available (MCT+ $n = 40$; control $n = 32$).
Results: The mean number of attended sessions was similar for the two groups. There were no differences in antipsychotic medication dose either at baseline or follow-up. Primary outcome analyses revealed a significant superiority for MCT+ regarding P1 (ITT $P = 0.03$, PP $P = 0.02$) and PSYRATS delusion score (ITT $P = 0.02$, PP $P = 0.018$), at a medium effect size (partial eta-squared = 0.08 in both cases). Secondary analyses revealed a numerical advantage of MCT+ for all symptom

dimensions of the PANSS which, however, did not reach significance (all $P > 0.2$). When analyses were repeated including only patients who attended at least 4 sessions of either intervention (MKT+ $n = 39$; control $n = 26$), all between-group effects increased in size, approaching a large effect size for delusions (partial eta-squared = 0.12) and a medium effect size in the case of PANSS positive ($P = 0.06$, partial eta-squared = 0.06), distress ($P = 0.06$, partial eta-squared = 0.06) and disorganization symptoms ($P = 0.04$, partial eta-squared = 0.07). Results were not affected by the presence or absence of current clinically relevant delusions at baseline (defined as P1 score ≥ 4).
Discussion: MCT+ was more effective in reducing delusions in patients with psychotic disorders compared to a control intervention (computerized cognitive remediation training), irrespective of delusion severity at baseline. This effect was more pronounced in patients who attended more sessions.

T216. Exercise improves clinical symptoms, quality of life, global functioning and depression in schizophrenia: a systematic review and meta-analysis

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Background: Physical exercise may be valuable for patients with schizophrenia spectrum disorders as it may have beneficial effect on clinical symptoms, quality of life and cognition.
Methods: A systematic search was performed using PubMed (Medline), Embase, PsychInfo, and Cochrane Database of Systematic Reviews. Controlled and uncontrolled studies investigating the effect of any type of physical exercise interventions in schizophrenia spectrum disorders were included. Outcome measures were clinical symptoms, quality of life, global functioning, depression or cognition. Meta-analyses were performed using Comprehensive Meta-Analysis software. A random effects model was used to compute overall weighted effect sizes in Hedges' g.
Results: 29 studies were included, examining 1109 patients. Exercise was superior to control conditions in improving total symptom severity (k = 14, $n = 719$: Hedges' g = .39, $P < .001$), positive (k = 15, $n = 715$: Hedges' g = .32, $P < .01$), negative (k = 18, $n = 854$: Hedges' g = .49, $P < .001$), and general (k = 10, $n = 475$: Hedges' g = .27, $P < .05$) symptoms, quality of life (k = 11, $n = 770$: Hedges' g = .55, $P < .001$), global functioning (k = 5, $n = 342$: Hedges' g = .32, $P < .01$), and depressive symptoms (k = 7, $n = 337$: Hedges' g = .71, $P < .001$). Yoga, specifically, improved the cognitive subdomain long-term memory (k = 2, $n = 184$: Hedges' g = .32, $P < .05$), while exercise in general or in any other form had no effect on cognition.
Discussion: Physical exercise is a robust add-on treatment for improving clinical symptoms, quality of life, global functioning, and depressive symptoms in patients with schizophrenia. The effect on cognition is not demonstrated, but may be present for yoga.

T217. Theta burst transcranial magnetic stimulation for auditory verbal hallucinations

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Background: Auditory verbal hallucinations (AVH) are a characteristic symptom of schizophrenia. In 25% of patients, these hallucinations are irresponsive to existing treatments such as antipsychotic medication. Repetitive Transcranial Magnetic Stimulation (rTMS) to the left temporoparietal region has been suggested to be a non-invasive treatment option for refractory hallucinations, but results up till now have been inconclusive. Recent studies with large sample sizes could not demonstrate efficacy of 1- Hz rTMS when compared to placebo. An alternative stimulation protocol using theta burst rTMS (TB-rTMS) may be a more effective treatment option.
Methods: In a double-blind sham-controlled design, seventy-one patients with AVH were randomly allocated to either TB-rTMS or placebo treatment. The TB-rTMS group received ten continuous TB-rTMS treatments over the left temporoparietal cortex distributed over five consecutive days. The placebo group received ten treatments of sham stimulation following the same procedures as the active treatment group. Severity of AVH was assessed at baseline, after five days of treatment, and during follow-up one month later using the Positive and Negative Symptom Scale (PANSS), Auditory Hallucinations Rating Scale (AHRS) and Psychotic Symptom Rating Scale (PSYRATS). Treatment effects on AVH were analyzed using a mixed design ANOVA.
Results: The severity of AVH did not significantly reduce after TB-rTMS compared to placebo, as no significant interaction effect between time and treatment group was found. A significant improvement in AVH occurred after treatment in general as measured by the AHRS ($p < .001$) and the PSYRATS ($p = .002$). Furthermore, the total ($p = .04$), positive ($p = .03$) and general ($p = .01$) PANSS score decreased significantly over time, but there was no significant decrease on the negative scale, neither a significant time by group interaction on the PANSS.
Discussion: As both treatment groups showed equal improvement, the results suggest AVH improvements were due to a placebo-effect rather than treatment-specific effects of TB-rTMS.

T218. Cognitive remediation group therapy reduces persistent negative symptoms in schizophrenia outpatients: RCT results

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Background: Negative symptoms often inhibit the social integration of people suffering from schizophrenia. Persistent Negative Symptoms (PNS) are consensus defined as primary negative symptoms or secondary symptoms not responding to usual treatment and interfering with patients' ability to perform role functions in clinically stabilized patients. The treatment of PNS is increasingly considered an unmet need, as very few interventions specifically addressing PNS exist up to date. Aim of this study was to investigate whether cognitive remediation therapy (CRT) supports remission of PNS.
Methods: The Integrated Neurocognitive Therapy (INT) represents a CRT group treatment approach designed for schizophrenia outpatients. We identified PNS outpatients of a data set from an international RCT comparing INT with Treatment as Usual (TAU). A total of 53 patients met inclusion criteria for PNS. A test-battery assessed baseline, end of therapy of 15 weeks (with bi-weekly sessions), and follow-up one year after baseline. Change in outcome between INT and TAU over treatment and follow-up was compared using GLM for repeated measurements. Remission rates of the two treatment conditions were compared using Chi-square tests.
Results: Remission rates of PNS (mild or no symptom severity) after therapy were significantly higher for INT compared to TAU after therapy and at follow-up. However, symptom reduction was associated only to the motivation factor (e.g., avolition, asociality) but not to the expression factor (e.g., blunted affect) of PNS. Furthermore, INT compared to TAU significantly increased functional outcome at follow-up. Regarding proximal outcome in cognitive domains, some significant effects were found in basic neurocognition (speed, attention, verbal memory). No effects in complex neurocognition and social cognition were evident in INT or TAU.
Discussion: INT seems to successfully reduce PNS and functional outcome deficits in PNS outpatients. To address individual deficits in specific negative symptoms such as blunted affect and alogia (expressive factor) as well as in complex cognitive functions, CRT should be combined with other therapy topics such as physical exercise and motivational techniques over a longer duration of therapy.

T219. Cognitive therapy and motivational interviewing: reducing cannabis consumption in individuals with psychosis

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Background: Cannabis dependence and abuse is a widely spread phenomenon among individuals with psychotic disorder. In vulnerable individuals, cannabis stimulates the development of psychotic symptoms and exerts a negative influence on the course of the disorder as well as treatment compliance. So far, only one treatment approach yielded promising results in the combined treatment of cannabis dependence and psychosis: Barrowclough's Cognitive Therapy and Motivational Interviewing (CT+MI). The aim of the current study is to test the efficacy of CT+MI in reducing cannabis consumption in individuals with psychosis.
Methods: Sixty patients were randomly assigned to CT+MI or a control condition (treatment as usual). CT+MI consisted of 24 individual sessions (45-60 min) spread over a period of 40 weeks, complemented by two booster sessions at weeks 5 and 10 after completion of treatment. Cannabis consumption (number of days abstinent from cannabis) was measured at baseline, post treatment, and at six and twelve months follow-up using the Time Line Follow Back method. An available case analysis involving 37 cases was carried out. In this preliminary sample, linear mixed effects models with random intercept were deployed to investigate the effect of treatment on cannabis consumption. Changes in cannabis consumption were tested both within treatment group and with a treatment*time interaction using a Wald test. Group differences in cannabis consumption were analyzed for each follow-up moment.
Results: In the treatment group, number of abstinent days significantly increased over time until six months after the intervention (post treatment: ß = 13.97, $P = 0.002$, 95% CI [5.08;22.68]; six month follow-up: ß = 11.92, $P = .014$, 95% CI [2.44;21.40]; 12 month follow-up: ß = 7.93;$P = .074$, 95% CI [-.76;16.63]). The difference in the number of abstinent days was slightly higher in the treatment group at end of treatment (ß = 3.29, $P = .65$, 95% CI [-11.03; 17.61]) and at six month follow-up: ß = 12.36, $P = .11$, 95% CI [-2.83; 27.55]), but this difference fell short of statistical significance at conventional levels. At 12 month follow-up, cannabis consumption did not significantly differ in the two groups (ß = .70, $P = .93$; 95% CI[-13.76;15.15]). There was no evidence of a time × group interaction ($\chi2(3) = 2.86$,$P = .41$). This suggests that, overall, group differences in cannabis consumption did not significantly vary over time.
Discussion: Initial evidence from the current data suggests that CT+MI does not reduce cannabis consumption in individuals with psychosis. Due to the small sample size, these preliminary results need to be interpreted with caution.

T220. An event-related potential EEG-neurofeedback training to treat auditory verbal hallucinations in schizophrenia patients

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Background: Previous studies have shown a global reduction of the event-related potential component (ERP) N100 in schizophrenia patients, which is even more pronounced during the event of auditory verbal hallucinations (AVH). This assumingly results from a dysfunctional activation of the primary auditory cortex by inner speech, which reduces its responsiveness to external stimuli.
The idea of this study is to enhance the responsiveness of the primary auditory cortex to external stimuli with an upregulation of the event-related potential component N100 through neurofeedback. Our main interest stands on the behavioral level, specifically in the change of the subjective intensity of AVH's.
Methods: Therefore, 15 healthy control subjects and 8 with chronic schizophrenia or schizoaffective disorder diagnosed patients underwent a neurofeedback training. Patients with an age range between 18 - 65 years have been randomly assigned to the treatment or the placebo group. Our design was scheduled with 16 training sessions starting and ending with a collection of questionnaires.
Results: We will present preliminary data of neurofeedback-trained schizophrenia patients and healthy control subjects. In controls, we generally found an unspecific habituation effect that lowered the N100 amplitude over time. Several subjects were able to compensate for this habituation with help of the given neurofeedback. In patients, a similar picture has been seen. On the behavioral level, one of the subjects in the training group reported that the negative impact of the voices decreased even further two weeks after the training.
Discussion: The training results of the healthy controls points at an important role of habituation in neurofeedback training on sensory ERP components. The patient data suggests that the chosen intervention may interact with AVH, but larger case numbers are necessary to draw well justified conclusions.

T221. Impact of psychosocial interventions on caregiver burden of schizophrenic outpatients. A systematic review of randomized controlled trials

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Background: Schizophrenia is a chronic disease that poses an important impact the family members and caregivers. These adverse consequences have been measured in studies of family/caregiver burden and it is expected that psychosocial interventions might reduce family burden. We systematically reviewed randomized controlled trials to evaluate the effectiveness of psychosocial interventions in reducing family burden of schizophrenia
Methods: A systematic review (following PRISMA Statement) of the main international databases, without language or period restriction, up to November 2015. Search terms: schizophrenia, caregiver, burden, outpatients, interventions, caregiving, treatment, psychoeducation. Inclusion criteria: randomized controlled trials (RCT), outpatients, use a rating scale or questionnaire designed to measure burden. Exclusion criteria: other trials (e.g., non-Randomized, observational, ongoing etc.). RCTs that used other rating scales, to indirect measure burden (e.g., quality of life scales, expressed emotion interviews
Results: Sixteen trials fulfilled our inclusion/exclusion criteria. They comprised 1341 individuals, 750 in the experimental, 591 in the control group. Sample size varied between 29 and 225 caregivers. Studies were conducted in the USA ($n = 1$), Italy ($n = 2$), Spain ($n = 2$), China ($n = 4$), Iran ($n = 4$), Pakistan ($n = 1$), India ($n = 1$) and Chile ($n = 1$). The mean age of the patients varied from 25 to 35 years, they had the diagnosis of schizophrenia (with one exception, DSM-IV). Duration of disease varied between 6 and 21 years. Most of the trials included as caregiver one family member (usually the mother); their age mean varied between 32 and 55 years. Caregivers spent between 7 hours/day and 35 hours/week with the patient. Randomization was described in 11 trials and blinding, in 6 studies. Instruments used to measure burden: Burden Assessment schedule (BAS), Caregiver Burden Scale (Zarit), Experience of Caregiving Inventory (ECI), Family Burden Interview Schedule (FBIS), Social Behaviour Assessment Schedule (SBAS), Family Burden Questionnaire (FBQ), Pai and Kapur Interview Schedule and Family Problems Questionnaire (FPQ).
Different methods of psychoeducation (including lectures, videos, booklets) was used in 10 trials, 5 trials combined psychoeducation with support groups and 1 trial applied Yoga. The duration of the intervention varied from 4 weeks to 12 months, usually once a week. The design of the trials usually included a baseline measure and a second measure at the end of the trial, 5 studies did a third evaluation 12 months after the end of the intervention, 3 studies after 18 months and 2 studies after 24 months. Control group is described as 'routine care' (psychiatric consultation for medication control) or 'waiting list'. In all trials, the intervention group obtained a statistically significant reduction of burden in comparison to control group.
Discussion: Our review suggests that psychosocial interventions are effective in reducing the burden of caregiving in schizophrenia. This reduction of burden lasted for 12 and 18 months after the end the intervention. Nevertheless it has to be considered that there are few RCTs on this subject and they usually are of relatively poor quality. The

use of 'routine care' as control group creates an unfair comparator to the intervention groups. More, well designed studies are needed to evaluate the impact of interventions in family burden of schizophrenia

T222. Comparing the efficacy of two types of cognitive remediation in schizophrenia: results from a two-site retrospective cohort study.

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Background: Cognitive remediation (CR) for schizophrenia uses a variety of methods that differ in terms of approach (computerized, paper and pencil), type of assistance (therapist-assisted, computer-assisted, unsupervised), and targeted domains. Here, we compared the impact on cognitive and clinical outcomes of two CR programs with similar duration and intensity: an unsupervised, computerized auditory targeted cognitive training (TCT) that was shown to improve global cognition and verbal learning and memory, and a therapist-assisted, paper and pencil, cognitive remediation therapy (CRT) that was shown to improve working memory, cognitive flexibility, negative and disorganized symptoms. We investigated whether these two interventions generated similar magnitudes of cognitive and clinical improvements.
Methods: Data were merged from two published RCTs. We compared 46 participants with schizophrenia who completed 50 hours of TCT, and 43 participants who completed 40 sessions of CRT. The cognitive outcome measures that could be compared between datasets were verbal fluency (Verbal Fluency Task FAS), verbal working memory (Letter Number Test), speed of processing and executive functioning (Trail Making Test A and B). Neither of the two cognitive remediation approaches was developed to specifically target these domains. For these variables, T scores were calculated using means and standard deviations from published normative data stratified by age and education. PANSS scores were coded using the Van Den Oord 6 factor solution. To determine statistically significant differences in cognitive and clinical outcomes, we conducted ANCOVAs on the post-treatment scores, with pre-treatment scores as covariates and group as an independent variable. Within-group effect sizes were computed by calculating the bias-adjusted standardized mean difference (Hedges'g). To examine whether gains between the two groups were statistically different, effect sizes were compared using Hedges'g confidence intervals.
Results: The two groups were matched on age, gender, education, and chlorpromazine equivalents. CRT participants had worse baseline speed of processing and executive functioning, compared to those in TCT. There were no statistically significant differences between cognitive improvements induced by TCT and CRT. Effect sizes were slightly larger for CRT (g = .17-.39) than for TCT (g = .13-.16), but their confidence intervals significantly overlapped. There were significant differences in clinical outcomes between TCT and CRT when adjusting for the baseline covariate. Although confidence intervals for effect sizes were not significantly different between the two groups, CRT improved negative symptoms (g = .28) and amotivation (g = .37), whereas TCT did not induce significant changes.
Discussion: Unsupervised TCT and therapist-assisted CRT induced similar cognitive improvements in the domains that were available for investigation, with small-moderate effect sizes. Since pre-treatment cognitive impairments may influence the response to different CR programs, we suggest that CR be tailored to the cognitive profile of each individual. When possible, multiple options should be offered to individuals with schizophrenia, according to their needs and goals. Therapist-assisted CRT induces improvements in negative symptoms and motivation, two critical domains for functional recovery in schizophrenia. Unsupervised TCT can be delivered remotely and implemented for individuals with schizophrenia who live in under-resourced areas and cannot reach mental health clinics, and for those who do not approach these treatment settings because of mental health stigma.

T223. Preliminary evidence for impaired object recognition as a neural correlate of visual derealisation phenomena in first episode schizophrenia patients

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Background: Perceptual closure, the ability to recognize an image based on partial information, and disturbances of self awareness (self-disorders, SDs), are important features of schizophrenia. The link between these two aspects has not been studied yet. We hypothesized that the generation of event-related potentials associated with perceptual closure (ERPs: P100, and Ncl) is impaired in first-episode schizophrenia patients (FEP), and that this deficit is associated with visual aspects of SDs in this group. The present research investigated perceptual closure in FEP, and the relationships between ERPs components and visual aspects of SDs, addressed by the Examination of Anomalous Self-Experience interview (EASE).
Methods: Nineteen FEP and twenty age and gender matched healthy controls were stimulated with images with different levels of fragmentation according to the Ascending Method of Limits (AML). Generators underlying perceptual closure were analyzed using source localization (Brain Electrical Source Analysis software: BESA). ERPS of first-episode schizophrenia patients were compared to those of healthy controls by t-test for independent groups. Relationships between SDs visual factors and ERP components were analyzed through the Spearman's correlation coefficient
Results: The amplitudes of P100 and Ncl components were significantly reduced in patients relative to controls ($F = 4.22$, $P < 0.05$; $F = 10.28$, $P < 0.05$ respectively), and the latency of Ncl component was significantly longer in patients ($F = 4.49$, $P < 0.05$). The EASE visual factor "distance to the world" was significantly correlated with the amplitude values of the Ncl component in patients ($P < 0.05$).
Discussion: The perceptual closure deficit in FEP might be associated with a subtype of derealisation phenomena characterized by visual experiences of being more distant to the world. Further research to confirm these findings is needed.

T224. Differences between patients with schizophrenia and unaffected controls in computationally derived acoustic phonetic parameters and measures of lexical variation and idea density

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Background: In recent years, computerized analysis of the speech of patients with schizophrenia has been shown to be a promising and objective means of evaluating both negative symptoms and language disturbances. In this study, funded by the U.S. National Institute of Mental Health (NIMH), we examined differences between patients and controls in a number of computationally derived linguistic parameters.
Methods: We collected diverse audiorecordings of spoken language (i.e., first, describing a line drawing; second, talking about a "perfect, most ideal day"; third, speaking about "the scariest, most frightening experience you've ever had"; fourth, reading aloud a neutral text passage; and fifth, reading aloud an emotionally stimulating text passage) from 98 patients and 102 controls, drawn from diverse sites in Washington, D.C. and New York City. We also measured IQ and neurocognition, and among patients, we collected extensive clinical phenotypic data with regard to negative symptoms and disorganization.

Results: Analyses pertaining to phonetic parameters (e.g., pitch variability, mouth opening variability, tongue movement variability, and "fraction voiced" or the amount of speaking (as opposed to pauses) during the recordings) revealed differences between patients and controls in specific measures. Furthermore, measures of lexical variation (moving average type-token ratio) and idea density also uncovered significant differences between the two groups.
Discussion: Patients with schizophrenia differ from unaffected controls in a number of computationally derived linguistic parameters that relate to both negative symptoms and disorganization.
Research such as this could represent a step toward developing new methods for measuring and tracking negative symptom severity and disorganization using computationally derived linguistic indices.

T225. Unawareness and misattribution of symptoms in schizophrenia: relationship with symptom clusters and socio-demographic variables

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Background: Previous studies suggest that poor insight in psychosis is not related or only modestly related to the severity of symptoms, leading to the conclusion that insight could be an independents phenomenological feature of schizophrenia or may have a non-linear relationship with symptoms severity. So far, little is known about insight into particular psychotic symptoms, whereas symptoms are different in nature and might be influenced by different socio-cultural, neurobiological or psychological factors.
The aim of this study is to describe and deeply explore the relationship between insight and psychopathology -considering the classical multiple dimensions of insight as well as unawareness and misattribution into particular symptoms - in a sample of schizophrenic patients.
Methods: A multicenter cross-sectional naturalistic study of 248 schizophrenic patients (180 men and 68 women) from different clinical settings was undertaken. Severity of psychopathology was assessed using Positive and Negative Syndrome Scale (PANSS) and Lindenmayer's Factors -Positive, Negative, Cognitive, Depressive and Excitement- were obtained. The deficit of insight and its three dimensions of awareness – of illness, of effects of medication, of social consequences- and the awareness and attribution of each different symptom were evaluated by the Scale of Unawareness of Mental Disorders (SUMD).Functionality was measured by GAF Scale. Pre-morbid IQ was estimated by verbal subscale of WAIS.
Stepwise regression models were performed including all the socio-demographic and clinical variables that were significant at the bivariant analysis.
Results: Conversion of the SUMD score of symptoms into dichotomic categories (aware or partial aware / unaware) shows that a high number of patients express some awareness of symptoms like hallucinations (62%), poor control of aggressive impulses (62%), apathy (76%), anhedonia (62%), attention problems (76%), and poor social relationships (70%); but few patients are total or partial aware of their delusion (37%), unusual appearance (28%), poor social judgment (34%) or unusual eye contact (37%).
General insight dimensions showed small significant correlations with positive, cognitive and excitement factors of psychopathology; whereas these symptom factors showed higher correlations with unawareness of particular psychotic symptoms (ranging from r = 0,2 to r = 0,4) as well as with the total unawareness of symptoms dimension (r = 0,3; $P < .000$)
Significant covariant variables were age, gender, IQ, inpatient vs outpatient and the positive, negative, cognitive and excitement factors.
Regression models showed a small significant predictive value of positive and cognitive symptoms in the three main insight dimensions as well as a moderate one in the prediction of awareness of particular symptoms.
Misattribution of symptoms seems to be independent from symptom severity and other psychosocial and clinical variables.
Discussion: Insight in schizophrenia is a multi-phased phenomenon that is more than "just psychopathology" and that the awareness of particular symptoms is the dimension most highly influenced by clinical severity. Symptoms have different degrees of opacity to awareness.
The positive and cognitive psychopathological factors are the most strongly linked to the phenomenology of insight, supporting the neuropsychological view of insight. The consistently reported relationship between insight and negative symptoms does in fact refer to cognitive aspects of negative symptoms rather than to affective ones such as emotional withdrawal or blunted affect.
Our results support findings reporting a lack of relationship between insight and depressive symptoms.

T226. Stress in those at risk for psychotic disorder: a possible role for momentary stress in the exacerbation of affective and psychotic symptoms.

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Background: Increased sensitivity to daily life stressors has been found in patients with psychotic disorder, as well as in individuals at (clinical high) risk for psychosis. Furthermore, recent studies with individuals at clinical high-risk for psychosis (CHR) have reported impaired tolerance and increased functional impairment in response to normal stress compared to healthy controls and higher self-reported psychosocial stress levels compared to first-episode psychosis patients, suggesting impaired stress tolerance is characteristic of CHR state.
Aim of this study was to further examine the association between momentary stress and both affective and psychotic symptoms in everyday life of CHR patients, compared to chronic psychotic patients and healthy controls, in search for evidence of early stress-sensitization.
Methods: The experience sampling method (ESM) was used to measure affective and psychotic reactivity to everyday stressful activities, events and social situations in 22 CHR patients, 24 chronic psychotic patients and 26 healthy controls. The data was analyzed in STATA with multivariate multilevel models, an extension of standard hierarchical linear models when analyzing multiple (correlated) outcomes. Models were fitted separately in the three groups (i.e., psychotic patients, CHR patients, and controls). To test whether the degree of association (i.e., correlation) between two outcomes differed between the groups at the beep level, the estimated correlations with their corresponding standard errors were extracted and entered in Wald-type tests.
Results: Levels of negative affect (NA) and momentary psychotic symptoms were similar in both patient groups. Additionally, group comparisons showed the association strength between NA and activity-related stress to be larger for CHR patients than for psychotic patients (0.1558 vs. 0.2764, $Z = -2.67$, $P = 0.008$), and larger for CHR compared to controls (0.2764 vs. 0.1128, $Z = 3.68$, $P = 0.0002$). Similarly, the association strength between activity-related stress and psychotic symptoms was larger in CHR than in patients (0.1357 vs. 0.2404, $Z = -2.29$, $P = 0.02$).
Discussion: The results suggest that those at CHR for psychosis are more sensitive to daily life stressors, in particular activity-related stress, than psychotic patients. Emotional and psychotic stress sensitization seems to occur prior to the development of a full-blow psychotic state and to play a role particularly in the early phase of the illness. These findings underscore the need for early intervention in CHR patients to help them to learn how to better cope with stressors and in turn lower both emotional and psychotic reactivity to these stressors.

T227. Reliability and validity of the Korean version of the motivation and pleasure scale-self report (MAP-SR), a self-report measure of negative symptoms

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Background: The Clinical Assessment Interview for Negative Symptoms (CAINS) is an empirically developed interview measure of negative symptoms in psychotic disorders. The Motivation and Pleasure Scale-Self-Report (MAP-SR) is a self-report measure that assesses the motivation and pleasure domain of negative symptoms based on the CAINS. This study examined the reliability and validity of a Korean version of the MAP-SR.
Methods: One hundred thirty nine patients with schizophrenia completed the 18-item MAP-SR, the CAINS, the Scale for the Assessment of Negative Symptoms (SANS), Brief Psychiatric Rating Scale (BPRS), Calgary Depression Scale for Schizophrenia (CDSS) and other measures of trait and cognitive function.
Results: Excluding poorly performed three items, the revised 15-item MAP-SR demonstrated good internal consistency and convergent validity with the clinician-rated Motivation and Pleasure scale of the CAINS as well as anhedonia/avolition subscale of the SANS. The scale also showed good discriminant validity, with little association with psychotic symptoms, agitation/mania and depression/anxiety. MAP-SR scores were related to Behavioral Activation System scales for trait measure and verbal fluency for cognitive measure.
Discussion: The Korean version of the MAP-SR is a promising self-report measure for examining severity of negative symptoms in schizophrenia.

T228. Experiences of antipsychotic treatment in clinical recovery from first episode psychosis

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Background: Recent studies have raised questions about the benefits, costs, safety and effectiveness of antipsychotic drugs. Further broad exploration of these issues is required, and must include the service user perspective. This explorative study investigates the experiences of 20 service users, all in symptomatic and functional remission, of using antipsychotic medications during and after a first episode of psychosis.
Methods: Thematic analytic approach within an interpretative-phenomenological framework. Analysis followed an established meaning condensation procedure.
Results: Main themes: (1) Use of antipsychotic drugs beyond the acute phase – Considered to compromise the contribution of individual effort in recovery; (2) Non-stigmatizing environments perceived to increase likelihood of successful use; and (3) Prolonged use of antipsychotic drugs perceived to reduce likelihood of functional recovery. Minor themes: (4) Trustful relationships considered more important than antipsychotic drugs; (5) Antipsychotic drugs reduce mental chaos during the acute phase; and (6) Antipsychotic drugs regulate mood swings and prevent further episodes of psychosis in cases of affective psychosis with mood incongruent psychotic symptoms.
Discussion: In this study, participants described acute phase anti-psychotic treatment as mostly advantageous, but costs were often seen as outweighing benefits with continued use beyond this stage. Echoing recent longitudinal study findings, this calls into question the position of continued maintenance treatment with antipsychotic drugs as the global, gold standard long-term treatment of psychosis. Findings clearly emphasize the need for a collaborative approach, involving service users in decisions concerning antipsychotic drug use, to be integrated across all phases of care.

T229. Paranoia and facets of self-esteem in early psychosis: associations across psychometric and real-life assessment methods

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Background: Paranoia and self-esteem have been widely associated in the literature; however, the precise nature of their association remains unclear. The present study investigated in a sample of at-risk mental state (ARMS) and first episode of psychosis (FEP) patients whether (i) global and specific facets of self-esteem (positive and negative self-beliefs) show differential associations with paranoia, and (ii) whether such distinction holds for momentary (Experience Sampling Methodology; ESM) and psychometric measures of trait self-esteem and paranoia.
Methods: 53 ARMS and 33 FEP patients were administered the Rosenberg Self-Esteem Scale (RSES) and the Positive and Negative Syndromes Scale (PANSS). Participants also received personal digital assistants that signaled them randomly eight times daily for one week to complete questionnaires about their thoughts, feelings, behaviors, and psychotic-like symptoms (momentary or ESM-paranoia and self-esteem measures).
Results: ESM-paranoia was inversely associated with ESM positive self-beliefs and positively associated with ESM negative self-beliefs in both groups. It was not associated with global ESM self-esteem in either of the two groups. ESM-paranoia was also inversely associated with total RSES in FEP patients, whereas a trend was present in ARMS patients. When the RSES facets were considered separately, ESM-paranoia was inversely associated with RSES positive self-beliefs in the ARMS group (the FEP group showed a trend), and positively associated with RSES negative self-beliefs in the FEP group. Finally, paranoia as assessed by the PANSS was inversely associated with total RSES in ARMS, but not FEP, patients. Likewise, PANSS paranoia showed an inverse association with RSES positive self-beliefs and a positive association with RSES negative self-beliefs in the ARMS group.
Discussion: ESM and questionnaire assessments of self-esteem and its facets showed distinct patterns of associations with momentary paranoia and clinician ratings of paranoia. It has been proposed that different assessment methods may tap different aspects of the self (e.g., ESM assessments would tap the "experiencing self" while psychometric measures would tap the "believing self"). The findings suggest that taking into account these different aspects of the self, as well as the different facets of self-esteem, is relevant for increasing our understanding of the role of the self in paranoia. Furthermore, delineating how these constructs are associated across the psychosis continuum is relevant for identifying risk factors and targets for intervention efforts.

T230. An embedded, embodied, enactive account to psychosis

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Background: Subjective experiences are the core of psychiatry. Patients suffer from feeling depressed, anxious or paranoid, they hear voices or see things that others cannot see. In this paper, I will argue that in order to make real progress in our understanding of psychopathology and more importantly in the development of new treatments, we need to put these experiences back at the core of our research rather

than moving away from them (for example as is being proposed in the RDOC criteria).
Methods: Within the field of Cognitive Science, an embedded, embodied, enactive approach to cognition and experience has been developed, which states that experiences can only be understood through studying how they arise out of interaction with the environment. I will apply this approach to the study of psychotic symptoms by using the Experience Sampling Method (ESM). ESM is a structured diary technique that allows assessing experiences as well as context in the realm of daily life. It is therefore ideally suited to examine psychopathological experiences from a person-environment interaction perspective.
Results: In this paper, I will discuss how interactional changes over time may be associated with moment-to-moment variation in psychopathology. For example, affective/subjective factors such as an increase in anxiety or the experience of subjective stress have been associated with increased levels of psychotic symptoms. Similarly, situational factors, such as social context (being with unfamiliar compared to being with familiar people) and lack of sleep have been associated with increased levels of paranoia. Secondly, I will provide two examples of newly developed real-life interventions that specifically focus on altering person-environment interactions, possibly fundamentally improving our clinical practice.
Discussion: The embedded, embodied, enactive approach may aid in improving our understanding of psychopathology. It provides a conceptual framework for a better understanding of existing data as well as for formulating new and possibly more accurate hypotheses. The picture that is emerging is that of psychopathology as a specific pattern of thoroughly context-sensitive interaction, related to but differing from non-pathological interaction. Following this approach may not only prove theoretically fruitful but might also have considerable applicable clinical benefits.

T231. The differences between individuals with persistent and non-persistent psychotic-like experiences: a follow-up study in the general population of Hong Kong

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Background: Psychotic-like experiences (PLEs) are poorly-understood phenomena referring to subclinical psychotic experiences that are reported by individuals without psychotic disorder. Most PLEs are transient, while persistent PLEs might increase the risk of developing psychosis. Examining the trajectory of PLEs and studying the differences between individuals with and without persistent PLEs could provide important insights on the development of psychosis as well as the significance of PLEs. Thus, the current study aims to: 1. explore the trajectory of PLEs over two years in the general population of Hong Kong; and 2. examine the difference of subjects with or without persistent PLEs in terms of demographics, mental health and neurological functioning.
Methods: Current on-going study is a 2-year follow-up on the participants who reported PLEs in the Hong Kong Mental Morbidity Survey 2010(HKMMS) – an epidemiological study carried out between 2010 and 2013 which targeted at general population aged 16-75 years old. The inclusion criteria were: 1. Participated in the HKMMS; 2. Endorsed one or more items in Psychotic Screening Questionnaire (PSQ); 3. No known psychotic disorder. 174 out of 5719 subjects of the HKMMS were eligible to take part in the current study.
PLEs were assessed by PSQ, where subjects endorsing one or more items at both baseline (HKMMS) and follow-up (current study) were considered as having persistent PLEs. Depression and anxiety symptoms (Hospital Anxiety and Depression Scale), social and occupational functioning (Social and Occupational Functioning Assessment Scale) as well as perceived social support of the subjects were also measured (Multidimensional Scale of Perceived Social Support).
Results: In the first 100 subjects, 63 (63%) were female, aged from 18-72 years (mean = 45.27, SD = 14.88). Mean years of education was 13.09 (SD = 5.05). 49/100 (49%) subjects had persistent PLEs at follow-up (endorsed ≥ 1 PSQ items at baseline and follow-up). It was found that subjects with persistent PLEs (PP) at follow-up endorsed significantly more PSQ items at baseline than the non-persistent subjects (NP) ($U = 950.50$. $P < 0.05$).
Baseline demographics were compared between PP and NP subjects. PP subjects were significantly older ($t = 0.98$, $P < 0.05$) than NP subjects. No significant difference were found in years of education ($t = -2.57$, $P = 0.25$), gender ($\chi 2 = 1.16$, $P = 0.28$) and immigrant status ($\chi 2 = 1.69$, $P = 0.28$).
Mental health related factors were also compared between PP and NP subjects. At follow-up, there were significant differences between the two groups in social and occupational functioning ($t = -1.14$, $P < 0.01$; PP < NP), depression symptoms ($t = 4.37$, $P < 0.05$, PP > NP) and anxiety symptoms ($t = 4.37$, $P < 0.05$, PP > NP) scores. There were no significant difference found in these factors at baseline. No significant difference of social support was found between the two groups at both time points.
For neurocognitive tests, PP subjects performed significantly worse in digit-symbol coding test ($U = 757.00$, $P < 0.01$), arithmetic ($U = 816.50$, $P < 0.05$) (WAIS-III) and verbal fluency ($U = 266.50$, $P < 0.01$) at follow-up.
Discussion: The number of PSQ items endorsed seems to affect the persistence of PLEs over two years' time. Differences in mood between PP and NP suggest potential link between mood, PLEs and development of psychosis. Also, despite being healthy, PP subjects seems to have some impairment in terms of mental health and neurological functions. Further investigation will be carried out to find out whether specific types of PLEs are more predictive of persistence than others, as well as exploring the potential relationship between persistent PLEs and impairment in mental health and neurological functioning.

T232. The course of acoustic verbal characteristics over time

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Background: Clinicians mainly deal with negative auditory verbal hallucinations (AVH). However, the majority of voice hearers have positive and useful AVH too. Assessment of the latter two is mandatory because of their clinical implications. Useful voices need to be cherished and fearing the loss of positive voices may cause patient drop-out. Because of these implications we studied the course over time of positive and useful AVH.
Methods: During 4 months all consecutive referrals to a psychiatric Out-Patient Department (OPD) were assessed for psychiatric diagnosis (DSM-IV-TR), AVH bij means of the AVHRS and PUVI.
AVH (Auditory Verbal Hallucinations Rating scale) is a structured 16-item interview. Inter-rater agreement scores (Cohen's kappa coefficients) are 0.84 and 0.88 respectively, internal consistency scores (Cronbach's alpha coefficients) 0.84 and 0.77).
PUVI (Positive and Useful Verbal hallucinations Inventory) is a 53-item self-report AVH inventory designed to assess socio-demographics and psychopathology (8 items), prevalence, course and characteristics of positive and useful AVH (15 items), and emotional attribution (9 items). Its internal consistency is good (Crohnbach's alpha = 0.925 for positive and 0.889 for useful voices).
Descriptive statistics, Chi-square tests, Mann-Whitney U tests and logistic regression models were used to analyze the data. For all tests, a two-tailed significance level of $P < 0.05$ was used.
Results: •One-hundred and sixty-six subjects (Ss) were included, thirteen Ss (7.8%) were excluded because of missing data leaving 153 patients for statistical analysis. Mean age was 38.41 years (S.D. = 13.3). Seventy-seven Ss (50%) had ever heard voices.
• Content of voices changed over time in 52% of the voice hearers.
Positive and negative AVH: 10% changed from positive towards negative, 20% from negative to positive, 22% changed in positive as well as negative voices,
Useful AVH: no change occurred in 67%, voices became not-useful in 12%,
not-useful voices became useful in 21%.
• Voice hearing subjects attributed changes in their voices to: social circumstances (15%), voice induced circumstances (8%), and treatment (77%).

• Command hallucinations commanded to: (i) commit suicidal behavior (52%), (ii) physically assault others (40%), (iii) stop talking about the voices (37.5%)
• AVH had (i) a trauma (35%) or sexual abuse related content (46%), (ii) were punitive (71%), (iii) sounded like the offender's voice or had (iv) the same gender as the offender (59%).
Discussion: This study shows that voice-characteristics change over time in a substantial number of voice hearers.
Positive voices have been reported in 35 to 75 percent of voice hearers depending on diagnosis and setting of the Ss. Assessment of positive voices is mandatory for two reasons. First, positive voices may be used against negative ones. Second, Quite a few patients fear that therapy may result in disappearance of these voices. It appeared that change in positive content occurred in 50% of the Ss.
Useful voices have been found in over forty percent of voice hearers. They may improve self-care and compliance. Changes were found in 33% of the Ss.
The clinical impact of these changes warrants further study.

T233. Quetiapine ER versus aripiprazole in children and adolescents with psychosis □ the randomised, blinded clinical tolerability and efficacy of antipsychotics (TEA) trial.

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Background: The evidence for choices between antipsychotics for children and adolescents with schizophrenia and other psychotic disorders is limited. The main objective of the TEA trial was to compare the benefits and harms of treatment with quetiapine extended release (ER) versus (vs) aripiprazole in children and adolescents with psychosis.
Trial registration: ClinicalTrials.gov: NCT01119014
Methods: The TEA trial is a Danish investigator-initiated, independently funded, multi-centre, blinded, randomised clinical trial (RCT). Patients aged 12-17 years with non-organic psychosis; antipsychotic-naïve or minimally treated were 1:1 randomised to a 12-week, double-blind intervention with quetiapine ER 600 mg/day vs aripiprazole 20 mg/day. Benefits and harms were assessed 2, 4, and 12 weeks after randomisation. The primary outcome was change in the positive symptom score of the Positive and Negative Syndrome Scale (PANSS). Key adverse outcomes were weight change; homeostatic model assessment of insulin resistance; akathisia (Barnes Akathisia Scale); and sedation (UKU (udvalget for kliniske undersøgelsesmetoder) side effects rating scale).
Results: Patients ($n = 113$), 82% with schizophrenia, 30% males, mean age 15.8 years (SD 1.36) were randomised, $n = 55$ to quetiapine ER and $n = 58$ to aripiprazole. There was no significant group difference on mean PANNS positive score after 12 weeks of intervention, but a significant effect of time for the whole group. The comparison on the four key adverse effect outcomes showed that the mean weight increased over time and more so with quetiapine ER than with aripiprazole. Insulin resistance was higher with quetiapine ER than with aripiprazole. Akathisia was more frequent with aripiprazole than with quetiapine ER. Frequency of sedation were similar between groups. There were no group differences on additional efficacy outcomes (PANSS negative, general, depressive or total symptoms; Global Assessment of Psychosocial Disability; Clinical Global Impression-Severity/Improvement; suicidality; or response-rates). Additional adverse outcomes showed more neurologic, autonomic, and total adverse reactions with aripiprazole than with quetiapine ER. More pronounced changes in metabolic variables were observed with quetiapine ER. There were no group differences on the counts of serious adverse reactions, serious adverse events, or adverse events.
Discussion: This RCT comparing quetiapine ER versus aripiprazole for early onset psychosis found no differences on the changes of PANSS positive symptoms. Akathisia was more frequent with aripiprazole, while weight increase and insulin resistance were higher with quetiapine ER. Additional analysis showed no group differences on other psychopathology and functional outcomes, but more neurologic, autonomic and total adverse reactions with aripiprazole, while metabolic variables increased more with quetiapine ER.

T234. Adolescent cannabinoid exposure increases the susceptibility for a schizophrenia-like phenotype in a novel rodent model

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Background: Schizophrenia is a debilitating disorder that affects over one percent of the population. Adolescent cannabis abuse is associated with an increased risk of developing schizophrenia. However, this is not a causal relationship as many adolescents use cannabis in a recreational setting and do not develop psychiatric illnesses. Thus, it is likely that cannabinoids increase the risk of developing schizophrenia only in individuals with an underlying predisposition. To explore this phenomenon, we have developed a model of "susceptibility" to schizophrenia-like symptoms. Specifically, the second filial (F2) generation of a developmental rodent model of schizophrenia [i.e. gestational methylazoxymethanol acetate (MAM) administration] show increased susceptibility to a schizophrenia-like phenotype. We believe that this "F2 MAM" model is unique in that it provides a model of susceptibility by which we can examine potential gene x environment interactions as they pertain to schizophrenia. Based on the relationship between cannabinoids and schizophrenia, we hypothesized that cannabinoid exposure during adolescence would increase the proportion of 'susceptible' F2 generation MAM rats displaying a schizophrenia-like phenotype while having no observable effects in control animals.
Methods: F2 MAM and F2 SAL rats were exposed in adolescence (postnatal days 35-45) to either a vehicle control or the synthetic cannabinoid WIN55,212-2 (0.2 mg/kg, i.p., 5 injections). In adulthood (postnatal days 70+) rats were tested at the behavioral (stimulant-induced hyperlocomotion), electrophysiological (extracellular dopamine recordings in the ventral tegmental area of anesthetized rats), and molecular (parvalbumin expression in the ventral hippocampus) levels.
Results: Our data shows that exposure to 0.2 mg/kg WIN55,212-2 during adolescence increases the proportion of 'susceptible' F2 MAM displaying a schizophrenia-like phenotype without producing noticeable deficits in control rats. Specifically, F2 MAM rats treated with 0.2 mg/kg WIN55,212-2 in adolescence (F2 MAM x WIN) show an increase in spontaneously active dopamine cells per vertical electrode track through the ventral tegmental area. Cells per track are as follows: F2 SAL x Veh had 1.134 ± 0.08 cells per track, F2 SAL x WIN had 1.084 ± 0.09 cells per track, F2 MAM x Veh had 1.319 ± 0.14 cells per track, F2 MAM x WIN had 1.642 ± 0.12 cells per track. A locomotor test revealed F2 MAM rats exposed to WIN during adolescence are more sensitive to a low dose of amphetamine (0.5 mg/kg, i.p.) than their F2 MAM x VEH and F2 SAL counterparts. Additionally, adolescent WIN treatment caused a decrease in ventral hippocampal parvalbumin expression which we have previously demonstrated to contribute to the aberrant dopamine system function observed in rodent models.
Discussion: Here we report on a novel model of schizophrenia susceptibility and demonstrate that this model is indeed sensitive to cannabinoid exposure during adolescence. Moreover, the locus of this affect may be the inhibitory parvalbumin containing interneurons in the ventral hippocampus. The F2 MAM rat may therefore be a useful model for exploring gene/environmental interactions as they pertain to schizophrenia.

T235. Potential drug-drug interactions in Mexican patients with schizophrenia.

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Background: Schizophrenia is a mental and chronic disease with a worldwide prevalence of approximately 1%. About 20-50% of patients with schizophrenia will not respond to the antipsychotic medication. Therefore, the use of multiple antipsychotics is a common practice in schizophrenia when a single drug doesn't relieve symptoms satisfactorily. Consequently, drug-drug interactions become inevitable. Thus, the aim of this study was to observed potential drug-drug interactions medications prescribed to Mexican schizophrenia patients.
Methods: We performed a retrospective and transversal study carried out in a clinic of the psychiatry. Only prescription of patients with schizophrenia with diagnoses based in DSM-IV was included in this study. The Drug Interactions Checker software was used in this study to analyze the potential drug-drug interactions. We also classified the potential drug- drug interactions by severity level and finally we analyzed the potential drug-drug interaction effect.
Results: Eighty six of one hundred twenty six patients were at risk of potential drug-drug interactions. Haloperidol and Biperiden was the most common drug pair of two hundred thirty two pairs observed. 13.8% of the drug-drug interaction showed major level of severity, whereas an 83.2% was moderate. Finally, the Central nervous System depression and anticholinergic effects were the principal's possible effect of drug- drug interaction.
Discussion: In the article, we detected a high number of patients with schizophrenia to be received two or more drugs. The potential drug-drug interactions observed in Mexican population are consistent with the prescription the concomitant use of antipsychotics, benzodiazepines and antidepressants in schizophrenia that could give a central nervous systems depression and anticholinergic effect. The drug-drug interaction could be considered when the patient with schizophrenia is prescript.

T236. The effects of positive allosteric modulator of α7 nicotinic receptors on cognitive and sensorimotor gating deficits in a schizophrenia-like model in rats.

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Background: Despite the urgent need, there is no effective treatment for cognitive deficits which are recognised as a core future of schizophrenia. Hence, the development of new treatments for these impairments are a research priority. Among the most promising targets for improving cognitive functions are alpha 7 nicotinic acetylcholine receptors (α7 nAChRs). α7 nAChRs are involved in the regulation of cognitive processes but also are associated with the pathophysiology of schizophrenia. Much of preclinical data indicated that orthosteric agonist produced procognitive effect, but their clinical efficacy in schizophrenic patients is equivocal. Positive allosteric modulation (PAM) is an alternative way to activate the α7 nAChRs. Based on the functional properties of modulation, α7 PAMs are divided into two groups, type I and type II. Both appear to increase receptor sensitivity to endogenous agonist. However, type I PAMs have little or no effect on desensitization processes, while the action of type II PAMs is accompanied by a retardation of the kinetics of desensitization. PNU12596 is one of the recently synthesized PAMs type II and its behavioural activity has not been yet extensively characterised. Thus, little is known about the potential efficacy of this compound on cognitive processes, particularly in the context of schizophrenia-like models. The aim of the current study was to evaluate the efficacy of PNU 120596, type II of α7 nAChRs PAMs, in reversing deficits of sensorimotor gating, attention, impulsivity and working memory (WM), which are all deficient in schizophrenia patients
Methods: Three cohorts of rats were tested in either the prepulse inhibition of startle response test (PPI), discrete paired-trial delayed alternation task in a T-maze or five choice serial reaction time task (5CSRTT). PPI is the reduction of rat's body response to an intense acoustic stimulus, when this stimulus is immediately preceded by a stimulus of lower intensity. In the 5CSRTT rats were required to correctly identify brief, flashing light, randomly presented in one of five apertures, in order to receive a food reward. Before each presentation of the stimulus, there is interval wherein the animal must withhold responses, and any responding during this period is recorded as a failure of inhibitory control (premature responses). The percent of correct choices and the percent of omissions was considered as a measure of attention while number of premature responses served as measure of impulsivity. The latency to respond reflects the speed of processing. In the discrete paired-trial delayed alternation task in T-maze rats are presented with a sequence of randomly chosen forced runs, each followed by a free choice run to find a food reward according to the non-match to sample rule. The percent of correct choices offers a measure of WM. Schizophrenia-like deficits in rats were evoked by administration of the NMDA receptor antagonist, MK-801.
Results: The present studies revealed that acute administration of PNU120596 (3 mg/kg) diminished PPI impairments in MK-801-based model. In addition, compound (in the same dose) was effective in reversing MK-801-evoked WM deficits, as assessed in a discrete paired-trial delayed alternation task. However, neither disturbed attention nor increased premature responses were counteracted by PNU120596 in 5CSRTT.
Discussion: The present study demonstrates the beneficial effects of type II α7 nAChRs PAM on sensorimotor gating and working memory in rats. Therefore, our results support the notion that α7 nAChRs allosteric modulation, may constitute a potential procognitive therapy in schizophrenia.
This study was supported by the Polish National Science Centre grants Opus 2012/07/B/NZ7/01150 and Preludium 2014/15/N/NZ7/02978.

T237. DRD2 co-expression network and a related polygenic score predict brain activity, behavioral phenotypes and treatment response linked to schizophrenia.

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Background: Genetic variants related to the dopamine D2 receptor gene DRD2 are associated with schizophrenia and its imaging phenotypes. However, genes do not work in isolation and DRD2 is likely part of a co-regulated genetic pathway associated with systems-level brain function. Here, we aimed at demonstrating that a co-expression gene set including DRD2 indexed by genetic markers is associated with prefrontal activity during working memory (WM) in healthy subjects (HC) and patients with schizophrenia (SZ) as well as with antipsychotic treatment response.
Methods: We used post mortem prefrontal (Brodmann Area 46) mRNA expression levels available in Braincloud dataset to run a weighted transcriptome wide co-expression network analysis. First, we identified a DRD2 co-expression gene set functionally enriched for schizophrenia. Second, we identified SNPs associated with the first principal component of the gene set co-expression matrix. Effects of these SNPs were summarized onto a polygenic score (PGS). With this aim, Sensitivity Index (D') of the Signal Detection Theory was computed for each SNP genotype distribution compared against major allele homozygous distribution of the same SNP. Thus, D' values were averaged within subjects to obtain the PGS, which was tested in a replication sample (Braineac). Then, we investigated association of the PGS with brain activity during WM performance in two independent samples of HC (discovery, $N = 124$; replication, $N = 244$) and in 29 SZ who performed the n-back task. We also tested association of the PGS

with antipsychotic treatment response as measured with PANSS in a sample of SZ treated with olanzapine in monotherapy ($N = 47$) as well as in a placebo-controlled cross-over double-blind study in SZ on atypical antipsychotics ($N = 40$).
Results: Gene set encompassed 85 genes and included 6 genes associated with schizophrenia in the Psychiatric Genomic Consortium study (hypergeometric test, $P = 0.0073$). We found 8 SNPs associated with gene set co-expression (FDR < 0.25).The PGS correlated with DRD2 gene set expression in both microarray samples (discovery, $R2 = 0.38$, $P = 3.6 \times 10\text{-}22$; replication, $R2 = 0.053$, $P = 0.05$). Predicted greater DRD2 gene set co-expression was associated with greater prefrontal activity. In the discovery imaging sample on healthy subjects we detected bilateral clusters in the superior and middle frontal gyri encompassing prefrontal cortex (BA 9/10/46) serving topological FDR corrected $P < 0.05$. In the replication sample, we found correlation between the PGS and signal change values extracted from the same clusters (corrected $P = 0.029$). In patients, clusters localization largely overlaps with that found in the discovery sample. Moreover, PGS was associated with a WM efficiency index (accuracy/reaction time). ANCOVA with LOAD (1-back, 2-back) as the within factor and efficiency index as the dependent variable showed a PGS × LOAD interaction ($P = 0.037$). Post-hoc regression yielded a significant fit for 2-back ($R2 = 0.035$, $P = 0.023$). Finally, PGS was associated with clinical improvement in terms of PANSS total score improvement in both datasets ($\rho = 0.39$, $P = 0.007$; $\rho = 0.27$, $P = 0.047$).
Discussion: Predicted greater DRD2 co-expression was associated with greater prefrontal activity, lower WM efficiency index and greater treatment response. We successfully replicated our findings in independent datasets. This study provides evidence that gene network of DRD2 modulates schizophrenia related phenotypes at the levels of brain circuits, behavior and clinical outcome. The molecular pathway co-regulated with DRD2 suggests novel potential entry points to target treatment of systems-level phenotypes and symptoms associated with schizophrenia risk.

T238. The effect of antipsychotic type and dose changes on dyskinesia and Parkinsonism in patients with a serious mental illness (SMI)

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Background: Despite the introduction of Second Generation Antipsychotics (SGAs) medication induced movement disorders are still highly prevalent. The two most common are parkinsonism and tardive dyskinesia. Current treatment recommendations for these disorders include lowering antipsychotic dose and switching to an SGA. However the efficacy of these treatments has not yet been studied in patients with severe mental illness (SMI).
Methods: An 18 year prospective study including all 223 SMI patients receiving care from the only mental-health service of the previously Dutch Antilles. Eight clinical assessments focused on movement disorders and medication use. Parkinsonism was scored on the Unified Parkinson's Disease Rating Scale (UPDRS) and dyskinesia on the Abnormal Involuntary Movements Scale (AIMS). Antipsychotics were classified into both FGA/SGA and high/low D2 affinity categories, the effect of switching within each category on subsequent movement scores was calculated separately by using time-lag multilevel logistic regression models (hereafter: the FGA/SGA-switch model and D2-affinity switch model).
Results: At baseline, the mean age was 50 years, 72% was male, and 80% had schizophrenia as a primary diagnosis. Average antipsychotic defined daily dose (DDD) was 2.09 (1.81 -2.32), which increased with each progressive time point. The mean prevalence of tardive dyskinesia and parkinsonism was 54 and 35%, respectively, with an average severity, for cases, of 9 points on the AIMS and 19 points on the UPDRS. Both disorders displayed a relapsing remitting course.
The (time-lag multilevel) regression models yielded significant coefficients, between a reduction in dyskinesia severity and starting/switching to an FGA ($B = -3.54$, $P < 0.001$), as well as starting/switching to a high D2 affinity antipsychotic ($B = -2.48$, $P < 0.01$); only in the FGA/SGA model adding an SGA to existing FGA treatment had a significant relationship with dyskinesia severity reduction ($B = -2.43$, $P < 0.01$). In the parkinsonism analyses stopping antipsychotics ($B = -7.76$, $P < 0.01$, FGA/SGA-switch model; $B = -7.73$, $P < 0.01$, D2-affinity switch model) was significantly associated with a reduction on the UPDRS; in the D2-affinty model there was also a significant relationship between an increase in parkinsonism severity and starting a high D2- affinity antipsychotic (3.29, $P < 0.05$, D2-affinity switch model).
Discussion: The results show that switching from an FGA to an SGA does not necessarily result in a reduction of dyskinesia or parkinsonism. Our study indicates that only stopping all antipsychotics reduces (the severity of) parkinsonism, and starting an FGA or a high D2-affinity antipsychotic may reduce (the severity of) dyskinesia in the next 1 -2 years.

T239. Treatment with antipsychotics in late-life schizophrenia

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Background: Very few studies are published on the treatment of schizophrenia in older patients. The only randomised controlled trials in older patients that have been published are in early-onset schizophrenia patients (EOS). RCTs in Late Onset Schizophrenia (LOS, first symptoms after 40 years) and Very Late Onset Schizophrenia-like Psychosis (VLOS, first symptoms after 60 years) are lacking. However, case series suggest that patients with LOS and VLOS may be effectively treated with lower doses of antipsychotics than EOS with the same age.
Methods: All patients with schizophrenia, admitted to an inpatient ward for older patients (55 years and older) with psychotic disorders between March 2011 and August 2013, were asked to participate in this study. The class (typical, atypical, clozapine) and dose (haloperidol equivalents) of antipsychotic agent were the primary outcome variables.
Results: We included 44 patients; 14 with EOS (8 male and 6 female, aged 65.6 ± 7.6 years), 17 with LOS (3 male, 14 female, aged 66.4 ± 7.3 years) and 13 with VLOS (5 male, 8 female; aged 74.8 ± 12.5 years).
There was no significant difference in antipsychotic class, but no VLOS patient received clozapine, in contrast to the EOS and LOS groups. The VLOS group received a lower dose of haloperidol equivalents compared to the EOS group, but this difference was not statistically significant (2.9 ± 2.4 mg. versus 5.0 ± 3.1 mg.; $P = 0.061$). There was no difference in dose between LOS and EOS patients (5.1 ± 3.9 mg. versus 5.0 ± 3.1 mg.; $P = 0.972$).
Discussion: VLOS patients were treated with a lower dose of haloperidol equivalents compared to EOS patients, but the difference of 2 mg/day was not statistically significant. This may be due to a lack of power. However, suboptimal treatment may also explain the differences in dose and in the lack of prescribing clozapine. Studies in LOS/VLOS patients that assess both efficacy (decrease in PANSS score) and side effects are necessary.

T240. Clinical and functional response to paliperidone palmitate in early schizophrenia – a retrospective observational study in newly diagnosed patients treated over a 12-month period

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Background: Data on clinical outcomes with long-acting antipsychotic treatment in young, newly diagnosed patients with schizophrenia is sparse.
Objectives: To explore hospitalization, drug utilization and clinical outcomes from medical records of newly diagnosed schizophrenia patients during the first 12 months of treatment with once-monthly paliperidone palmitate (PP).
Methods: International, multicenter, retrospective, observational study. Outcomes presented here: baseline (BL) characteristics and

demographics, clinically relevant improvements in disease severity (ie ≥20% decrease in PANSS or BPRS total score or CGI-S Change ≥-2 or CGI-C ≥3, with no score showing worsening) and clinically relevant functional improvement (ie change in PSP total score ≥+7 points or change in GAF total score ≥+20 points, with no score showing worsening) from BL to last-observation-carried-forward endpoint (LOCF-EP) within 12-month documentation period, mean mode PP dose and adverse drug reactions.
Results: 84 patients analyzed: 69% male, mean age at initiation of PP was 24.1(SD2.7) years, Mean BL weight was 78.7(SD16.0)kg and 80.0 (SD14.7)kg at LOCF-EP, with a mean change of 1.2(SD3.9)kg; mean time from first psychotic episode to initiation of PP was 5.5 (SD3.3) months. At LOCF-EP 86.6% achieved a clinically relevant improvement (71/84, Kaplan-Meier median time from initiation of PP: 52.4 days). 63.4% achieved a clinically relevant functional improvement (52/84, Kaplan-Meier median time from initiation of PP: 53.1 days). PP mean mode maintenance dose was 96.4(SD19.8) mg. ADRs reported in ≥5% of patients were weight increase 9.1% and hyperprolactinemia 5.7%.
Discussion: Treatment with once-monthly PP was well tolerated and associated with clinically relevant improvements in disease severity and functioning in young, newly diagnosed schizophrenia patients.

T241. Effectiveness of antipsychotics used in first episode psychosis: a naturalistic cohort study

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Background: Continuous antipsychotic treatment for at least one year from symptom remission is an arguable gold standard following a first episode of psychosis. Whilst a range of antipsychotics used in routine practice have demonstrated similar clinical efficacy in first episode, understanding which are most likely to be continued may better inform prescribing practice and offer comparative effectiveness evidence incorporating efficacy, tolerability and other complex qualitative factors.
Methods: A retrospective, cohort study examined the naturalistic 1-year treatment of all patients accepted by early intervention in psychosis services across 7 sites in Sussex, Coventry and Warwickshire, UK, between February 2009 and February 2012. Electronic case notes and clinical files of patients were examined from the point of treatment initiation to any-cause discontinuation or for a period of one year (which ever occurred sooner). Kaplan-Meier survival analysis and a Cox-proportional hazards regression model were used to determine and compare the median survival time and rate of discontinuation at one year for the different treatment groups.
Results: Out of 460 patients prescribed treatment, 61 were prescribed Aripiprazole, 185 prescribed Olanzapine, 116 prescribed Quetiapine and 88 prescribed Risperidone. The greatest risk of treatment discontinuation was in the first 3 months of treatment for all medications. Risperidone had the longest median time to discontinuation at 165.0 days (95% CI 97.1-232.9) followed by Quetiapine with 135.0 days (95% CI 77.6-192.4), Aripiprazole with 118.0 days (95% CI 63.0-173.0), and Olanzapine with 109.0 (95% CI 85.4-132.6) days. Highest rates of discontinuation by one year were seen with Olanzapine (140/179, 78.2%) and Aripiprazole (43/56, 76.8%), followed by Quetiapine (74/107, 69.2%) and Risperidone (53/80, 66.3%), after excluding missing variables. There was only a significant difference between Risperidone and Olanzapine on log rank pairwise comparison of survival distribution between medications ($\chi^2 = 4.34$; $P = 0.037$). Covariate analysis revealed a significant effect of duration of untreated psychosis and geographic location on survival distribution, although these factors did not appear to influence overall antipsychotic group effect. Reasons for discontinuation were most commonly poor patient adherence (without clear association with adverse effects) and lack of efficacy. Specific adverse events causing discontinuation differed by medication, and followed established literature.
Discussion: This inclusive study suggests that of all antipsychotics currently used clinically in the UK at this time, risperidone has greater effectiveness than olanzapine as measured by median survival time to all cause discontinuation, in the treatment of first episode psychosis. Our findings may influence clinicians' first prescribing decisions. Reasons for discontinuation are complex but appear most frequently not clearly associated with medication properties, highlighting the importance of collaborative decision making with the patient and adherence orientated interventions.

T242. A systematic review and meta-analysis of treatments for clozapine-induced obesity and metabolic syndrome: evidence from randomised-controlled trials

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Background: Average life expectancy in people with schizophrenia is about 20 years shorter than the general population – this difference is largely attributed to increased mortality from chronic physical conditions such as heart disease and diabetes mellitus (Saha *et al.*, 2007). Cardiometabolic complications such as weight gain, obesity, metabolic syndrome and diabetes mellitus are well recognized side effects of antipsychotics particularly the atypicals which are widely used today (De Hert *et al.*, 2011).
Clozapine is generally regarded as the most efficacious antipsychotic drug (Leucht *et al.*, 2013), but has been associated with the highest risk for developing obesity and metabolic complications compared with other atypical antipsychotics (Allison *et al.*, 1999; Bodén *et al.*, 2013; Gianfrancesco *et al.*, 2002). It is estimated that the prevalence of metabolic syndrome in long-term clozapine users ranges from 28 to 45% (Bai *et al.*, 2011; Bodén *et al.*, 2013). Clozapine is the gold standard for managing treatment-resistant schizophrenia, which comprises approximately 25% of all patients with this condition (Brenner *et al.*, 1990). Clozapine is the only antipsychotic approved by the US Food and Drug Administration (FDA) for treatment-resistant schizophrenia (Novartis, 2002). Similarly, the UK national institute for health and care excellence (NICE) recommends clozapine as the treatment of choice for patients who do not respond to two antipsychotics (NICE, 2014). Clinicians, therefore, are faced with a difficult choice between efficacy and long-term cardiometabolic complications when choosing clozapine. We present a systematic review and meta-analysis of pharmacological and non-pharmacological treatments for clozapine-induced obesity and metabolic syndrome.
Methods: Two researchers independently searched PubMed and Embase for randomised controlled trials (RCTs) of treatments for clozapine-induced obesity or metabolic syndrome. All other types of studies were excluded. We only included RCTs where more than 50% of participants were taking clozapine.
Results: We identified 13 RCTs. Effective pharmacological treatments for clozapine-induced obesity and metabolic syndrome include metformin, aripiprazole, and Orlistat (in men only). Meta-analysis of three studies showed a robust effect of metformin in reducing body mass index and waist circumference but no effects on blood glucose, triglyceride levels, or HDL levels. In addition, there is limited evidence for combined calorie restriction and exercise as a non-pharmacological alternative for the treatment of clozapine-induced obesity, but only in an in-patient setting. Rosiglitazone, topiramate, sibutramine, phenylpropanolamine, modafinil, and atomoxetine have not shown to be beneficial, despite reports of efficacy in other populations.
Discussion: Randomised-controlled trial data supports the use of metformin, aripiprazole, and Orlistat (in men only) for treating clozapine-induced obesity. Calorie restriction in combination with an exercise programme may be effective as a non-pharmacological alternative. Findings from trials in different populations should not be extrapolated to people being treated with clozapine. Further trials focusing on clozapine-induced obesity and metabolic syndrome are needed.

T243. A novel KV3 positive modulator augments rodent prefrontal fast network oscillations *in vitro* following sub-chronic PCP treatment.

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Background: Cortical networks produce synchronized fast network oscillations in the beta (20-30 Hz) and gamma (30-80 Hz) frequency band that are critical for a range of different cognitive functions. Numerous studies have shown that this neuronal network activity is orchestrated by GABAergic inhibitory mechanisms. Within this context, perisomatic targeting fast-spiking parvalbumin-containing (PV+) interneurons are capable of sustaining action potential output in the gamma frequency range. PV+ interneurons entrain the population of cortical pyramidal neurons via gamma frequency inhibition. Previous studies in patients suffering from schizophrenia (1) and putative animals models (2) of the condition demonstrate an inability of cortical networks to generate coherent gamma frequency oscillations. The Kv3-family of potassium channels, including Kv3.1, are selectively expressed in PV+ interneurons in the cortex. Kv3 channels allow fast-spiking PV+ interneurons to fire accurately at high frequencies to orchestrate the activity of cortical networks. Such high rates of firing, with high temporal accuracy, are required for the generation of gamma rhythms. Post-mortem studies using cortical tissue obtained from patients with schizophrenia report reductions in PV+ and in the expression of Kv3.1 channels in the remaining PV+ interneurons.
Methods: For in vitro slice experiments from drug naïve rats slices were obtained from male Lister Hooded rats (2 months old), whereas for chronic PCP slices 60 female Lister Hooded rats were used for these experiments. Rats were housed in groups of 3 under standard laboratory conditions under a 12hr light: dark cycle, lights on at 0700hr. Behavioural testing and slice preparation were carried out in the light phase.
Results: Targeting Kv3 channels, and enhancing the activity of PV+ interneurons, has potential as a pharmacological treatment for schizophrenia. We have, therefore, examined the effect of a novel Kv3 modulator (AUT00206) in an established pre-clinical model of schizophrenia. We first used sub-chronic treatment of rats with phencyclidine (PCP) (2 mg/kg, i.p. twice daily for 7 days) to confirm that a significant deficit in the novel object recognition (NOR) task ($n = 24$ animals; $P < 0.05$) could be achieved. Prefrontal cortex slices containing the prelimbic (PrL) and infralimbic (IL) subregions were then prepared from PCP and vehicle treated rats that had undergone behavioural testing. Fast network oscillations were elicited by the application of carbachol (10 microM) and kainate (200 nM) in slices from PCP and vehicle treated animals. The amplitude of fast network oscillations in recordings in PCP treated PrL ($n = 7$) and IL ($n = 6$) slices were significantly increased following the application of AUT00206 (10 microM; Prl, 1.73 ± 0.72 μV2 v. 2.49 ± 1.03 μV2; IL, 0.55 ± 0.2 μV2 v. 0.74 ± 0.34 μV2). In comparison in slices taken from saline treated animals which showed no cognitive deficit ($n = 22$ animals; $P > 0.05$), in the NOR behavioural task application of AUT00206 (10 microM) had no effect on the fast network oscillation power in either the PrL (1.51 ± 0.3μV2 v. 1.32 ± 0.5 μV2; $P > 0.05$, $n = 6$) or IL (0.25 ± 0.1 μV2 v. 0.21 ± 0.1 μV2; $P > 0.05$, $n = 3$) subregions.
Discussion: In summary these results demonstrate that AUT00206 significantly increases the power of fast network oscillations in the PrL and IL subregions of the rat medial prefrontal cortex only in slices obtained from sub-chronic PCP treated rats which have also shown a robust cognitive deficit in the NOR behavioural task. Our results suggest that, modulation of Kv3 channels by this novel modulator, may have the potential to correct disruptions in neuronal synchronization in schizophrenic patients by augmenting gamma frequency oscillations.

T244. The effect of cumulated estrogen exposure and other female hormonal events on clinical trajectories and antipsychotic response in postmenopausal schizophrenia women

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Background: Estrogens have a positive influence on mental health and antipsychotic response in schizophrenia women, and may confer a protection against the onset of the disorder between puberty and menopause. The loss of estrogens in the menopausal period would imply a high vulnerability for psychotic relapses, poor outcomes and the need of higher doses of antipsychotics. However, the relationship between cumulative estrogen exposure and clinical trajectories has been poorly studied. We aimed to investigate potential symptomatic domains of antipsychotic response in postmenopausal schizophrenia women, and correlate female reproductive events with clinical outcomes.
Methods: Sixty-one postmenopausal schizophrenia women (DSM-IV-TR) were included in a 12-week prospective observational study. Menarche age, menopause age and other female hormonal factors were recorded. Duration of reproductive years (menopause age-menarche age) was considered as an indirect measure of lifetime cumulated exposure to estrogens. Psychopathological assessment included the Positive and Negative Syndrome Scale (PANSS; 5-factors), the Personal and Social Performance Scale (PSP) and the Clinical Global Impression-Schizophrenia (CGI-SCH). Response was defined as a reduction of $\geq 30\%$ of PANSS total scores. Antipsychotic compliance was assessed by plasma level monitoring. First analysis: (Responders vs. Non-responders): Analyses of Covariance (ANCOVA) and non-parametric tests when necessary. The association between reproductive factors and clinical variables were investigated by using partial correlational analyses.
Results: 39 patients (63.9%) were antipsychotic responders. Non-responders had higher scores in the PANSS cognitive subscale ($P = 0.017$) and a tendency toward higher negative symptoms. Responders needed higher doses of antipsychotics ($P = 0.045$) and showed a higher improvement in CGI-SCH positive subscale ($P = 0.005$). When corrected for influencing factors, responders showed higher improvement in the PANSS excitement subscale ($P = 0.20$) compared to improvement in terms of the other four subscales (e.g. positive, negative, depressive, cognitive). Later menarche tended to be positively associated with number of psychotic episodes ($P = 0.07$) and cumulative estrogen exposure was negatively correlated with higher duration of first-episodes ($P = 0.06$). No other correlations were found between cumulated estrogen exposure and improvement in the five PANSS factors.
Discussion: To our knowledge, this is the first study to highlight the clinical relevance of the excitement dimension in antipsychotic response among postmenopausal schizophrenia women. A shorter interval between menarche and menopause would be associated with higher duration and number of psychotic episodes, which is line with the estrogen protection hypothesis.

T245. Clinical risk factors associated with clozapine induced neutropenia

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Background: Clozapine is the only drug with established efficacy in treatment-resistant schizophrenia.

The use of clozapine is limited due to the occurrence of the rare but life threatening adverse event of agranulocytosis, an event which occurs in approximately 0.8% of clozapine users. In all cases this is preceded by a drop in neutrophil count, which triggers cessation of clozapine treatment. Further, neutropenia can occur during clozapine treatment, which can also necessitate the discontinuation of clozapine.
We currently do not know how clozapine causes these adverse reactions, but the risk appears to be greatest within the first 18 weeks of treatment. Not all risk factors are the same for agranulocytosis and neutropenia; this implies that there may be distinct mechanisms for the two.
The sociodemographic characteristics associated with CIA and neutropenia, along with their incidence is reasonably well established. However, there is little epidemiological research into clinical factors which may impact on this risk. The use of concurrent medication and the risk for the development of CIA and neutropenia has not been examined in a large cohort of patients.
Methods: The principal objective of this research is to examine and identify clinical risk factors associated with the onset of clozapine induced agranulocytosis (CIA) and neutropenia (CIA). A retrospective review of electronic health records was undertaken. The utlilised the Case Register Interactive Search (CRIS) system, which has been developed to allow for the search and retrieval of anonymised electronic clinical records of patient data within SLaM.
All patients who discontinued Clozapine due to a neutropenic event were included for analysis. Patients with a reference to word "red" or "neutropenia" not in a context of a neutropenic event were excluded. A control sample was constructed from all patients with a documented Clozapine exposure at the time of the Clozapine neutropenic event of the case patient.
Results: 101 cases and 101 controls were included in this study.44% ($n = 44$) developed neutropenia within the first 6 months of clozapine treatment, 16% during 6–12 months of treatment, and 40% after one year of treatment
We found significant associations between Clozapine associated neutropenia and the concurrent use of Sodium valproate when adjusted for age and ethnicity (Odds ratio (OR) 1.98, 95%CI: 1.02-3.86; $P = 0.043$). A dose dependent relationship between Clozapine associated neutropenia and higher doses of sodium valproate was also significant. (OR-12.26, CI:-1.77-84.89 $P < 0.011$).
We also observed an inverse relationship between Clozapine dose and risk of developing Clozapine associated neutropenia within the first month of clozapine use (T = -1.642, $P = 0.001$). A higher risk of Clozapine associated neutropenia was seen in younger patients (OR 0.93, CI 0.91-0.96, $P < 0.001$), and especially in those aged 17-29 (OR 11.13, CI 2.05-60.5, $P < 0.001$) when compared to those aged >50. The risk of neutropenia was also increased in those of black ethnicity (59.4%) compared to (31.0%) in controls (OR 2.80, CI 0.90-8.71; $P = 0.04$).
We found that 55% of our 55 patients those who were re-challenged were unsuccessful and had a second neutropenic event. This was more common in patients of white ethnicity (53%) compared to black ethnicity (40%)(x2 = 5.420, $P = 0.026$*).
Discussion: This is the first case-control study, and largest study to identify an association between clozapine associated neutropenia and the concurrent use of sodium valproate. We recommend that consideration for the discontinuation of sodium valproate be made prior to the initiation of Clozapine. Patients should be also considered for re-challenge if the first neutropenic event was deemed to be sodium valproate related.

T246. Screening for antipsychotic drugs which do not interact with monoamine receptors

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Background: Phenotypic screening approaches have proven successful in delivering first-in-class drugs. The current project used SmartCube®, a state-of-the-art behavioral primary screening platform in mice, to discover new potential treatments for psychiatric indications (Alexandrov *et al.* 2015, Eur J Pharmacol). We used SmartCube® as the starting point for an exploratory phenotypic screening approach in which we generate in vivo signatures of molecules without any a priori biological constraints. Instead, the criteria for compound selection were CNS drug-like properties *in silico*, manual selection by experienced CNS chemists, and availability of sufficient high-grade powder from our compound library. Compounds with a desired in vivo profile were then screened in vitro for absence of binding to monoamine receptors. To confirm their psychoactive profile, compounds were tested in our rodent pharmacological MRI (phMRI) platform. The pattern of brain activity induced by novel compounds was assessed by arterial spin labeling (ASL) MRI and compared to those patterns elicited by known antipsychotics chosen from our reference database (Bruns *et al.* 2015, Neuroimage).
Methods: Compounds were tested in C57/Taconic mice in SmartCube® 15 min after acute i.p. dosing. The behavioral signatures were calculated by a proprietary algorithm using a reference compound database. The in vitro binding profile of the compounds was assessed for dopamine, serotonin and adrenergic receptors. For phMRI, compounds were administered acutely via the i.p. route in Sprague Dawley rats; after 30 min the animals were lightly anesthetized with isoflurane and submitted to MRI acquisition. Using continuous ASL, changes in blood perfusion, a surrogate for changes in neural activity, was measured in more than 60 brain regions-of-interest (ROI) and these were compared to those elicited by typical and atypical reference antipsychotics (Bruns *et al.* 2015, Neuroimage) using multivariate analysis.
Results: Testing for significant behavioral activity in SmartCube gave a hit rate of approximately 20%. One of these hits was identified as a starting point for a program, because of its attractive SmartCube profile (antipsychotic-like without side-effects across a large dose range), phMRI pattern (atypical antipsychotic-like) and lack of inhibition of monoamine receptor binding. This hit was expanded into a series which was further optimized for antipsychotic-like properties using SmartCube as the primary screen. For selected compounds, the antipsychotic-like signature in SmartCube was generally confirmed in the reference system used for multivariate profiling phMRI.
Discussion: Screening and optimizing, using the in vivo SmartCube platform as primary screen and an in vitro target panel as the secondary screen, has led to the identification of compounds with antipsychotic-like properties, in the absence of effects on monoamine receptors. Using multivariate profiling of phMRI activation patterns as a secondary unbiased platform, provided additional confidence in the antipsychotic-like properties of these compounds. This approach suggests that it is possible to engineer serendipity into phenotypic screening and to integrate this into rational drug design.

T247. Inhibition of PDE1 leads to memory improvement in animal models related to cognitive symptoms of schizophrenia via enhancement of dopamine D1 receptor signaling

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Background: Cognitive dysfunction in schizophrenia is believed to result - at least in part - from prefrontal dopaminergic hypo-functionality resulting in insufficent dopamine D1 receptor signaling. D1 receptors are stimulatory Gs coupled receptors which activate adenylyl cyclase resulting in the increased synthesis of cAMP. Phosphodiesterase-1 (PDE1) hydrolyzes both cAMP and cGMP and is expressed in cortical and striatal areas of the brain at which it is suggested to play a role in D1 receptor signaling (Duinen *et al.*, 2015). Thus, in the present study, co-localization studies by immunofluorescence staining of PDE1 and D1 receptor were performed using rat and human brain section. Additionally, the impact of PDE1 inhibition on brain cAMP/cGMP elevation was studied as well as its behavioral consequences in animal cognition tasks. Further experiments are underway to evaluate the interaction of PDE1 and D1 receptor

mechanistically in prefrontal cortical slices by electrophysiology and to assess the impact of PDE1 inhibition on attentional performance.
Methods: Rat and human brains tissues fixed with formalin were sliced for double immunofluorescence staining using antibodies for PDE1B, D1 receptor and pre-/post-synaptic markers. Analysis of staining was performed by confocal microscopy. Potency of the PDE1-inhibitor (PDE-I: WO2013/192556) was determined in PDE assays using recombinant human PDE1A, 1B and 1C expressed in a baculoviral system. Interaction of PDE1 and D1 receptor on neuronal transmission was assessed by using extracellular recordings from layer 5 of rat prefrontal slices. Adult male mice were administered with the PDE-I, and the increase of cAMP/cGMP was determined in prefrontal cortex via ELISA technique. Memory performance was tested in the mouse T-maze continuous alternation task after administration of the PDE-I, and attention was assessed in the rat 5-choice serial reaction time task.
Results: Double immunofluorescence analysis revealed co-localization of PDE1 and D1 receptors in neurons of prefrontal and other cortical areas of rat and human brain. PDE-I showed almost equally high potency on PDE1A, 1B and 1C (IC50 = 31-75 pM), and PDE-I administration to mice led to a dose-dependent increase of cAMP and cGMP in the prefrontal cortex. Regarding cognition, PDE1 inhibition showed efficacy in terms of reversal of MK-801 induced memory impairment in the mouse T-maze alternation test.
Discussion: As demonstrated in this study, PDE1B is co-expressed with D1 receptors in neurons of the prefrontal cortex, which indicate an involvement of PDE1B in regulating D1 receptor signaling by modulating cAMP levels. Indeed, cAMP but also cGMP levels in the prefrontal cortex were increased after treatment with the PDE1 inhibitor, and memory performance could be improved in a working memory task (T-maze) which is related to prefrontal cortical function. Thus, our data further support the use of PDE1 inhibitors as potential approach for the treatment of disorders with cognitive dysfunction such as schizophrenia.
References:
1. Duinen *et al.* (2015), Curr. Phar. Des. 21, 3813-3828.

T248. Informing clinicians, patients and guidelines. Network meta-analysis on 24 antipsychotic drugs and a broad range of important outcomes for schizophrenia - a protocol

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Background: The evidence base concerning differences between individual neuroleptic drugs is sparse. Network meta analysis provides the possibility to rank individual drugs for efficacy, tolerability and acceptability domains.
Methods: We developed a protocol to do a network meta analysis examining twelve second- and twelve first-generation antipsychotic drugs in acute treatment of schizophrenia. Included studies must be randomized and at least single blind. Data sources will be the Cochrane Schizophrenia Group's specialized register, MEDLINE, EMBASE, CENTRAL, ClinicalTrials.gov and the FDA website, supplemented by requests to study authors. Outcomes will be overall efficacy (primary outcome), responder rates, drop-out rates, positive, negative and depressive symptoms, quality of life, and side-effects. Data extraction will be done by two persons independently.
Results: After elimination of duplicates or search yielded 16419 hits. Outcomes are currently extracted.
Discussion: Our final results will expand the evidence base for the treatment of schizophrenia. Especially the huge amount of tolerability and acceptability data presented will help to find the best drug for the individual patient.

T249. Effects of N-acetylcysteine in schizophrenia-like behaviors induced by a progressive regimen of amphetamine sensitization in mice

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Background: A process of 'endogenous sensitization' is thought to drive the mesolimbic dopamine hyperfunction that underlies psychotic symptoms in schizophrenia patients. This sensitization is the basis for the enhanced striatal dopamine release in response to an acute amphetamine challenge observed in such patients. The heightened sensitivity to amphetamine can be modeled in rodents by repeated exposure to psychostimulants, resulting in a long-term sensitization where increased behavioral response to the drug is observed at a subsequent exposure. N-acetylcysteine (NAC) has been proposed as an adjunctive treatment for neuropsychiatric disorders and assessed in several clinical trials, including in patients with schizophrenia. Given the relevance of antioxidant, anti-inflammatory and glutamate-modulating properties for schizophrenia, we here explored the potential of NAC in the context of early intervention. We used amphetamine sensitization in an escalating dose protocol proposed to mimic the graded progression from the prodromal state to full-blown schizophrenia. This protocol leads to changes that resemble several of the neurochemical findings observed in patients with schizophrenia and at-risk subjects.
Methods: Amphetamine was administered to adult male C57BL/6 mice three times per week during 3 weeks; the dose was weekly increased from 1 to 3 mg/kg. NAC (60 mg/kg) was given immediately before saline or amphetamine during the second and third weeks. All solutions were injected intraperitoneally. Latent inhibition (conditioned active avoidance in a two-way shuttle box) and locomotor response to amphetamine challenge were assessed after 4 weeks of washout.
Results: The progressive amphetamine regimen disrupted latent inhibition and induced locomotor sensitization to an amphetamine challenge. NAC disrupted latent inhibition in control animals, and failed to prevent the amphetamine-induced disruption. In sensitized animals, NAC attenuated the enhanced locomotor response to amphetamine.
Discussion: NAC administered along with amphetamine partially protected against the locomotor effects induced by amphetamine sensitization. Glutamate pathways are involved in the neurochemical mechanisms that underlie sensitization, since activation of NMDA receptors is required for inducing sensitization. NAC increases extrasynaptic glutamate by activating the cystine-glutamate antiporter, resulting in stimulation of metabotropic glutamate receptors 2/3 that inhibit synaptic glutamate release. This glutamate modulation mechanism might account for the protective effects of NAC against the locomotor effects of amphetamine sensitization. NAC lacks acute effects when administered before amphetamine or MK-801 challenges, which suggests that NAC is more effective in counteracting the long-term adaptations induced by repeated psychostimulant administration than as a classic antipsychotic in an animal model of positive schizophrenia symptoms. However, data from a range of doses and administration intervals is needed before a definitive conclusion can be reached. We have previously shown that NAC prevents the increased sensitivity to amphetamine in social isolation-reared mice. This study complements that data and supports the idea that NAC may be useful in preventing the neurochemical changes that are thought to precede full-blown schizophrenia. Given this protective effect is especially relevant to at-risk subjects, and considering the safety profile of NAC, clinical trials are warranted.

T250. Pattern of antipsychotic prescription among patients with schizophrenia at a Nigerian neuropsychiatric hospital

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Background: Psychotropic medication have been identified as a key component in the management of patients with schizophrenia.

Several psychotropic medication as well as other medication are available for use to patients with schizophrenia both as over-the-counter and prescription. It has been widely documented that indiscriminate use of medication particularly antipsychotic medication has the potential to result in unpleasant side effects and has been implicated in poor adherence to treatment regimen. Coupled to this is the enormous cost that may arise from such inconsiderate prescriptions, particularly in an environment where most of payment for healthcare is out-of-pocket. This study set out to examine the pattern of antipsychotic medication use among patients with schizophrenia at a Nigerian Neuropsychiatric hospital.
Methods: The study which was part of a larger study was a descriptive cross-sectional study. Three hundred and seventy consecutive clinic attendees with a Diagnostic and Statistical Manual of mental disorders (DSM-IV) diagnosis of schizophrenia confirmed with the Structured Clinical Interview for DSM-IV axis I disorders (SCID-I) and aged between 18 and 64 years of age were recruited at the outpatient clinic of the Federal Neuropsychiatric Hospital, Yaba, Lagos. The respondents were interviewed using a questionnaire that assessed socio-demographic and clinical variables. A medication use recall questionnaire assessed medication use recall in the 24- hour period prior to data collection as a predictor of medication use behavior. Monotherapy was defined as a single antipsychotic medication, whereas polypharmacy was defined as having two or more antipsychotics. Data was analyzed using SPSS-20 to generate frequency tables. Ethical approval was sought from the health research and ethics committee of the study centre while a written informed consent was obtained from each subject that participated in the study.
Results: The mean age of patients was 37.87 (SD = 11.24), with a male to female ratio of 1:1. The mean (SD) age at onset of mental illness was 26.46 (SD = 7.84) years. The average monthly cost of treatment was 19.86 US Dollars, while the median monthly income was 500 US Dollars. Only about a fifth (18.4%) of the respondents were directly responsible for paying for their treatment despite 45.7% of them being employed. The most common route of administration of antipsychotic medication was oral (52.5%). One hundred and eighty three (49.5%) of the respondents were on monotherapy, 47% were on a combination of oral and depot medication, while about a fifth (21.4%) of them were on a combination of both typical and atypical medication and 53.5% were on only typical medication. The average number of medications taken on a daily basis was 2.4 (SD = 1), while the mean medication use recall score was 69.4%. The most common depot preparation was fluphenazine decanoate. About a third (33.8%) of the respondents experienced various types of medication side effects with 15.9% of all the patients experiencing extrapyramidal side effects.
Discussion: The finding in this study suggests that physicians in our environment have a slightly high preference for polypharmacy, although it is known that other factors such as response to treatment may account for this. Additionally, conventional antipsychotics are still commonly used in this environment which isn't surprising considering the socioeconomic circumstances of majority of the patients. It is however important to consider the limitations of this study while interpreting observations.

T251. Treatment-resistant schizophrenia: simple pairwise and network meta-analysis of all antipsychotics

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Background: Although clinicians often deal with patients suffering from refractory forms of schizophrenia, an up-to-date systematic review and meta-analysis on the effects of the various antipsychotic drugs in treatment-resistant schizophrenia is not available; the last one, already fifteen year-old, was by Chakos *et al.* (2001) concluding that clozapine -the gold standard- was more efficacious and better tolerated than first-generation antipsychotics (FGAs) such as haloperidol and chlorpromazine. But given the restrictions of clozapine's use due to its many side-effects and in light of a continuously increasing number of new randomized controlled trials (RCTs) on other antipsychotics, we decided to perform simple pairwise and network meta-analysis (NMA) of all antipsychotics in treatment-resistant schizophrenia.
Methods: We searched Medline, Embase, Biosis, PsycINFO, Pubmed, the Cochrane Central Register of Controlled Trials, WHO International Trial Registry and ClinicalTrials.gov. At least two independent reviewers selected published and unpublished blind RCTs and extracted all data. The primary outcome was efficacy as measured by mean overall change in symptoms of schizophrenia. Secondary outcomes were mean change in positive and negative symptoms, categorical response to treatment, dropouts due to any reason and due to inefficacy of treatment, and important adverse events. We also assessed the effect of potential moderator and quality variables on the primary outcome by several meta-regression, subgroup and sensitivity analyses. All analyses were performed in a Bayesian setting.
Results: This was the first and large (40 RCTs, 5172 patients) meta-analysis of blind trials on treatment resistant schizophrenia applying the modern methodology of NMA. For the primary outcome, in the pairwise meta-analysis, only olanzapine was significantly better than haloperidol (SMD -0·29, 4 RCTs, $n = 693$). In the NMA, olanzapine was significantly more effective than quetiapine (SMD -0·29), haloperidol (-0·29) and sertindole (-0·46); clozapine was more effective than haloperidol (-0·22) and sertindole (-0·40); and risperidone was more effective than sertindole (-0·32). Few significant differences were found among antipsychotics in the remaining outcomes. Altogether, there was a certain pattern of superiority for olanzapine, clozapine and risperidone which were significantly better than other antipsychotics in various efficacy outcomes such overall and positive symptoms, response rates and drop-outs due to inefficacy, but the results were not consistent and the effect sizes were small. The most surprising finding was that clozapine was not significantly better than most other drugs in both the pairwise and the NMA.
Discussion: There is at present insufficient evidence on which antipsychotic drug is more efficacious for patients with treatment-resistant schizophrenia. Clozapine's superiority over FGAs has been repeatedly demonstrated establishing clozapine as the gold standard treatment in this specific population, but blinded randomized trials-in contrast to unblinded effectiveness studies- provide little evidence for the superiority of clozapine compared to other second generation antipsychotics. Based on the above results and given the high risk profile of clozapine, treatment attempts with olanzapine or risperidone could be warranted, before moving on to clozapine. Nevertheless, our meta-analysis is not definitive due to several limitations such as limited or no data for specific SGAs and differences in the criteria of treatment resistance and clozapine dosing between studies; thus, more trials comparing clozapine with other SGAs in more severely ill patients and using high clozapine doses are warranted.

T252. Treatment strategies in case of non-response in schizophrenia: meta-analytical assessments of increasing the antipsychotic dose and switching the antipsychotic drug versus continuation of the same andipsychotic dose and drug.

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Background: Many patients with schizophrenia do not reach a satisfying clinical response with a standard dose of an initially prescribed antipsychotic drug. In such cases, clinicians face the dilemma of increasing the antipsychotic dose beyond regular thresholds in order to enhance antipsychotic efficacy. Another treatment option would be to switch the initial antipsychotic drug to another compound. Nevertheless, the evidence on these two treatment strategies is scarce. Therefore, we decided to conduct two separate systematic reviews and meta-analyses; one examining whether increasing the antipsychotic dose rather than maintaining it and one examining whether switching the antipsychotic drug rather than maintaining it could benefit patients who do not respond to their initial antipsychotic treatment.
Methods: We searched the Cochrane Schizophrenia Group Trials Register up to October 2015. References of all included studies were examined for further trials. All relevant randomized controlled trials (RCTs) were selected and all data were extracted by two independent

researchers. For dichotomous outcomes, random-effects relative risk (RR) and 95% confidence intervals (CI) were estimated. For continuous outcomes, weighted mean differences (MD) based on a random-effects model were used. Since both reviews are ongoing, hereby we could only present the results on the two primary dichotomous outcomes.
Results: In the first review comparing increasing the antipsychotic dose rather than maintaining it, nine relevant RCTs with 557 participants were included; the small sample sizes per trial limited the overall quality of the evidence. No significant difference was found between groups in terms of the number of patients who responded (7 RCTs, $n = 407$, RR 1.11, CI 0.78 to 1.58) or left the study early (4 RCTs, $n = 250$, RR 1.14, CI 0.78 to 1.68). In the second review comparing switching the antipsychotic drug rather than maintaining it, ten relevant RCTs with 928 participants were included; the small sample sizes again limited the overall quality of the evidence. No significant difference was found between groups in terms of the number of patients who responded (5 RCTs, $n = 596$, RR 1.17, CI 0.94 to 1.45) or left the study early (4 RCTs, $n = 437$, RR 1.05, CI 0.79 to 1.39).
Discussion: There was not even a single study in favor of the dose increase strategy in case of non-response in schizophrenia. As for the switching strategy, a recent unpublished trial supports its effectiveness but data from previous trials are not consistent. The overall quality of the meta-analytic results is low, mainly due to the limited evidence base; there is an urgent need for further trials in order to determine the optional treatment strategy in case of non-response to the initial antipsychotic treatment in schizophrenia.

T253. A molecular imaging study of postsynaptic density transcripts in antipsychotic-naïve vs. antipsychotic-exposed animals. a molecular explanation for discrepancy in treatment responses depending on treatment history

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Background: Partial or non-response to antipsychotics, the mainstay treatment of schizophrenia, is a major concern in schizophrenia therapy. Switching from one antipsychotic to another is a common psychiatric practice, mostly in those people that are non-responders. However, no study has so far investigated whether the molecular effects of an antipsychotic are affected by a previous treatment. The aim of this study will be to evaluate whether a prolonged treatment with an atypical antipsychotic, i.e. amisulpride, has divergent molecular effects when given in antipsychotic-naïve subjects compared to subjects who had a prolonged treatment with a typical antipsychotic, i.e. haloperidol. We investigated the effects of these procedures on the expression of genes of the post-synaptic density (PSD). These molecules have been found modulated by antipsychotic treatments and have been implicated in synaptic plasticity processes and schizophrenia pathophysiology.
Methods: Sprague Dawley rats ($n = 36$) were randomly assigned to receive 15- day haloperidol 0.8 mg/kg (HAL) or vehicle (NaCl 0.8%; VEH) by intraperitoneal (ip) injection. On day 16, animals in each treatment arm were randomly assigned to receive VEH, HAL or amisulpride 35 mg/kg (AMS) by ip injection. Therefore, six treatment groups were obtained ($n = 6$ each): VEH+VEH; VEH+HAL; VEH+AMS; HAL+VEH; HAL+HAL; HAL+AMS. In Situ Hybridization Histochemistry was used to assess the expression of the immediate-early genes Homer1a and Arc and of the constitutive PSD genes Homer1b/c and PSD-95. One-way ANOVA and Tukey's post hoc tests were used to analyze treatment effects. Head-to-head comparisons were carried out by Student's t test. In all tests, significance was set at $P < 0.05$ (two-tailed).
Results: Homer1a expression was significantly higher in the VEH+AMS group compared to the HAL+AMS group in all cortical and in several caudate-putamen regions. Notably, VEH+AMS treatment significantly induced Homer1a expression in the cortex compared to both VEH +VEH and VEH+HAL. Both VEH+AMS and VEH+HAL significantly induced Homer1a expression in striatum compared to VEH+VEH. On the contrary, HAL+AMS did not significantly induce the gene in the cortex or in the striatum. Homer1a was significantly induced by HAL +HAL in the striatum compared to both HAL+VEH and HAL+AMS.
Arc expression was not significantly different when the groups pretreated by VEH were compared with the corresponding groups pretreated by HAL. Arc expression was significantly induced by VEH +HAL compared to VEH+VEH in the striatum, but no significant differences were found with VEH+AMS. The gene was significantly induced by HAL+HAL in the striatum compared to both HAL+VEH and HAL+AMS.
In sharp contraposition with Homer1a, expression of Homer1b/c by AMS was significantly higher in the VEH+AMS group compared to the HAL+AMS group. Notably, Homer1b/c expression was significantly increased by HAL+AMS only compared to both HAL+VEH and HAL +HAL. PSD-95 expression was not significantly different between VEH +AMS and HAL+AMS.
Discussion: These results demonstrate that the molecular effects of amisulpride are strongly divergent in antipsychotic-naïve animals compared to animals that received a prolonged treatment with haloperidol. Further studies are needed to evaluate whether these observations can be generalized to the other antipsychotic compounds and to which extent can be translated to human therapy. Nonetheless, our study may shed a light on some forms of treatment resistant schizophrenia.

T254. Different receptor profile and dose of antipsychotics induce differential changes in level and topography of postsynaptic density transcripts associated to psychosis pathophysiology.

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Background: Postsynaptic density (PSD) proteins have been involved in psychosis pathophysiology and antipsychotic treatment. Antipsychotics impact differentially the expression, level and topography of PSD transcripts after acute administration, depending on receptor profile and dose administered. However, a direct head-to-head comparison of first and second-generation antipsychotics at different doses in a chronic paradigm is still lacking. To fill this gap, we evaluated the expression of key PSD transcripts, i.e. Homer1a, Arc, Homer1b, PSD-95 and Shank after chronic treatment with haloperidol and asenapine, a first and second-generation antipsychotic, respectively. Olanzapine was used also, as an internal comparator.
Methods: Male Sprague-Dawley rats were assigned to the following treatment groups: Vehicle (VEH); Haloperidol 0.25 mg/kg (HAL0.25); haloperidol 0.5 mg/kg (HAL0.5); haloperidol 0.8 mg/kg (HAL0.8); asenapine 0.05 mg/kg (ASE0.05); asenapine 0.1 mg/kg (ASE0.1); asenapine 0.3 mg/kg (ASE0.3); olanzapine 2.5 mg/kg (OLA). Drugs were dissolved in saline, adjusted to physiological pH, and subcutaneously injected for 21 days (one injection/day). Ninety minutes after the last injection, animals were sacrificed, and brains were processed for in situ transcript mapping and level analysis. Treatment effect on gene expression was analyzed by ANOVA.
Results: Asenapine administration reduced Homer1a expression in several brain regions compared to VEH. In the striatum, ASE0.1 and ASE0.3 reduced Homer1a expression only in the ventromedial caudate putamen compared to VEH. Arc expression was reduced by almost all treatments in both cortical and striatal regions explored. Homer1b expression was increased by ASE0.05 in multiple cortical regions and in the nucleus accumbens, while OLA and HAL0.5 increased Homer1b expression only in the nucleus accumbens compared to VEH. Shank expression was poorly affected in all treatment groups. PSD-95 expression was reduced by ASE0.1 in cortical areas and in the medial regions of the caudate putamen compared to VEH. Among all treatments, only OLA administration induced PSD-95 expression in the ventrolateral caudate putamen and in the nucleus accumbens.
Discussion: The expression of genes relevant to synaptic plasticity at the PSD was differentially modulated after chronic administration of typical and atypical antipsychotics compounds as well as by the same compound administered at different doses. Asenapine impacted gene expression mostly in cortical regions, haloperidol mainly in striatum.

These results are consistent with the observed effects of asenapine on the glutamatergic system (i.e. enhancement of NMDA-mediated currents in pyramidal cortical neurons and decrease NMDA receptor activity in the striatum) and with the well known action of haloperidol on the dopaminergic nigro-striatal pathway.

T255. Prevention of disability in treatment resistant schizophrenia (TRS) needs individuation of factors contributing to social impairment. Results from a pilot study using a stringent operative procedure to categorize TRS patients.

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Background: Treatment Resistant Schizophrenia (TRS) is diagnosed in patients who did not respond or respond poorly to adequate antipsychotic treatments. TRS causes severe disability in people who are affected. It has been demonstrated that TRS patients have more limited achievements in functional milestones of everyday living even compared to schizophrenia responder patients (RP). In this work, we aimed at investigating the factors that are associated with impaired global and area-specific social performances in TRS patients, with the scope of individuating a set of modifiable factors that could be addressed to prevent severe disability.
Methods: We included 118 psychotic and non-psychotic consecutive patients with a significant impairment on the Personal and Social Performance (PSP) scale (defined as a total score < 80). Diagnosis of TRS was made according to a multistep procedure whose main points were: 1) reliable reconstruction of pharmacological history of the patient, to confirm that he/she had already received (and did not respond) at least two adequate antipsychotic treatments; 2) evaluation of actual psychotic symptoms (patients were considered actively psychotics whether they had a Positive and Negative Syndrome Scale, PANSS, total score >70); 3) assessment of factors of pseudo-pharmacoresistance; attempts to their correction, if possible; re-categorization of the patient after correction; 4) additional prospective antipsychotic trial, to assess the condition of non-response or sustained partial response. Patients under clozapine were categorized as TRS. All patients were administered the PSP and underwent a panel of assessments exploring demographic, clinical, psychometric, social and cognitive variables. ANOVA and linear regression were used.
Results: PSP total score, PSP Area1 (Social Useful Activities), Area2 (Personal and Social Relationship), and Area3 (Self-Care) subscale scores were significantly different among diagnostic groups, while Area4 (Disturbing and Aggressive Behavior) subscale score was not. PSP total, Area1, and Area3 subscale scores were significantly higher in TRS than in RP and NSP, while Area2 subscale score was not significantly different compared to RP but was higher than in NSP.
PSP total score in TRS patients was significantly associated to: occupation status; age at onset; adherence to therapy; PANSS negative score. These factors produced a model whose adjusted R2 was 0.57, therefore accounting for more than half of PSP total score variance in these patients. Factors associated to PSP total score were sharply different in RP and NSP and gave models that accounted for a minor part of PSP total score variance.
The same factors were significantly associated with Area1 score, providing a model whose adjusted R2 was 0.54. Area2 score significantly associated with use of first-generation antipsychotics and adherence to therapy. Area3 score significantly associated with use of first-generation antipsychotics, adherence to therapy, Verbal Fluency, and PANSS total score. In both cases, backward stepwise regression showed that adherence to therapy was the only predictor surviving the procedure. Both models showed low (< 0.2) adjusted R2.
Discussion: These results confirm previous reports on the most relevant social impairment in TRS patients compared to non-TRS patients. High levels of negative symptoms, younger age at onset, poor vocational status, and poor adherence to therapeutic advice were relevant factors of social impairment. Specifically, these factors appeared implicated in impaired social useful activities. Impairment in social relationship and self-care were only limitedly associated to poor adherence, as other factors presumably contribute to these alterations.

T256. Symptomatic remission status in patients with schizophrenia treated with paliperidone palmitate (1-month and 3-month formulations)

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Background: In this double-blind (DB), parallel-group, multicenter, phase-3 study (EudraCT no: 2011-004889-15), symptomatic remission was analyzed in patients (age 18-70 years) with schizophrenia following treatment with paliperidone palmitate (1-month [PP1M] and 3-month [PP3M] formulation).
Methods: Patients previously stabilized on PP1M and treated with fixed doses of PP3M (175, 263, 350, or 525 mg eq. deltoid/gluteal) or PP1M (50, 75, 100, or 150 mg eq. deltoid/gluteal) for 48 weeks were included in this analysis. Symptomatic remission was assessed according to Andreason's criteria ($\leq$3 score on all positive and negative symptom score [PANSS] items: P1, P2, P3, N1, N4, N6, G5, and G9 for the last 6 months of DB treatment, with no excursion allowed). Functional remission was also assessed.
Results: Consistent with the primary efficacy endpoint with similar relapse rates in both treatment groups (PP3M: $n = 37$, 8%; PP1M: $n = 45$, 9%; difference in relapse-free rate: 1.2% [95% CI:-2.7%; 5.1%]), the percentage of patients who showed symptomatic remission was similar and $>50\%$ in both groups (PP3M: $n = 243/483$, 50%; PP1M: $n = 260/512$, 51%; relative risk of remission [95% CI]: 0.98 [0.87, 1.11]). Among the remitters at entry into DB phase, percentage of patients who met the symptomatic remission criteria was similar in both groups across 48 weeks. Proportion of patients who maintained symptomatic remission and functioning remission (PSP score >70 during the last 6 months of DB treatment) was similar between both groups (PP3M: $n = 121/483$, 25%; PP1M: $n = 136/512$; 27%).
Discussion: Patients treated with PP demonstrated higher symptomatic remission compared with remission rates published elsewhere (Beitinger, 2008) with similar rates in both treatment groups across all 48 weeks. PP3M can thus be considered as a unique option for symptomatic remission in patients with schizophrenia previously stabilized on PP1M.
Beitinger, R., *et al.* Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2008. 32(7): p. 1643-1651.

T257. Resilience in individuals clinically at high risk for psychosis - first results from the PRONIA study

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Background: Resilience describes individual conditions considered as protective factors with respect to the occurrence or course of mental illness. The aim of this study was to investigate levels of resilience in patients clinically at high risk for psychosis (CHR) in comparison to patients suffering from psychosis and, or depression.
Methods: PRONIA ('Personalized Prognostic Tools for Early Psychosis Mangement') is a prospective collaboration project funded by the European Union under the 7th Framework Programme (grant agreement no 602152). Considering a broad set of variables (sMRI, rsMRI, DTI, psychopathological, life event related and sociobiographic data, neurocognition, genomics and other blood derived parameters) as well as advanced statistical methods, PRONIA aims at developing an innovative multivariate prognostic tool enabling an individualized prediction of illness trajectories and outcome. Seven university centers

in five European countries and in Australia (Munich, Basel, Birmingham, Cologne, Melbourne, Milan/Udine, Turku) participate in the evaluation of three clinical groups (subjects clinically at high risk of developing a psychosis [CHR], patients with a recent onset psychosis [ROP] and patients with a recent onset depression [ROD]) as well as healthy controls; planned sample size is $n = 1700$.
In a first interim analysis, we investigated data from the 'Resilience Scale for Adults' (RSA) developed by Odin Hjemdal and Oddgeir Friborg, a self-report instrument with six factors: perception of self, planned future, social competence, family cohesion, social resources and structured style.
Results: Group comparisons revealed a significant difference between patients and healthy controls. Healthy controls showed higher total scores on the RSA than CHR, ROP and ROD participants. Further, CHR patients scored significantly lower than ROD on RSA total. The ROP sample showed significantly higher scores on the RSA factor perception of self compared to ROD and CHR as well as a significant higher score on planned future than CHR participants.
Discussion: The results of the current study support the notion that lower resilience is associated with mental illness. This was already observable in a population clinically at risk for psychosis, who scored even lower than the recent onset depression group. The lower scores on the RSA factors perception of self and planned future might reflect a higher impact of depression compared to the recent onset psychosis group.

T258. Peer problems and low self-esteem mediates the schizotypy – reactive aggression relationship in adolescents

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Background: Very little prior research exists on aggressive behavior in children with schizotypal and paranoid features, and almost no research on factors that may help explain this relationship. This study assesses whether paranoid and non-paranoid features of schizotypy are particularly associated with reactive forms of aggression, and if peer problems and low self-esteem mediate this relationship.
Methods: 1,301 schoolchildren aged 8-14 years were assessed on the child version of the Schizotypal Personality Questionnaire (SPQ-C) and the Social Mistrust Scale (SMS). Aggression was assessed using the Reactive-Proactive Aggression Questionnaire (RPQ). A serial multiple mediation model was tested with a hypothesized causal flow from schizotypy / suspicious schizotypy to peer problems to low self-esteem to increased aggression.
Results: Increased schizotypy and suspicious schizotypy were both associated with increased aggression, particularly the reactive form. Peer problems and self-esteem mediated the relationships between schizotypy and reactive, but not proactive, aggression. Specifically, children with higher levels of schizotypy were more likely to have peer problems which in turn were associated with lower self-esteem which in turn was associated with reactive aggression.
Discussion: Results provide an initial explanatory model of why children with paranoid and non-paranoid schizotypal features are more likely to be reactively aggressive. Therapeutic implications to enhance self-esteem in schizotypal adolescents may help reduce their co-morbid reactive aggressive behavior.

T259. Social and role functioning in a high risk child and adolescent sample

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Background: Functioning in daily life and social functioning, as well as global functioning ability are one of the core features of psychotic illness. Early stages of psychosis are associated with poor functioning in adolescents (Grano *et al* 2011). Premorbid functioning, such as early adolescent social dysfunction were suggested as an early predictor of conversion (Tarabox *et al*, 2013). Nevertheless, there are only few studies attending to this topic in child and adolescent population, despite its importance.
Methods: A prospective, naturalistic and multicentric study from Hospital Clinic and Hospital Sant Joan de Déu of Barcelona conduced in help-seeking children and adolescents (10-17 years) and healthy controls (HC). Inclusion criteria: 1) Attenuated positive or negative symptoms in the previous 12 months 2) Brief limited intermittent psychotic symptoms 3) First or second degree relative with schizophrenia or schizotypical disorder plus impairment of functioning. Exclusion criteria: IQ < 70 and a diagnosis of neurodevelopmental disorder. Prodromal symptoms were assessed by The Semistructured Interview for Prodromal Syndromes (SIPS). Functioning ability was assessed by the Global Assessment of Functioning (GAF), the Global Functioning Role Scale (GFRS) and the Global Functioning Social Scale (GFSS). Scores assess functioning at the time of evaluation, and better and worst scores in the last year.
Results: A total of 128 subjects were included. 89 were UHR patients, mean age 15,09 ± 1,72 and 58,42% girls. 39 were HC, with mean age 15,50 ± 1,50, and 66,6% were females. No age ($P = 0{,}207$) and gender ($P = 0{,}379$) differences were found between the two samples. All scores on functioning scales were significant lower in UHR patients than in HC at baseline.
Of the UHR sample, 10 individuals had converted to psychotic disorder during the follow-up visits. There were no baseline differences between converted and non-converted individuals at baseline in terms of function ability.
Discussion: High risk child and adolescent samples show worse global functioning, social functioning and role functioning than healthy controls at baseline, as observed in previous literature (Grano *et al.*, 2011). In terms of predictive value, functioning not seems to be a good discriminative between converters and non-converters, since no baseline differences were founded between these two samples.

T260. Comparing domains of functioning in clinical high risk subjects, recent onset psychosis and recent onset depression patients - first results from the PRONIA study

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Background: Decreased global functioning was reported in several studies on clinical high risk (CHR) states of developing a first psychotic episode. In a considerable proportion of CHR individuals, functional deterioration remains even after (transient) remission of symptomatic risk indicators. Moreover, low levels of functioning are predictive for a later transition to psychosis. Furthermore, intervention trials demonstrated a favorable effect on transition rates, but not on functioning. Thereby, previous studies used rather global measures of functioning. However, for evaluating the mechanisms underlying functional decline and for an improved definition of targets for intervention, a more detailed analysis of the affection of the different domains of functioning and its illness-related pattern is required.
Methods: PRONIA ('Personalized Prognostic Tools for Early Psychosis Mangement') is a prospective collaboration project funded by the European Union under the 7th Framework Programme (grant agreement n° 602152). Considering a broad set of variables (sMRI, rsMRI, DTI, psychopathological, life event related and sociobiographic data, neurocognition, genomics and other blood derived parameters) as well as advanced statistical methods, PRONIA aims at developing an innovative multivariate prognostic tool enabling an individualized prediction of illness trajectories and outcome. Seven university centers in five European countries and in Australia (Munich, Basel, Birmingham, Cologne, Melbourne, Milan/Udine, Turku) participate in the evaluation of three clinical groups (subjects clinically at high risk of developing a psychosis [CHR], patients with a recent onset psychosis

[ROP] and patients with a recent onset depression [ROD]) as well as healthy controls; planned sample size is $n = 1700$.
In a first interim analysis, we analyzed data from the 'Functional Remisson of General Schizophrenia' Scale (FROGS), comprising five subdomains (daily life, activities, relationships, quality of adaption, health and treatments), the 'Global Functioning: Social and Role' Scale (GF S/R) and a disability/impairment score derived from the 'Global Assessment of Functioning' Scale (GAF).
Results: Compared to healthy controls, CHR, ROP and ROD showed lower functioning scores on all scales. Among the patient groups, ROP scored significantly lower than the two other groups on the GAF as well as on the GF scales and all domains of the FROGS. Comparisons of CHR and ROP groups revealed no significant difference on the GAF or the GF scales. However, the FROGS revealed a differential pattern with lower scores of the domains 'quality of adaptation' and 'health and treatments' in the CHR group.
Discussion: Compared to healthy controls, CHR subjects showed a deterioration of functioning, which was comparable to that observed in the patient groups with a recent onset of psychosis or a recent onset of depression. The global assessments did not detect a difference in functioning between CHR and ROD, however with the FROGS, lower scores could be demonstrated in two of five domains. Follow-up assessments will enable us to investigate the predictors of further deterioration in other domains and the predictive value of the observed pattern for the functional and symptomatic outcomes in the CHR group.

T261. The bullying scale - first results from the PRONIA study

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Background: Bullying is a major public health problem (Nansel *et al.* 2004). Nearly 30% of American adolescents have got moderate experiences with bullying (as the bully, the victim, or both) (Nansel *et al*, 2001). A review of Wolke & Lereya (2015) considers the importance of bullying as a major risk factor for poor physical and mental health and reduced adaptation to adult roles including forming lasting relationships, integrating into work and being economically independent.
Methods: PRONIA ('Personalized Prognostic Tools for Early Psychosis Mangement') is a prospective collaboration project funded by the European Union under the 7th Framework Programme (grant agreement no 602152). Considering a broad set of variables (sMRI, rsMRI, DTI, psychopathological, life event related and sociobiographic data, neurocognition, genomics and other blood derived parameters) as well as advanced statistical methods, PRONIA aims at developing an innovative multivariate prognostic tool enabling an individualized prediction of illness trajectories and outcome. Seven university centers in five European countries and in Australia (Munich, Basel, Birmingham, Cologne, Melbourne, Milan/Udine, Turku) participate in the evaluation of three clinical groups (subjects clinically at high risk of developing a psychosis [CHR], patients with a recent onset psychosis [ROP] and patients with a recent onset depression [ROD]) as well as healthy controls; planned sample size is $n = 1700$. To assess bullying in PRONIA, a modified, considerably shorter version of the Bully Survey was developed (Swearer & Carey, 2003, Swearer, Turner, Givens & Pollack, 2008). Among other modifications, the PRONIA version enables a differentiation between experiences at school or within the current living situation and between onset before or after the age of 17.
Results: Subjects clinically at high risk for psychosis as well as patients with a recent onset psychosis or patients with a recent onset depression reported significantly more bullying experiences than healthy controls. Moreover, CHR subjects experienced significantly more bullying than ROD and ROP patients. Furthermore, compared to healthy controls, the CHR as well as the ROP and the ROD groups reported a significantly higher subjective burden due to the bullying experience. Again, this burden was significantly more pronounced in the CHR than in the ROD and ROP group, and ROP patients got significantly more problems than ROD patients.
Discussion: Our results underline the importance of bullying prevention with regard to mental health. The fact that CHR patients reported more severe bullying experiences than the ROD and ROP groups, may indicate a higher sensitivity for stressful social experiences in this group. The prospective design of PRONIA will enable us to further elucidate the impact of bullying experiences on the symptomatic and functional outcome of all three groups, including the impact on a later progression to psychosis in the CHR group.

T262. Self-stigma and its relationship with victimization, psychotic symptoms and self-esteem among people with schizophrenia spectrum disorders.

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Background: Self-stigma is highly prevalent in schizophrenia and can be seen as an important factor leading to low self-esteem. It is however unclear how psychological factors and actual adverse events contribute to self-stigma. This study empirically examines how symptom severity and the experience of being victimized affect both self-stigma and self-esteem.
Methods: Persons with a schizophrenia spectrum disorder ($N = 102$) were assessed with a battery of self-rating questionnaires and interviews. Structural equation modelling (SEM) was subsequently applied to test the fit of three models: a model with symptoms and victimization as direct predictors of self-stigma and negative self-esteem, a model with an indirect effect for symptoms mediated by victimization and a third model with a direct effect for negative symptoms and an indirect effect for positive symptoms mediated by victimization
Results: Results showed good model fit for the direct effects of both symptoms and victimization: both lead to an increase of self-stigma and subsequent negative self-esteem. Negative symptoms had a direct association with self-stigma, while the relationship between positive symptoms and self-stigma was mediated by victimization.
Discussion: Our findings suggest that symptoms and victimization may contribute to self-stigma, leading to negative self-esteem in individuals with a schizophrenia spectrum disorder. Especially for patients with positive symptoms victimization seems to be an important factor in developing selfstigma. Given the burden of self-stigma on patients and the constraining effects on societal participation and service use, interventions targeting victimisation as well as self-stigma are needed.

T263. Mentalizing ability as a mediator between reported childhood abuse and non-affective psychotic disorder.

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Background: A number of studies have identified reported childhood abuse as an important risk factor for nonaffective psychotic disorder (NAPD). Interestingly, van Os and colleagues (Nature, 468(7321), 2010) have suggested that a reduced mentalizing ability may be one of the mechanisms underlying the effect of childhood abuse on the risk of NAPD. Indeed, there is some evidence for an association between mentalizing ability and severity of social dysfunction, positive and negative symptoms. It is therefore possible that mentalizing ability (partially) mediates the effect of childhood abuse on social functioning, negative symptoms and positive symptoms. The current study tested this hypothesis.
Methods: Sixty-two patients with NAPD were recruited from Rivierduinen mental health care institute. Participants were interviewed with the Childhood Experience of Care and Abuse, the Social Functioning Scale, and the Positive and Negative Syndrome Scale. The Hinting Task

was used to measure mentalizing ability. Three mediator models were tested using a bootstrapping procedure with reported childhood abuse as independent variable, mentalizing ability as mediator and social functioning, positive symptoms and negative symptoms as dependent variables.
Results: 30.6% (19) of the respondents reported no childhood abuse, 45.2% (28) reported mild childhood abuse, 19,4% (12) reported moderate childhood abuse, and 4,8% (3) reported serious childhood abuse. Contrary to expectations, childhood abuse did not significantly predict social functioning or positive symptoms, but there was a significant relationship between childhood abuse and negative symptoms ($\beta = .14$, $p = .01$). Further regression analyses showed that childhood abuse was related to mentalizing ability ($\beta = -.08$, $p < .01$), and that mentalizing ability was related to negative symptoms ($\beta = -.85$, $p < .001$). The bootstrapping results showed a significant indirect effect of childhood abuse through mentalizing ability on negative symptoms (LLCI = .0032; ULCI = .19), which was also reflected in a significant result on the Sobel test ($\beta = .07$, $p < .05$). The effect of childhood abuse on negative symptoms ($\beta = .21$, $p < .001$) was reduced when mentalizing ability was accounted for ($\beta = 0.14$, $p < .05$), indicating that the effect of childhood abuse on negative symptoms is partly mediated by mentalizing ability.
Discussion: Previously reported associations between childhood abuse and level of social functioning and severity of positive symptoms were not found. However, a positive association was found between childhood abuse and severity of negative symptoms. The results furthermore suggest that a deficit in mentalizing ability accounts for a part of the pathway from childhood abuse to negative symptoms. The implications are twofold. Firstly, mentalizing ability may protect against the development of negative symptoms. Secondly, treatments that target mentalizing ability may be successful in reducing negative symptoms.

T264. Language disturbance and functional capacity in early psychosis

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Background: The role of language disturbance in predicting functional outcomes in psychosis is a neglected area of research. Bizarre idiosyncratic thinking (BIT) is a type of language disturbance that may predict clinical course in psychosis. BIT has been criticised for lacking validity as measures of language disturbance, although very few studies have evaluated its clinical utility. We aimed to investigate the utility of BIT with respect to functional capacity following first episode psychosis (FEP) and compare it to that of formal thought disorder (FTD).
Methods: Participants were recruited through the DETECT Early Intervention in Psychosis Service in Dublin, Ireland between January 2013 and July 2014. Those diagnosed with a first episode of affective or non-affective psychotic disorder were included. BIT was evaluated with 12 proverbs adapted for use in an Irish sample and the total score ranged from 0-36. FTD was evaluated dimensionally: its factor structure was established in another study and comprised disorganised, verbose and impoverished speech domains (disFTD, verFTD and povFTD respectively). Functional capacity was evaluated with the UPSA-B which was adapted for use in an Irish setting; it evaluates an individual's ability to perform everyday tasks e.g. using a telephone. Analyses were controlled for premorbid IQ, diagnosis, duration of untreated psychosis and diagnosis. The MIRECC GAF was employed as a measure of social and occupational functioning although it was not the primary endpoint of interest in the current study. Funding was provided for this study by the Health Research Board of Ireland.
Results: A total of 108 individuals had a functional capacity evaluation at baseline and 88 at 1 year follow-up. The prevalence of BIT at FEP was 29% at baseline and 20% at 1 year compared with 55% and 30% respectively for the presence of any FTD dimension. The concordance between BIT and FTD was poor for all dimensions of FTD. There was no significant change in total scores between baseline and one year in relation to functional capacity ($r = 0.15$, $P = 0.06$) or BIT ($r = -0.01$, $P = 0.89$) unlike FTD dimensions, which all improved significantly. Higher UPSA-B scores were associated with financial independence and non-schizophrenia spectrum diagnosis but not with residential independence or with MIRECC GAF occupational or social functioning sub-scale scores (rho = 0.14 and rho = 0.10 respectively, both P = NS). BIT severity was significantly associated with functional capacity on multivariate analysis at FEP presentation (beta = -0.22, $P < 0.05$) but not at 1 year. BIT severity was not significantly correlated with either social or occupational functioning (rho = -0.16 and rho = -0.13 respectively, P = NS). None of the FTD dimensions had a concurrent or predictive relationship with functional capacity. Functional capacity at 1 year was predicted by premorbid IQ, female gender and baseline functional but not negative symptoms. The multivariate models explained 33% and 45% of the variance in functional capacity, at baseline and 1 year respectively.
Discussion: Functional capacity was associated with BIT at FEP but not at 1 year in this study and it showed no association with FTD. The validity of functional capacity in FEP has previously been questioned and, in addition to its temporal stability, this should be considered in its future use in clinical trials. The validity and generalisability of BIT as a measure of language disturbance is questionable in FEP although this study was somewhat under-powered for some analyses.

T265. Predicting psychosocial functioning in schizophrenia: the role of clinical symptoms and the awareness of illness

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Background: Schizophrenia is a disabling mental disorder with a chronic course that often leads to significant impairments in psychosocial functioning. These functional deficits are considered to be important prognosis factors whose comprehensive treatment should go beyond just the psychotic symptoms. There are many studies that link negative symptoms with their impact on the daily functioning of patients with schizophrenia but only a few include the lack of insight as a variable to analyze. This study aims to examine the concomitant relationships between psychopathological symptoms, the awareness of mental illness and the functional impairment.
Methods: Fifty adult patients meeting the ICD-10 criteria for schizophrenia were consecutively recruited for this study following their admission into a Mental Health Rehabilitation Centre. Their clinical features and psychosocial functioning data were collected with the following psychometric instruments: Brief Psychiatric Rating Scale (BPRS), Scale to assess Unawareness of Mental Disorder (SUM-D) and the Social Performance Scale (PSP). For methodological purposes, the BPRS scores were grouped into three dimensions: positive symptoms, negative symptoms and general psychopathology (which included the rest of the items). In addition, only the global scores for PSP and SUM-D were taken into account in the study. Correlation coefficients and multiple regression analysis were performed to measure the strength of association between the quantitative variables. Statistical analysis was carried out using MedCalc software and the significance level was set at $P < 0.05$.
Results: The mean age of the patients was 39.96 years (SD = 9.07), and 26% of the patients were female. The mean duration of illness was 17.28 years (SD = 8.14). A univariate analysis yielded statistical inverse correlations between global functioning and positive symptoms (rho = -58; $P < 0.0001$), negative symptoms ($r = -0.43$; $P = 0.0018$), general psychopathology ($r = -0.59$; $P < 0.0001$) and awareness of illness (rho = -0.54; $P < 0.0001$). In a logistic stepwise regression analysis, psychosocial functioning was significantly predicted by negative symptoms and general psychopathology ($P = 0.0009$). Positive symptoms were included in the model but did not show a significant association ($P > 0.05$). Unawareness of Mental Disorder was not included in the model.
Discussion: The negative symptoms - as well as other psychopathological features, such as a lack of insight - undermine the functional outcomes in patients with schizophrenia. In all likelihood, if psychometric instruments to assess the deficits in cognitive function and social cognition had been applied, our findings would likely have been more determinant and would have showed a stronger and more accurate correlation between these factors and global psychosocial functioning.

T266. Recovery in schizophrenia: a natural 5-year follow-up study in a private practice

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Background: Follow-up studies have found that a substantial number of patients with schizophrenia achieve recovery (i.e., sustained improvement in both symptoms and social/vocational functioning). The aim of this study was to determine recovery rates and related factors in schizophrenia outpatients.
Methods: A sample of 61 consecutive outpatients (schizophrenia = 42, schizoaffective disorder = 19) who followed-up for five years was examined in the study. Psychopathological status was evaluated by means of standardized symptomatic remission criteria based on Positive and Negative Syndrome Scale (PANSS), and Clinical Global Impression severity (CGI-S). Functionality of the patients was evaluated by means of Global Assessment of Functioning (GAF) and informations from family members. Recovery required remission of positive and negative symptoms and adequate social/vocational functioning (fulfillment of age-appropriate role expectations, performance of daily living tasks without supervision, and engagement in social interactions) for at least 24 months. Demographic and clinical variables were compared using one-way analysis of variance for continuous variables and χ2 test for dichotomous ones. Binary logistic regression was performed to find the predictors of recovery.
Results: After 5 years, 67.2% of the patients achieved symptom remission at some point, and 39.3% had adequate social functioning at least for 2 years. Only 27.9% of subjects met recovery criteria for more than 2 years. Late onset of illness (22y↑), being schizoaffective disorder, and being first episode were predictors of recovery. Schizophrenic and schizoaffective patients were characterized by an overlapping age at onset, mean duration of illness, mean duration of untreated psychosis and common sociodemographic characteristics. More than half of the patients were taken intramuscular injection antipsychotic drugs any time of the treatment period. The mean number of visits was 16.3 ± 5.8 that is 3-4 meeting in a year.
Discussion: The proportion of patients who met recovery criteria is not low. This finding might be interpreted as a result of same physician treatment, intramuscular drug applications, and regular meetings. Compared to schizophrenic patients, schizoaffective patients may be considered as a subgroup of psychotic patients displaying several specific characteristics in terms of clinical course, clinical and functional outcome and treatment.

T267. Attempts of suicide in first episode of psychosis and psychosocial functioning

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Background: The adverse impact of attempts of suicide on psychosocial functioning and symptomatic remission hasn´t been well documented. However, the determinants and levels of psychosocial functioning and symptomatic remission remain poorly understood in people experiencing FEP. This study aimed to study the effects of attempts of suicide after first episode of psychosis on psychosocial functioning and symptomatic remission one year after first episode of psychosis.
Methods: Sixty-five first-episode patients participated in this study. Baseline demographic clinical data and information about suicide attempts previous at FEP were collected in the first contact with mental health services. Sociodemographic and clinical data were collected from information provided by the patients and their relatives. We used Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) to screen for psychotic symptoms which were then used for diagnosis. Information about suicide attempts previous at FEP was collected using Schedules for Clinical Assessment in Neuropsychyatry SCAN. This clinical interview contains a question about attempted suicide. At 12 months after first episode of psychosis WHO-DAS-S was used to assess psychosocial functioning. Is a semi-structured interview to screen psychosocial functioning in four dimensions: personal care, occupation, family and household and broader social context. This interview is recommended by OMS to evaluate difficulties caused for physical and mental problems. We defined remission according to PANSS operational criteria set up by the Remission in Schizophrenia Working Group. The symptomatic criterion includes eight core PANSS items (delusion, unusual thought content, hallucinatory behaviour, conceptual disorganization, manner-ism/posturing, blunted affect, social withdrawal, lack of spontaneity) with a score ≤ 3. The duration criterion is symptomatic remission maintenance over 6 consecutive months.
Results: Significant correlation ($P < 0.001$) was found between disability in personal care and number of attempts of suicide after first episode of psychosis (r = 0.52). Disability in family and household correlated significantly ($P < 0.005$) with number of attempts after first episode of psychosis (r = 0.29). Multivariable analysis were done for analyse the relationship between disability in personal care and family and household with number of attempts of suicide. In the linear regression we included covariates. These covariates were: age, gender and diagnosis. Number of attempts of suicide explaining 20% of the variance in the disability of personal care and 14% of the variance in the disability of family and household.
Discussion: Suicide attempts impacted negatively on personal care and family and household disability. These findings have significant implications for early, targeted interventions for this vulnerable group.

T268. Cannabis use and attempts of suicide in first episode of psychosis

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Background: Substances taking is common in patients with a diagnosis of eschizophrenia. The prevalence of substances taking in this group of patients is estimated between 40-50%, in contrast with a 16% that is estimated in general population.
The objective of the present study consists in analyse the influence of cannabis taking in suicide attempts that occur during a year in persons who have suffered a first psychotic episode.
Methods: The sample of the study consists on 65 patients who have suffered a first psychotic episode. Sociodemographic and clinical information was managed at moment of admission and after stabilization.
Results: Significant relations were found between cannabis taking and suicide attempts at 12 months ($P < 0.05$). However there is no relationship between cannabis taking and suicide attempts previous at first admission. Mann-Withney test showed significant differences ($P < 0.05$) between the users/no users of cannabis in the suicide attempts at 12 months. These differences did not take place in consumers/no consumers in the attempts of suicide previous the debut of schizophrenia.
Discussion: There are only a few studies concerning the influence of use of cannabis in suicide attempts in different temporary moments. The results explained here show how the use of cannabis is associated with suicide attempts, but only at 12 months, nevertheless such relation does not exists in the other temporary moments considered in the study.

T269. Validation and implementation of the individual recovery outcomes counter (I.ROC) in an SMI population in the Netherlands – research plan

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Background: To be in control of one's own life has become leading in policy plans and health care development in the Netherlands. Recovery plays an important role in gaining control over one's life,

especially in people with a serious mental illness (SMI). People with an SMI should have more opportunities to take care of themselves in their own environment. Provided help should become more recovery focused.
The Individual Recovery Outcomes Counter (I.ROC), developed at Penumbra in Scotland, is a recovery focused instrument, fitting very well in the recovery vision. The I.ROC assesses recovery in twelve domains of life through twelve questions, the outcome provides starting points for recovery focused help. The psychometric properties of the I.ROC are already investigated in Scotland, with good results. The newly translated Dutch version however still needs validation. Within the Netherlands a consortium has been formed (including Phrenos, Pro Persona, GGZ Drenthe, Indigo, GGZ Friesland, Lentis Groningen, GGz Breburg) with main aim establishing the psychometric properties of the Dutch I.ROC in various health care populations. The psychometric properties in the SMI population will be investigated by GGZ Drenthe, Lentis Groningen, GGZ Friesland and GGz Breburg. In order to use the results of the I.ROC in mental health care, outcomes are further shaped in the HOPE toolkit, which is directly connected to the twelve measured domains. The toolkit consists of guidance plans, tools, wellbeing tips and links to other resources. If the psychometric properties of the Dutch I.ROC are sufficient, the HOPE toolkit will be implemented in several FACT teams in Drenthe, the Netherlands for an effect evaluation.
Methods: In the Netherlands, mental health care users are evaluated once every year with a standard set of instruments, during these yearly evaluations, people with an SMI using health care at GGZ Drenthe, GGZ Friesland, Lentis Groningen or GGz Breburg will be asked to fill out the I.ROC for the first time. The inclusion will take place from January until December 2016, in this period we hope to include a minimum of 400 people with an SMI. Participants fill out an I.ROC every six months during one year, adding up to three assessments for each participant.
Several other instruments will be used to compare the results of the I.ROC to (e.g. Honos, Mansa). We will look at validity, reliability and factor structure. The effectiveness of the HOPE toolkit will be investigated in up to five FACT teams in Drenthe, with the implementation of the toolkit in some teams and care-as-usual in other teams. Participants will fill out an I.ROC every three months during at least one year. Besides that, various other instruments will be completed and interviews will be held with both participants and health care workers.
Results: If present at the time, first results will be presented at the poster. Otherwise the poster will give an overview of our I.ROC research plans.
Discussion: First results will be discussed if present at the time.

T270. Health related quality of life in schizophrenia and other psychoses: AQOL-4D findings from the second Australian National Survey of Psychosis

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Background: Multi-attribute utility instruments are generic health-related quality of life (HRQoL) measures that enable valuation of health states relative to death (0.0) and full health (1.0). The usefulness of one such instrument, the AQoL-4D, was tested in a population with psychosis to confirm whether it has adequate lower end sensitivity to provide meaningful HRQoL valuations in this population, and to assess utility values across demographic, general and illness-related health categorizations.
Methods: A nationally representative sample of participants in the Second Australian National Survey of Psychosis ($N = 1,825$) were asked to complete the AQoL-4D as one of 32 assessment modules encompassing demographic, diagnostic, clinical, cognitive, physical health, independent functioning and service use measures. A standard algorithm was applied to responses to each of 12 items in the instrument.
Results: Utility values were assessed for 1793 participants (98.2%). The AQoL-4D gave rise to no ceiling effects. Only 6.6% of participants scored in the top decile of HRQoL (0.9-10.0]. In contrast, 10.8% scored in the lowest decile [-0.04-0.10], a floor effect observed in 0.4%. The mean utility value was 0.49 (95%CI: 0.48-0.51), significantly lower than the Australian population norm of 0.81 (95%CI: 0.81-0.82). Greatest impacts on HRQoL were for diminishing independent functioning (ES: 0.68-2.24), self-rated mental health (ES: 0.15-1.65) and physical health (ES: 0.11-1.21). Strong effects were also observed for course of disorder (ES: 0.08-1.13), current suicidal ideation (ES: 0.76-1.08), and labor force participation (ES: 0.11-0.97).
Discussion: The AQoL-4D had good lower end sensitivity in a psychosis sample and demonstrated responsiveness across subjective, objective and symptom measures. The HRQoL impacts of psychosis are profound. The greatest losses were associated with poorer independent functioning, self-rated mental and physical health, course of disorder and current suicidal ideation.

T271. Reliability and validity of the specific levels of function scale - Japanese version; relation to cognitive insight

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Background: Improving functional outcomes in work, residential and social issues provides ultimate goals in the treatment of psychiatric diseases, such as schizophrenia. There have been efforts to identify assessment tools adequately measuring "real-world functional outcomes", which is linked to neurocognition and daily activity skills. In this respect, the Specific Levels of Function (SLOF) has been reported to be a promising measure of social function (Harvey *et al.* Am J Psychiatry 2011). In addition to cognitive function, there have been suggestions that the lack of insight, a core feature of schizophrenia, also influences outcome. Therefore, the aims of this study were; 1) to determine reliability and validity of the Japanese version of SLOF, and 2) to determine if cognitive insight, a component of metacognition, would affect social function, as measured by the SLOF.
Methods: This study was a multi-center trial involving 10 medical facilities in Japan, in which 58 Japanese patients meeting DSM-IV-R criteria for schizophrenia participated. The study protocol was approved by the ethics committees of participating institutions. The Social Functioning Scale Individuals' version modified for the MATRICS-PASS (Modified SFS for PASS) - Japanese version (Sumiyoshi *et al.* Schizophr Res Cogn 2015) was used as a self-report measure of social function. Neurocognition and functional capacity (daily activity skills) were evaluated by Japanese versions of the Brief Assessment of Cognition in Schizophrenia (BACS) and the UCSD Performance-based Skills Assessment-Brief (UPSA-B), respectively. We also assessed cognitive insight (metacognition) by means of the Beck Cognitive Insight Scale (BCIS). Severity of symptoms was measured by the Positive and Negative Syndrome Scale (PANSS). All of these clinical scales have been validated. The SLOF Japanese version, developed based on the original English version, was also administered. Interviewer-rated summary scores of the SLOF, based on its three domains, e.g. Interpersonal Functioning, Everyday Activities, and Vocational Functioning, were obtained (Sabbag *et al.* Schizophr Res 2011; Strassnig *et al.* Schizophr Res 2015).
Results: Cronbach alpha for the SLOF Japanese version was 0.80. The one-week test-retest reliability of the scale was acceptable ($\tau = 0.81$,

$P < 0.001$). Pearson's correlation coefficients indicated significant relationships between scores of the SLOF vs. those of the SFS (r = 0.56, $P < 0.01$), BACS (r = 0.56, $P < 0.01$), UPSA-B (r = 0.65, $P < 0.01$), BCIS (r = 0.30, $P < 0.05$) and PANSS (r = -0.59, $P < 0.001$). Further analysis indicated that the correlation between performance on the UPSA-B and scores of the SLOF was significantly more robust compared to the correlation between performance on the UPSA-B and scores of the SFS (z = 2.30, $P < 0.05$). Similarly, the correlation between scores of the BACS and SLOF tended to be more robust than that between the BACS and SFS (z = 1.89, $P = 0.059$). Importantly, while the correlation between scores of the BCIS and SLOF reached significance, it was not so between scores of the BCIS and SFS (r = 0.17, P = n.s.).
Discussion: These results suggest the SLOF Japanese version, reported here, provides a valid and reliable measure of social consequences in patients with schizophrenia. The positive relationship between cognitive insight and social function evaluated by the SLOF (interviewer-rated), but not SFS (self-reported) is consistent with the observation that ratings with the former scale were more strongly associated with performances on objective functional measures (i.e. BACS and UPSA-B).

T272. What do service users want from a smartphone app for psychosis?

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Background: Schizophrenia affects 2% of the population. The majority of people who experience a first episode of psychosis (FEP) reach remission within 12-months of intervention. However, the early course of psychosis is characterised by repeated relapse; 80% of those experiencing a first episode of psychosis will relapse within 5-years of their initial episode, adversely impacting on their psychosocial development. National and international guidelines recommend a combination of pharmacological and psychosocial intervention in the treatment of schizophrenia. However, many service users are not compliant with their prescribed medication and a shortage of trained clinicians, resource pressures, long waiting lists, to name a few mean that of people with psychosis who could benefit, relatively few service users have access to helpful psychosocial packages, often resulting in relapse indicators being missed. Accordingly, there is an urgent need to improve access to helpful intervention packages that can be delivered in a timely manner.
Methods: Using framework analysis, this presentation will focus on the findings from two large qualitative studies carried out in the UK, whereby first episode psychosis service users ($n = 20$) and early intervention service clinicians ($n = 40$) were interviewed to elicit views about the feasibility and acceptability of mobile health (mHealth) approaches to delivery psychosocial interventions in psychosis. Data regards the necessary features of Smartphone-based apps for will be presented.
Results: Participants interviewed ranged between 16-34 years in age. Based on qualitative interviews with service users, there was an overarching view that smartphone technology is an acceptable and relevant way for service users to manage their mental health problems. Service users used technology for a variety of reasons, including help-seeking and gathering information regards their mental health problem. Participants felt that apps could overcome many of the barriers to traditional service set up and was an easy point of access with high ecological validity, extending the reach of service delivery and circumventing waiting times. There were many important features considered necessary to app design and development, including language, the ability to personalise the app and to maximise the functionality of the app. Empowerment, control and choice and the de-stigmatising nature of apps also reinforced their utility. Barriers to use were also identified and will be presented.
Discussion: The presenter will compare and contrast service user vs clinician views and attitudes about app-based interventions and will conclude by presenting the key factors necessary first episode psychosis service users consider to be important when designing and implementing apps in early psychosis.

T273. Quality of life assessment in schizophrenia diagnosed patients with predominant negative symptoms

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Background: Negative symptoms have a significant impact over the schizophrenia diagnosed patients overall functionality, including work performance, social interactions, self-care, academic achievements etc. Assessing the impact of the negative symptoms over the patients everyday life activities from the psychiatrists point of view, integrating caregivers opinion and the patients own perspective, could be an useful process in order to establish reintegration programs and making therapeutic decisions.
Methods: This is an observational, open-label trial, consisting in a group of 34 patients, 22 male and 12 female, diagnosed with schizophrenia (according to DSM 5 criteria), that presented predominant negative symptoms, as defined by a Positive and Negative Syndrome Scale (PANSS) Negative Subscale score higher than 25 and a PANSS Positive Subscale of maximum 20, were evaluated longitudinally for 24 weeks, using PANSS, Scale for Assessment of Negative Symptoms (SANS), Quality of Life Inventory (QoLI), Clinical Global Impression- Severity (CGI-S), Global Assessment of Functioning (GAF), Visual Analogic Scale (VAS) scored 1 to 10 for the caregiver's perception of the patient's overall improvement. All the psychometric scales were applied every 4 weeks. Patients included in this trial maintained their initial treatment (atypical antipsychotics- olanzapine $n = 16$, ziprasidone $n = 8$, aripiprazole $n = 6$, quetiapine $n = 4$) during 24 weeks, except for cases of psychotic decompensations, when hospitalisation and antipsychotic switch/augmentation was considered appropriate. All patients that developed acute psychotic episodes and necessitated antipsychotic changes had been eliminated from statistical processing.
Results: After 24 weeks, data from 24 patients were processed. Scales for negative psychotic symptoms recorded minor variations compared to baseline (SANS -8.9+/-1.2, and PANSS- Negative Subscale -3.6 +/-0.9), demonstrating a high stability in time. No differences between patients' evolution on PANSS-Negative Subscale or SANS were detected depending on the antipsychotic used. CGI-S and GAF registered variations of 1.2+/-0.3, and 7.7+/-1.7, respectively. QoLI evaluations detected a worsening in several dimensions- "satisfaction with social relations" (-10.5%), "satisfaction with mental and physical health" (-7.7%) and "satisfaction with life in general" (-5.2%). On VAS, the caregivers reported more frequent a deterioration of the global clinical status (58.4% versus 41.6%) of minimal (-1 to -3 points, $n = 8$) or moderate (-3 to -5 points, $n = 6$) severity.
Discussion: Evaluation of the quality of life in patients with schizophrenia and predominant negative symptoms is important because it could not be inferred from other clinical scales for psychotic symptoms, like PANSS or SANS, and neither from global functioning scales like GAF. This could be a reflection of the fact that small scale variations on clinical scales for psychosis have a high resonance both at the patient's perception of his/her life quality, and at the caregiver's perception of the patient's overall functioning. This could be the base for establishing psychotherapy programs focused on enhancing the patients' sense of self-efficacy through social reintegration and working skill training.

T274. Assessing the relevance of the subjective well-being under neuroleptics–short form in schizophrenia: patient and caregiver perspectives

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Background: Aripiprazole once-monthly 400 mg (AOM 400) is a long-acting injectable (LAI) antipsychotic treatment for adults with schizophrenia. In a recent 28-week, head-to-head clinical trial (the QUALIFY study) against paliperidone palmitate, patients taking AOM 400 showed superior improvements of health-related quality of life (HRQOL) and functioning (Naber *et al.*, 2015). One of the study's

secondary endpoints was the Subjective Well-being Under Neuroleptics–Short Form (SWN-S). The 20-item SWN-S is a patient-reported instrument designed to measure subjective effects of neuroleptic drugs on psychopathology and HRQOL over the past week in patients with schizophrenia (Naber, 1995). Higher scores on the SWN-S denote better subjective well-being and fewer overall negative impacts from medications and disease. The SWN-S provides a total score and individual scores for 5 domains: Mental Functioning, Self-control, Emotional Regulation, Physical Functioning, and Social Integration. The objective of the current study was to gain a better understanding of the importance and relevance of the SWN-S items and domains to patients and caregivers.
Methods: Individual interviews with adults with schizophrenia and focus groups with caregivers of adults with schizophrenia were conducted in two locations in the US (Raleigh, NC, and St. Louis, MO). Semi-structured interview guides incorporating content from the SWN-S were used to direct the discussions, including questions on the meaning of the instrument's items and domains and those that were most likely/ prone to change based on the level of patient functioning. Patients and caregivers were also asked to rank-order the SWN-S domains according to their perceptions of importance and their contribution to patients' QOL and functioning.
Results: A total of 12 interviews with patients and 4 focus groups with caregivers ($n = 17$) were conducted. Patients were 58% male with a mean age of 42 years (range, 25-62) and diagnosed with schizophrenia for a mean of 16 years (range, 2-47). Caregivers were primarily female (71%) with a mean age of 46 (range, 24-70). The domain Mental Functioning (e.g., being able to think clearly, easily, and quickly) was deemed most important by patients and caregivers and was also considered the domain most likely/prone to change. Emotional Regulation (e.g., hope for the future, confidence) and Physical Functioning (e.g., comfortable with body) were second and third most important to patients, respectively, whereas Social Integration (e.g., interacts with others, makes social contact) and Self-control (e.g., feelings and behavior are appropriate to situations) were second and third most important to caregivers, respectively.
Discussion: Content measured on the SWN-S was considered relevant, important, and with propensity to change and improve. Concepts related to the patient's cognitive functioning, such as the ability to think clearly, were strong drivers toward overall HRQOL. These findings help to establish the content relevance in supporting the QUALIFY study's findings.

T275. Measuring well-being in chronic schizophrenia: the significance of positive symptoms

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Background: Well-being perception differs from quality of life concepts and has been less explored in schizophrenia patients. A recurrent limitation is the reduced number of tools available for assessing well-being in this population group. This cross-sectional study sought to compare subjective well-being scores in a group of chronic schizophrenia patients ($N = 142$) receiving clozapine treatment with those of a general population sample using a new scale, and to explore which clinically recognised factors may predict subjective well-being amongst chronic schizophrenia patients.
Methods: The Short Warwick-Edinburgh Mental Well-being Scale (SWEMWBS) was used to measure well-being. We compared subjective well-being distribution between patients and general population using a t test, and then correlated SWEMWBS scores and 27 clinically recognised factors, spanning socio-demographics, symptom severity scores, physical health diagnosis, clozapine side effects, habits and prescribed medication. Factors with a $P < 0.2$ correlation were then included as a predictors in a linear regression model.
Results: Patients were found to have a significantly lower mean SWEMWBS score compared to that of the general population distribution ($P < 0.0001$). Ten factors were included in the linear regression model, however only positive symptom severity was a significant predictor of SWEMWBS score ($P < 0.003$).
Discussion: These results suggest that the SWEMWBS is an efficient tool for assessing subjective well-being in schizophrenia patients. This study also suggests that greater levels of clinical attention given to positive symptoms compared with other symptoms and aspects of well-being, during biomedical treatment for chronic schizophrenia, may partially explain the finding that only positive symptoms significantly predicted patient perceptions of low well-being in this study.

T276. Does functioning and life satisfaction differ for schizophrenia patients with co-morbid depression?

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Background: The negative relationship between depression and ratings of life satisfaction in schizophrenia is well established. However, the relation between depression and objective functioning in the disorder is still relatively unclear. There is evidence for this relationship in other disorders (e.g., cancer, OCD). The inherent differences between individual measures of functioning (e.g. social relationships and physical health) and their consolidation into composite objective quality of life (QoL) scores have further complicated the issue. This study sought to examine the differences in objective QoL between schizophrenia patients with (DP) and without (NDP) co-morbid depression. This was done separately for 5 noted individual measures of functioning: daily activities and functioning (DAF), frequency of family relations (FAM) and social relations (SOCREL), safety (SAF) and health state (HEALTH). Life satisfaction ratings (subjective QoL) for these domains were also compared. We hypothesized that both objective and subjective QoL in depressed schizophrenia patients would be lower than NDP.
Methods: 57 patients with schizophrenia/schizoaffective disorder were recruited and administered the MADRS. MADRS scores were used to distinguish 31 patients with current clinical depression ($M = 45.81$, $SD = 10.29$) and 26 without ($M = 40.54$, $SD = 11.00$). Objective and subjective QoL was assessed using Lehman's (1988) QoL Interview (QoLI) with the PANSS for current symptomatology. z-scores were created for each domain (objective and subjective) based on the responses of 44 healthy control participants ($M = 39.80$, $SD = 13.94$).
Results: Objectively, there was a trend to poorer functioning for DP to NDP patients in only the SOCREL domain ($P = .02$, corrected for multiple comparisons). This contrasted with significantly reduced subjective life satisfaction between groups in the DAF ($P = .01$), SOCREL ($P = .03$ - trend) and HEALTH ($P = .000$) domains.
Discussion: Depressive symptoms do not appear to have a broad effect on daily functioning in schizophrenia, though there is some evidence they might influence interpersonal interaction. The broad impact of depression disproportionately reducing life satisfaction is supported. The overall findings reinforce the need to address depression in schizophrenia in terms of improving their subjective experiences. On a functional level, this may help improve interpersonal interaction and facilitate efficacious re-integration into the workplace and broader society.

T277. Association of knowledge and causal explanation of schizophrenia students' attitude towards service users: a comparison between nursing and medical undergraduates

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Background: People with severe mental disorders are prone to face negative attitudes in general health care settings, with significant implications in terms of under-diagnosis and under-treatment of physical illnesses (Thornicroft *et al.*, 2007). Although several authors argued that a better knowledge of the disease and its biological causes and mechanisms would have led to a more positive view of patients with schizophrenia and less social distancing, studies yielded mixed findings, particularly amongst medical doctors and students (Serafini *et al.*, 2011; Magliano, 2013, 2014). The aim of this study is to

compare the attitudes towards service users expressed by nursing and medical students and to explore the relation between knowledge of schizophrenia, causal explanation, and participants' and perceived social view of the disorder.
Methods: The study involved 59 medical students and 161 nursing students attending the third year of their BSc who have not attended yet a Psychiatry course. Socio-demographic information was collected using an ad-hoc questionnaire, participants' view about people affected with schizophrenia was assessed using the Opinion on Mental Illness Questionnaire (OQ, Magliano, 2004, 2011), and perceived devaluation of service users by the community was assessed using the Devaluation Consumers Scale (Struening *et al.*, 2001). Between groups differences and associations between categorical and continuous variables were tested using Student's t test and ANCOVA. Nursing and medical students were similar in terms of self-reported ethnicity and education, but different in terms of gender distribution, age, and father social class; therefore, these variables were used as potential confounders.
Results: Medical students were more able to identify as schizophrenia a clinical vignette of a patients affected by delusions and hallucinations (36 [61.0%] vs. 36 [22.4%], chi sq 29.306, $P < 0.001$). Furthermore, a greater proportion of them chose biological causes (i.e. heredity, chemical imbalance, or obstetrical complications) as more frequent cause of schizophrenia (25 [43.4%] vs. 30 [18.6%], chi sq 12.978, $P < 0.001$). After adjusting for potential confounders, nursing students showed a more optimist view on recovery from schizophrenia (F 11.922, p 0.001), effectiveness of available treatments (F 48.187, $P < 0.001$), and community's attitude towards patients affected by severe mental disorders (F 5.268, p 0.0223). Among nursing students, only those who correctly identified schizophrenia reported reduced confidence in recovery (F 9.225, p 0.003) and were more conscious about community's devaluation of patients with schizophrenia. Moreover, in the same group, psychosocial explanation of schizophrenia (i.e. stress, family conflicts, or disillusionment in love) were associated to a more optimistic view towards social equality of service users, though this relation became non-significant after adjusting for confounders.
Discussion: Our preliminary findings show that medical students express higher level of stigma against schizophrenia and perceived greater community's devaluations against service users. On the other hand, nursing students generally showed a more optimistic view about schizophrenia, which was particularly pronounced among those who shared a psychosocial explanation of the disease. This is partially consistent with the literature and underline the relevance of education intervention and stigma-reduction programs about health science students.

T278. An audit of clozapine use in first episode psychosis

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Background: Clozapine is a second generation antipsychotic medication consistently shown to be more efficacious in treatment-resistant schizophrenia (TRS). It is estimated that 30% of people with schizophrenia will not respond to standard therapeutic treatment. Along with reducing positive and negative symptoms, Clozapine has also been reported to reduce risk of suicide and reduce hospitalisation rates. Guidelines have been developed internationally for treating those with TRS. The UK National Institute for Health and Care Excellence (NICE) first published guidelines for the treatment of schizophrenia in 2002. It recommends using Clozapine for treatment resistant schizophrenia. The guidelines state that Clozapine should be offered after two adequate 4-6 week trials of different antipsychotics, of which one must be an atypical. However, adherance to these guidelines have been consistently poor in the US, Canada, New Zealand and Australia.
Methods: Ethics and audit committee approval was received. Data were collected from the paper and electronic records of people who originally presented with first episode psychosis between 1995 and 1999 ($N = 166$). Information was gathered from paper charts and electronic records (inpatient and outpatient). Data were collected from the time of first presentation up to the end of December 2013, or until the patient was discharged or transferred to another service. Information on service use and physical health was gathered using a data collection template designed specifically for this audit.
Results: A total of 28/166 participants were prescribed Clozapine. Of this Clozapine subsample 23/28 (82%) were male. The mean age at baseline was 23.11 years for the Clozapine subsample and 29.13 for the entire sample. The most prevalent diagnosis of the cohort prescribed Clozapine was schizophrenia (82%). The mean time to first trial of Clozapine was 6.7 years. The mean number of hospital admissions reduced from 6.04 per year to 0.88 per year, following the initiation of Clozapine. 11 participants (46%) had their Clozapine prescription augmented with another medication, including mood stabilisers and typical and atypical antipsychotics. 87.5% of patients had side effects as a result of Clozapine initiation. The mean number of anti-psychotics prescribed before a Clozapine trial was 4.85.
Discussion: Nearly one in five of the original cohort was considered to have a suboptimal response to trials of antipsychotic medication. Similarly to other studies we found that barriers to treatment with Clozapine exist. Clozapine for treatment resistant schizophrenia is underutilised and better understanding of this is necessary given the implications for patient's quality of life and hospital admission rates.

T279. Does long acting aripiprazole improve outcomes in routine clinical practice?

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Background: Ablify Maintena (AM) is a long acting injection of aripiprazole that received marketing authorisation in the UK in January 2014. Long acting injections have theoretical advantages over their oral equivalents but this is difficult to demonstrate in short randomised controlled trials. However, observational studies have shown better outcomes (Tiihonen *et al*, 2011). AM is costly compared to first generation antipsychotics (FGAs) LAIs and there are no robust trials comparing AM with FGA LAIs. We examined the effectiveness and use of AM in a mental health trust as well as the characteristics of patients prescribed AM. Previous research in North Staffordshire has demonstrated that AM is cost effective and significantly reduces bed occupancy.
Methods: We identified all consecutive patients prescribed AM in North Staffordshire (population 470 000) since launch and examined records for demography, diagnosis, bed and medication use as part of a service evaluation. We examined the effectiveness of AM using routinely collected data. The main outcome measure was the Health of the Nation Outcome Scale (HONOS). This 12 item instrument measures behaviour, impairment, symptoms and social functioning (Wing, Curtis & Beevor, 1996). Secondary outcomes included serum lipids, glucose and prolactin levels.
Results: 30 patients received AM in a time frame allowing a one year follow up. 69% were male and the mean age was 39 years. Over half were detained under the 1983 Mental Health Act and 30% were inpatients on a psychiatric intensive care unit when AM was started. The median dose was 400 mg. Clinical teams judged that 80% of patients had improved. HONOS scores reflected this with a mean total score of 13.3 (SD 6.3) before starting AM and 8.5 (SD 5.5) at one year follow up ($P = 0.0001$). All subscores showed statistically significant improvement except the impairment subscale. Mean prolactin levels were 254.9mIU/L (SD 317.7) and all mean lipid measures were in the normal range as was blood glucose.
Discussion: Within the limitations of the methodology and sample our results show clinical improvement following the use of AM in a routinely collected outcome measure (HONOS) after one year. The patient population demographics were similar to that seen in clinical trials but around half were detained patients suggesting a difficult to manage population. Serum glucose, lipids and prolactin parameters were within the normal range which is reassuring given concerns regarding metabolic syndrome and premature mortality in this population. In conclusion the use of AM has resulted in reduced bed occupancy which is mirrored by improved clinical outcomes.

T280. Five-year outcomes of FEP patients receiving integrated vs. functional mental health care. A pilot study from the PICOS

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Background: No consensus currently exists on whether mental health care should be provided through 'functional' (i.e., transition of patients between different psychiatric services is coordinated through a network of regulated referrals) or 'integrated' (the same mental health staff delivers to patients all the different interventions across in-patient and out-patient settings) systems. This study aimed to compare, in a sample of first episode psychosis (FEP) patients, integrated and functional mental health care systems with regard to a range of subjective, clinical and social outcomes at 1-, 2- and 5 years from illness onset.
Methods: This study was conducted in the context of the Psychosis Incident Cohort Outcome Study (PICOS), a multisite naturalistic research on FEP patients treated within the public psychiatric sector in the Veneto Region (Italy). Assessment was performed used a comprehensive set of standardized measures. Patients were recruited from 23 public community mental health services, which were retrospectively stratified as having provided functional or integrated care according to the definitions operationalized in the COFI (COmparing policy framework, structure, effectiveness and cost-effectiveness of Functional and Integrated systems of mental health care), a EU funded multisite research comparing functional (i.e., care is provided by different clinicians/teams in in-patient and out-patient services) and integrated (i.e., care is provided by the same responsible clinician across in-patient and out-patient services) systems across five European countries.
Results: A total of 397 FEP patients were assessed at baseline. Preliminary analysis revealed that patients treated within integrated systems had more engagement with services over time than those treated by functional ones (respectively, 100% vs. 86% at 2 years; 90% vs. 69% at 5 years). Regression analyses showed that receiving continuity of care helped in reducing the level of needs in different domains of the Camberwell Assessment of Needs (CAN) at each follow-up point and, in particular, had a significant effect in reducing the level of unmet health needs at 2 years, also after having controlled for baseline differences between groups.
Discussion: This study provides some initial empirical findings on which kind of mental health care system (functional vs. integrated) may be most beneficial for patients experiencing their first episode of psychosis. Our results indicate that integrated care is more effective in reducing patients' levels of needs, especially needs relative to the health domain. In recent years the concept of needs for care has been proposed as a new paradigm in both planning mental health service interventions and assessing the outcome of care provided. Integrated model seems to be the most adequate service configuration to specifically address this important subjective outcome. Additional variables should be selected in future studies to detect possible differences between integrated vs. functional systems on FEP patients.

T281. Free associations as both a verbal and nonverbal phenomenon in dance/movement therapy - a case study with patients diagnosed with schizophrenia and varying degrees of related forms of psychiatric diagnoses.

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Background: The purpose of this paper is to explore the connection between the psychoanalytical idea and method of free associations and their kinesthetic analogues in self-expression through dance and movement, as they appear in Dance Movement/Therapy (DMT) processes. The paper provides a brief theoretical review of the psychoanalytic concept of free association represented in the Christopher Bolas (2002) book "Free Association," and a case study that analyzes a single DMT session with patients diagnosed with schizophrenia and varying degrees of related forms of psychiatric diagnoses, to demonstrate how free associations can reveal one's unconscious and inner world through movement and within DMT sessions. The application of free association and its' relevance to the dance movement therapy will also be demonstrated.
Methods: This case study analyzes a single session of Dance Movement/Therapy (DMT) with patients diagnosed with mental disorders, especially those on the schizophrenia spectrum. Participants: 40 patients (ages 18 to 56) diagnosed with mental disorders, recovering from active psychosis into more residual stages of disability, attending Daily Psychiatric Rehabilitation Unit in one of the hospitals in Poland.
Free Association - a technique used in psychoanalysis, psychoanalytical and psychodynamic approaches to therapy - was used to analyze DMT session.
Results: - Interpreting the free associations of both the group members' verbal and nonverbal expression allowed therapist to deepen understanding of group dynamics.
- Movement reflects internal processes and shed light on relational processes.
- DMTs note transient body rhythms, changes in muscular tensions, and the varying shapes, postures, or body attitude that they see in their patients. They also work from the premise that movement helps to release creativity. Together, these observations show that DMTs, whether they are aware of it, or not, support free associating. Therefore, one may conclude that moving and talking freely can yield information about one's emotional state, ability to express oneself, regulate, and identify shifts in internal self organization.
- Moving and talking freely can yield information about one's emotional state, ability to express oneself, regulate, and identify shifts in internal self-organization.
Discussion: As described in the vignette portraying a conflict between group members and dance/movement therapist, one can see that in DMT movement serves as a relational process. Free association technique has been used as a way to encourage patients to talk freely about what was on their minds, moving from one object to another, not following any plan or hidden agenda, and later unpacking unconscious meaning, revealed and helped to explain individual and group dynamics. This was unearthed not only in words, but also in movement and gesture. Patients related, unconsciously, to what was going on within them, and in their life stories - the fundamental need for secure attachments. Clients and therapists engaged in empathic creative process using body movement and dance to assist integration of emotional, cognitive, physical, social and spiritual aspects of self (Meekums, 2002). By intentionally incorporating free associations into DMT practice, one can reveal the hidden logic of the unconscious, express deeper layers of own being, disclose mental content that has been forbidden. Such findings, for both therapist and client, including patients in psychiatric, care can result in becoming more aware of one's own nonverbal and verbal expressions, thoughts, feelings, internal images and sensations, and, with time and increased exposure to free association, result in initiation of personal and interpersonal change.

T282. The Moray Psychosis Survey: prevalence, demographics and treatment characteristics in a rural cohort of patients diagnosed with schizophrenia

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Background: There is a paucity of contemporary data on prevalence, demographics and treatment characteristics of psychotic disorders in rural areas. We identified a cohort of individuals with a lifetime diagnosis of schizophrenia on the caseload of mental health teams in rural North Scotland. We sought to estimate prevalence and to measure demographic and treatment characteristics across the natural course of the disorder.
Methods: The study used a proforma to extract casenote data ($n = 139$). Demographic variables measured included employment, housing and age at onset, Treatment characteristics including admission at onset, medication changes and access to psychological therapies were also measured. Data were extracted for selected time points up to 15 years

post diagnosis and at time of audit. Measures of symptomatic and functional recovery were also measured.
Results: We identified $n = 139$ cases. The prevalence rate for a schizophrenia diagnosis within the working age population was 2.48 cases per 1000. The gender ratio was 60:40 (M:F). The average age of onset was 28.98 years (Range = 14-54). With regard to treatment, 67% of cases were admitted to hospital at onset. The average number of medication changes was 11 (Range = 0-44). For psychological therapies 33% were offered psychological input, and 12% of the sample were offered CBT. With regard to recovery rates it was found that 15% ($n = 21$) were employed, 1% ($n = 2$) were in education or training and the remaining 84% of the sample were unemployed. For symptomatic recovery 33% ($n = 46$) were in full recovery, 25% ($n = 35$) were in partial recovery, 1% were in relapse at point of audit and 39% ($n = 55$) presented with chronic symptoms of schizophrenia. Full symptomatic recovery was associated with being employment or training (Chi-Squared = 17.7, $P = .0001$).
Discussion: This case-note study provides an overview of patient characteristics and treatment of schizophrenia in rural Scotland. Our data are comparable with urban datasets and can also be compared with rural Schizophrenia surveys conducted in Scotland in the early 1980's. Findings can inform the treatment pathway for individuals with schizophrenia living in rural areas our data also highlight the need to develop interventions focused on both symptomatic and functional recovery, including employment and training pathways.

T283. Meta-analysis of oxytocin in schizophrenia: effects on social cognition

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Background: There is considerable evidence that affiliative and social cognitive processes are linked to oxytocin (OXT). There is evidence that oxytonergic systems are involved in psychosis and emerging evidence that synthetic OXT may represent a novel treatment paradigm. Meta-analytic findings for the relationship of OXT to symptom reduction are mixed. However, the literature on the effects of OXT on social cognition and emotion recognition has yielded promising results in non-clinical samples and where OXT has been used to enhance psychological interventions. As treatment trials of OXT in human clinical samples increase, we conducted a meta-analysis to estimate an effect size for OXT treatment on social cognition and emotional recognition.
Methods: Published trials of OXT vs. Placebo in schizophrenia were identified. Participants had a diagnosis of Schizophrenia or psychosis and the outcome variables explored the effects of OXT in relation to social cognition and emotional recognition. Effect sizes for OXT on were converted to Hedge's 'g'. Meta-analyses were conducted with both fixed and random effects meta-analyses, incorporating assessment of heterogeneity, publication bias and influence bias.
Results: OXT administration versus placebo was associated with a moderate effect on improved emotion recognition SMD = -0.36; 95%CI = -0.80 to 0.08, $P = 0.03$), a minimal non-significant effect on trust (SMD = -0.17; 95%CI = -0.57 to 0.22; $P = 0.47$); a moderate non-significant effect on empathy (SMD = -0.27; 95%CI = -0.80 to 0.26; $P = 0.98$); and a minimal non-significant effect on trust (SMD = -0.17; 95%CI = -0.53 to 0.20; $P = 0.49$). Heterogeneity indicated substantial methodological variation in the studies that were analyzed.
Discussion: Preliminary evidence suggests there is currently limited evidence to support the effectiveness of OXT administration on improving social and emotional cognition in schizophrenia. Effect sizes are mainly small in magnitude and non-significant. Results suggest there may be promise in closer examination of the effects of OXT on emotion recognition. However, results are compromised by heterogeneity in study methodologies and the lack of standardized batteries for measuring social and emotional cognition.

T284. Predictors of pre-diabetes in overweight or obese schizophrenia patients treated with clozapine or olanzapine: baseline results from an ongoing randomised controlled trial

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Background: Obesity, metabolic disturbances and diabetes among antipsychotic-treated patients are major health problems as well as known risk factors for cardiovascular disease. The reasons underlying these associations most likely consist of interactions of antipsychotic medications, genetics and unhealthy lifestyle. Especially two of the most efficacious antipsychotics, clozapine and olanzapine, cause the most weight gain and metabolic disturbances. The glucagon-like peptide-1 (GLP-1) analogue liraglutide improves glycaemic control and induces weight loss in diabetic patients.
Methods: We report screening/baseline results from a 16-week, double-blinded, randomised, parallel-group, placebo-controlled clinical trial, designed to evaluate the effects of liraglutide on glycaemic control compared to placebo in overweight (body mass index ≥ 27 kg/m2), pre-diabetic, schizophrenia patients on stable treatment with clozapine or olanzapine.
Results: One-hundred-and-ninety-five schizophrenia patients treated with clozapine or olanzapine were screened. Fifty-six patients were excluded following the initial screening. The remaining 139 patients had a 75 g-oral glucose tolerance test (OGTT) performed. Ninety-five of these patients (68.3%) had pre-diabetes. Pre-diabetic and non-diabetic/non-pre-diabetic individuals did not differ regarding demographic, illness and treatment variables, including age, gender, antipsychotic treatment, alcohol intake or psychopathological scores. However, the pre-diabetic patients had significantly higher waist circumference (116.2 ± 14.1 vs 109.3 ± 13.4 cm, $P = 0.008$), two-hour plasma glucose during OGTT (9.71 ± 1.8 vs 6.4 ± 1.0 mmol/L, $P < 0.0001$), glucose metabolism markers (HbA1c 37.0 ± 4.3 vs 34.9 ± 3.2 mmol/mol, $P = 0.005$; fasting plasma glucose 5.7 ± 0.6 vs 5.2 ± 0.4 mmol/L, $P < 0.0001$, C-peptide: 1324 ± 505 vs 974 ± 381 pmol/L, $P < 0.0001$), were more insulin resistant, and had higher triglycerides levels (2.26 ± 1.2 vs 1.62 ± 0.9 mmol/L, $P = 0.002$) and liver transaminases (alanine transaminase: 37.9 ± 21.2 vs 25.6 ± 11.9 U/L, $P = 0.0005$, aspartate transaminase 28.0 ± 9.8 vs 23.2 ± 6.0 U/L, $P = 0.004$) compared to the non-diabetic/non-pre-diabetic patients.
Discussion: In a group of overweight or obese schizophrenia patients treated with olanzapine or clozapine 68.3% were pre-diabetic. The pre-diabetic group had significantly higher waist circumference, liver transaminases and triglycerides levels and showed many signs of poorer glycaemic control, putting them at very high risk for development of diabetes.

T285. Catatonia in first episode of psychosis: correlations with hyperprolactinemia and DUP

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Background: Hyperprolactinemia may be present in patients with schizophrenic psychoses independent of antipsychotic medication. It might be stress induced. As enhanced prolactin can increase dopamine release through a feedback mechanism. Motor abnormalities, such as catatonia, may be also present even in drug-naive psychotic patients. To our knowledge there are no previous studies exploring the relationship between prolactine serum levels and catatonia in first episode psychosis
In the present study, prevalence of catatonia in first episode psychosis was investigated. In addition, correlations between catatonia and porlactin serum levels, and between catatonia and DUP were explores.
Methods: Design: one phase observational study

- Sample: Inclusion criteria: patients between 16-55 year-old, who were admitted in the Psychiatric acute ward of Parc Sanitari Sant Joan de Déu. First episode psychosis, drug-naive patients. A total of 32 patients were included in the study.
- Instruments: Prolactine serum levels were obtained before starting antipsychotic treatment, within first 24 hours of hospitalisation. Catatonia was assessed by means of the Bush Francis Catatonia Rating Scale (BFCRS), during first days of hospitalisation. Duration of Untreated Psychosis was also obtained.
-Statistical Analysis: T-test and lineal regression models were conducted. SPSS 20.0
Results: SOCIODEMOGRAPHIC FEATURES
Genre: 71% Male / 29% Female.
Age: Mean (SD): 27.59 (+/- 9.08).
DUP: Mean (SD): 13.44 months (+/- 15.91).
REGRESSION MODEL:
Catatonia-Prolactine serum level: B = -0,087; $P = 0,58$
Catatonia-DUP: B = 0,175; $P = 0,487$
Discussion: We did not find correlation between catatonia and prolactin serum levels. We did not find either association between catatonia and DUP. Nevertheless, we are still including patients in our sample, hence these are preliminary results. In addition, some more additional analysis will be done.

T286. Preliminar results of the effectiveness of the MCT group in people with psychosis in rehabilitation services

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Background: The psychotic spectrum disorders course with a common feature, the presence schizophrenic-like positive symptoms. Usually, cognitive biases such as jumping to conclusions, self-service bias or close pressure, are underlying positive symptoms and, it is know that difficult the community functioning of people that show them (Garety *et al.*, 2005; Moritz & Woodward, 2006). Metacognition training is a group standardized treatment addressed to treat specifically cognitive biases in people with positive psychotic symptoms. This tool was created by Moritz & Woodward (2007), and studies had been described a positive results compared with other cognitive programs to reduce cognitive bias or that usual treatments to reduce positive psychotic symptomatology (Moritz *et al.*, 2011).
Methods: A crossed clinical trial randomized controlled with a Rehabilitation Treatment as Usual. A total of 21 persons between 18-60 years old, with diagnosis included in the spectrum psychotic disorders, with a score > 3 in the PANSS delusion, grandiosity or suspiciousness subscale and < 5 in the subscale of Hostility of the PANSS in the last year and, without any factor that affect cognition were included in the study.
All participants signed an informed consent. After, they were aleatorized to control (CG) or experimental (EG) group. The intervention (module A with 8 sessions) was first done in the EG while the CG received treatment as usual in the rehabilitation services. Evaluation was done in the baseline and post-treatment (after the module A).
All participants were evaluated in all assessment moments with the following instruments:
-Internal, Personal and Situational Attributions Questionnaire (IPSAQ) (Diez-Alegría, 2006).
- Rosemberg Self-esteem Scale
- Beck Cognitive Insight Scale (Beck *et al.*, 2004)
Comparisions between groups (EG or CG) were done by the difference of means of the Student t-test implemented in the SPSS/PC (version 22).
Results: A total of 21 people with psychosis were included, 8 (38.1%) women and 13 (61.9%) men. Mean age of 48 years old (SD = 10.38). Only 15 subjects completed two assessments of the study. No differences were found in the BCIS [EG:-.71+/-3.35; CG:1.6+/-7.9]; Rosenberg self-esteem questionnaire [EG:1.33+/-4.0; CG:6.5+/-5.4]; total scores and in the subscales of BCIS, self-certainty [EG:.57+/-3.7; CG:-.14+/-4.1] and self-reflectiveness [EG: 7.5+/-5.2; CG:6.0+/-4.3] and in the two subscales of the IPSAQ, externalized bias [EG:1.0+/-7.3; CG:-.57+/-5.0], personalized bias [EG:.18+/-1.8; CG:-1.1+/-1.0] between two groups.
Discussion: Our preliminary results showed that the two groups did not differ in psychotic positive symptomatology and in levels of self-esteem after the completion of the module A of the metacognition programme. These are preliminary results; however these are not into agreement with other studies. Nevertheless, this is the first time that this programme was implemented in persons that received rehabilitation treatment, and our results are done in a preliminary sample. It is possible that in this case, both modules (A and B) should be carried out to find improvement in positive psychotic symptoms and metacognitive variables.

T287. Risk of psychosis and internal migration: results from the BOLOGNA first episode psychosis study

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Background: Incidence of psychotic disorders is higher in many migrant groups; however little is known about internal migrants (IM). This study aims to describe the IR in natives (NA), IM and external migrants (EM) in Bologna, North Italy
Methods: All patients aged 18-64 years, with First Episode Psychosis (FEP), who made contact with the Bologna West psychiatric services, between 2002 and 2010, were included.
Results: 187 cases were included. Age and sex adjusted IR of psychosis per 100.000 per year were: 12.6 for NA, 25.3 for IM and 21.4 for EM. The IRR was 1.93 (1.19-3.13, $P = 0.007$) for IM and 1.79 (1.06-3.02, $P = 0.03$) for EM compared to NA.
Discussion: Rates of psychosis were significantly elevated in IM as well as in EM. This result adds evidence as to the role of migration itself (versus ethnicity) on the risk of psychosis.

T288. Anthropometric values in naïve first episode of non affective psychosis: the role of weight at birth

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Background: Patients with schizophrenia exhibit a reduced life expectancy mainly due to medical-related pathologies, such as cardiovascular diseases or type 2 diabetes mellitus. Actual body of knowledge supports that those medical conditions might have been initiated due to stressful events during fetal development. Indeed intra-uterus growth patterns do predict anthropometric measures in adulthood, which have been described as risk factors for schizophrenia and metabolic side effects. We aim to evaluate anthropometric values in a cohort of naïve patients with non affective psychosis and correlated them with a surrogate marker of the fetal environment such as weight at birth.
Methods: Weight at birth and anthropometric values from 61 naïve patients with a first episode of non affective psychosis and 87 matched controls by age and gender were evaluated.
Results: Patients show a decreased weight at birth, weight and body mass index at onset compared with controls while no differences were found in height. In a regression model, height was significantly associated with weight at birth, gender, diagnosis and the interaction of weight at birth by diagnosis; weight with age and weight at birth while body mass index with age. Weight at birth positively correlates with height in patients. Significant differences applied to gender.

Discussion: Our results support a systemic disease concept, confirming body differences (anthropometric) values at the onset while highlighting the role of a fetal environment marker, weight at birth, as a predictor of baseline characteristics implied in future metabolic risk factors.

T289. Metabolic syndrome or glucose abnormalities in first episode of psychosis?

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Background: Patients with schizophrenia exhibit a reduced life expectancy mainly due to diverse medical conditions such as cardiovascular diseases, type 2 diabetes mellitus and metabolic syndrome. Besides pharmacological secondary side-effects and unhealthy lifestyle, studies in naïve patients reflect diverse abnormalities at the onset. Although patients with a first episode of psychosis display a wide scope of metabolic abnormalities, ranging from normality till pathological values depending on the parameters studied, metabolic syndrome is the regular evaluation investigated and might not display the biochemical complexity underlying patients.
Methods: We evaluate the metabolic syndrome and glycemic homeostasis in a subset of 84 naïve patients with a first episode of non-affective psychosis. Patients and matched controls underwent an oral glucose tolerance test after an overnight fast.
Results: Patients showed a similar metabolic syndrome prevalence compared with a matched control sample (6% vs 4% $P = 0.562$) while glucose homeostasis values differed significantly (14% vs 5% $P = 0.034$).
Discussion: Our results suggest that metabolic syndrome is not a useful marker in patients before pharmacological treatment as glucose abnormalities are not detected. Abnormal glycemic homeostasis at the onset of the disease requires specific preventive measures in order to avoid future cardiovascular events. New strategies must be implemented in order to evaluate the cardiovascular risk and subsequent morbidity in patients at the onset of the disease.

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