

ABSTRACTS OPEN

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Monday, 4 April 2016
11:00 a.m.–1:00 p.m.
Poster Session/Lunch II

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M1. Childhood adversities in first episode psychosis

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Background: Childhood trauma experiences and negative life events are risk factors for psychosis. A meta-analysis found psychosis patients to have exposed to such adversities 2.7 times more likely compared to control subjects. The objective of this study was to explore negative life experiences among first episode psychosis (FEP) patients compared to control participants.

Methods: The participants were adult FEP patients ($n=67$) with first psychiatric contact for psychosis in Helsinki, Finland. They were interviewed as soon as possible after entering treatment. A matched control sample collected from the civil register ($n=41$) was also included. Symptomatology was assessed with Brief Psychiatric Rating Scale (BPRS) and other validated instruments. 11 negative childhood experiences were surveyed in a questionnaire, including financial troubles of the childhood family, frequent unemployment of parents, and parental divorce. Serious illnesses of parents and the respondent, and parents' problems with mental health or with alcohol were also inquired, as well as severe conflicts at home and school bullying.

Results: 81% of the patients and 54% of the controls reported at least one childhood adversity. The number of adverse experiences was higher among psychosis patients (mean 2.3) than among controls (mean 1.1), $P=.002$. There were no gender differences. Specifically, conflicts within the family, bullying at school, and own and parents' serious illness were reported by patients more often than controls. In the FEP group, BPRS last week 1-24 sum score, anxiety (assessed with Beck Anxiety Inventory), and obsessive-compulsive symptoms (assessed with Obsessive-Compulsive Inventory – Revised) were positively correlated with the number of adverse life events. Patients with positive mania screen result (Mood Disorder Questionnaire) reported more childhood adversities compared to screen negatives. Level of functioning, depression (assessed with Beck Depression Inventory) or BPRS suicidal symptoms were not associated with exposure to childhood adversities.

Discussion: A majority of the patients with FEP reported exposure to childhood adversities, the patients reporting more adversities than controls. These results are in line with earlier studies on the association between psychosis and childhood trauma. Compared to controls, the patients in this sample were especially exposed to serious illness, parents' serious illness, bullying, and conflicts within the family. Associations of childhood adversities with BPRS, anxiety, mania, and obsessive-compulsive symptoms were also found. Detailed results will be presented and discussed in the meeting. Understanding the association between negative life events and psychosis is important in treating FEP patients, with a possible impact on the prognosis of the illness.

M2. Clozapine as a treatment for tardive dyskinesia: a meta analysis

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Background: Tardive dyskinesia (TD) is a drug-induced movement disorder that typically occurs after long term exposure to antipsychotic drugs. Meta-analyses have investigated several TD treatment strategies and none of these strategies led to a significant overall decrease in severity. Switching to clozapine is often suggested as a treatment for TD. However, no meta-analysis to validate this intervention has been published yet.

Methods: An electronic search was carried in the PUBMED, PsycINFO, and Embase databases. As clozapine has been studied extensively and TD is frequently assessed as a secondary outcome we performed the search using a broad set of terms related to TD and clozapine. This study is being conducted in accordance to the MOOSE guidelines.

Results: Of the 8009 articles that were found 205 potentially relevant articles were selected based on their title and abstract. 58 of these articles may contain relevant information and are now being analyzed. A secondary search is also being performed on the articles published after 2013.

Discussion: The final overall results and discussion of these articles, and will be presented at the conference.

M3. Impact of adverse childhood experiences on psychotic-like symptoms and stress reactivity in daily life in nonclinical young adults

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Background: There is increasing interest in elucidating the association of different childhood adversities with psychosis-spectrum symptoms as well as the mechanistic processes involved. The present study used Experience Sampling Methodology to examine (i) associations of a range of childhood adversities with psychosis symptom domains in daily life; (ii) whether associations of abuse and neglect with symptoms are consistent across self-report and interview methods of assessment; and (iii) the role of different adversity subtypes in moderating affective, psychotic-like, and paranoid reactivity to situational and social stressors.

Methods: A total of 206 nonclinical young adults were administered self-report and interview measures to assess childhood abuse, neglect, bullying, losses, and general traumatic events. Participants received personal digital assistants that signaled them randomly eight times daily for one week to complete questionnaires about current experiences, including symptoms, affect, and stress.

Results: Self-reported and interview-based abuse, and neglect were associated with psychotic-like and paranoid symptoms, whereas only self-reported neglect was associated with negative-like symptoms. Bullying was associated with psychotic-like symptoms. Losses and general traumatic events were not directly associated with any of the

symptom domains. All the childhood adversities were associated with stress reactivity in daily life. Interpersonal adversities (abuse, neglect, bullying, and losses) moderated psychotic-like and/or paranoid reactivity to situational and social stressors, whereas general traumatic events moderated psychotic-like reactivity to situational stress. Also, different interpersonal adversities exacerbated psychotic-like and/or paranoid symptoms in response to distinct social stressors.

Discussion: The findings contribute to our understanding of how childhood adversity subtypes impact the expression of spectrum symptoms in the real world and lend support to the notion that stress reactivity is a mechanism implicated in the experience of reality distortion in individuals exposed to childhood trauma. Investigating the interplay between childhood experience and current context is relevant for uncovering potential pathways to the extended psychosis phenotype.

M4. Sexual dysfunction in patients with schizophrenia: is antipsychotic medication to blame?

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Background: Sexual dysfunction (SD) is a common side effect of antipsychotic medication, and the occurrence is often linked to prolactinaemia and the degree of dopamine D2 receptor blockade. Recent studies have described a high prevalence of SD in unmedicated patients. This challenges the current notion of SD as merely a side-effect of antipsychotic medication. The present study aims to characterize the prevalence of SD in a large group of antipsychotic-naïve schizophrenia patients before and after first antipsychotic treatment. Further, we explored a possible effect of gender on SD and prolactinaemia.

Methods: As a part of a large multimodal study (the PECANS study), a total of 69 patients were examined before and after six weeks of monotherapy with the relatively selective D2 receptor antagonist, amisulpride. Data on SD were obtained from UKU (Udvalget for Kliniske Undersøgelser) and fasting, morning values of S-prolactin (s-prl) were obtained.

Results: Baseline

SD: UKU was available on 51 patients (21 females). Increased sexual desire was reported by 9 patients (18%), whereas 17 (36%) reported decreased sexual desire and 11 (41%) reported orgasmic dysfunction. Gynecomastia and galactorrhoea was reported by 7 (12.1%) respectively 4 (6.1%). There were no gender differences in the report of sexual dysfunctions. Prolactin: S-prl was measured in 56 patients (21 females), mean 0.28 IU / L (SD±0.17). Six patients (10%) had hyperprolactinaemia. There was no gender effect on s-prl. S-prl correlated positively with orgasmic dysfunction at baseline ($P=0.003$). **Follow-up:** SD: UKU was available on 42 (18 females). Orgasmic dysfunction was the only SD with a significant change (decrease) over time ($P=0.024$). Gender separate analyses, revealed that females had an increase in the prevalence of gynecomastia ($P=0.021$) and galactorrhoea ($P=0.003$). Prolactin: S-prl level was available in 37 patients (17 females). Repeated measures ANOVA showed significant effect of gender ($P=0.009$) and time ($P<0.001$), as s-prl increased over time, with largest increase in females. There was no interaction ($P=0.161$). At follow up, there was a positive correlation between s-prl and galactorrhoea ($P=0.001$), and gynecomastia ($P=0.014$), but no correlation with any other symptoms of SD or amisulpride dose.

Discussion: We found a high prevalence of SD at baseline, and contrary to the conventional notion, we found no relation between antipsychotic induced s-prl increase and SD in general. There was a significant effect of amisulpride treatment on s-prl, which correlated with galactorrhoea and gynecomastia, primarily observed in females. Since SD is a common reason for discontinuation of antipsychotic treatment, our findings stress the importance of clarifying the degree of SD before initiating antipsychotic treatment.

M5. The effect of childhood abuse on outcome in individuals at ultra high risk for psychosis

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Background: The association between childhood abuse and psychosis has been demonstrated in previous research (Bendall *et al.*, 2008, Varese *et al.*, 2012). However, the effect of childhood abuse on transition to psychosis and other outcomes in individuals at Ultra-High Risk (UHR) for psychosis is not clear yet. The present study aimed to examine the effect of childhood abuse on transition to a first episode of psychosis in UHR subjects and aimed to examine the effect of childhood abuse on other clinical and functional outcomes.

Methods: Participants were UHR subjects of the EDIE-NL study. Structured Equation Modeling (SEM) was used to examine the effects of childhood abuse on transition to psychosis, depression, anxiety, and functional outcome at 4-year follow-up.

Results: Twenty-three participants transitioned to psychosis (21.9%). None of the childhood trauma domains were significantly associated with transition to psychosis. Physical abuse was associated with higher depression rates ($b=0.420$, $P=0.003$) and lower social functional outcome ($b=-0.243$, $P=0.011$) at follow-up. In addition, emotional neglect was negatively associated with social functioning ($b=-0.287$, $P=0.025$).

Discussion: Our results indicate that childhood trauma is more strongly associated with depression and social functioning than with transition to psychosis at 4-year follow-up, suggesting that childhood trauma may not be specifically associated with higher transition rates for subjects in the UHR phase.

M6. Is it worth to give clozapine a second chance? A series of 12 subjects rechallenged with clozapine following a neutropenia

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Background: The superiority of Clozapine over other antipsychotics in treatment resistant schizophrenia has been consistently replicated in many studies. Despite its propensity to induce serious side-effects, Clozapine still remains the antipsychotic of choice in such population. Yet, according to the product monograph, Clozapine must be immediately discontinued if a patient develops significant leukopenia or neutropenia, and further treatment with clozapine is contraindicated.

Methods: The aim of this study is to describe characteristics and trajectories of Clozapine treated patients who have been rechallenged to a second trial of clozapine following the occurrence of a significant neutropenia (i.e., neutrophil count $<1.5 \times 10^9/L$). We reviewed all situations in which patient treated at Institut Universitaire en Santé Mentale de Québec between 1 January, 1998 and 31 January, 2013 underwent a second clozapine trial following a significant neutropenia.

Results: Among twelve patients who were rechallenged, 1 (8.3%) experienced a second significant neutropenia that was eventually reversed by two consecutive doses of filgrastim; this patient has remained on Clozapine for the last five years without any other complication. Nine (82%) subjects were still receiving clozapine at the time of data collection, and one patient died from medical conditions deemed unrelated to Clozapine use. Median clozapine exposure after rechallenge was 4.7 years (0.1 to 14.7 years). All patients who underwent this rechallenge improved on the CGI-S subscale indicating a positive clinical response.

Discussion: As shown by our results, clinical benefits from Clozapine rechallenge after neutropenia may outweigh the risks for some patients. Further studies are needed to determine with greater certainty which patients are the best candidates for a rechallenge with clozapine after neutropenia.

M7. Risk factors for tremor in a population of patients with severe mental illness: an 18-year prospective study in a geographically representative sample

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Background: Tremor is one of the most common movement disorders in psychiatry and can be an important reason for treatment non-compliance. Despite a wealth of knowledge on the drugs that can cause or exacerbate tremors, little research has been done into risk factors that influence their development in chronically medicated psychiatric populations.

Methods: A prospective study of SMI patients receiving care from the only mental health service of the previous Dutch Antilles. Eight clinical assessments, over 18 years, focused on movement disorders and medication use. Incidence and prevalence of resting tremor (RT), and (postural) action tremor (AT) were assessed, as were current and previous, time-lagged, risk factor associations.

Results: Yearly tremor incidence rate was 2.9% and mean tremor point-prevalence was 18.4%. Over a third of patients displayed tremor during the study. AT was less prevalent and less persistent (5.2% and 25.0%, respectively) than RT (17.1% and 65.3%).

Having RT was associated with age (OR=1.07 per year; 95% Confidence Interval 1.03-1.11), sex (OR=0.17 for males; 0.05-0.78), cocaine use (OR=10.53; 2.22-49.94), dyskinesia (OR=0.90 per unit; 0.83-0.97), and bradykinesia (OR=1.16 per unit; 1.09-1.22). Developing RT was strongly associated with previous measurement RT (OR=9.86; 3.45-17.94), as also with previous measurement RT severity (OR=1.22 per unit; 1.05-1.41) and higher anticholinergic load (OR=1.24 per point; 1.08-1.43). Having AT was associated with tremor-inducing medication (OR=4.54; 1.90-10.86), cocaine use (OR=14.04; 2.38-82.96), and bradykinesia (OR=1.07 per unit; 1.01-1.15). Developing AT was associated with, previous AT severity (OR=2.62 per unit; 1.64-4.18) and tremor reducing medication (OR=0.08; 0.01-0.55).

Discussion: Long-stay SMI patients are very prone to developing tremors, which show a relapsing-remitting course. Differentiation between RT and AT is important as risk factors differ, and they require different prevention and treatment strategies.

M8. The effect of childhood trauma and five-factor model personality traits on exposure to adult life events in patients with psychotic disorders

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Background: Recent life events are associated with transition to and relapse in psychosis. General population studies show that childhood trauma and personality characteristics play a role in proneness to adult life events. Little is known about the contribution and interrelatedness of these characteristic in psychotic disorders. Knowledge about pathways to adult life events may provide information relevant for relapse prevention programs and treatment. Therefore, we investigated in patients with psychotic disorders whether Five-Factor Model personality traits and childhood maltreatment predict adult life events, and whether the effect of childhood maltreatment on life events is mediated by personality traits.

Methods: 163 patients with psychotic disorders were assessed on the Five-Factor Model personality traits neuroticism, extraversion, openness, agreeableness, conscientiousness, recent negative and positive life events, and history of childhood abuse and neglect.

Results: Negative life events were significantly correlated with childhood abuse ($r=0.251$), openness to experiences ($r=0.229$), and extraversion ($r=0.219$), and openness to experiences was significantly correlated with abuse ($r=0.157$). The relationship between abuse and adult life events ($b=0.25$) was partly mediated by openness to experiences: this indirect effect was tested with use of 10,000 bootstrapped samples. The bootstrapped unstandardized indirect effect was 0.07, and the 95% confidence interval ranged from 0.008 to 0.182. Thus, the indirect effect was statistically significant. Positive life events were significantly positively correlated with openness to experiences ($r=0.181$) and extraversion ($r=0.209$). Neglect increased the chance for experiencing less positive events ($r=-0.157$). Neglect was also negatively correlated with extraversion ($r=-0.214$). As such we explored mediation of the effect of neglect on positive life events by extraversion whilst including age as a covariate. Results indicated that the association between neglect and positive life events was no longer significant after age was included as covariate.

Discussion: Findings suggest that childhood trauma predisposes to experiencing more negative adult life events and fewer positive adult life events, suggesting that childhood adversities contribute to a propensity that a person encounters later adversities (environment-environment correlation). This effect is partly mediated by personality. Our findings stress the importance of trauma based therapies in psychosis; also, future research could focus on mechanisms leading to positive life events, as positive life events may buffer against mental problems.

M9. Cabergoline use to counteract antipsychotic symptomatic related hyperprolactinemia: a retrospective longitudinal case-series

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Background: Cabergoline, a dopaminergic agonist, is currently used to correct hyperprolactinemia secondary to antipsychotics use in clinical setting. However, the risk/benefit ratio of such a practice is not well documented.

Methods: Our main objective is to describe the 12-month clinical evolution of patients in whom cabergoline was used as an add-on to antipsychotics to reverse symptomatic antipsychotic-related hyperprolactinemia. We identified 44 cases from the Institut universitaire en santé mentale de Québec for whom Cabergoline was introduced between January 1, 2000 and December 31, 2014. Prolactin levels pre- and post introduction of Cabergoline were compared and CGI-S were retrospectively rated, at baseline, 1, 3, 6, and 12 months.

Results: Following cabergoline addition, significant mean prolactin level reductions were observed at 3 and 6 months (respectively, 25.8% $P=0.0019$ and 37.8% $P=0.0045$) but for only 6/44 patients, normalization was reached over 12 months. Although reasons to introduce cabergoline were initially documented, lack of further documentation of hyperprolactinemia-induced side-effects was highlighted in this review. Overall, psychopathology severity was not affected by cabergoline use, as assessed by Clinical Global Impression scores since mean CGI-S scores remained stable between 3.1 and 3.7/7, thorough the following year.

Discussion: In this case series, use of cabergoline was associated with a modest but statistically significant reduction of prolactin levels without any deterioration of psychopathological symptoms. However, this review emphasizes the difficulty for clinicians to document hyperprolactinemia-induced side-effects, even in patients for whom a decision was made to add cabergoline in such situation.

M10. Differential effects of childhood trauma and cannabis use disorders in patients suffering from non-affective psychosis

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Background: Childhood trauma (CT) and cannabis use are both environmental and modifier risk factors for schizophrenia. However,

little is known about how they interact together. We examined the main effect of each of the two environmental factors on the course, the clinical expression of the disease, and its psychosocial repercussions using a large set of variables, and we tested whether and how cannabis and CT interact together to influence these outcomes.

Methods: A sample of 366 subjects who met the DSM-IV-TR criteria for schizophrenia or schizoaffective disorder has been recruited through the FACE-SCZ (Fondamental Advanced Centre of Expertise – Schizophrenia) network. Patients fulfilled a large standardized clinical evaluation including Structured Clinical Interview for DSM Disorders-I (SCID-I), Positive and Negative Symptoms Scale (PANSS), Global Assessment of Functioning (GAF), Short-Quality of Life-18 (S-QoL-18), and Medication Adherence Rating Scale (MARS). We assessed CT with Childhood Trauma Questionnaire and cannabis status with SCID-I.

Results: After adjustment on age and gender, CT significantly predicted number of hospitalizations, PANSS total, positive, and general scores, GAF, and S-QoL-18 scores. Cannabis use disorders significantly predicted age of onset, and MARS score. We did not observe any significant interaction between CT and cannabis use disorders on our variables of interest. However, we found evidence for a correlation between the two risk factors.

Discussion: CT and cannabis have differential deleterious effects on clinical and functional outcomes in patients with schizophrenia. CT exposure is associated with more hospitalizations, more severe positive and general symptoms (i.e. depression, anxiety, disorganization, and impulsivity-related symptoms), and worsen functioning and quality of life. Cannabis abuse was associated with an earlier age of onset and a worsen adherence to treatment. Our results shed new light on the deleterious impact of CT and cannabis use disorders of schizophrenia often considered in isolation, and reiterate the importance to study different risk factors together. They also highlight the need to systematically assess with patients their history of traumatic experiences and cannabis use disorders to adopt suitable therapeutic interventions.

M11. Childhood maltreatment, antenatal attachment, and symptom severity in women at risk of postpartum psychosis

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Background: Postpartum or Puerperal Psychosis (PP) is the most severe psychiatric disorder associated with childbirth. Women with a diagnosis of bipolar affective disorder, schizoaffective disorder or previous postpartum psychosis have up to 50-70% probability to develop the illness after giving birth, with devastating consequences for both mother and child. Still, no study has examined antenatal attachment in women at risk of this disorder. This study aimed to investigate antenatal attachment in women at risk of PP and its association with a history of childhood maltreatment and clinical symptoms around the birth.

Methods: 34 women at risk of PP and 41 healthy controls were included in the study. Childhood maltreatment was investigated using the Childhood Experiences of Care and Abuse Questionnaire (CECA-Q) (Bifulco *et al.* 2005) at 25-30 weeks gestation. Antenatal attachment was assessed using the Maternal Antenatal Attachment Scale (MAAS) (Condon *et al.* 1993) in the third trimester of pregnancy. This scale provides an overall measure of attachment (Total attachment), as well as measures of quality of the affective experience towards the baby (Quality of attachment) and of the time spent thinking about the baby/intensity of preoccupation (Time spent in attachment). Sub-clinical symptoms in the week before and after delivery were assessed using the Beck Depression Inventory-BDI (Beck *et al.* 1996); the Highs Scale (Glover *et al.* 1994), the Prodromal Questionnaire Brief Version-PQ-B (Loewy *et al.* 2011) and the State-Trait Anxiety Inventory-STAI (Spielberger *et al.* 1970).

Results: Results showed that women at risk of PP (47.1%) were more likely to experience childhood maltreatment than healthy controls (17.9%) ($N=73$, $\chi(1)^2=7.1$, $P<0.05$). In particular, significantly more women at risk of PP (30.3%) experienced sexual abuse compared to healthy controls (2.4%) ($N=74$, $\chi(1)^2=11.2$, $P<0.01$). Women at risk of PP (24.2%) were also more likely than healthy controls (7.7%) to have experienced antipathy ($N=72$, $\chi_{-1}^2=23.8$, $P=0.052$). There were

no significant differences between the groups in rates of neglect and physical abuse.

Among women at risk, those who had experienced sexual abuse had more "Time spent in attachment" than those who had not experienced it, albeit at trend level (Mean = 30.4, SD = 3.4; Mean = 28, SD = 2.5, respectively, $t(20)=1.9$, $P=0.076$). There was no significant difference in "Time spent in attachment" for the other types of abuse. "Quality of attachment" and "Total attachment" were not significantly different between women who had experienced childhood maltreatment and those who had not. Most women at risk of PP also had low "Quality of attachment" and high "Time spent in attachment", resulting in an anxious, ambivalent or affectless preoccupation towards their babies. Women at risk of PP also showed a negative correlation between "Quality of attachment" and depressive (both during the week before and after the delivery), manic (in the week before the delivery) and anxiety symptoms (at 6 days postpartum). Furthermore, "Total attachment" was significantly correlated with higher anxiety.

Discussion: Results showed that women at risk of PP, particularly those who have experienced sexual abuse, have high levels of anxiety towards their babies. As such, this preoccupation may affect the positive aspects of attachment, as evidenced by the anxious style of attachment that these women are showing towards their babies. Moreover, high attachment could be a protective factor for maternal wellbeing around the birth. Therefore, preventive interventions during pregnancy may focus on helping mothers to have more positive experiences and less preoccupation towards their babies.

M12. Adjunctive aripiprazole for risperidone/paliperidone induced hyperprolactinemia. effect of functional polymorphisms in dopamine-related genes

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Background: Hyperprolactinemia (HPR) is an adverse effect associated with risperidone/paliperidone administration. In addition, HPR may be attenuated by adjunctive treatment with aripiprazole. We aim to evaluate if functional polymorphisms in dopamine-related genes may be associated to both effects.

Methods: Forty two schizophrenic patients, 30 men and 12 women, who were receiving risperidone (20 men and 8 women) or paliperidone (10 men and 4 women) for at least three weeks, were included. Serum prolactin (PRO) was assessed before (D0) and after 7 (D7), and 28 days (D28) of treatment with 5 mg/day of adjunctive aripiprazole.

We genotyped the following polymorphisms: catechol-O-methyltransferase (COMT) ValMet, Monoamine Oxidase A (MAOA) promoter VNTR, and D2 dopamine receptor (D2DR) Taq1A.

Results: Values are presented as mean and 95%CI. HPR was present in 38 patients on D0, 32 patients on D7 and 28 patients on D28. Serum PRO decreased significantly from D0 to D28 (repeated analysis of variance, $n=42$: $F=9.69$, $P<0.001$. PRO D0≠D7 and D28), although normalization was achieved only in 10 patients. In men, mean PRO concentration was 43ng/ml [37-49] on D0, 32 ng/ml [27-38] on D7 and 32 ng/ml [25-38] on D28. In women, mean PRO values were 108 ng/ml [67-150] on D0, on 92 ng/ml [51-133] D7 and 56 ng/ml [35-77] on D28. In men, the concentrations of PRO on D0 (52 ng/ml; 31-45) and on D7 (41 ng/ml; 30-52) were higher in the patients treated with paliperidone than in those receiving risperidone (D0: 38 ng/ml, 43-62. D7: 28 ng/ml, 22-35) (rank test $P=0.023$ and 0.028 , respectively). The concentration of PRO on D28 was lower in male patients with low-activity genotypes in MAOA VNTR polymorphism than in the high-activity genotypes carriers (MAOA gene is in chromosome X) (Rank test $P=0.037$). Finally, only 11 patients presented adverse events potentially related to HPR. All of them had the CC genotype in D2DR Taq1A polymorphism (Fisher Exact Test, $P=0.007$).

Discussion: The effect of 5 mg/day adjunctive aripiprazole treatment on serum PRO concentrations and HPR normalization is consistent with other studies. Higher rates of HPR normalization have been reported in some studies, using higher doses or longer duration of

aripiprazole treatment (1,2). It is possible that patients carrying the low-activity MAOA VNTR genotypes, maintained somewhat higher dopamine levels and would normalize the HPR with lower doses of aripiprazole. The association between HPR related symptomatology and D2DR Taq1A polymorphism is different from other reports, and needs further investigation. It has been reported a lack of association (3) or association of the D2DR Taq1A T allele with HPR related symptomatology (4).

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M13. Second-generation antipsychotic combination is a major risk factor for akathisia and long-term benzodiazepines don't help. Results from the FACE-SZ Cohort

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Background: The main objective of this study was to determine the prevalence of akathisia in a community-dwelling sample of patients with schizophrenia, and to determine the effects of treatments and the clinical variables associated with akathisia.

Methods: 372 patients with schizophrenia or schizoaffective disorder were systematically included in the network of FondaMental Expert Center for Schizophrenia and assessed with validated scales. Akathisia was measured with the Barnes Akathisia Scale (BAS). Ongoing psychotropic treatment was recorded.

Results: The global prevalence of akathisia (as defined by a score of 2 or more on the global akathisia subscale of the BAS) in our sample was 18.5%. Patients who received antipsychotic polytherapy were at higher risk of akathisia and this result remained significant (adjusted odd ratio=2.04, $P=0.025$) after controlling the influence of age, gender, level of education, level of psychotic symptoms, substance use comorbidities, current administration of antidepressant, anticholinergic drugs, benzodiazepines, and daily-administered antipsychotic dose. The combination of second-generation antipsychotics was associated with a 3-fold risk of akathisia compared to second-generation antipsychotics used in monotherapy.

Discussion: Our results indicate that antipsychotic polytherapy should be at best avoided and suggest that monotherapy should be recommended in cases of akathisia. Long-term administration of benzodiazepines or anticholinergic drugs does not seem to be advisable in cases of akathisia, given the potential side effects of these medications.

M14. Birth by cesarean section and schizophrenia. Results from the multi-center FACE-SZ dataset

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Background: Children born by cesarean section ("c-birth") are known to have different microbiota and a natural history of different disorders including allergy, asthma, and overweight compared to vaginally born ("v-birth") children. C-birth is not known to increase the risk of schizophrenia (SZ), but to be associated with an earlier age at onset. To further explore possible links between c-birth and SZ, we compared clinical and biological characteristics of c-born SZ patients compared to v-born ones.

Methods: 454 stable community-dwelling SZ patients (mean age = 32.4 years, 75.8% male gender) were systematically included in the multicenter network of FondaMental Expert Center for schizophrenia (FACE-SZ).

Results: Overall, 49 patients (10.8%) were c-born. These patients had a mean age at schizophrenia onset of 21.9+/-6.7 years, a mean duration of illness of 10.5+/-8.7 years and a mean PANSS total score of 70.9 +/-18.7. None of these variables was significantly associated with c-birth. Multivariate analysis showed that c-birth remained associated with lower peripheral inflammation (aOR=0.07; 95%CI 0.009-0.555, $P=0.012$) and lower premorbid ability (aOR= 0.945; 95%CI 0.898-0.994, $P=0.03$) independently of age, age at illness onset, sex, education level, psychotic and mood symptomatology, antipsychotic treatment, tobacco consumption, birth weight, and mothers suffering from schizophrenia or bipolar disorder.

Discussion: Altogether, literature data as well as our results suggest that c-birth is associated with lower weight gain and lower inflammation in schizophrenia, which could be explained by microbiota differences. Further studies should take into account c-birth when exploring the role of microbiota in SZ patients.

M15. Peripheral sub-inflammation is associated with antidepressant consumption in schizophrenia. Results from the multi-center FACE-SZ dataset

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Background: The relation between C-Reactive Protein (CRP), depression, and antidepressant consumption has been well explored in major depressive disorders but not in schizophrenia, which has a high rate of depression comorbidity. The objectives of this study were: (i) to determine the prevalence of abnormal CRP levels, depression, and antidepressant consumption in a multicenter community-dwelling sample of subjects with schizophrenia (ii) to determine the association between abnormal CRP levels, depression, and antidepressant consumption in schizophrenia.

Methods: 219 stable patients with schizophrenia (mean age = 31.6 years, 75.3% male gender) were systematically included in the multicenter network of FondaMental Expert Center for schizophrenia (FACE-SZ) and assessed with a dedicated electronic medical record including the Structured Clinical Interview for DSM-IV Axis I Disorders and Calgary Depression Scale for depression. High sensitivity CRP (hs-CRP) was measured with an assay using nephelometry (Dade Behring). Abnormal CRP level was defined by levels >3 mg/L. Current medication was recorded.

Results: Overall, 63 subjects (28.8%) were found to have abnormal CRP levels, 43 (20.1%) received a diagnosis of comorbid current depression, and 51 (31.9%) had ongoing antidepressant treatment. In univariate analysis, abnormal CRP levels were found to be significantly associated with body mass index (BMI) ($P < 0.0001$), hypertriglyceridemia ($P=0.0015$), high waist circumference ($P < 0.0001$), metabolic syndrome ($P=0.0011$), abdominal obesity ($P < 0.0001$), and with antidepressant consumption ($P=0.01$), while depression, psychotic symptomatology, age of onset, illness duration, sociodemographic characteristics, current tobacco or cannabis status, hypertension or high fasting glucose were not (all $P > 0.05$).

In a multivariate model, abnormal CRP was associated with antidepressant consumption independently of other confounding variables (adjusted Odds Ratio=2.8, 95% confidence interval 1.22-6.62). Metabolic syndrome was also independently associated with abnormal CRP (adjusted Odds Ratio=2.6, 95% confidence interval 1.01-6.71).

Discussion: Abnormal CRP levels in schizophrenia were found to be associated with antidepressant consumption, but not with current depression. Several potential mechanisms may be suggested. Altogether, these results suggest that inflammation may explain resistance to antidepressant treatment in schizophrenia. Antidepressant consumption should also be systematically recorded in future studies exploring inflammation in schizophrenia as a potential confounding factor.

M16. Early cognitive inflammaging in schizophrenia

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Background: Inflammation (measured by blood C-reactive protein (CRP) level) was associated with cognitive decline in healthy aging populations ("cognitive inflammaging"). High rates of abnormal CRP levels were described in schizophrenia (SZ), with inconsistent associations with impaired cognitive functions. The aim of the present study was to investigate the cognitive impairment associated with abnormal CRP levels in a large multi-centric sample of community-dwelling subjects with schizophrenia, using a comprehensive one-day-long neuropsychological battery.

Methods: 369 community-dwelling stable young SZ subjects (76.2% men, mean aged 32.7 years) were included in this study. A comprehensive battery of neuropsychological tests was detailed. Abnormal CRP level was defined as > 3 mg/L.

Results: Multiple factor analysis revealed that abnormal CRP levels, found in 104 patients (28.2%), were associated with impaired General Intellectual Ability and Abstract Reasoning (aOR=0.56, 95%CI 0.35-0.90, $P=0.014$), independently of age, sex, education level, psychotic symptomatology, treatments, and addiction comorbidities. Abnormal CRP levels were also associated with the decline of all components of working memory (respectively $P=0.033$, 0.04, 0.006 and 0.004) and a wide range of other impaired cognitive functions including memory ($P=0.026$) and learning abilities ($P=0.035$), semantic memory ($P=0.026$), mental flexibility ($P=0.044$), visual attention ($P=0.004$), and speed of processing ($P=0.04$).

Discussion: Combined with non-SZ literature data, our results suggest that abnormal CRP level is associated with early cognitive impairment in schizophrenia that shares some similarities with CRP-associated cognitive decline described in aging populations. The evaluation of the effectiveness of neuroprotective anti-inflammatory strategies is needed to prevent cognitive inflammaging in schizophrenia.

M17. Can lessons learnt from cardiac stress testing be applied to the early identification of psychosis?

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Background: There is an urgent need to develop methods to identify individuals at risk for psychotic disorders with greater precision and as early as possible. Schizophrenia is a complex disorder that shares some similarities with coronary artery disease (CAD) including the existence of modifiable (e.g. drug use) and non-modifiable (e.g. genetics) risk factors. Existing screening programs identify vulnerable populations primarily based on family history or attenuated psychotic symptoms, which is analogous to relying on family history of CAD or symptoms (chest pain) to identify those at risk for CAD. At present, a prerequisite for a diagnosis of schizophrenia is the occurrence of a psychotic episode. Therefore, attempting to detect schizophrenia on the basis of psychosis is analogous to diagnosing CAD after the occurrence of a myocardial infarction (MI). The introduction of cardiac stress testing (CST) has revolutionized the detection of CAD and the prevention, and management of angina and MI.

Methods: In CST an individual's cardiovascular system is stressed either through physical exercise, pharmacological stimulation or both so as to unmask coronary hypoperfusion; the latter manifests as physical symptoms, and changes in vital signs and/or EKG, and is predictive of MI. CST is clinically useful even though it does not reveal the primary pathophysiology of CAD i.e., plaque, but rather unmasks the consequences of plaques i.e. coronary hypoperfusion. By analogy, a stress test designed to unmask the risk for psychotic disorder might do so by manifesting the consequences of the underlying pathophysiology without revealing the precise pathophysiology. This is important given that the precise pathophysiology of psychotic disorders remains elusive and thus, its elucidation might not be a necessary prelude to developing a screening test that is clinically useful.

Results: We suggest that analogous to CST for CAD, a psychosis stress test (PST) can be developed. But like CST, for PST to become a clinically useful tool, will involve the selection and testing of suitable stimuli, outcome measures, and target population. An ideal PST will be one with high sensitivity, specificity, and positive and negative predictive value in identifying at-risk individuals. An ideal stimulus for PST should have the following properties: 1) measurable dose, 2) uniform delivery, 3) good dose-response, 4) repeatability, 5) good test-retest reliability, and 6) good safety and tolerability.

Discussion: Furthermore, a preferred and accepted stimulus for PST would be one that is known to be experienced by the population being tested outside of testing conditions – like physical exertion for CST. Psychosocial stress stimuli have been shown to induce transient psychological stress in healthy subjects as well as patients with schizophrenia and individuals with a family history of psychosis. Such stress paradigms would have great acceptability because the stress induced is modest, transient and well-tolerated. However, psychosocial stress stimuli are difficult to quantify and dose, have limited repeatability and may not elicit a large enough or specific enough response to identify risk of schizophrenia. Pharmacological stimuli offer some advantages over psychological stimuli such as measurable dose, uniform delivery method, measurable dose-response and repeatability. Thus far, psychological and pharmacological stimuli have been directed towards studying the pathophysiology of schizophrenia but not for the early detection and risk stratification of at-risk for psychosis individuals. Like with CST, an iterative process may be expected in refining the group who would benefit most from a PST. Finally, a clinically useful PST will need to have an established risk/benefit.

M18. Predicting transition to psychosis on the basis of electrophysiological self-suppression abnormalities in ultra-high risk individuals

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Background: There is strong evidence that people with schizophrenia fail to suppress the sensory consequences of their own actions. These self-suppression abnormalities represent a plausible biomarker for the disorder as they provide a prima facie explanation for some of the most characteristic symptoms of schizophrenia which involve the misattribution of self-generated thoughts and actions to external sources. The present study investigated (1) whether self-suppression abnormalities are present in non-psychotic individuals at ultra-high risk (UHR) of developing a psychotic disorder, and (2) whether they are more severe in UHR individuals who subsequently transition to full-blown psychosis.

Methods: Twenty-eight individuals deemed at UHR of developing a psychotic disorder (on the basis of CAARMS criteria) were recruited from the PACE Clinic, OYRGEN, Melbourne. These participants were followed up for 24 months and psychosis transition was assessed. The UHR participants were compared to a matched group of 28 healthy control individuals. Participants were asked to press a button at will which resulted in a simple tone (1000 Hz) being presented to their headphones (Self condition). The comparison condition was of the tones being generated automatically by the computer (External condition) Electroencephalographic data were recorded continuously (64 channels, re-referenced to mastoids). The dependent variable was N1-suppression, which was calculated as the amplitude of the N1-component in the External condition minus the Self condition.

Results: The 28 UHR participants exhibited lower levels of N1-suppression compared to the 28 healthy controls. Furthermore, when the UHR group was divided into the 7 participants who transitioned to psychosis (UHR+) and the 21 UHR participants who did not (UHR-), the UHR+ group was found to exhibit lower levels of N1-suppression compared to both the HC and UHR-groups.

Discussion: The results indicate that (1) reduced levels of electrophysiological suppression to self-initiated sensations are present in UHR individuals, and (2) these reductions are more severe in UHR individuals who subsequently transition to full-blown psychosis

relative to those who do not. This finding is significant as it suggests that electrophysiological self-suppression deficits could represent a theoretically-grounded and empirically useful biomarker for predicting which individuals will subsequently transition to psychosis, and who would thus benefit most from prophylactic treatment.

M19. Cytokine dysregulation in cerebrospinal fluid of patients with schizophrenia

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Background: The inflammatory hypothesis of schizophrenia has gained considerable traction over the last few years given data that has recently emerged. In addition to the increased risk of schizophrenia associated with prenatal infections with Influenza, T. Gondii, or Herpes Simplex Virus type 2, recent data obtained from large scale GWAS studies have consistently reported a genome-wide significant association between the Major Histocompatibility Complex and schizophrenia. Moreover, celecoxib and aspirin, both anti-inflammatory medications, when used as add-on treatment to antipsychotic medications, have shown to be partially useful, especially in patients in the early psychosis phase.

Given that the inflammatory response is mediated by cytokines, some authors have measured cytokine levels as biomarkers in peripheral blood and cerebrospinal fluid (CSF). However, very few studies have been conducted so far, and to date, only one meta-analysis has reported pooled data of cytokines measured in cerebrospinal fluid in schizophrenia. Therefore, our goal is to twofold: 1) to report on cytokine levels in CSF of a group of ten patients with chronic schizophrenia and ten healthy volunteers (The Zucker Hillside Study), and 2) to conduct a meta-analysis of cytokines in CSF of patients with schizophrenia which will include all new relevant data.

Methods: In the Zucker Hillside Study ten patients with a schizophrenia spectrum disorder diagnosis and ten healthy volunteers underwent a lumbar puncture. 20-25 mls of CSF were obtained from each subject. Cytokine analyses were conducted using the Q-plex Human Cytokine Screen array. For the meta-analysis, a literature search was conducted using PubMed, Google Scholar, and ISIS web of Knowledge. Any study that reported cytokine levels in CSF in patients with a schizophrenia spectrum diagnosis was included in the analysis. Statistical analyses were conducted using STATA 11.2 using the Metan, metafunnel, and metabias commands.

Results: In the Zucker Hillside study, levels of IL-1 β were significantly higher in patients with schizophrenia compared to controls (mean = 15.3 pg/ml, SD = 1.9 vs. mean = 13.1 pg/ml SD = 2.1; $P = 0.02$). The same was observed with IL-8 (mean = 31.0 pg/ml, SD = 2.3 vs. mean = 18.8 pg/ml, SD = 1.3; $P = 0.0002$). Even though IL-6 was also elevated in patients compared to controls (mean = 1.7 pg/ml, SD = 0.4 vs. mean = 1.0 pg/ml, SD = 1.3), it did not reach statistical significance ($P = 0.08$). Thirteen studies were included in the meta-analysis. Random effect analysis showed that IL-6 was significantly higher in patients with schizophrenia compared to healthy controls (6 studies, SMD = 0.49, 95%CI = 0.22, 0.75, $P < 0.001$). IL-8 levels were also significantly higher in patients vs. controls (3 studies, SMD = 1.75, 95% CI = 0.13, 3.38, $P = 0.034$). There were no statistically significant differences between patients and controls in IL-1 A (2 studies), IL-1B (4 studies), IL-2 (4 studies), TGF-B1 (2 studies), and TGF-B2 (2 studies).

Discussion: Levels of IL-1B and IL-8 were significantly higher in our sample of 10 patients with schizophrenia compared to 10 healthy controls. Levels of IL-6 were also higher and approached statistical significance. Results from the meta-analysis showed that levels of IL-6 and IL-8 were significantly higher in patients compared to controls. In conclusion, pro-inflammatory cytokines seem to be elevated in CSF of patients with schizophrenia and provide support to the inflammatory hypothesis in schizophrenia. More studies, including longitudinal studies, are need to understand the role of cytokines and neuroinflammation in schizophrenia.

M20. Antioxidative function of albumin may stratifying two different groups in first-episode, drug-naive schizophrenic patients

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Background: Metabolic processes are changed in the patient with schizophrenia even in first episode of disease. It is important to investigate the pathophysiological mechanisms of the first episode of schizophrenia (FES). The aim is to investigate some biochemical and biophysical parameters in FES patients.

Methods: The group of patients who were investigated clinically and biochemically consists of 26 persons (11 women and 15 men, average age 28.2 ± 9.5 years) with the first psychotic episode (F20.0; F20.3). Some biochemical parameters, representing the aminergic systems (semicarbazide-sensitive amine oxidase), and antioxidant function of albumin (concentration of SH-groups), the main source of thiols of plasma, were studied. Concentration of malondialdehyde (end product of lipid peroxidation processes) was measured. These parameters in all patients were estimated following the admission and prior to any treatment.

Results: The severity of the disorder on admission to the clinic according to PANSS score was 75.5 ± 2.2 (i.e., moderately severe). Patients with FES were characterized by a significant decrease of serum semicarbazide-sensitive amine oxidase activity (by 29%; $P < 0.001$) in comparison to the controls ($n = 10$). Kinetic coefficient, KV, - reactivity of SH-group of serum albumin - was measured in reaction with thiol-specific reagent - dithiobisnitrobenzoic acid. It was decreased in FES patients (by 24%; $P < 0.05$) in comparison to controls. In the group of patients negative correlation of concentration of malondialdehyde and negative PANSS score was observed ($r = -0.55$; $P < 0.01$). Moreover, patients with FES can be divided into two groups - with high KV (0.38 ± 0.02 ; $n = 6$) and with low KV (0.12 ± 0.01 ; $n = 21$), both $P < 0.05$ comparing with control group (0.27 ± 0.03 ; $n = 10$).

Discussion: These results show that FES patients are characterized by pronounced metabolic disturbances and they are correlated with clinic severity of the disorder. Further, group of patients with FES is heterogeneous, that may probably lead to differences in therapy in future and can serve as potential biomarkers.

M21. The state of antioxidant enzyme activities in patients with chronic schizophrenia under antipsychotic treatment

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Background: To investigate antioxidant enzyme activities in red blood cells (RBC) of schizophrenic patients under pharmacotherapy with traditional antipsychotics.

Methods: There were investigated 26 patients with following diagnosis (according to ICD-10): F20.0 -paranoid schizophrenia; F20.5 - residual schizophrenia and F20.6 - simple schizophrenia. Biochemical parameters - glutathione peroxidase (GP), glutathione reductase (GR), glutathione-S-transferase (GT), catalase (CAT), and glucose-6-phosphate dehydrogenase (G-6-PD) activities - were estimated spectrophotometrically in RBC before and after 6 weeks of pharmacotherapy with traditional antipsychotics in forms of mono- or combined therapy. Control group consists of 39 mentally and somatically healthy persons.

Results: Severity of disorder on admission according to PANSS score was 51.2. After treatment there were revealed strong, moderate, and minimal clinical improvement in 8, 46, and 38% of patients, respectively, according to GCI Scale. CAT activity of patients at admission was significantly higher than in controls. Treatment with antipsychotics normalized this index. GP activity did not change. Affinity of CAT for H₂O₂ is higher than of GP. H₂O₂ is predominantly destroyed by CAT and not by GP. G-S-T activity was significantly lower

before and after treatment in comparison with controls. G-6-PD activity was significantly lower at admission as compared with controls. After treatment G-6-PD activity continues to decline ($P=0.05$). GR activity was significantly higher before treatment and after pharmacotherapy its activity was significantly lower in comparison with values both at admission and in controls.

Discussion: It is supposed that before pharmacotherapy on background of decreased G-6-PD activity compensatory increased GR activity continues to maintain enough high GSH (reduced glutathione) level. After pharmacotherapy G-6-PD activity continues to decline that is accompanied by further decrease of NADPH synthesis.

In spite of improvement of clinical status of patients after pharmacotherapy there are no signs of normalization of metabolic processes.

M22. Differential peripheral biomarkers of negative dimension in schizophrenia

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Background: Schizophrenia is not only a mental disorder but also has other components affecting the physical part of the body (1). Numerous technologies have been employed in search of schizophrenia biomarkers (2). Some studies have suggested that some metabolic traits (3) and neuroinflammatory processes (4) may be associated with negative dimension in patients with schizophrenia. The aim of this poster is to find biomarkers of the negative dimension in schizophrenia. We present the biological parameters of patients with schizophrenia and according to the lab results.

Methods: Cross-sectional, naturalistic study. Inclusion criteria: DSM-IV diagnosis of schizophrenia; age > 17 years; and written informed consent given.

Results: 123 patients with schizophrenia. Mean age 40.75 (10.37), 67.5% males. Psychopathology: PANSS negative subscale and Marder negative factor. Laboratory tests: red cells, hemoglobin, leukocyte, platelets, glucose, urea, creatinine, uric acid, cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, GPT, AP, CA, P, FE, insulin, HbA1c, and TSH. Furthermore, homocysteine and C-reactive protein (CRP) as oxidative and inflammatory parameters. Partial correlation coefficients adjusted for age, gender, years of illness, number cigarettes/day, number of antipsychotics and BMI showed relationship between negative dimension and some lab results: in males, PANSS negative scale and insulin ($r=-0.28$, $P=0.026$), and, urea ($r=0.27$, $P=0.030$); Marder negative factor and insulin ($r=-0.29$, $P=0.023$). In females, Marder negative factor and total cholesterol ($r=0.37$, $P=0.040$), and, LDL cholesterol ($r=0.40$, $P=0.024$). A stepwise regression analysis was performed with these independent variables. In males, urea ($B=0.186$) accounted for 9.2% of the PANSS negative scale variance (model $df=1$, $F=7.355$, $P=0.008$) and insulin ($B=-0.063$) accounted for 6.9% of the PANSS Marder negative factor variance (model $df=1$, $F=5.421$, $P=0.023$).

Discussion: In males, higher concentrations of urea and lower concentrations of insulin could predict more severity of the negative dimension in schizophrenia. However, in females none parameter could predict it.

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M23. Autoantibody profiling in patients with schizophrenia

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Background: Schizophrenia affects approximately 1% of the world population and therefore is considered as a major chronic mental illness. In the recent years a number of studies have showed a correlation between higher levels of autoantibodies and the frequency of autoimmune disease in patients with schizophrenia compared to healthy individuals. However, a disease associated biomarker has so far not been identified. In this study we used a targeted proteomics approach to validate the autoantibody reaction in patients with psychotic features.

Methods: In this study several disease associated cohorts, with different sample types have been used to study an autoimmune reaction in psychotic patients. In total we analyzed more than 500 samples in a first discovery phase. Based on previous studies of autoantibodies in psychosis, we selected approximately 250 protein fragments from the Human Protein Atlas with a length of roughly 100 amino acids. Autoimmunity profiling was performed using the suspension bead array technology and IgG reactivity was measured in patients and controls. Additionally a selected screening was performed. Here antigen arrays including 42000 unique protein fragments covering 19000 ENSG-IDs which correspond to 94% of the gene centric proteome were used.

Results: Our findings clearly indicate altered immune response in patients with chronic mental illness compared to healthy controls. In our study we identified potential predictive biomarkers for schizophrenia which are of interest for further studies in the field of psychiatry.

Discussion: By further validating these putative autoimmunity targets, we could gain insights into the autoantigens associated to chronic mental illnesses. Furthermore we can characterize the biological function of our findings in this disease.

M24. Association of serum sFlt-1 with progressive reduction in cortical thickness: a preliminary longitudinal study of familial high risk for psychosis subjects

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Background: Current research supports the idea that peripheral angiogenic factors are altered in schizophrenia. Angiogenic factors (e.g. VEGF, sFlt-1) can regulate microvascular change, blood flow, and energy metabolism. Some of these markers have been associated with symptom severity, cognitive decline, and brain structure in schizophrenia. We recently demonstrated that sFlt-1 is significantly elevated (1.7 fold, $ES=0.8$) in subjects at familial high risk for psychosis (FHR). It is unclear whether angiogenic disruption in antipsychotic-naïve FHR subjects has an effect on clinical and neuroimaging measures. Thus, we hypothesize that elevated sFlt-1 correlates with baseline and longitudinal changes in medial temporal lobe structures (MTL), symptomatology, and cognition.

Methods: Human growth factor panel was used to measure baseline levels of sFlt-1 in plasma from individuals with FHR (age = 17 ± 0.6 , $n=35$) and healthy controls (HC, age = 25 ± 1 , $n=39$) using a multiplex immunoassay system with Meso Scale Discovery's multi-array technology. In FHR subjects, schizotypal symptoms were rated using Chapman psychosis proneness scale. In the two groups, baseline cognitive (Wisconsin Card Sorting Test, perseverative error score), soft neurologic signs (Neurologic Evaluation Scale, total score), and structural brain imaging (1.5 T T1-weighted MRI) was obtained. For a subgroup of FHR subjects, there were three years of longitudinal data available. Baseline data was analyzed using Pearson's correlations between sFlt-1 and clinical/imaging measures followed by Benjamini and Hochberg correction. Longitudinal data was analyzed using linear mixed model ANOVA (sFlt-1 was median split in the FHR group) to

determine the effects of baseline sFlt-1 level on symptomatology, cognition, soft neurologic signs, and MTL structure.

Results: As previously demonstrated, sFlt-1 was significantly increased in FHR subjects when compared to healthy controls. At baseline, sFlt-1 was significantly correlated with soft neurologic signs ($r=0.27$, $P=0.02$, $q=0.09$), but not symptomatology, cognition or MTL structure. Longitudinal examination in the FHR group demonstrated that high levels of sFlt-1 were significantly associated with worsening schizotypal symptoms ($t=1.9$, $P=0.01$) and reduced left parahippocampal cortical thickness ($t=-2.3$, $P=0.05$) when compared to low levels of sFlt-1 expression. No differences were noted for cognition, soft neurologic signs, and other MTL structures.

Discussion: These findings suggest an association between sFlt-1 and structural abnormalities in the parahippocampus of people at familial high risk for psychosis. The increased levels of sFlt-1 are consistent with the hypothesis of altered microvascular circulation in schizophrenia and those at risk.

M25. Combined effect of genetic variants in GluN2B coding gene (GRIN2B) on prefrontal function during working memory performance

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Background: The GluN2B subunit of NMDA glutamate receptors is involved in the physiology of the prefrontal cortex (PFC) during working memory (WM): in layer III of the PFC, GluN2B selective blockade impairs WM performance (Wang *et al.*, 2013). Moreover, genetic variants in GluN2B coding gene (GRIN2B) have been associated with cognitive impairment and increased risk for neuropsychiatric diseases in humans, possibly mediated by regulation of activity of transcription factors affecting GRIN2B function (Traynelis *et al.*, 2010). However, it is unclear how GRIN2B genetic variation affects gene expression and prefrontal cognitive processing. Using a composite score, we aimed to assess the combined effect of GRIN2B variants on PFC activity during WM performance in healthy subjects. We hypothesized that greater putative GRIN2B transcription levels in PFC would predict enhanced PFC activity during WM and greater WM performance.

Methods: We used a sample including 148 subjects in order to compute a composite score (D' GS) to combine the effects of single nucleotide polymorphisms on post-mortem prefrontal GRIN2B mRNA expression: greater D' GS predicted greater GRIN2B expression levels. We assessed GRIN2B expression in peripheral blood to provide a biological test of the predictive power of D' GS in 46 healthy Caucasians. We then computed the D' GS in independent samples of healthy participants: 116 healthy unrelated adult Caucasians, which were recruited for a WM behavioral study (n-back including 0-, 1-, 2-, and 3-back (Weinberger *et al.*, 1996)), and 122 healthy Caucasian subjects who underwent functional magnetic resonance imaging during performance of the n-back WM task (0-, 1-, and 2-back). Thus, we used a D' GS linear and quadratic term in a within-subjects factorial model to test its association with PFC activity and behavior during WM.

Results: Five polymorphisms were associated with GRIN2B expression: rs2160517, rs219931, rs11055792, rs17833967, rs12814951 (all corrected $p < .05$). D' GS reliably indexed gene expression (linear regression t -value = -6.25, $R^2=0.21$, $P=4.23 \times 10^{-9}$). D' GS also predicted peripheral GRIN2B expression (Pearson's $r=-0.26$, $R^2=0.068$, $P=.04$), WM behavioral efficiency ($F(1, 110)=4.1$, $P=0.044$, partial $\eta^2=0.036$), and PFC activity (BAs 6, 8). Moreover, there was a non-linear association between GRIN2B genetic score and PFC activity: both high and low D' GSs were associated with high BOLD signal in the PFC (BAs 6, 9, 10, 44).

Discussion: These results suggest that alleles associated with moderate transcription levels of GRIN2B predict lower PFC activity during WM performances. Even controlling for this effect, alleles associated with greater GRIN2B transcription levels in the post-mortem PFC are also associated with WM efficiency. The selected SNPs are localized in the same LD block of several SNPs associated with neuropsychiatric disorders, like schizophrenia (Weickert *et al.*, 2013) and major depression (Zhang *et al.*, 2014). Overall, the present findings indicate

that genetic regulation of GRIN2B transcriptional levels is associated with prefrontal physiology during WM in human adults.

M26. Odor deficits in chronic schizophrenia –relationship to cognition, symptoms, and epigenetic markers

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Background: Deficits in Odor identification and discrimination have been found in previous studies of patients with schizophrenia (SZ), and structural and functional abnormalities in the olfactory system of schizophrenia are well documented. Some studies have reported relationship between odor deficits in SZ and negative symptoms. We investigated these questions in a new sample of chronic SZ and controls who are also participating in a study of epigenetic markers in the lymphocytes of SZ. Sequencing of activation and silencing of gene methylation by methylating enzymes (DNMT1 3a) and change in histone acetylation may be involved in epigenetic modifications of the development of the olfactory system

Methods: In this initial group of sample we studied 39 patients with chronic SZ and 33 controls. Odor identification discrimination was assessed with Sniff n Sticks smell test battery for Odor Identification and Odor Discrimination. Current psychiatric symptoms were assessed with PANSS interview. Cognition was assessed by MATRCIS battery. A blood sample was drawn for measurement of mRNA of enzyme related to methylation of genes (DNMT, TET 1) and genes products heavily regular by promoter methylation (BDNF, glucocorticoid receptor), by QPCR assays, although assays on these samples have not been completed at this time, but data will be presented.

Results: SZ had significantly lower scores than controls on the odor identification ($P=0.012$) and odor discrimination tests ($P < 0.1$) of the Sniff n Sticks battery. However, on the odor identification, but not on discrimination, there was a significant subject type by sex effect ($P=0.022$), with identification being deficient in male SZ but not females. There were no differences between male vs. female controls on the odor tests. There was a modest association between scores on odor discrimination and scores on the MATRCIS battery (Overall Composite $r=0.31$, $P=0.066$, and Working Memory $r=0.32$, $P=0.048$), but this association was stronger in the small number of female SZ (r 's=0.9) than male SZ (r 's= 0.2). In controls there was only a significant association with higher odor discrimination with better scores on the MCCB domain of working memory ($r=0.32$, $P=0.048$) and no sex difference. In SZ patients poorer performance on odor discrimination tended to be weakly associated with higher scores on Negative symptoms ($r=0.30$, $P < 0.07$). Relationships to biological markers are being analyzed but have not been completed at this time.

Discussion: This current research confirms the previously reported deficits in olfaction in schizophrenia, and the relationship of olfactory deficits to negative symptoms. It suggests that sex differences may be important in odor identification test, but not the odor discrimination test in SZ. This is the first study to show olfactory deficits related to performance on the MATRCIS battery and suggest that there may be a sex difference in the strength of this relationship. Relationship to epigenetic markers are being explored.

M27. Association between erythrocyte membrane fatty acids and psychopathology in individuals at ultra-high risk for psychosis

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Background: This study investigated the relationship between erythrocyte membrane fatty acid (FA) levels and the severity of symptoms of individuals at ultra-high risk (UHR) for psychosis.

Methods: The study sample consisted of 80 neuroleptic-naïve UHR patients. Associations between baseline erythrocyte membrane FA levels, measured by gas chromatography, and scores on the Positive and Negative Syndrome Scale (PANSS), the Global Assessment of Functioning Scale, and the Montgomery–Asberg Depression Rating Scale (MADRS) were investigated. After correlation analysis in all participants, subjects were divided into three groups according to the predominance of positive or negative symptoms based on PANSS subscale scores; membrane FA levels in the three groups were then compared.

Results: PANSS negative symptom scores were negatively correlated with two saturated FAs (myristic and margaric acids), one ω -9 monounsaturated FA (MUFA; nervonic acid), and one ω -3 polyunsaturated FA (PUFA; docosapentaenoic acid). Negative symptom scores were positively correlated with two ω -9 MUFAs (eicosenoic and erucic acids) and two ω -6 PUFAs (γ -linoleic and docosadienoic acids). PANSS positive symptom scores were correlated only with nervonic acid. No associations were observed between FAs and MADRS scores. In subjects with dominant negative symptoms, the sum of the ω -9 MUFAs and the ω -6: ω -3 FA ratio were both significantly higher than in those with dominant positive symptoms, whereas the sum of ω -3 PUFAs was significantly lower.

Discussion: Abnormalities in FA metabolism may contribute to the neurobiology of psychopathology in UHR individuals. In particular, membrane FA alterations may play a role in negative symptoms, which are primary psychopathological manifestations of schizophrenia-related disability.

M28. Prediction of functional outcome in the early onset psychosis and psychosis prodrome using neuroanatomical and resting state pattern classification

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Background: To date, research into the biomarker-aided early recognition of psychosis has focused on pre-dicting the transition likelihood of clinically defined individuals with different at-risk mental states (ARMS) based on structural and functional brain changes. However, it is currently unknown whether neuroimaging patterns could be identified to facilitate the individualized prediction of symptomatic and functional recovery.

It is noteworthy that recent studies have shown that ARMS individuals, who ultimately did not convert to psychosis, remained at a lower level of functioning compared to non-psychiatric comparison subjects. The aim of this study was to investigate whether cortical surface and resting state (RS) fMRI functional connectivity alterations analyzed by means of multivariate pattern recognition methods can individually predict subsequent functional outcome in individuals with different ARMS for psychosis.

Methods: Firstly, we investigated whether cortical surface alterations analyzed by means of multi-variate pattern recognition methods could enable the single-subject identification of functional outcomes in twenty-seven ARMS individuals.

Subjects were dichotomized into 'good' vs. 'poor' outcome groups on average 4 years after the baseline MRI scan using a Global Assessment of Functioning (GAF) threshold of 65.

Secondly, we investigated whether RS fMRI functional connectivities analyzed by means of multivariate pattern recognition methods could enable the single-subject prediction of functional outcomes in 54 early psychosis spectrum (EPS) patients at the six-months follow-up (PRONIA-Personalized Prognostic Tools for Psychosis Recognition).

Results: Cortical surface-based pattern classification predicted good vs. poor outcome status at follow-up with an balanced accuracy of 82% (sensitivity 78.6% and specificity 84.6%) as determined by nested leave-one-cross-validation. Neuroanatomical prediction involved cortical area reductions in superior temporal, inferior frontal, and inferior parietal areas, and was not confounded by functional impairment at baseline or antipsychotic medication and transition status over the follow-up period. RS-based pattern classification yielded a slightly lower balanced accuracy of 67% (sensitivity 74.1% and specificity 59.3%) when predicting good vs. poor outcome in EPS patients. Both cortical

surface and RS prediction models' decision scores were correlated with positive and general symptom scores at follow-up.

Discussion: These neuroimaging findings support the concept that the ARMS for psychosis is frequently associated with poor clinical courses associated with enduring functional disability, irrespective of an ultimate transition to the full-blown illness. In addition, our results are supporting the assumption that poor functional outcome might be predicted from the brain signature by using different neuroimaging modalities. These findings also suggest that poorer functional outcomes are associated with non-resolving attenuated psychosis and could be predicted at the single-subject level using multivariate neuroanatomical risk stratification methods. However, the generalizability and specificity of the suggested prediction model should be thoroughly investigated in current and future large-scale and cross-diagnostic MRI studies.

M29. Pro- and anti-inflammatory cytokines in young people in ultra-high risk of developing schizophrenia and bipolar disorder

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Background: Immune imbalances have been implicated in late stages of schizophrenia and bipolar disorder, but very few is known about the immunological changes before the onset of disease. This work aimed to analyze serum levels of pro- and anti-inflammatory cytokines in young people in ultra-high risk (UHR) of developing psychosis and bipolar disorder.

Methods: Twenty two young UHR and 22 age- and sex-matched healthy controls were enrolled in this study. Clinical evaluation was composed by psychiatric diagnosis using Structured Clinical Interview for DSM-IV (SCID-1), Community Assessment of Psychic Experiences (CAPE), Montgomery Asberg Depression Rating Scale (MADRS), Young Mania Rating Scale (YMRS), Comprehensive Assessment of At-Risk Mental States (CAARMS), Childhood Trauma Questionnaire (CTQ) and Cannabis Experiences Questionnaire. A blood sample was withdrawn, serum was isolated levels of IL-2, IL-4, IL-6, IL-10, TNF, IFN- γ , and IL-17 was measured by flow cytometry using the Th1/Th2/Th17 cytometric bead array.

Results: All subjects were already evaluated and had their serological cytokines measured. We are proceeding with the analysis of cytokines and their relation with clinical variables.

Discussion: The analysis of biological correlates, like cytokines, before illness onsets are of great scientific value, since the knowledge of these changes allow earlier intervention and ultimately disease prevention.

M30. Effects of omega-3 PUFA on markers of immune function in individuals at ultra-high risk of psychosis

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Background: Alterations of immune function have been repeatedly reported in schizophrenia and caused several trials to study the possible benefit of anti-inflammatory agents. In individuals at ultra-high risk (UHR) to develop psychosis first studies also suggest marker properties of cytokines in terms of transition to psychosis risk and treatment response. Meanwhile, a randomized controlled trial could show effects of omega-3 polyunsaturated fatty acid (PUFA) supplementation on transition risk and symptomatology in UHR patients. In this study we therefore investigated the effects of PUFA supplementation on markers of immune function.

Methods: In a randomized controlled design we measured the serum levels of interleukine (IL)2, IL6, and soluble intercellular adhesion molecule-1 (sICAM-1) in 81 help-seeking UHR individuals (13–25 years of age) using commercially available assays. Inflammatory markers were compared before and after 12 weeks of treatment with either 1.2 g/d omega-3 (PUFA) or saturated fatty acids (SFA).

Results: In multivariate tests, the effects of omega-3 PUFA and placebo (SFA) were significantly different in terms of IL6 ($P=0.041$), but showed no difference in terms of IL2 and sICAM-1. On IL6 placebo caused a significant decrease ($P=0.016$), while the omega-3 PUFA condition did not cause a significant change. In univariate tests, only the omega-3 PUFA condition increased sICAM-1 ($P=0.022$).

Discussion: The omega-3 PUFA condition obviously did not act on IL6 which counts as state marker during the acute exacerbation of schizophrenia. As a new finding, omega-3 PUFA increased the serum concentration of sICAM-1, which belongs to the Ig superfamily and serves as a counter-receptor for the lymphocyte function-associated antigen (LFA-1). The LFA-1/ICAM-1 interaction is important in a variety of cellular events including Ag-specific T cell activation and leukocyte transendothelial migration. Therefore we speculate that modulating effects of PUFA supplementation on cell mediated immune function might contribute to its clinical effectiveness.

M31. Retinal anomalies in schizophrenia patients and regular cannabis users: a potential way to a biological marker?

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Background: Cannabis is a neuromodulator substance and its regular use is associated with an increased risk of schizophrenia in a specific high risk population. However, the precise underlying mechanisms are still debated. There is therefore a need to develop new methods assessing the neurobiological underpinning of brain dysfunctions in schizophrenia as well as the brain neurotoxicity of cannabis in order to provide biological markers allowing the screening of nonaffected cannabis users at high risk of schizophrenia. The retina is an anatomical and developmental extension of the central nervous system and the retina and the brain display similar properties, especially in terms of neurotransmission. This structure is organized in several layers of cells, mainly the photoreceptors—rods and cones—, bipolar, and ganglion cells. The functional properties of these cells can be evaluated by objective retinal electrophysiological measurements such as the flash (fERG) and the pattern (PERG) electroretinogram. Each one of these techniques allows for the assessment of specific cell types of the retina and gives different information on the pathophysiology. In this study, we used fERG and PERG measurements as indirect ways to explore neurotransmission signaling pathways in schizophrenia patients and regular cannabis users.

Methods: Recordings of fERG and PERG were performed in 9 patients with schizophrenia, 30 regular cannabis users and 30 healthy controls using guidelines of the International Society for Clinical Electrophysiology of Vision (ISCEV) for the fERG and the PERG. Measurements of fERG were performed in scotopic and photopic conditions, and the amplitude and implicit time of the a-wave and b-wave were measured. A constant luminance white area was used for PERG recordings, and the amplitude and implicit time of the P50 and N95 were assessed.

Results: Anomalies in functional properties of photoreceptor, bipolar and ganglion cells were observed with fERG and PERG recordings, and were detected in both schizophrenia patients and regular cannabis users, compared to controls. Several of these retinal dysfunctions were specific of each group of patients, but, interestingly, schizophrenia patients and regular cannabis users also displayed similar retinal abnormalities.

Discussion: These results are a preliminary analysis extracted from a larger sample whose recruitment is yet ongoing. We confirm herein some retinal anomalies reported in previous studies but we also found significant novel retinal dysfunctions in schizophrenia. Importantly, similar and different retinal abnormalities found in schizophrenia patients and cannabis users suggest common as well as separated pathophysiological mechanisms. Additionally, these results support that the retinal function could reflect brain neurotransmission in neuropsychiatric disorders and consequently could represent an early and sensitive biological marker.

M32. Markers of the glutathione antioxidative defense system are associated with structural brain changes in untreated first-episode schizophrenia

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Background: Regional structural brain changes are among the most robust biological findings in schizophrenia, yet the underlying pathophysiological changes remain poorly understood. Oxidative stress and impairment of the glutathione antioxidative defense system (AODS) were also reported several times in schizophrenia and linked to hyperexcitation, cytotoxicity, and abnormal neuronal/dendritic plasticity.

Methods: The study involved 27 first-episode schizophrenia patients (FEP), who were either drug-naïve or off antipsychotic medication, and 31 healthy controls (HC). In a first step we examined whether markers of the glutathione AODS (total glutathione (GST), oxidized glutathione (GSSG), reduced glutathione (GSR)) show group differences. In a second step we investigated associations between the effect of illness on the AODS marker and focal gray matter density using voxel-based morphometry (VBM) analysis of T1-high-resolution MRI-images with the altered AODS marker as independent covariate.

Results: In FEP we found GSSG activity increased and GSR decreased, consistent with previous findings. VBM group comparisons showed in FEP abnormalities of left frontal and left medial temporal cortices/insula. Brain-wide VBM interaction analysis with peripheral markers as covariable disclosed an influence of illness on associations between GSSG or GSR and gray matter density at left superior temporal cortex.

Discussion: Our findings support the notion of oxidative stress as potential pathomechanism for brain structural abnormalities in the early phase of acute schizophrenia, and in particular in the left temporal cortex.

M33. Niacin skin sensitivity decreased in close to psychosis ultra-high risk groups and associated with prepsychotic symptomatology – an optical reflection spectroscopy study

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Background: Decreased or zero response to niacin skin stimulation has been reported in 30-50% of patients suffering from schizophrenia. In individuals of risk populations to develop psychosis, so far available niacin test results are still inconclusive. To our best knowledge there is no study by this point that includes patients of different ultra-high risk (UHR) groups and first-episode schizophrenia patients (FEP), and that investigates associations between niacin sensitivity (NS), symptom severity and transition to psychosis status.

Methods: We compared NS of 84 UHR individuals, 105 FEP and 180 healthy controls (HC). In terms of UHR subgroups according to PACE criteria or transition to psychosis status (transition/non-transition), we compared NS of individuals with attenuated psychotic symptoms ($n=45$), those with Brief Limited Intermittent Psychotic Symptoms (BLIPS) ($n=12$), those at a genetical risk ($n=27$) as well as non-transition individuals ($n=13$) vs transition individuals ($n=39$). Response to skin stimulation with aqueous N-methyl nicotinate (niacin) in three concentrations (0.1-0.001M) was assessed by optical reflection spectroscopy (ORS), analyzed by repeated measure ANOVA, and referred to psychopathology by correlation analysis.

Results: I. FEP showed significantly decreased NS as compared to HC and UHR individuals. II. Individuals of the attenuated symptoms and BLIPS group showed significantly less NS as individuals of the genetical risk group. III. Transition patients showed decreased NS as compared to HC. IIII. Correlation analysis revealed inverse correlations between NS and positive symptom scores in individuals of the BLIPS and FEP group.

Discussion: NS seems to be decreased in risk stages near to psychosis (attenuated symptoms, BLIPS state), but unchanged or even increased

in risk states far from psychosis (genetical risk stage). Results further support our notion, that NS is rather a state than a trait marker. It could be applicable either to characterize the intensity of a distinct pathomechanism in the immediate advance of psychosis or to identify UHR individuals that might benefit from fatty acid or antioxidant supplementation. Further studies should include more individuals of UHR subgroups and follow-up investigations.

M34. The Dutch bipolar and schizophrenia offspring study; psychopathology outcome during early adolescence

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Background: Schizophrenia and Bipolar Disorders aggregate in families and show overlapping symptom patterns. Children and adolescents with an affected parent are at increased risk to develop these disorders themselves, but also other psychopathology. Cross diagnostic studies in adolescents at familial high risk are scarce. Here, we examine behavioral and cognitive functioning of adolescents with a parent diagnosed with schizophrenia (SZ) or bipolar disorder (BD) compared to aged matched community controls. In addition the effect of family history load for mood disorders, psychosis, and substance use disorders on symptom level outcome in these three groups is explored.

Methods: The study presented is part of an ongoing prospective study among BD and SZ offspring and Controls (aged between 8 and 18 years) in the Netherlands. All 181 subjects were recruited between 2010 and 2015. Symptoms and diagnoses according to DSM-IV criteria were assessed using the Kiddie Schedule of Affective Disorders and Schizophrenia Present and Lifetime Version (K-SADS-PL).

For child behavior ratings, mothers filled in the Child Behavior Check List for children between (CBCL/6-18). The CBCL rates the child's competence and emotional and behavioral problems in the last 6 months. Cognitive functioning (IQ) was estimated by 4 subtests, Information, Vocabulary, Block Design and Picture Completing, of the Dutch Wechsler Intelligent Scale for Children III (WISC III NL). The FIGS was used to construct a familial loading index; information regarding the number of affected and unaffected relatives, the age and sex of the relatives, and whether they are first-degree or second-degree relatives was collected. Data Analyses: Statistical analyses were performed using the SPSS 15.0 package for Windows (SPSS Inc., USA). Correction for multiple testing was applied. Our calculation of the Familial Loading index for schizophrenia and mood disorders was based on a well-established algorithm in which individual likelihood ratios are based on the proband being a sporadic of familial case.

Results: Lifetime Axis I diagnoses according to DSM-IV, IQ, and CBCL scores were collected in three groups with a mean age of 13.1 years (SD 2.5); 45 SZ offspring, 86 BD offspring and 47 Controls. SZ offspring show the highest lifetime prevalence of psychopathology with 64.4% any axis I disorder versus BD offspring 48.3% and Controls 17%. Also, Total IQ score is significant lower in SZ and BD offspring compared with Controls. Mood disorders are in both SZ and BD offspring the most frequent diagnosed disorder. Moreover, SZ offspring show significantly more major mood disorders (20%) and autism spectrum disorders (13,3%) compared to both BD offspring and Controls. With respect to ADHD both SZ and BD offspring show higher prevalence rates than Controls. On emotional and behavior problems SZ and BD offspring are rated significantly ($P < 0.001$) higher by their mothers compared to Controls. An high Familial Load index for mood in all participants is significantly associated with total symptom score.

Discussion: Adolescent SZ and BD offspring have a higher prevalence of DSM IV Axis I diagnoses compared to Controls. The expression of psychopathology shows considerable overlap in both index offspring groups, with the highest prevalence for mood, behavior, and autism spectrum disorders. In addition, compared to Controls, parent ratings of behavioral and emotional problems are rated higher in SZ and BD offspring. During early adolescence no specific symptomatic prodrome can be determined, but in general SZ offspring show on all measures the poorest outcome. Other risk factors need to be included to construct future individual risk profiles.

M35. Age differences in the diagnostic stability of patients with psychosis nos: a meta-analysis

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Background: Psychotic Disorder Not Otherwise Specified (PsyNOS) and Brief Psychotic Disorder (BrPsy) involve the presence of positive psychotic symptoms without fulfilling criteria for other psychotic disorders (DSM-III-R to DSM-IV-TR, ICD-9, and -10). Therefore, they are usually diagnoses of exclusion and transition in clinical practice, and are often neglected in research and literature.

Methods: We systematically searched PUBMED and PsycInfo from database inception until 8/2015 for articles reporting on diagnostic stability of PsyNOS or BrPsy. Authors were contacted to obtain unpublished/missing data. A meta-analysis was conducted to characterize this population socio-demographically and clinically, and to determine the progression to other diagnostic entities during follow-up, stratifying results by age group.

Results: Altogether, 39 studies were included encompassing 628 individuals from 21 non-overlapping samples. Subjects were mainly male (50.8%) and 26.0 ± 9.2 years old. During 30.6 ± 9.1 months (range = 1-11.5 years) follow-up, only 39.8% kept the same diagnosis, 6.1% were in full remission (without requiring pharmacological treatment) and 54.1% changed to another diagnosis, mainly schizophrenia (17.6%), bipolar disorder (12.0%), schizoaffective disorder (6.3%), depression (3.5%), and to other psychotic (7.2%) or non-psychotic diagnosis (6.9%).

Samples were divided by age: 8 youth samples (mean age < 19 years old; 118 subjects), 12 adult samples (mean age 19-65 y.; 438 subjects), and an elderly sample (mean age > 65 y.; 72 subjects). Youth were mainly boys (66.7%) aged 14.6 ± 2.2 years old, adults were mainly women (57.5%) aged 35.2 ± 12.3 y. and the elderly were also mainly women (56.6%), aged 75.4 ± 9.3 y. Ages of onset differed expectedly between youth and adults (8.3 ± 3.1 years vs 35.3 ± 11.7 years, $P < 0.0001$), and drug-abuse comorbidity (6.0% vs. 29.9% respectively, $P = 0.0001$), without data for the elderly group. During follow-up (youth = 40.3 ± 19.3 months; adults = 28.3 ± 3.8 m.; elderly = 30 m.) only 22.6% vs 45.8% vs 31.9%, respectively, kept the same diagnosis ($P = 0.0001$); and 8.7% vs 6.4% vs 0% were in full remission (youth = adults > elderly; $p \leq 0.0006$). The change to affective dis. was 37.4%, 12.1% and 0.0% in each ascending age group ($P < 0.0001$); being more frequent to bipolar dis. (youth: 29.4%; adults: 9.2%, $P < 0.0001$) than depression (youth: 8.0%; adults: 2.9%, $P < 0.001$). In contrast, the change to a schizophrenia spectrum diagnosis was common across age groups, being 25.2%, 23.3%, and 31.9% respectively (youth = adults > elderly; $p \leq 0.02$). Transition to schizophrenia was 19.1%, 14.7% and 31.9% ($P < 0.009$); to schizoaffective dis.: 6.1%, 7.4%, and 0% (youth = adults > elderly; $P < 0.0001$); to delusional dis.: 0%, 1.2%, and 15.3% ($P < 0.0001$); and the other psychotic diagnosis 0%, 3.1%, and 20.8% ($P < 0.0001$).

Discussion: According to the very scarce literature, over an average of 2.5 years, 54% of subjects diagnosed with PsyNOS/BrPsy developed a different severe mental disorder, pointing to it as a mostly transient condition. In exploratory subgroup analyses of (somewhat overlapping) age groups, earlier-onset of PsyNOS/BrPsy was associated with a higher probability of developing an affective disorder. The youth-group had the longest follow-up, which should be taken in to consideration given that it also had the highest instability of diagnosis; and only one study could be included for over 65-aged sample. Since final diagnosis, remission and diagnostic stability will vary depending on longer-term outcomes, more research is needed to identify markers and predictors of transition to specific conditions by age group and to test safe and effective interventions to improve overall outcomes.

M36. Adverse childhood events and adult psychosis

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Background: Adverse childhood events can have lifelong health consequences. Early abuse has been linked to a range of adult psychiatric problems but diagnosis-specific associations remain elusive. The risk for schizophrenia (SZ) is increased in those who were sexually or physically abused but this risk is not unique to SZ and the role of other early stressors is poorly understood. The purpose of this study was to identify the psychopathological correlates of adverse childhood circumstances.

Methods: The downtown east side (DTES) is the poorest neighborhood in Vancouver and carries a disproportionate burden of the city's mental and physical health problems. This study included 421 DTES residents (male = 330, female = 91, mean age = 41, living in poverty = 91%). A large proportion were disadvantaged from an early age. Half (54%) saw their parents separate, 57% experienced maternal separation for more than a year, 33% were placed in government care at some time, and 50% had three or more changes in caregiver. Sexual (33%) and physical (38%) abuse were common and 65% reported drug or alcohol abuse within the family. Only 18% spent their entire childhood with the same caregivers and also experienced no physical or sexual abuse. Most (84%) had a current or past DSM-IV defined major psychiatric disorder. This included non-affective psychosis for 59% (SZ 10%, schizoaffective [SZA] 6%, PNOS 13%, substance induced psychosis [SIP] 30%). Mood disorder with or without psychosis occurred in 57% (Bipolar disorder [BD] 12%, Major depression [MD] 32%, Substance induced mood disorder [SIM] 13%). Comparisons were made between each diagnosis and a those who had none of these diagnoses ($N = 64$).

Results: Drug use (99%) a history of homelessness (74%) and criminal convictions (86%) were common. Adverse childhood events did not predict who had these difficulties but there was an association with the age at onset of the problems. The number of different caregivers, parental neglect, physical abuse, and sexual abuse each significantly predicted the age at leaving home, age at first drug use, age at first conviction, age first became homeless, and age at the onset of a persistent decline in functioning (all $P < 0.05$). The non-psychiatric control group had fewer changes to their caregivers than those with SZ-SZA (1.8 vs 2.4; OR = 2.5, 1.3-4.8) or an anxiety disorder (1.9 vs 2.5; OR = 1.5, 1.0-2.4) but did not differ from PNOS, BD, MD, SIP or SIM. Sexual abuse was less common in controls than in BD (22% vs 52%; OR = 3.7, 1.9-7.1), MD (22% vs 37%; OR = 2.0, 1.1-3.4), and anxiety (28% vs 44%; OR = 2.0, 1.1-3.8) but not SZ-SZA, PNOS, SIP or SIM. Physical abuse was associated with BD (43% vs 65%; OR = 2.4, 1.2-4.6) but no other diagnosis. Neglect was not associated with any diagnosis. Childhood events were not associated with age at onset of psychosis but the number of caregivers, neglect and physical abuse predicted age at first depression.

Discussion: Findings suggest that a range of adverse childhood circumstances influence the age at onset of several aspects of a dysfunctional lifestyle in this marginalized population. Consistent with previous results, childhood sexual abuse was associated with mood disorders and anxiety during adulthood. However, this abuse did not predict psychosis. The finding of an association between multiple caregivers and psychosis suggests that environmental instability may be a risk for psychosis. Childhood adversity has many inter-related aspects and the psychopathological consequences are numerous and poorly understood.

M37. The link between bullying victimization and psychotic-like experiences: an exploratory view in the young adolescent population

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Background: Being bullied has been increasingly recognized as a risk factor for the development of psychiatric disorders, and scientific literature is focusing on the association between adverse event and bullying victimization (BV) with Psychotic-Like Experiences (PLEs). However studies on young adolescents population are limited and a definite association between a specific type of BV with a specific PLEs has not been investigated yet.

Methods: For the recruiting we used the Adolescent Psychotic-Like Symptom Screener and the cut off was set on a score of 2 points. To assess the bullying victimization we used the Multidimensional Peer Victimization Scale (MPVS) composed by 16 items with a possible score 0-32. MPVS is formed by four subscales: Physical victimization scale, Verbal victimization scale, Social manipulation scale and Attacks on property scale. To assess the PLEs we used the Specific Psychotic Experiences Questionnaire (SPEQ) composed by 6 types of PLEs: paranoia, hallucinations, cognitive disorganization, grandiosity, anhedonia, all assessed via self-report, and negative symptoms via parent report. To assess the depression we used the Children's Depression Inventory (CDI) while for the anxiety disorders we used the Multidimensional Anxiety Scale for Children (MASC). The procedures for descriptive statistics have been used for the socio-demographics and clinical characteristics. Regression analyses have been used for the association between our variables of interest.

Results: The sample consisted in 27 patients divided in 15 males (55,6%) and 12 females (44,4%), mean age 16,7mmt \pm 20,9. The mean of MPVS was 15,4(\pm 7,5) with a verbal bullying mean 5,4 (\pm 2,7), a social manipulation bullying 4,2 (\pm 2,2) a physical bullying 1,9 (\pm 2,6) and an attack property bullying 3,7 (\pm 2,3). The mean of the SPEQ was found 99,5 (\pm 33,5) with a Paranoia 29,6 (\pm 18,4), Hallucination 14,7 (\pm 9,6), Grandiosity 8,1 (\pm 6,6) Cognitive disorganization 7,6 (\pm 2,7) anhedonia 27,6(\pm 10) a negative symptoms 11,4(\pm 7,4). The linear regression between MPVS-tot and the SPEQ-tot has resulted in a positive coefficient of 2,27 ($P < 0,05$). The coefficient has been controlled for sex, depression, anxiety disorders. From the correlation between the different types of bullying victimization and the different psychotic phenomena a coefficient $> 0,6$ ($P < 0,05$) between the verbal victimization and the paranoia has been found positive for a further linear regression; the result was a crude positive coefficient of 4,2 $P < 0,01$, and it is not changed after the subsequent control for confounders.

Discussion: In our sample the most represented bullying victimization and Psychotic-Like Experiences were the verbal victimization and the Paranoia. An higher score at the MPVS was associated with a doubled score at the SPEQ. The current study add the evidence that bullying victimization can be associated with a cause-effect relation to the PLEs. Finally we have assessed that a higher score at the Verbal Victimization Scale can be associated with a score four times higher at the Paranoia Scale. This result is new in the current literature. This is a pilot study we have decided to enrich our sample till 50 patients and to add a group control.

M38. Emotion recognition and social skills in child and adolescent offspring of parents with schizophrenia

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Background: Although there is substantial evidence for emotion recognition deficits in people with schizophrenia, a smaller body of literature has investigated the presence of emotion recognition impairments in first-degree relatives of people with schizophrenia. To date, the findings have been mixed, with some studies finding evidence of deficits in facial affect recognition speed and/or accuracy

in relatives compared to controls (Leppanen *et al.*, 2008) and some studies finding no evidence of deficits (Bolte & Poustka, 2003). Emotion recognition deficits in people with schizophrenia may contribute to social dysfunction (Addington *et al.*, 2006); however no studies of which we are aware have examined the link between emotion recognition and social functioning in offspring of parents with schizophrenia.

Methods: The present study examined emotion recognition and social functioning deficits in 16 child and adolescent offspring of parents with schizophrenia (HR) compared to 34 age- and sex-matched healthy controls (LR; ages 5–19). We examined facial affect recognition using the Penn Emotion Recognition Test (PERT, Kohler *et al.*, 2003), a task which rates participants' response time and accuracy in identifying pictures depicting five basic emotions and a neutral condition. Social functioning was examined using the parent- and child-report versions of the Social Skills Rating System (SSRS; Gresham & Elliot, 1990), which provides age- and sex-normed total, and subscale scores in assertion, empathy, self-control, responsibility, and cooperation domains.

Results: As hypothesized, HR children exhibited impaired PERT performance in accuracy and response time relative to controls. Furthermore, HR children identified significantly fewer fearful faces compared to LR. There were no other group differences in accuracy or response time. As reported previously for this sample, HR children reported significantly worse overall social skills than their HC counterparts. In contrast, there were no group differences in parent-reported social skills; however, HR parents rated their children as having significantly more internalizing problems. In terms of the relation between PERT score and social functioning for both groups, age-adjusted PERT accuracy score predicted parent's overall rating of their child social skills, particularly within the domains of assertion and responsibility.

Discussion: This study provides further support for the presence of emotion recognition deficits— including less accuracy and slower response time—in child and adolescent offspring of parents with schizophrenia. This is the first known study to suggest the presence of these deficits in non-symptomatic HR children as young as five, given that prior studies of first-degree relatives have included older relatives who are within the typical window of risk for schizophrenia onset; thus, their emotion recognition skills may be affected by clinical symptoms and/or medication use. Emotion recognition deficits in the HR group were greatest in the domain of fear processing, consistent with one recent study which attributes this impairment to selective amygdala dysfunction in at-risk groups which could underlie clinical symptoms (Kohler *et al.*, 2014). The present study suggests a relationship between emotion recognition abilities and real-world social functioning in children. It also highlights the need for future studies of at-risk children to include both parent and child reports of child social skills, as they may differentially relate to risk factors. Improved characterization of social cognitive and functioning deficits in HR children could inform future efforts to develop more specific and individually-tailored targets for early intervention.

M39. Cognitive development and the emergence of psychotic experiences in children at high risk of schizophrenia: a longitudinal study of 22q11.2 deletion syndrome

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Background: The developmental course of premorbid cognitive deficits in patients diagnosed with schizophrenia is not fully known. 22q11.2 Deletion Syndrome (22q11.2DS) represents one of the strongest genetic risk factors for development of schizophrenia and following children and adolescents through the period of risk can provide insights into this issue. Previous studies have identified premorbid cognitive decline in IQ but the cognitive mechanisms underlying decline remain unknown. Decline in IQ score could be due to a developmental lag (growth that is slower relative to healthy comparison subjects) or developmental deterioration (absolute decline in cognitive ability).

Methods: 70 children with 22q11.2DS and 29 intrafamilial controls were assessed twice (2.5 year gap; time 1 = 10.0 years, time 2 = 12.5

years). Psychotic phenomena, IQ, and specific cognitive functions were assessed. Cognitive trajectories were fitted using multilevel modeling. To understand the mechanisms underlying cognitive decline in 22q11.2DS, cognitive development in 22q11.2DS relative to controls was tested against proposed developmental deficit (static cognitive impairments that emerge early and remain stable), developmental lag and developmental deterioration hypotheses for cognitive development in schizophrenia. Variability in cognitive development was characterized and related to the emergence of psychotic phenomena.

Results: No individual met criteria for psychotic disorder but psychotic experience prevalence increased from 2.9% to 21.4% in 22q11.2DS ($P < 0.001$). Significant cognitive deficits across all cognitive domains were found in 22q11.2DS relative to controls, including a deficit of -33.2 IQ points (95%CI = -38.4, -28.0, $P < 0.001$). Magnitude of cognitive deficits differed by cognitive domain; IQ, sustained attention, and set shifting ability deficits were twice the magnitude of deficits in processing speed, spatial planning, and spatial working memory. A decline in IQ of 1 point per year was observed in 22q11.2DS ($P = 0.002$). The longitudinal course of deficits differed across cognitive domains. A developmental deficit was observed for VIQ, executive function and sustained attention. Decline was observed for PIQ, which was found to be a developmental lag rather than developmental deterioration of absolute ability. Development of sustained attention was more variable in 22q11.2DS compared to controls ($P = 0.034$), but no difference was found for IQ, executive function, and processing speed. Deficits in spatial working memory ($P = 0.020$) and decline in sustained attention ($P = 0.020$) were associated with the emergence of psychotic experiences.

Discussion: The presence of a mix of developmental deficits and developmental lags in children with 22q11.2DS indicates genetic risk for schizophrenia is associated with both processes that emerge early in development and those that manifest later during childhood and adolescence. A large proportion of children with 22q11.2DS display psychotic experiences and our analysis indicates that spatial working memory and sustained attention are both linked to their emergence. 22q11.2DS is a powerful genetic model for understanding the processes that precede schizophrenia development.

M40. Neurotoxic autoantibodies and familiar history of autoimmune disease in acute child and adolescent psychopathology

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Background: A growing body of literature is investigating the association between psychopathology, autoimmunity and inflammation, also in young population

In parallel, research in a classic autoimmune process, Systemic Lupus Erythematosus (SLE), has identified a subset of the anti-dsDNA autoantibodies (Ab), as possible causal agents for the psychiatric symptoms in SLE: the anti-DWEYS Ab. It is Abs that cross-react against the NR2 subunit of the NMDA receptor (NMDAR), causing neuronal damage and apoptosis. The target in the NMDAR would be a pentapeptide consensus sequence, identified as DWEYS. **PURPOSE:** to explore whether acute psychiatric young patients might have higher serum concentrations of virtually neurotoxic antibodies, and higher rate of personal and family history for autoimmune/allergic diseases.

Methods: Sample: patients (P, $n = 81$, mean age 15.7, %female 59%), controls (HC, $n = 34$, mean age 15.1, %female 48%). No significant sociodemographic difference was found between the two groups. Data were collected on:

- antibodies (Ab): antistreptolisin (ASLO), common Lupus & autoimmune disease Ab; anti-NR2-Ab, described in bipolar affective disorder, and anti-DWEYS-Ab;
- Personal and family history of infectious, autoimmune and allergic disease.

Blood sample were collected in fasting status and afterwards frozen at -80° . Statistical analysis was run with SPSS.20.

Results: 1. Patients had significantly higher concentrations of anti-DWEYS antibodies: median (IQ range) in P 0,069 (0,054-0,098), in HC 0,105 (0,082-0,138), $P < < 0.001^{**}$.

Anti-DWEYS concentrations positively correlate with anxiety and depression scales:

● SCARED (Screen for Child Anxiety Related Disorders) scale.: SCARED Total Score (Spearman's Rho – $R=0.393$, $P=0.004^{**}$); subscales somato-psychic anxiety ($R=0.444$; $P=0.001^{**}$), generalized anxiety ($R=0.365$; $P=0.008^{**}$); Social Phobia ($R=0.418$; $P=0.002^{**}$) and Separation Anxiety ($R=0.267$; $P=0.058$).

● CDI (Child Depression Inventory) ($R=0.384$; $P=0.036^{*}$) and BDI (Beck Depression Inventory) scale ($R=0.485$; $P=0.009^{**}$).

2. Personal allergies and tonsillectomy showed a tendency to be higher in Patients. Autoimmune and allergic disease were significantly higher in mothers of P than of HC, and nearly significantly higher in 2nd degree relatives on maternal side of P.

Table 1. Significant/nearly significant differences in personal and family history of infectious & autoimmune disease

Personal history of tonsillectomy: HC: 3,3%; $P=16.9\%$; $P=0.063$

Personal history of allergies: HC: 16,1%; P: 31,4%; $P=0.109$

History of autoimmune disease (AD) in mothers: HC: 21,2%; P: 41,8%; $P=0.042^{*}$

History of AD in maternal 2nd degree relatives: HC: 36,4%; P: 56,7%; $P=0.056$

No other significant differences were found in autoimmune/allergic markers or personal and familiar history.

Discussion: Results suggest possible differences in autoimmune personal and familiar load between acutely ill patients and HC.

To note:

- The anti-DWEYS Ab, possibly neurotoxic and related to psychiatric symptoms in SLE patients, was higher in P than in HC, with a positive correlation to anxiety and depression scales. If confirmed, it should be determined whether the Ab influences psychopathology, or is just a marker of an immunity status. Increased stress levels in the P group could have contributed to damage the blood-brain-barrier and allow the Ab to access the brain.

- The higher prevalence of autoimmune disease in P's maternal history supports the hypothesis of a link between psychopathology and autoimmunity. No higher prevalence on the paternal side might be explained by incomplete information in the P group, where parents were often separated and mothers, who were mostly the informers, might not be fully aware of the fathers' history.

M41. Significant differences in substest Ralvt between a PEP's group and controls

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Background: Episodic memory impairment, linked to abnormal activation in the medial temporal lobes is one of the most robust and reliable cognitive difficulties experienced by individuals with and an important predictor of social and community functioning and quality of life. Consequently, the assessment of episodic memory functioning should be an essential component of routine clinical evaluation for individuals with schizophrenia. The recovery of the abilities after a First Episodic Psychotic (PEP) is important for a good prognosis.

Methods: A sample of 41 FEPs and 39 healthy subjects were evaluated. The variables assessed were verbal and visual memory, attention, and working memory (substest WISC and RALVT)

Results: The patients with PEP's group had significant differences ($p \leq 0,003$) with controls in substest Delayed free recall (RALVT).

Discussion: It is clear that there is a deterioration in the memory function in patients who have suffered a PEP.

Synaptic transmission between the hippocampus and prefrontal cortex is required for many executive cognitive functions. It is believed that disruption of this communication contributes to symptoms observed in psychiatric disorders including schizophrenia.

Investigation about the connexion between these areas and their role in the development in psychosis should be a priority to investigate.

M42. Adolescent trajectories of motor function and risk for psychosis

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Background: Evidence indicates that individuals who subsequently develop schizophrenia/ schizophrenia spectrum disorders (SDD) in adulthood display poorer motor function during early and middle childhood than individuals who do not develop these disorders. However, among individuals who develop schizophrenia/SSD in adulthood, motor dysfunction is not apparent at all stages of childhood development and may reduce with increasing age. Currently, little is known about the developmental trajectories of motor function in adolescence among youth at-risk for the disorder.

Methods: 94 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 the Purdue Pegboard assessment, comprising four subtests: dominant hand, non-dominant hand, both hands, assembly subtest. Motor function between ages 9-16 years was compared between youth characterized by a triad of well-replicated developmental antecedents of schizophrenia (ASz, $N=29$); youth with a least one affected relative with schizophrenia or schizoaffective disorder (FHx; $N=26$); and typically developing youth (TD, $N=42$).

Results: Longitudinal mixed models for repeated measures data indicated significant improvements with age in TD youth on the assembly subtest only. Relative to TD youth, FHx children exhibited an early deficit on the dominant hand and both hand subtests which was followed by faster rates of improvement with age, but a stable impairment on the assembly subtest across adolescence. In contrast, compared to the TD group, ASz youth showed an early deficit followed by significant improvements for the assembly subtest, but a stable impairment on the dominant hand and both hand subtests across adolescence.

Discussion: Findings are consistent with existing literature indicating that risk for schizophrenia/SSD is associated with delayed motor development. The motor dysfunction observed in both at-risk groups may reflect cerebellar dysfunction, and provides additional support for a cognitive dysmetria model of schizophrenia.

M43. Negative symptoms at first episode and their impact on treatment outcomes in early-onset psychosis

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Background: The severity of negative symptoms (NS) at the onset of illness have been consistently associated with poor outcomes in adult onset psychosis. Less is known about the impact of NS on later clinical outcomes in child and adolescent onset psychosis. Furthermore, very little is known about the effect of NS at first presentation on the response to antipsychotic medications in children and adolescents. Using a large electronic mental health record database, we aimed (i) to investigate the presence of NS in a historical cohort of children and adolescents with early-onset psychosis and (ii) to determine if their presence around the first psychotic episode was prospectively associated with initial treatment failure (ITF), as defined by initiation of a third trial of novel antipsychotic treatment for psychotic symptoms.

Methods: Data were obtained from a first episode psychosis (FEP) cohort of 602 children (51% male), mean age 16.0 (SD 1.6, range

10–17 years), referred to inpatient and community based Child and Adolescent Mental Health services in South London, UK. Using the Clinical Record Interactive Search system (CRIS) and previously validated natural language processing tools (NLP), we extracted, from electronic health records, a number of individual and treatment characteristics including age at presentation, sex, ethnicity, adaptive function, co-morbid ICD-10 diagnoses, negative symptoms at presentation (the seven items of the PANSS Marder Negative Symptoms Factor were used as a framework), and the number of unique antipsychotic medications prescribed over a 5 year observation period. We modeled the effect of 2 of more Marder Negative Factors at first presentation on antipsychotic treatment failure over a 5-year period using Cox regression.

Results: Of the 602 children and adolescents who presented with FEP, 220 (36.5%) had two or more NS items at first presentation, and 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. A fully adjusted cox proportional hazards model found that the presence of two or more NS at the first episode doubled the rate of iTF (aHR 2.05, 95% CI: 1.21-3.49), presence of a comorbid diagnosis of autism spectrum disorders (aHR 1.96, 95% CI: 1.07-3.61) were also associated with an increased risk of developing iTF. **Discussion:** NS could be used as a marker, at first presentation of psychosis, to identify a subset of children and adolescents who will respond poorly to antipsychotic medication. Optimization of current treatment strategies in this subset of patients with psychosis, and research involving agents that target both the negative and the positive symptoms, are warranted.

M44. From neurological soft signs to functional outcome in young individuals in treatment with secondary services for non-psychotic disorders

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Background: Functional decline among patients with mental illness is not unique to individuals with psychotic disorders. Despite this, research on early predictors of functional outcome mainly focused on individuals thought to have an "At Risk Mental State" (ARMS) for psychosis. There is evidence suggesting that certain early vulnerability markers, such as neurological soft signs (NSS), may explain variability in functional outcomes independent of the level of psychosis risk and the traditional diagnostic classification.

Methods: Structural equation modeling was applied to baseline data from a prospective longitudinal study of 138 young individuals in treatment with secondary services for non-psychotic disorders. We evaluated theoretically based models of pathways to functional outcome starting from NSS. The intervening variables were established according to previous evidence and drawn from two general categories: cognition (neuro- and social-) and negative symptoms (expressive and experiential).

Results: A final trimmed model was a single path running from NSS to neurocognition to experiential negative symptoms to outcome. It could not be improved by adding or dropping connections that would change the single path to multiple paths. The indirect effect from NSS to outcome was significant. The validity of the model was independent of the ARMS status and the psychiatric diagnosis.

Discussion: Our results provide evidence for a single pathway model in which the starting and intervening variables represent modifiable trans-diagnostic therapeutic targets to improve functional trajectories in young individuals with a recent onset psychiatric diagnosis and different levels of psychosis risk.

M45. Theory of mind as a mediator variable between neurocognition and functioning in young individuals in treatment with secondary services for non-psychotic disorders

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Background: A large body of studies provides evidence for a link between neurocognition, theory of mind (ToM) and functioning in psychotic spectrum disorders (PSDs), with ToM mediating the impact that neurocognition has on functioning. These three constructs and the related mediation effect may characterize different psychiatric syndromes other than PSDs. Despite this, research on early predictors of functional outcome mainly focused on individuals thought to have an "At Risk Mental State" (ARMS) for psychosis.

Methods: Structural equation modeling (SEM) was applied to baseline data from a prospective longitudinal study of 138 young individuals in treatment with secondary services for non-psychotic disorders. Using SEM, we tested the hypothesis that ToM mediates the effect of neurocognition on functioning independent of the level of psychosis risk and the traditional diagnostic classification.

Results: In the mediation model the bootstrapping estimate revealed a significant indirect effect that was the association of social cognition with neurocognition and with functional outcome ($\beta=0.055$, 95% CI=0.001 to 0.202, $P=0.043$). ToM was significantly associated with neurocognition ($\beta=-0.21$, $P=0.044$) and the path from neurocognition to functioning was no longer significant as soon as the mediator (ToM) was entered into the mediation model ($\beta=-0.15$, $P=0.077$), consistent with a complete mediation effect through ToM. This mediation was independent of the ARMS status and the psychiatric diagnoses, highlighting the need for a broad trans-diagnostic approach to early detect and intervene on functional recovery.

Discussion: Our results provide useful information on a young psychiatric sample, in which specific therapeutic interventions have the potential to significantly limit functional disability.

M46. Nucleus reuniens regulation of ventral tegmental area dopamine neuron activity: relevance to psychosis

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Background: Excess dopamine (DA) signaling, ie "hyperdopaminergic states," are thought to underlie psychosis in a variety of psychiatric conditions, including schizophrenia, schizotypal personality disorder, bipolar disorder, and temporal lobe epilepsy. Previous work from our group has described a tripartite circuit comprised of the ventral subiculum (vSub), nucleus accumbens (NAc), and ventral pallidum (VP), which governs the proportion of ventral tegmental area (VTA) DA neurons that are spontaneously active, ie "population activity." Population activity is a key parameter of VTA DA neuron activity: DA cells can only exhibit burst firing if they are spontaneously active. Therefore, population activity serves as a means of adjusting the amplitude of rapid, phasic DA system responses. For example, our group and others have observed aberrantly high population activity in the methylxozymethanol acetate (MAM) model of schizophrenia. More recently, our group reported that inhibition of the infralimbic subdivision of the medial prefrontal cortex (ilPFC) increases DA neuron population activity, and that this effect depends on vSub. However, there is no direct projection from ilPFC to the ventral hippocampus. We propose that communication between the two structures is mediated by the nucleus reuniens of the midline thalamus (RE). Several anatomical studies have characterized dense, reciprocal connections between RE and ilPFC/vSub, suggesting that RE could be involved in controlling VTA DA neuron population activity, and that ilPFC might exert its influence on VTA via RE. We hypothesize that RE governs VTA DA neuron population activity via the ilPFC-RE-vSub circuit, and altered signaling in this circuitry contributes to hyperdopaminergic states.

Methods: Electrophysiological studies: recordings of VTA DA neurons were performed in anesthetized rats following intracranial infusion of pharmacological agents into RE, ilPFC, and/or vSub just prior to recordings. DA neurons were identified using well-established electrophysiological criteria. Three parameters of DA neuron activity were measured: (1) population activity (number of spontaneously firing DA neurons per electrode track, i.e. cells/track), (2) firing rate, and (3) the percentage of action potentials occurring in bursts. Population activity was determined by counting the number of spontaneously firing DA neurons encountered while making 6–9 vertical passes (tracks) through the VTA. Behavioral studies: locomotor activity was measured in an open field immediately following amphetamine administration in animals receiving intracranial infusion of NMDA or vehicle into RE.

Results: We show that pharmacological inhibition of ilPFC enhances VTA DA neuron population activity, but this effect does not occur if RE is also inhibited. Furthermore, we show that pharmacological stimulation of RE enhances VTA DA neuron population activity, and that this effect is prevented if vSub is also inhibited. Finally, we demonstrate that pharmacological stimulation of RE enhances amphetamine-induced hyperlocomotion, a behavioral indicator of an over-responsive DA system.

Discussion: These findings suggest that increased DA neuron population activity following inhibition of ilPFC may occur via disinhibition of RE, enhancing DA system gain. Indeed, dysfunction in prefrontal cortex, as well as hyperactivity in thalamus and ventral hippocampus, are thought to underlie the psychotic symptoms of schizophrenia and other disorders, and show activation with psychotomimetic drugs. Therefore, loss of prefrontal regulation via disruption of ilPFC-RE communication could lead to a dysregulated hyperdopaminergic state, and may play a role in psychotic disorders.

M47. Behavioral effects of D-amphetamine applied to the associate striatum of the rat as a circuitry paradigm of psychosis

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Background: Based on the mesolimbic hypothesis of psychosis, and the antipsychotic effects of dopamine antagonists, d-amphetamine (AMPH)-induced hyperactivity in rodents has been used as a screening assay for detecting antipsychotic-like effects since several decades. However, recent human studies have shown that dopaminergic hyperactivity in the dorsal, associative, striatum rather than the ventral, mesolimbic, striatum underlies psychosis in patients with schizophrenia. Since there is no clear understanding which, if any, systemic AMPH-induced behaviors are dependent on the associative striatum, we infused AMPH in a homologous area in the rat and made a detailed behavioral assessment. To confirm that the observed effects were mediated by the specific area, we then co-infused sulpiride which is known to diffuse very little in the striatum, to examine whether the behaviors could be reversed by local D2 receptor blockade.

Methods: Stereotaxic implantation of a guide cannulae was performed bilaterally into the dorsomedial striatum in rats. After a 2 weeks recovery period, a first bilateral intra-striatal infusion of either CSF, AMPH 10 or 20 µg (per side) was applied to awake rats. Animals were immediately transferred in an open field box, where specific behaviors were registered for 40 minutes. One week later, the animals were infused a second time with either AMPH 20 µg, sulpiride 50 ng or a cocktail AMPH/sulpiride (per side) (animals were randomized). The rats were observed again for 40 minutes. The locomotor activity was automatically measured by light beam interruptions. Manual scoring was done for specific behaviors such head weaving, scratching, wet dog shaking, and grooming.

Results: AMPH did not alter locomotor activity, including forward locomotion, stereotypy, and rearing. The only behavior that was dose-dependently induced by AMPH was head weaving (i.e. slow horizontal head movements). Sulpiride, when combined with AMPH, did not alter locomotor activity but almost completely blocked head weaving induced by AMPH.

Discussion: Dopaminergic stimulation involving D2 receptors in the dorsomedial striatum of rats induced a specific stereotyped behavior,

i.e. head weaving. Interestingly, head weaving was also observed following systemic AMPH, and could be blocked by superior colliculus lesions (Pope *et al* 1980 Psychopharm), in line with a dorsal striatum – nigrotectal pathway. These data suggest that head weaving induced by (systemic) AMPH could serve as an improved paradigm for psychosis as compared to the mesolimbic mediated hyperactivity assays.

M48. A new insight at the interaction between mGlu4 and 5-HT1A receptors in animal models of schizophrenia disorders

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Background: Variety of our previous studies showed that glutamatergic system plays a significant role in the pathophysiology of schizophrenia. Recently, the mGlu4 receptor was determined as a one of the most promising antipsychotic drug target. In the present studies we focused on the antipsychotic action of the latest agonist of mGlu4 receptor, LSP4-2022 and the involvement of serotonergic system in its activity. We used standard pharmacological tools, such as 5-HT1A antagonist, WAY100635, and the agonist, (RS)-8-OH-DPAT. We also tried to establish the neurochemical background of that interaction.

Methods: Several behavioral tests to study antipsychotic-like activity of compounds, such as MK-801-induced hyperactivity and DOI-induced head twitches, social interactions, and novel object recognition test were used. The neurochemical and physiological backgrounds of mGlu4-5-HT1A interaction was investigated with the use of patch clamp recordings, in the model of DOI-induced spontaneous excitatory postsynaptic currents (EPSCs) in frontal cortex, and with microdialysis *in vivo*, to investigate the release of dopamine (DA), glutamate (Glu), and gamma-aminobutyric acid (GABA) in freely moving rats. Moreover, the level of second messenger (cAMP generation) was established in chopped slices from rat prefrontal cortex.

Results: In all behavioral tests, the administration of WAY100635 blocked LSP4-2022-induced antipsychotic effects. Moreover, the co-administration of subeffective doses of LSP4-2022 with a subeffective dose of (RS)-8-OH-DPAT induced an antipsychotic action similar to that observed by LSP4-2022 when given alone. LSP4-2022 decreased the amplitude and frequency of DOI-induced spontaneous EPSCs. The administration of WAY100635 antagonized LSP4-2022-induced effect on frequency, but not the amplitude of sEPSCs. In the microdialysis studies administration of MK-801 significantly increased the release of all investigated neurotransmitters (DA, Glu, GABA). This effect was decreased by administration of LSP4-2022. Furthermore, the administration of 5-HT1A antagonist blocked the LSP4-2022 effect on these releases. In the second messenger generation studies mGlu4 agonist decreased forskolin-stimulated increased in cAMP accumulation, and WAY100635 administration had no influence on that effect.

Discussion: The present studies indicate and confirm our earlier results, that activation of mGlu4 receptor by selective orthosteric agonist – LSP4-2022 is promising target in antipsychotic drug discovery. Moreover, the simultaneous modulation of 5-HT1A receptors may contribute to observed LSP4-2022-induced antipsychotic effect, and facilitate its action. Electrophysiological and neurochemical data indicate, that the mGlu4-5-HT1A interaction involves large neuronal loops rather than intracellular signaling within a single neuron.

M49. α5 Nachr modulation of cortico-mesolimbic circuitry and function

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Background: Cholinergic signaling is central to the control of cognitive processes and reward-focused behaviors. Hypotheses concerning a cholinergic contribution to schizophrenic symptomology have been

built around potential aberrations in cholinergic neurotransmission as a source of cognitive and negative symptoms associated with this disorder. Furthermore, the strong prevalence of nicotine abuse in this patient population has been proposed to be indicative of an attempt at self-medication via stimulation of nicotinic acetylcholine receptors (nAChR, D'Souza and Markou, 2012). The $\alpha 5$ nAChR is an auxiliary subunit, and while it does not sit directly in the binding pocket, it can potentially affect the function of heteromeric nAChRs. It is found throughout cortical-mesolimbic circuitry in association with $\alpha 4\beta 2$ ($\alpha 5$) nAChRs, including presynaptically on dopamine (DA) terminals in the ventral striatum, as well as in layer 6 of the prefrontal cortex (PFC), giving it the capacity to contribute to nAChR modulation of striatal DA release and cortical information processing, respectively. In the present studies, we sought to characterize the role of the $\alpha 5$ nAChR subunit in modulating ventral-striatal DA release, PFC circuitry, as well as top-down control of attentional performance.

Methods: An RNAi strategy was developed to manipulate $\alpha 5$ expression in-vivo. A lenti-viral vector carrying a shRNA directed against $\alpha 5$ was then infused into the DA cell bodies in the ventral tegmental area (VTA), or locally in the medial PFC. In experiment one, we used fast-scan cyclic voltammetry to monitor stimulated DA release in the core of the nucleus accumbens, both in intact anesthetized rats and in striatal slices, following $\alpha 5$ knockdown in the VTA. In experiment two, the effect of PFC $\alpha 5$ knockdown on the response of layer 6 pyramidal cells to ACh and nicotine was assessed in rat cortical slices. In a separate cohort of animals, the impact of this same PFC knockdown on attentional performance and resilience to distraction was tested.

Results: $\alpha 5$ knockdown in the VTA potentially attenuated stimulation-evoked accumbens dopamine release and clearance, as well as the modulation of dopamine release by nicotine ($n = 5$ for knockdown and luciferase control conditions), both in vivo and ex vivo. In pyramidal cells from layer 6 of the PFC, $\alpha 5$ knockdown reduced the inward current evoked by local application of ACh and augmented the rate of desensitization following nicotine as previously reported in $\alpha 5$ developmental knockout mice (Bailey *et al.*, 2010). In rats performing an attention task, PFC $\alpha 5$ knockdown had no impact on standard task performance or the acute impact of a distracter challenge. However, PFC $\alpha 5$ knockdown did reduce the animals' capacity to recover performance to pre-distracter levels in the days following the challenge ($n = 12$, 11 for knockdown and control, respectively).

Discussion: The $\alpha 5$ nAChR plays a critical role in the regulation of nucleus accumbens dopamine release, both at baseline and in response to a nicotine challenge. At the level of the PFC, $\alpha 5$ nAChRs potentially modulate the impact of ACh and nicotine on pyramidal cells. Functionally, such loss of PFC $\alpha 5$ signaling specifically impaired attentional performance in the days following a distracter-induced increase in error rates, suggesting that $\alpha 5$ nAChRs normally support a form of cognitive resilience or top-down preservation of attentional performance in the face of violations of task expectancies. Combined, via its ability to contribute to nAChR modulation of striatal dopamine release and cortical circuitry, the $\alpha 5$ nAChR could represent a novel target for treatment of cognitive, motivational, and reward processes known to be impaired in schizophrenia.

M50. The reliability of the remission and exacerbation criteria (REC) of schizophrenia and schizoaffective disorders using the standard for clinicians' interview in psychiatry (SCIP)

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Background: The Clinical Global Impressions (CGI) scale provides a qualitative judgment of overall patient improvement, placing patients into one of seven categories (very much improved, much improved, minimally improved, no change, minimally worse, much worse, and very much worse) (1). The psychometric properties of the CGI have not been tested at the outset and it has not been revised or quantified since 1976. There is an urgent need to assess mental disorders and the response to treatment using a dimensional model (2-6).

Methods: The Standard for Clinicians' Interview in Psychiatry (SCIP) was developed and tested between 2000 and 2012 to assess mental disorders using reliable dimensions based upon reliable symptoms and signs (7-9). The total psychosis score (TPS) is the sum of the

hallucinations, delusions and disorganization dimensions. Based upon the TPS, the Remission and Exacerbation Criteria (REC) is defined as the percent change in the core symptoms and signs (dimension) between a baseline assessment and a subsequent assessment. Compared to the baseline assessment, the REC at a subsequent assessment can be categorized as one of the following: (1) Substantial improvement: >70% decrease in dimension score, (2) Moderate improvement: 20% to 70% decrease in dimension score, (3) Minimal improvement: <20% decrease in dimension score, (4) No change from the baseline score, (5) Minimal worsening: <20% increase in dimension score, (6) Moderate worsening: 20% to 70% increase in dimension score, and (7) Substantial worsening: >70% increase in dimension score. Inter-rater reliability of the TPS and kappa for REC between two raters were calculated.

Results: Participants were thirty seven patients from two inpatient psychiatric units who had been diagnosed with schizophrenia or schizoaffective disorders (mean age=37, 49% male, 92% White). Patients were interviewed by two raters upon admission and upon discharge. The two raters demonstrated good agreement on patients' TPS, $r=0.92$. There was also substantial agreement between the two raters on REC categories, kappa=0.71.

Discussion: The REC is a quantitative and reliable method of assessment of improvement or worsening of patients with schizophrenia and schizoaffective disorders over time.

M51. Investigation of "critical period" in the treatment for first-episode schizophrenia: analysis of the association between duration of untreated psychosis and clinical outcome

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Background: The duration of untreated psychosis (DUP) has been identified as an independent predictor of poor outcome in first-episode psychosis. Indeed, meta-analysis studies have demonstrated an association between the longer DUP and the poorer prognosis. Early intervention programs have been prompted in many countries based on the critical period hypothesis. However, the range of critical period is controversial because the precise length of DUP associated with outcome has not been clarified.

The aim of this study was to clarify the association between the DUP and clinical features in a prospective longitudinal study examining patients with first-episode schizophrenia. Additionally, to define the critical period, we examined the outcome by subdividing the length of DUP.

Methods: The subjects were recruited at the Toho University Omori Medical Center, Tokyo. The subjects fulfilled the following inclusion criteria: (i) age between 16 to 55 years at the time of their first visit to the hospital; (ii) meeting the ICD-10 criteria for schizophrenia, schizotypal, and delusional disorders (F2); (iii) no previous adequate treatment for psychosis; and (iv) no history of a psychotic condition associated with substance-related disorders, mental retardation, and/or organic diseases.

The subjects were followed for over 36-months. Psychotic symptoms, cognitive function, and social functioning were assessed at baseline and at 12, 24, and 36-months follow up points. Global social functioning was measured using the Global Assessment of Functioning (GAF). The overall severity of disease was measured using the Clinical Global Impression (CGI). The doses of antipsychotic drugs were calculated according to their chlorpromazine equivalent (CP mg equivalent). Psychiatric symptoms were measured using the Positive and Negative Syndrome Scale (PANSS). Quality of life (QOL) was evaluated based on the mean WHOQOL-26 score. Cognitive function was evaluated using the Schizophrenia Cognition Rating Scale (SCoRS). Social functioning was evaluated using the total score of the Social Functioning Scale (SFS). This protocol was approved by the Ethical Research Committee of Toho University School of Medicine.

Results: A total number of 54 patients (31 female and 23 male, with a mean [SD] age at onset of 30.2 [9.9] years, with a mean [SD] age at first visit of 32.3 [9.6]) with first-episode schizophrenia were assessed. The

mean [SD] of DUP was 22.1 [46.9] months, and the median DUP was 3.3 months. It was suggested that shorter DUP could be more improved than longer DUP. Furthermore, shorter DUP predicted improvement, when DUP was analyzed as a dichotomous variable divided at 1 year.

Discussion: The length of DUP could be correlated with the prognosis of the first-episode schizophrenia. To define the critical period, more precise examination of the association between DUP and the outcome has been demanded. The more precise critical period could be useful for effective strategies in early intervention of first-episode schizophrenia.

M52. PANSS-6 measures the severity of schizophrenia using only six items

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Background: The 30-item Positive and Negative Syndrome Scale (PANSS-30) is among the most widely used outcome measures in clinical trials of schizophrenia, but is considered to be too time consuming for routine use in clinical practice. Therefore, shorter versions of the scale have been proposed, including the PANSS-14 (Santor *et al.*) and PANSS-8 (Andreasen *et al.*). However, none of these PANSS versions have been subjected to validation by means of the parametric Rasch rating scale model, which evaluates "scalability". Scalability is a statistical prerequisite for using the total score of a rating scale as a measure for the severity of the disorder being rated. In this study, we therefore tested the scalability of PANSS-30, PANSS-14, and PANSS-8.

Methods: We tested the scalability of PANSS-30, PANSS-14, and PANSS-8 using the item response theory analysis (ad modum Rasch) based on data from two randomized controlled trials (RCTs) in schizophrenia (Zimbroff *et al.* & van Kammen *et al.*). Furthermore, using analysis of covariance (ANCOVA), we tested whether a scalable version of PANSS could separate the effect of sertindole and haloperidol from that of placebo in the RCTs.

Results: Our item response theory analysis showed that PANSS-30, PANSS-14, and PANSS-8 were not scalable. Two items from PANSS-8 were responsible for the lack of scalability of this scale, namely "G5 - Mannerisms and posturing" and "G9 - Unusual thought content". When removing these two items, the resulting 6-item scale (PANSS-6) became scalable. PANSS-6 consists of the following items: P1 - Delusions, P2 - Conceptual disorganization, P3 - Hallucinations, N1 - Blunted Affect, N4 - Social withdrawal, N6 - Lack of spontaneity & flow of conversation.

The ANCOVA showed that PANSS-6 was able to separate the effect of sertindole and haloperidol from that of placebo.

Discussion: In this analysis, we identified a scalable schizophrenia severity rating scale consisting of only 6 items (PANSS-6). While further studies of its validity are needed, we are optimistic that PANSS-6 will turn out to be a sound alternative to the longer PANSS versions. Indeed, a 6-item rating scale seems ideal for facilitation of measurement-based care of schizophrenia in clinical practice.

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NB: An article based on the findings outlined above is in press in *Acta Psychiatrica Scandinavica* (DOI: 10.1111/acps.12526). Parts of this abstract are excerpted from that article.

M53. Electronic cigarettes as a harm-reduction strategy in people with serious mental illness: a pilot clinical trial

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Background: Electronic cigarettes have been shown to be just as effective as nicotine patches in the general population. But research has been done as to whether they may affect the physical health, smoking patterns, and psychiatric symptoms in people with serious mental illnesses. This pilot trial aimed to investigate the effect of electronic cigarettes on psychiatric symptomatology, physical health, and cigarette consumption in psychosis patients over 24 weeks, as well as electronic cigarette acceptability.

Methods: Patients aged 18-70 with a diagnosis of schizophrenia, bipolar disorder, schizoaffective or schizophreniform disorders were enrolled onto a 24 week trial, including a 6 week intervention period, where patients were given free electronic cigarettes. They were encouraged to replace as much of their tobacco smoking as possible with the electronic cigarettes. Cigarette and electronic cigarette use per day was collected by self-report, and psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS). Carbon monoxide levels and peak expiratory flow rate was also used to monitor respiratory effects. Acceptability for the electronic cigarette was assessed using a visual analog scale and the E-Cig ITC questionnaire. Participants were assessed weekly for 12 weeks, and a follow-up was conducted at 24 weeks.

Results: All data reported is preliminary, as the trial is still on-going. Cigarette use significantly reduced after the first week of electronic cigarette distribution and was maintained at 24 weeks. Conversely, electronic cigarette use did not significantly change over the trial period, and no significant variation in peak expiratory flow rate or carbon monoxide levels were detected. Reduction in cigarette use was significantly associated with a reduction in positive psychotic symptoms as measured by the PANSS.

Discussion: These findings support the idea that electronic cigarettes may significantly reduce tobacco consumption in people with psychosis, without exacerbating psychiatric symptomatology. One explanation for the non-detection of changes in respiratory function may be that the majority of patients in the study were dual users of both tobacco and electronic cigarettes. Tobacco specific nitrosamines are to be analyzed from urine samples at baseline and at the end of the free electronic cigarette distribution period. Further study is needed to develop understanding of the impact of electronic cigarettes in this population.

M54. An assessment of injection site reactions and injection site pain of once-every one month and three-month long-acting injectable formulations of paliperidone palmitate (PP1M vs PP3M)

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Background: Injection site reactions and pain associated with long-acting antipsychotics is of interest to healthcare professionals. Safety data of a randomized, double blind (DB), parallel group, multicenter, non-inferiority study (NCT01515423) evaluated PP3M and PP1M injection site reactions and pain.

Methods: Patients (N = 1429) with schizophrenia were initially treated with PP1M (50-150 mg eq.) in a 17 week open-label (OL) phase. Upon meeting clinical stabilization criteria, patients were randomized 1:1 to PP1M or PP3M in a 48 week DB phase. Patients assigned to PP3M received a 3.5 multiple of the PP1M dose received at week 13; patients in the PP1M group continued to receive the same dose as week 13. Injections occurred every month with PP3M patients receiving placebo injections to maintain blind. Investigators assessed injection site reactions within 30 minutes of each injection. Patients assessed

pain using a visual analog scale (VAS; 0 [no pain] to 100 [maximum pain]).

Results: Overall, injections were well-tolerated. Incidence of induration, redness, and swelling were low in the OL (9-12%) and DB (7-13%) phases, and mostly mild in severity. Mean (SD) visual analog scale (VAS) pain scores decreased from 22.0 (21.6) at OL baseline to 19.2 (20.8) at OL week 17. At DB baseline mean (SD) VAS scores for PP3M and PP1M were 19.5 (20.7) and 18.4 (20.4), respectively; at DB endpoint mean (SD) VAS scores were 15.6 (17.9) and 15.5 (18.3) respectively. No notable changes in injection site reactions or pain were observed by injection site location (deltoid vs gluteal) during the OL and DB phases or by final OL dose (50-75 mg eq., 100 mg eq. or 150 mg eq.) of PP1M during the DB phase.

Discussion: Injection site reactions and pain were low and similar between PP1M and PP3M, regardless of last dose of OL PP1M.

M55. Validation of the Korean version of the clinical assessment interview for negative symptoms (CAINS)

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Background: Negative symptoms are highly resistant to available treatments despite their close associations with functional outcome in schizophrenia. Clinical Assessment Interview for Negative Symptoms (CAINS) has been recently developed to improve its measurement and is a promising negative symptoms instrument with sound psychometric properties. In the current study, we performed a multi-site study to validate the Korean version of the CAINS (CAINS-K).

Methods: One hundred eighty schizophrenia patients diverse in age, symptoms, and illness duration were recruited from four mental clinics. The CAINS-K, the Scale for the Assessment of Negative Symptoms (SANS), Brief Psychiatric Rating Scale (BPRS), Calgary Depression Scale for Schizophrenia (CDSS), self-report measure of behavioral inhibition and activation (BIS/BAS), and neurocognitive tasks were administered.

Results: The CAINS-K demonstrated a high internal-consistency ($\alpha=.916$) and inter-rater agreement ($\alpha=.782$). Exploratory Factor Analysis replicated a two-factor structure of the original scale which includes motivation/pleasure and expression deficits. No gender difference was found on the total and sub-scale scores of the CAINS-K. It showed an adequate convergent validity with the total and sub-scale scores of the SANS, negative symptoms of BPRS, and self-report measure of behavioral activation. The CAINS-K also exhibited strong divergent validity as it was minimally related with positive symptoms of the BPRS, depression of the CDSS, and neurocognitive tasks.

Discussion: The CAINS-K demonstrated an excellent reliability and validity. It is expected to facilitate studies on the etiology, mechanism, and treatment of negative symptoms in Korean population with schizophrenia.

M56. Drug development strategies for schizophrenia using a novel PDE10A inhibitor: TAK-063

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Background: Translational studies in phase I are important to establish key information about a compound such as demonstration of adequate exposure at the target site of action, binding to the pharmacological target, and demonstration of pharmacological activity to prevent costly phase II/III failures. In preclinical studies, doses of TAK-063 that achieved ~30% occupancy of phosphodiesterase 10A (PDE10A) in striatum produced antipsychotic-like effects, enhanced various cognitive functions, normalized pre-pulse inhibition, and reversed ketamine-induced increases in gamma power. To date,

no PDE10A inhibitors have demonstrated clinical efficacy in the treatment of schizophrenia, and, therefore, relationships between preclinical and clinical effects have not been established. The strategy for the TAK-063 phase I program was developed to obtain this key information and used for phase 2 dose selection.

Methods: The TAK-063 phase I program consisted of four clinical trials. Two were placebo-controlled, double blind, dose-escalation studies (single and multiple dose). The single dose study was conducted in Japanese and non-Japanese healthy volunteers (HVs). The multiple dose study was conducted in schizophrenia subjects and Japanese HVs dosed once daily for seven days. An open-label, single-dose PET study to evaluate the target occupancy of TAK-063 was conducted. In addition, a randomized, placebo-controlled, 3-period, incomplete crossover study was conducted to evaluate the effects of single doses of TAK-063 on ketamine-induced changes in fMRI. In all studies, appropriate safety and PK were assessed. In addition, most studies also included exploratory measures of cognition, EEG, and other biomarkers established by preclinical studies.

Results: TAK-063 was safe and generally well tolerated in all studies. There were no serious adverse events (AEs). Single doses of TAK-063 were well tolerated up to 1000 mg in healthy subjects. Somnolence was the most common AE. The pharmacokinetics were dose-proportional up to 30 mg, with a half-life suitable for once-daily dosing. Food increased absorption. In the MRD study, TAK-063 (administered with food for 7 days) was tolerated at all doses. At 30 mg and above, more moderate to severe AEs were observed in subjects with schizophrenia. Though a maximum tolerated dose was not defined, somnolence was considered to be potentially dose-limiting. Modeling was used to explore relationships between plasma concentrations and adverse effects. Restoration of gamma synchrony with increases in alpha and decreases in slow waves were observed in electroencephalographic recordings most consistently at 20 mg. Single doses of TAK-063 reversed the ketamine-induced increases in BOLD signal in brain regions in which risperidone has previously shown to have similar effects. The largest and most consistent effects on BOLD were observed in the 30 mg group, which approximates steady-state exposures of 20 mg.

A relationship between plasma concentrations and target occupancy in putamen was observed in the PET study. These data were used to predict the steady state target occupancy of TAK-063 using C_{max}, AUC, and C_{min}. Doses of 20 mg were predicted to achieve an average target occupancy greater than 30%. Based on these results, 20 mg was considered to be the highest, best tolerated dose that achieved relevant target occupancy, exposures, and produced consistent effects on exploratory biomarkers.

Discussion: These data provide an understanding of the safety, pharmacology, and PK of TAK-063. Based on these data, a proof of concept study has been initiated to determine the efficacy of 20 mg of TAK-063 administered nightly with food in the treatment of schizophrenia.

M57. Joint modeling of dropout and outcome in three pivotal clinical trials of schizophrenia

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Background: Dropout is a serious challenge to the success of clinical trials. However, standard outcome analyses with mixed models do not account for dropout. Joint models use dropout from a survival model to adjust the outcome from a mixed model, but are untested in clinical trials of schizophrenia. We aim to compare mixed and joint models in three acute phase pivotal placebo controlled clinical trials of schizophrenia.

Methods: Data were reanalyzed on 611 trial participants with acute schizophrenia who participated in three pivotal randomized controlled trials (RCTs) that compared olanzapine or risperidone with placebo (dropout rates placebo: 62.6% and medication: 37.4%). The outcome measures were BPRS or PANSS total change scores. Mixed-effects models for repeated measures and joint models were computed and compared to examine the time-treatment interaction. Effect size comparisons were made.

Results: Antipsychotic treatment was superior to placebo across analyses. Time treatment interactions were statistically significant ($P < 0.05$) for both mixed ($\beta = 2.33$) and joint ($\beta = 2.62$) models. Compared with mixed modeling, joint modeling reduced the estimated change score for treatment (21.24 vs 19.74) and placebo (1.64 vs -1.11). The effect size differences between placebo and treatment groups were greater for joint ($ES = 0.89$) than mixed ($ES = 0.83$) models. Sensitivity analyses replicated this trend of results within each of the three trials.

Discussion: Compared to mixed models, the results of joint models provide a greater separation between treatment and placebo groups. This offers preliminary evidence that joint modeling may be useful in the analysis of antipsychotic placebo controlled RCTs.

M58. A possible role for prolactin in emerging psychosis

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Background: Hyperprolactinemia is frequently found in patients with schizophrenic psychoses and is usually considered to be an adverse effect of antipsychotic medication. However, there have also been recent reports on hyperprolactinaemia in antipsychotic-naïve first-episode psychosis (FEP) patients and in antipsychotic-naïve at-risk mental state (ARMS) individuals.

Prolactin secretion is not only stimulated by sucking, but also by psychosocial stress. The main regulatory mechanism acting on prolactin is the inhibition of its synthesis by dopamine. Furthermore, there is strong evidence that psychosocial stress is implicated in the development of psychotic symptoms. To corroborate the role of prolactin in emerging psychosis we want to i) replicate the existing findings of elevated prolactin levels in ARMS and FEP subjects (% hyperprolactinaemia) ii) analyze if FEP patients have higher prolactin levels than ARMS individuals, and iii) analyze if prolactin levels differ between men and women after normalization.

Methods: The data analyzed in this study were collected within the prospective Früherkennung von Psychosen (FePsy) study, which aims to improve the early detection of psychosis. From January 2012 until October 2015, 38 antipsychotic-naïve ARMS individuals and 12 antipsychotic-naïve FEP patients met the requested criteria for prolactin analyses and agreed to special blood withdrawal. This took place between 8 and 10 a.m. after overnight fast and 30 min of rest. Patients were asked to avoid stress, sports, physical activity, stimulation of the breast and smoking during at least 12 hours before blood taking. For analyses with continuous variables, we normalized prolactin values to correct for the biological variation between the sexes. We performed an ANOVA analysis to evaluate the main effects of group (ARMS, FEP) and sex (men, women), as well as their interactions on prolactin levels.

Results: Hyperprolactinaemia, i.e. blood levels higher than the normal range, was shown in 24% of ARMS individuals (22% of men and 33% of women) and 8% of FEP patients (0% of men, 50% of women). Mean prolactin values did not show a difference between ARMS and FEP subjects ($F = 0.122$; $P = 0.727$) but there was a main effect of sex ($F = 5.2533$; $P = 0.023$) describing higher normalized prolactin levels in women as compared to men. There was no interaction effect of group (ARMS, FEP) and sex (men, women).

Discussion: We could replicate the finding of elevated prolactin levels in ARMS individuals and FEP patients with a relatively high percentage of hyperprolactinemia using very sound methodology when taking blood samples and regarding exclusion criteria. These findings support a possible role for prolactin in emerging psychosis. The fact that we could not find higher prolactin levels in FEP than in ARMS individuals might be due to methodological problems, as we could not examine the FEP patients directly in their acute psychotic episode. We could also show that prolactin values are higher in our female as compared to our male patients even after correcting for the normal biological variation between the sexes. Thus, it could be speculated that stress, which can induce hyperprolactinaemia, has a stronger effect on women than on men with emerging psychosis.

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M59. Enhancing computer-assisted cognitive remediation for schizophrenia: an open-label study with anodal tDCs on left lateral prefrontal cortex

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Background: The aim of this study was the application of a specific intervention that combined a neuromodulation technique (transcranial Direct Current Stimulation, tDCS) and a computer-assisted cognitive remediation (CACR) strategy in order to obtain a fast and long-lasting cognitive enhancement in people affected by Schizophrenia (SCZ).

Methods: A group (enhanced CogPack[®], eCP group) of fourteen SCZ patients was treated for eight sessions (twice-weekly) of anodal tDCS over F3, roughly corresponding to the lateral prefrontal cortex (electrode delivering cathodal tDCS was placed on the ipsilateral arm; stimulation intensity: 1mA; duration: 20'), followed by a CACR intervention with CogPack[®] (duration: 50'-60'). A second group (CP group) of fifteen SCZ patients was treated with eighteen CogPack[®] sessions without neuromodulation (twice-weekly). Clinical, cognitive, and functioning assessments were done the week before (T0) and after (T1) the CACR intervention, as well as three and six months after the CACR end (respectively, T2 and T3).

Results: At T0, clinical, cognitive and functioning indices did not differ between eCP and CP groups. Respect to T0, a significant improvement in several cognitive domains and in the functioning was observed at T1, T2, and T3 for both intervention groups, as revealed by the repeated measures ANOVA models. No difference emerged in the efficacy on the cognitive and functioning indices between the two intervention group, as indicated by the absence of significant group \times time interaction effect ("eCP vs. CP" \times "T0 vs. T1 vs. T2 vs. T3").

Discussion: Anodal tDCS possibly enhanced cognitive performance during CogPack[®], reducing the amount of time needed to elicit a significant, long-lasting effect using CACR treatment in Schizophrenia. The present findings confirmed cognitive remediation intervention as potentially activating learning processes, with tDCS amplifying such effect by means of neuroplasticity mechanisms leading to a substantial shortening of the time required to induce clinically appreciable effects.

M60. Safety, tolerability, and pharmacokinetics of a novel PDE10A inhibitor, TAK-063, following multiple dosing in subjects with stable schizophrenia and healthy Japanese subjects

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Background: TAK-063 selectively inhibits phosphodiesterase 10A (PDE10A), which hydrolyzes both cyclic adenosine monophosphate and cyclic guanosine monophosphate. PDE10A inhibition may aid schizophrenia treatment by modulating, indirectly or directly, the effects of glutamatergic and dopaminergic systems. The objective was to characterize the safety, tolerability, and pharmacokinetics (PK) of TAK-063 following repeated dosing.

Methods: This was a randomized, double-blind, placebo-controlled, multiple-dose study in stable schizophrenia subjects washed out of their current antipsychotic medications ($n=47$) and healthy Japanese subjects ($n=30$). Ten subjects per cohort were enrolled and randomized to either TAK-063 or placebo (8 active and 2 placebo). Schizophrenia subjects were dosed once daily (QD) 3, 10, 20, 30, and 100 mg, and healthy Japanese subjects were dosed 3, 10, and 20 mg TAK-063 or placebo QD in the fed state using tablets for 7 days. Safety assessments were recorded throughout; serial plasma and urine samples were collected on days 1 and 7, with predose plasma samples on days 4, 5, and 6.

Results: TAK-063 was safe and generally well tolerated in both groups. There were no serious adverse events (AEs). Most AEs were of mild or moderate intensity. Somnolence, the most frequent AE in both treatment groups, was especially prevalent in schizophrenia subjects following 100 mg QD. Extrapyramidal syndrome (EPS), mainly dystonia, was observed in 14 schizophrenia subjects and 1 healthy Japanese subject treated with TAK-063. EPS was also observed in 1 schizophrenia subject in the placebo group. No clinically significant changes in the physical examination, clinical laboratory tests, or ECGs were observed. Blood pressure and pulse rate parameters were consistent with treatment-emergent AEs of orthostatic tachycardia and orthostatic hypotension and were similar between placebo and treatment groups. In the two groups, PK was broadly similar; in addition to TAK-063, a metabolite (M-I) was also quantified and exhibited a similar profile to TAK-063. TAK-063 was absorbed with a median T_{max} of 1.5 to 4 hours. C_{max} and AUC₂₄ values of TAK-063 and M-I increased in a dose-related manner up to 30 mg in schizophrenia subjects and up to 20 mg in Japanese subjects, with modest accumulation upon repeat dosing. At doses of 30 to 100 mg, the increase in exposure was less than dose proportional. Renal clearance was a minor elimination route ($< 0.1\%$ of dose).

Discussion: TAK-063 was safe and well tolerated in schizophrenia and healthy Japanese subjects at all doses tested; somnolence was the most commonly observed AE. At equivalent doses, reports of EPS were higher in subjects with schizophrenia than in healthy Japanese subjects, despite similar PK between groups. At doses of 30 to 100 mg, the increase in exposure was less than dose proportional, likely due to solubility-limited oral bioavailability.

M61. Stability in a 52-week schizophrenia extension study of treatment with long-acting injectable aripiprazole lauroxil

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Background: Aripiprazole lauroxil (AL; ARISTADA™, Alkermes, Inc.), a long-acting injectable antipsychotic, is approved for the treatment of schizophrenia. Clinical stability is a highly desirable treatment outcome, as it can predict better long-term outcomes including reduced hospitalizations. We assessed symptom stability in schizophrenia patients treated with AL in an efficacy study as well as the long-term safety extension study.

Methods: In a double-blind placebo-controlled study of acutely ill patients diagnosed with schizophrenia, subjects ($N=622$) were randomized to receive AL 441 mg, AL 882 mg, or placebo intramuscular injection (IM) once-monthly. Subjects received daily oral aripiprazole (15 mg) or matching placebo for the first 3 weeks after randomization, and continued with IM treatment for 12 weeks. Both new subjects with stable schizophrenia and those who completed the study were eligible to enroll into a 1 year active treatment extension study ($N=478$). New subjects received monthly injections with AL 882 mg, and rollover subjects received monthly injections with either AL 441 mg or AL 882 mg, depending on the treatment in the preceding trial. Subjects from the placebo arm received 441 or 882 mg corresponding to low/high placebo volume treatment. Similar to the 12-week randomized study, all new and placebo rollover subjects also received oral aripiprazole (15 mg) for 3 weeks. The exploratory analysis of the 1-year extension study included subjects who met two stability criteria: Positive and Negative

Syndrome total Score (PANSS) ≤ 80 and PANSS ≤ 4 on each of items P2, P3, P6, and G9 simultaneously for 12 continuous weeks. For subjects who were stabilized, remission and relapse rates were assessed using the Schizophrenia Working Group remission criteria (SWGRC). Remission was defined as a PANSS ≤ 3 for each of items P1, G9, P3, P2, G5, N1, N4, and N6 for ≥ 6 continuous months. Relapse criteria was defined as an increase of 10 points or more in PANSS total score from the end of the stabilization period.

Results: The full analysis set contained data from 462 subjects; 396 (86%) subjects reached stabilization within a median time of 85 days, while 66 subjects never met stability criteria. Among 396 stabilized subjects, 383 (97%) remained stable for the entire study, only 39 (10%) relapsed after achieving stabilization, and 233 (60%) achieved symptom remission. Among the 66 subjects who did not meet stability criteria, 30 subjects were not treated for a sufficient period as they discontinued before day 85. For the other 36 subjects, treatment emergent adverse events included schizophrenia (17%) and insomnia (11%). Overall, 318 subjects completed the entire long term safety extension study and 313 (98%) stayed stable after achieving stabilization.

Discussion: The majority of subjects with schizophrenia who were treated with AL achieved response and remained stable for ≥ 52 weeks. As most safety extension studies have the limitation of selecting for responders, about half the study subjects were treated de novo. Nonetheless, over half of the subjects achieved remission.

M62. Specificity and prognostic accuracy of the basal screening instrument for psychosis (BSIP) and the so far often neglected problem of false negatives

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Background: Previous research on the prospective clinical assessment of the prodromal period of schizophrenic psychoses has mainly focussed on transition rates of individuals considered being in an at-risk mental state for the disease. By contrast, relatively little attention has been paid to the clinical outcome of individuals who were referred to early detection centers, but initially not considered to be at increased risk of psychosis. Incorrect classification of individuals as being "not at-risk" may, however, have severe consequences such as a delay of adequate treatment. Therefore, we conducted a comprehensive 4-year follow-up clinical assessment of individuals initially not considered to be at increased risk of psychosis on the basis of the Basel Screening Instrument for Psychosis (BSIP) [1]. Moreover, we evaluated the specificity, sensitivity, and positive and negative predictive value of the BSIP.

Methods: 87 individuals were screened with the BSIP as part of the prospective 'Früherkennung von Psychosen' (FePsy; early detection of psychosis) study [2]. 64 of these were classified at baseline as being in an at-risk mental state and followed up at regular time intervals for at least 2 and up to 5 years to determine whether transition to psychosis had occurred. 23 subjects were classified at baseline as not at-risk and re-assessed after 4 years. Clinical characteristics of these were analyzed descriptively. Moreover, sensitivity, specificity, and positive and negative predictive value of the BSIP were computed.

Results: During the follow-up period, none of the individuals initially classified as not being at increased risk of psychosis in fact did transition to psychosis. At follow-up, the majority of this study group was diagnosed with depressive or anxiety disorders. The average psychopathological symptom severity of these individuals corresponded to "mildly ill" and the average level of functioning to "some difficulty in social or occupational functioning". In contrast, of the individuals positively identified as being in an at-risk mental state at baseline, 21 had developed psychosis. The sensitivity of the BSIP was 1.0, the specificity 0.35.

Discussion: Misclassification of individuals as being not at increased risk of psychosis appears to be relatively rare. These individuals mainly suffer from depressive and anxiety disorders years after initial assessment and show varying degrees of symptom severity and

levels of functioning. The prognostic accuracy of the BSIP for detecting the prodromal phase of psychosis is compelling, with an excellent sensitivity and a specificity similar to other risk instruments and the advantage of a relatively short interview duration.

References:

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M63. A phase 3 study to determine the antipsychotic efficacy and safety of ALKS 3831 in adult subjects with acute exacerbation of schizophrenia

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Background: ALKS 3831 (a combination of olanzapine [OLZ] and samidorphan [SAM]) is currently under investigation for the treatment of schizophrenia. The combination formulation is intended to address metabolic issues such as weight gain frequently observed in patients treated with olanzapine. A recently completed 12-week phase 2 study demonstrated similar efficacy and safety of ALKS 3831 compared to olanzapine, while subjects demonstrated significantly less weight gain on ALKS 3831 compared to olanzapine. This protocol, which is a part of the ENLIGHTEN study program, is designed to further study the efficacy and safety of ALKS 3831, and olanzapine versus placebo in acutely ill subjects with schizophrenia.

Methods: This 4-week study is a placebo- and active-comparator controlled, multi-center, multi-national, double-blind study (planned N=390) that has recently begun enrollment of subjects with acute schizophrenia demonstrating unstable symptomology. Inclusion criteria include men and women 18-70 years of age (inclusive) with DSM-5 diagnosis of schizophrenia, a Positive and Negative Syndrome Scale (PANSS) score ≥ 80 and Clinical Global Impression-Severity (CGI-S) Score ≥ 4 at screening and baseline, BMI between 18 and 40 kg/m², and have a stable living environment (when not hospitalized) as well as a designated caregiver or informant in countries where a caregiver is required. Exclusion criteria include diagnosis of additional psychiatric conditions, use of prohibited or contraindicated drugs, pre-existing medical conditions, and abnormal lab results during screening. The SAM 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. Subjects will be randomized 1:1:1 into ascending-dose treatment with olanzapine (10 or 20 mg), ALKS 3831 [10 mg OLZ+10 mg SAM (10/10) or 20 mg OLZ+10 mg SAM (20/10)] or placebo for a 4-week double-blind period. All subjects will receive 1 tablet daily. Subjects will be inpatients for at least the first 2 weeks of the double-blind period and on day 3, the daily dose of olanzapine will be increased from 10 to 20 mg in the relevant study arms. Decrease in olanzapine dose will be allowed up to day 15, then stay fixed for the remaining 2 weeks. After treatment, subjects will enter a 2-week safety follow-up period unless they continue into the extension study.

Extension Study: After 4 weeks of double-blind treatment with study drug, subjects will be eligible to continue in an open-label, long-term safety study (ALK3831-A306) and continue to receive ALKS 3831 for up to 52 weeks.

Results: The primary efficacy endpoint will be the change from baseline in PANSS total score at Week 4. The key secondary efficacy endpoint will be the change from baseline in Modified Overt Aggression Scale (MOAS) total score at Week 2. Other parameters that will be measured include movement disorders and pharmacokinetics/pharmacodynamics. Subjects in the extension study will be assessed for durability of effect (PANSS, CGI-S) and safety (including AEs, laboratory, weight, vitals and ECG parameters), Columbia Suicide Severity Rating Scale, and movement disorders.

Discussion: (This is an ongoing study)

M64. A phase 2, efficacy, safety, and tolerability study of ALKS 3831 in schizophrenia with alcohol use disorder

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Background: Alcohol use disorder (AUD) occurs commonly in the schizophrenia population and worsens the course of schizophrenia. There is currently no approved treatment specifically for schizophrenia with AUD. ALKS 3831 is composed of the established antipsychotic drug olanzapine and, samidorphan. ALKS 3831 is being developed for the treatment of schizophrenia. It is intended to have utility in treatment of schizophrenia with AUD and for addressing olanzapine-induced weight gain. The objectives of the current study are to evaluate the efficacy, safety, and tolerability of ALKS 3831 compared with olanzapine in subjects with schizophrenia and AUD.

Methods: This is an ongoing phase 2, randomized, active comparator-controlled, multi-center, multi-national study. There is an initial 4-week open-label olanzapine treatment period followed by a 2-week open-label ALKS 3831 period. The double-blind treatment period then begins for up to 15 months' duration where subjects (planned N=270) will be randomized 1:1 to receive either daily flexible dose olanzapine or ALKS 3831 (olanzapine+10 mg samidorphan). Inclusion criteria include men and women, 18-65 years of age (inclusive), a DSM-IV-TR diagnosis of schizophrenia, a DSM-5 diagnosis of AUD, meeting pre-specified symptom severity criteria including a recent (within 6 months) exacerbation of schizophrenia symptoms and have experienced at least 10 drinking days in the 30 days prior to screening (as measured by the Timeline Follow-Back [TLFB] method), with at least 2 of these drinking days meeting criteria for a heavy drinking day (4 drinks in a day for women and 5 drinks in a day for men). The primary efficacy measure will be an event of disease exacerbation symptoms based on the occurrence of pre-specified events indicative of exacerbation of disease symptoms (confirmed by an independent adjudication committee [IAC]). Other efficacy measures include Positive and Negative Syndrome Score (PANSS), Clinical Global Impression-Improvement and -Severity (CGI-I, CGI-S), TLFB assessment of alcohol drinking, and visual analog scale (VAS) for perception of desire for alcohol. Safety assessments will include parameters for suicide, vitals, weight and movement disorders. Other analyses may include pharmacokinetic and pharmacodynamic parameters. An interim analysis for futility will be completed after approximately 35 subjects with disease exacerbation have been confirmed. As of November 9, 2015 preliminary data include the following baseline demographics: Subjects enrolled n=205 (United States [n=161], Bulgaria [n=41], Poland [n=3]), 80% male, age (mean \pm SD)=46 \pm 10 years, White 38%, Black or African American 58%, weight (mean \pm SD) 87 \pm 19 kg, PANSS total score (mean \pm SD): 70 \pm 9. Average drinks/day: 4.6; 13.6 heavy drinking days over the previous 30 days. Exacerbations: 80 days prior [hospitalization (35%), aggression/intentional injury (12%), change in medication (37%), ER visit (25%)], randomized to ALKS 3831 or olanzapine n=127.

Results: The demographics will be updated when the study is complete.

Discussion: (This is an ongoing study)

M65. Safety, tolerability, & Pk of multiple rising doses of BI 425809 tablets given orally once daily for 12 days to young healthy male & female volunteers: a randomized, double-blind, placebo-controlled, within-dose groups, 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, and (2) characterise the pharmacokinetic (PK) properties of BI 425809 after multiple doses in young healthy volunteers.

Methods: The trial was a randomized, double-blind, within-dose group, placebo-controlled, multiple rising dose trial conducted at a single center. Five dose groups of BI 425809 (10, 25, 50, and 75 mg once daily [qd] and 75 mg twice daily [bid]) were treated for 12 days. Drug: placebo ratio was 3:1 across the dose groups. 60 healthy volunteers (12 subjects per dose group) between 18 and 50 years of age participated in the trial. Safety was evaluated with adverse event (AE) monitoring, clinical laboratory assessments, vital signs, 12-lead ECG, physical examinations, ophthalmologic tests, visual analog scales (VASs) of psychiatric effects (B&L, Bowdle), and suicidality assessments (C-SSRS). Plasma PK was characterized.

Results: The most common treatment-emergent AEs were headache (approximately 30% across the dose groups) and dizziness (10%-30% across doses). There was no trend for dose dependency in the frequency and severity of AEs. All AEs were of mild to moderate intensity. No severe or serious AEs were observed. There was no safety-related finding of clinical significance in the clinical laboratory evaluation, ECG, vital signs, VAS, or ophthalmologic tests. No suicidal ideation or behavior was observed during the trial.

Tmax was about 4 hours, half-life was approximately 45 hours, and steady state was reached within 8 days. Accumulation ratios of 2.0-2.3 × for Cmax and 2.3-3.0 × for AUC were observed with repeated dosing. A trend towards a less than dose-proportional increase in exposure was observed at higher dose levels (starting at 50 mg). While the linearity index was around one for doses up to 75 mg qd, it was clearly decreased in the 75 mg bid dose group.

Discussion: BI 425809 was generally well tolerated in all dose groups. The less than proportional increase in exposure at higher doses is likely due to the low intrinsic dissolution rate of the compound. At exposures achieved in the 75 mg bid dose group, BI 425809 metabolism might be induced as suggested by the decreased linearity index.

M66. Metabolic syndrome in patients with schizophrenia receiving long-term treatment with lurasidone, quetiapine XR, or risperidone

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Background: Patients with schizophrenia are at high risk for developing metabolic syndrome, a constellation of metabolic symptoms that includes central obesity, dyslipidemia, hypertension, and hyperglycemia. The risk of developing metabolic syndrome may be compounded in these patients because of treatment with antipsychotic agents. Lurasidone has demonstrated low propensity for metabolic disturbance in adult patients with schizophrenia in short-term, 6-week studies. This analysis evaluated metabolic syndrome occurrence during long-term treatment of schizophrenia with lurasidone or other antipsychotic agents.

Methods: Metabolic syndrome rates (as defined by the US National Cholesterol Education Program-Adult Treatment Panel III without using drug treatment criteria) were evaluated in adult patients with schizophrenia treated with lurasidone in 2 long-term, active-controlled studies (quetiapine XR or risperidone). In the quetiapine XR-controlled study, patients completing a 6-week, double-blind, placebo-controlled, fixed-dose trial of lurasidone (74 mg/d or 148 mg/d) or quetiapine XR (600 mg/d) continued on double-blind, flexibly dosed lurasidone (37-148 mg/d) or quetiapine XR (200-800 mg/d) for up to 12 months. In the risperidone-controlled study, patients received double-blind, flexibly dosed lurasidone (37-111 mg/d) or risperidone (2-6 mg/d) for up to 12 months.

Results: Among patients without metabolic syndrome at baseline in the quetiapine XR-controlled study, 2.4% (2/84) of patients treated with lurasidone and 7.4% (2/27) of patients treated with quetiapine XR developed metabolic syndrome at month 12 ($P=NS$). Of patients without metabolic syndrome at baseline in the risperidone-controlled study, 10.3% (12/117) of patients treated with lurasidone and 23.2%

(16/69) of patients treated with risperidone developed metabolic syndrome at month 12 ($P=0.02$).

Discussion: Long-term treatment with lurasidone was associated with lower rates of metabolic syndrome in patients with schizophrenia compared with treatment with quetiapine XR or risperidone.

Sponsored by Sunovion Pharmaceuticals Inc.

ClinicalTrials.gov identifiers: NCT00789698 and NCT00641745.

M67. Positive phase 3 clinical trial of ITI-007 for the treatment of schizophrenia: secondary endpoints and subgroup analyses 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-HT_{2A} 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 GluN_{2B} receptor phosphoprotein modulator and a serotonin reuptake inhibitor. Phase 2 clinical trial (ITI-007-005) data indicated that 60 mg ITI-007 was effective in reducing symptoms of schizophrenia with a safety and side effect profile similar to placebo (Lieberman *et al.*, Biological Psychiatry, 2015 online ahead of print). A Phase 3 clinical trial (ITI-007-301) was conducted to evaluate the efficacy and safety of ITI-007 for the treatment of schizophrenia.

Methods: In the Phase 3 trial (ITI-007-301) patients with an acutely exacerbated episode of schizophrenia were randomized to receive one of three oral treatments once daily for 4 weeks: 60 mg ITI-007, 40 mg ITI-007, or placebo in a 1:1:1 ratio. The primary endpoint was change from baseline on the Positive and Negative Syndrome Scale (PANSS) total score at Day 28 compared to placebo. The key secondary endpoint was the Clinical Global Impression scale for Severity of Illness (CGI-S). Additional analyses on secondary endpoints and patient subgroups were conducted.

Results: In this trial, once-daily ITI-007 60 mg met the primary endpoint and demonstrated efficacy with statistically significant superiority over placebo at Day 28 as measured by the PANSS total score ($P=0.022$). Moreover, ITI-007 60 mg showed significant efficacy as early as week 1 on both the PANSS total score and PANSS Positive Symptom subscale score, which was maintained at every time point throughout the entire study. ITI-007 60 mg also met the key secondary endpoint of statistically significant improvement on the CGI-S ($P=0.003$). Consistent with previous studies, ITI-007 was safe and well-tolerated. [Please see companion abstract/poster for more details on safety.] Additional analyses on secondary endpoints and patient subgroups will be presented.

Discussion: These findings confirm and extend the positive results demonstrated at 60 mg in the Phase 2 study. Taken into context with data from another clinical trial (ITI-007-008) in which ITI-007 60 mg was associated with a mean of approximately 40% striatal dopamine D₂ receptor occupancy using positron emission tomography (PET), ITI-007 demonstrated efficacy at relatively low striatal D₂ receptor occupancy, lower than the occupancy range required by most other antipsychotic drugs. Unlike any existing schizophrenia treatment, this dopamine receptor phosphoprotein modulator, or DPPM, acts as a pre-synaptic partial agonist and post-synaptic antagonist at D₂ receptors. This mechanism along with potent interactions at 5-HT_{2A} receptors, serotonin reuptake inhibition and indirect glutamatergic modulation likely contributes to the efficacy with improved psychosocial function. ITI-007 further exhibits improvements with a differentiated profile on important secondary endpoints and in patient subgroups who represent particularly vulnerable populations in need of improved treatment. As such, ITI-007 represents a novel approach to the treatment of schizophrenia.

M68. Using an mhealth approach to deliver a psychosocial intervention in early psychosis: preliminary results from the actissist trial

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Background: Psychosocial interventions are recommended for the treatment of psychosis; however, only a small proportion of service users have access to intervention packages offered by mental health services. Given advancements in mobile phone technology, it is possible to provide ecologically-valid interventions via smartphones. Smartphones have become everyday devices that an increasing number of people routinely keep about themselves. Indeed, there is emerging evidence which suggests that smartphone technology using software applications (apps) could increase access to psychological approaches for psychosis. This paper reports the protocol for a clinical trial of smartphone-based intervention for early psychosis and will report preliminary findings regards feasibility and acceptability of this approach.

Methods: We conducted a single-blind randomized controlled trial comparing a cognitive behavior therapy-informed software application (Actissist) plus Treatment As Usual (TAU) with a symptom monitoring software application (ClinTouch) plus TAU in early psychosis over a 12-week intervention period. We randomly assigned 36 participants registered with early intervention services (EIS) across the North West of England, UK in a 2:1 ratio to each arm of the trial. Our primary objective was to determine whether in people with early psychosis the Actissist app is feasible to deliver and acceptable to use. Secondary aims are to determine whether Actissist impacts on predictors of first episode psychosis (FEP) relapse and enhances user empowerment, functioning and quality of life. Assessments were conducted at baseline, 12 weeks (post-treatment) and 22-weeks (10 weeks post-treatment) by assessors blind to treatment condition. The trial will report on the feasibility and acceptability of Actissist and compare outcomes between the randomized arms.

Results: The presenter will report the preliminary findings regards feasibility and acceptability of the intervention and this approach.

Discussion: This randomized controlled trial tests the feasibility, acceptability, uptake, attrition, and potential efficacy of a CBT-informed smartphone app for early psychosis. Mobile applications designed to deliver a psychologically-informed intervention offer new possibilities to extend the reach of traditional mental health service delivery across a range of serious mental health problems and provide choice about available care.

M69. Which are the most important first-generation antipsychotic drugs? Survey of international schizophrenia experts

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Background: Although in many industrialized countries "atypical", second-generation antipsychotic drugs (SGA) are nowadays the mainstay of treatment of schizophrenia, "typical", first-generation antipsychotic drugs (FGA) are still very frequently used in developing countries. Moreover, studies such as CATIE and CUTLASS have shown that at least some first-generation are not inferior to SGAs. But which among the more than 50 FGAs listed by the WHO are the most important one and might thus be still worthwhile examining?

Methods: To find out which FGAs might be worthwhile further investigation, we conducted a survey of more than 50 international schizophrenia experts from all continents. They were sent the names of 52 first-generation antipsychotics listed by the World Health Organization's Collaborative Center for Drug Statistics Methodology. All participants had 10 votes which they could use to indicated 10 antipsychotics which they considered most important. We summed the votes to derive a hierarchy of the most important first-generation antipsychotics.

Results: The ten most frequently selected first-generation antipsychotics were chlorpromazine, flupenthixol, fluphenazine, haloperidol,

loxapine, perphenazine, pimozide, sulpiride, thioridazine, zuclopenthixol.

Discussion: The choice of antipsychotic drugs is very much driven by marketing. Once a drug loses its patent and cheap generics become available, pharmaceutical companies quickly lose their interest in these compounds, there is no marketing around them and psychiatrists use them less and less. Like this potentially useful antipsychotics get forgotten and patients cannot benefit from them. In this survey we therefore present the drugs that international schizophrenia experts still find important according to a survey. This is important information for decision makers, trialists, and meta-analysts.

M70. Reduce - a randomized clinical trial to evaluate gradual neuroleptic discontinuation in chronic stable schizophrenic patients

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Background: The evidence base for maintenance treatment of chronic schizophrenic patients is sparse. New results from drug reduction in first episode patients suggested better social functioning in the long term. Guided discontinuation in chronic schizophrenic patients has not been examined yet.

Methods: We are conducting a randomized, rater blind pilot study to examine guided discontinuation in stable chronic schizophrenic patients (Register Number: DRKS00006878). We include chronic stable schizophrenic patients (no hospitalization in the last three years), Age 18-65, treated with at least one neuroleptic except clozapine. Trial is duration is 26 weeks with visits every two weeks. Primary outcome is staying in remission according to Andreasen criteria. Further outcomes are PANSS, CGI, PSP, and SWN.

Results: First patient was included January 2015. So far we have included 20 patients and are still recruiting. We had more relapses in the discontinuation group, but by raising the medication again patients got stabilized again and no hospitalization was needed.

Discussion: This is a pilot to check the feasibility of guided discontinuation in stable chronic schizophrenic patients. Our preliminary results look promising. If the final results show the same tendency, we will conduct a large multicenter trial to confirm the results.

M71. More pronounced cognitive deficits in adolescent subjects at clinical high risk of psychosis

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Background: Cognitive deficits are central manifestations of individuals at clinical high risk (CHR) of psychosis. Few studies have directly reported the pattern of cognitive deficits among CHR adolescents. The goal of this study was to investigate the cognitive deficits among CHR adolescents, compared with CHR adults.

Methods: CHR subjects were recruited using a 2-step method. They were first screened for presence of subclinical psychotic symptoms using the Prevention Through Risk Identification Management and Education (PRIME) and then those with a positive screening score were assessed further with the SIPS/SOPS (Structured Interview for Prodromal Symptoms/Scale of Prodromal Syndromes). Twenty three CHR adolescents (mean age, 15.8 years (ys), age range 14-17 ys) and 29 CHR adults (mean age, 24.6 ys, age range 18-37 ys) were included. The control groups consisted of 25 adolescent controls (mean age, 16.2 ys, age range, 14-17 ys) and 35 adult controls (mean age 25.4 ys, age range 18-41 ys). Cognitive functioning was assessed using the Chinese version of MATRICS Consensus Cognition Battery (MCCB).

Results: CHR adolescents have more severe cognitive deficits of verbal learning (CHR adolescents, z-score = -1.53 ± 1.90, CHR adults, z-score = -0.22 ± 1.02, t = -2.989, df = 31.894, P = 0.005), working memory (CHR

adolescents, $z\text{-score} = -1.07 \pm 1.38$, CHR adults, $z\text{-score} = -0.10 \pm 0.92$, $t = -2.893$, $df = 36.619$, $P = 0.006$), and attention/vigilance (CHR adolescents, $z\text{-score} = -1.41 \pm 0.84$, CHR adults, $z\text{-score} = -0.60 \pm 1.42$, $t = -2.557$, $df = 46.530$, $P = 0.014$), as comparing with CHR adults. Among the CHR adolescents, the performance on verbal learning task was correlated with negative symptoms measured by SIPS/SOPS (Spearman's $\rho = -0.618$, $P < 0.01$).

Discussion: CHR adolescents have more severe cognitive deficits as compared with CHR adults. The correlation of their verbal learning task with negative symptoms supported the neural developmental hypothesis of schizophrenia.

M72. Effects of cognitive training using brain training games on brain structure in patients with schizophrenia

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Background: Cognitive impairment is one of the core symptoms of schizophrenia that significantly impacts patients' social outcomes and quality of life. Cognitive remediation, of which a main component is repetitive cognitive training, is a promising approach to improve cognitive impairment. Though, its effect on the brain structures of patients with schizophrenia has not been investigated enough. In this study, we used brain training games on a portable game device (Brain Age, Nintendo) as a cognitive training program; this approach allowed patients to perform the cognitive training tasks at home. In addition to measuring the change in cognitive performance from pre- to post-intervention, we investigated the influence of cognitive training on gray matter structures.

Methods: Thirty-two participants with schizophrenia, aged 18–39 years were randomly assigned to either training or control group. Training group engaged in cognitive training using video games for 30 minutes/day, 4 times/week, for 8 weeks at home, while control group played visuospatial puzzle games. Assessment on cognitive performance and imaging on magnetic resonance imaging scanner were performed at the beginning and end of the intervention.

Results: Participants in the training group showed significantly greater improvement in processing speed and executive function compared to the control group. In addition, the improved cognitive performance was accompanied by regional gray matter volume reduction.

Discussion: These findings suggest that cognitive training using video games can be an option for patients with schizophrenia and that it not only influences the performance on cognitive measures, but also patients' neural structures.

M73. Use of prior knowledge in perceptual inference dissociates computational mechanisms of anomalous perceptions and delusions

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Background: Anomalous perceptions (APs) and delusional ideation (DI) occur in the general population and in patients with psychotic disorders. Recent advances in computational theories of brain function offer a framework within which to understand both phenomena in terms of disrupted predictive processing. APs are caused by excessive influence of prior knowledge that shapes sensory data to conform to expectations, while DI are caused by excessive prediction error that causes aberrant learning about the world. We explored these possibilities by characterizing the use of prior knowledge in relation to APs and DI in healthy people.

Methods: 40 healthy participants completed a novel visual task that provides an index of the use of prior knowledge in perceptual inference. Participants were asked to make decisions about degraded images before and after they had acquired prior knowledge about image content from non-degraded versions (Before and After trials, respectively). Participants therefore made decisions with varying

amounts of prior knowledge while sensory input was kept constant. The effect of prior knowledge was measured within-subject (After – Before). The task contained two interleaved conditions. In the Global condition, coarse prior knowledge of global image structure was sufficient to guide decision-making. In the Local condition, precise knowledge of local image detail was required. Using multiple linear regression and objective performance measures derived from signal detection theory (d'), we examined whether self-report APs and DI predict the effects of prior knowledge on performance. Additionally, we used a diffusion-drift model within a hierarchical Bayesian framework to model the effects of prior knowledge on drift rate (rate of evidence accumulation towards a decision) and decision threshold (evidence required to make a decision).

Results: In the Global condition, d' (After) – d' (Before) showed a slight association with APs ($t = 2.173$, Cohen's $D = 0.73$, $P = 0.04$) and no significant association with DI. In the Local condition, there were opposing effects of APs and DI, despite them being highly correlated ($r = 0.67$). d' (After) – d' (Before) was positively associated with APs ($t = 4.226$, Cohen's $D = 1.42$, $P = 0.0001$), but negatively associated with DI ($t = -4.475$, Cohen's $D = 1.51$, $P < 0.0001$). Modeling of reaction times showed that prior knowledge greatly increases drift rate (v) and slightly decreases decision threshold (a). In the Local condition, v (After) – v (Before) was positively associated with APs ($t = 3.861$, Cohen's $D = 1.31$, $P = 0.0005$) and negatively associated with DI ($t = -4.267$, Cohen's $D = 1.44$, $P = 0.0001$).

Discussion: We found dissociable changes in visual information processing associated with APs and DI. APs are associated with a greater influence of prior knowledge on perception. In contrast, DI is associated with normal performance when decisions require knowledge of global image properties, but a disadvantage when knowledge of fine details is needed. Taken together, these findings support and refine accounts of psychosis as disrupted predictive processing. In line with previous research, we suggest that perception in people prone to APs is more reliant on prior knowledge. They therefore more readily learn and use information from the non-degraded image in this task. This is consistent with atypicalities in low-level visual processing associated with psychosis. Conversely, our results suggest that DI is associated with aberrant learning from the non-degraded image, such that people prone to DI are able to extract the gist but have difficulty learning the details. These findings provide novel insights into computational mechanisms that might underlie anomalous experiences and beliefs associated with psychosis.

M74. Does change in cognition affect psychosocial functioning after cognitive remediation for schizophrenia?

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Background: Deficits in cognition have been well established in patients with schizophrenia. There has been significant research showing a relationship between cognitive function and psychosocial functioning, such as community adjustment, acquisition of social skills and positive vocational outcomes. However, there is limited empirical evidence of the specific links between improvements in cognitive functioning and social performance. The goals of the current study were to examine cognitive mediators associated with domains of psychosocial functioning and the effects of changes in cognition after 12 weeks CRT on changes in overall and specific psychosocial domains.

Methods: Following screening, patients were randomized to either COGPACK or PositScience for 36 sessions (12 weeks). Assessments were completed at baseline and endpoint and included the MCCB MATRICS battery for neurocognition, the Personal and Social Performance scale (PSP) for functional outcomes in socially useful activities, personal and social relationships, self-care, and disturbing and aggressive behaviors, and overall function. All patients were stable and on antipsychotic medication regimens throughout the intervention. A patient was considered improved on psychosocial functions if his or her overall PSP score moved into at least one 10-point range higher than the baseline range. A GLM Model was conducted to assess which MCCB domain contributes to the improvement of overall PSP scores.

Results: 63 in- and outpatients with DSM IV-TR schizophrenia or schizoaffective disorder completed CRT. There was a significant improvement in the overall MCCB T-Score ($P=0.020$). Two MCCB domains showed significant improvement, the Letter Number Span test and the domain of working memory ($P=0.006$ and $P=0.001$ respectively). There was a significant improvement in overall PSP score from baseline to endpoint ($P=0.021$). Chi-Square test revealed a significant difference from baseline to endpoint in PSP domains A (socially useful activities) ($P=0.012$), B (Personal and Social Relationships) ($P=0.008$), and D (disturbing and aggressive behaviors) ($P=0.012$), but not in domain C (self-care) ($P=0.222$). After the CRT intervention, significant correlations were found between baseline TMT ($r=0.395$, $P=0.001$), BASC ($r=0.315$, $P=0.012$), verbal fluency ($r=0.457$, $P<0.001$), speed of processing ($r=0.436$, $P<0.001$), verbal learning ($r=0.251$, $P=0.048$), overall MCCB T score ($r=0.289$, $P=0.022$) and endpoint overall PSP scores. GLM model analysis showed significant associations of overall PSP score with baseline TMT scores, baseline fluency scores and baseline total PANSS scores. ($P=0.037$, $P=0.025$, and $P=0.041$ respectively).

Discussion: We found that verbal fluency, speed of processing and verbal learning, as well as degree of illness were significantly associated with improvement in social functioning. These results suggest the importance of training in the cognitive domain of speed of processing and fluency, in order to obtain improvements in psychosocial functioning for individuals with schizophrenia.

M75. Emotional intelligence deficits in schizophrenia: the impact of non-social cognition

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Background: Previous studies using the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) revealed significant performance deficits across all areas of Emotional Intelligence (EI) in schizophrenia patients compared to healthy controls. However, none of these studies has investigated a potential influence of non-social cognition on these findings.

Methods: 58 schizophrenia outpatients and 85 control subjects were investigated using the MSCEIT and the Brief Assessment of Cognition in Schizophrenia (BACS). Analyses of covariance were performed with adjustment for the BACS composite score and education. To investigate this issue in more detail, a mediation analysis was conducted.

Results: Patients showed significantly lower EI and non-social cognition levels compared to healthy controls. After adjustment for BACS composite score and education, only the group difference in the "managing emotions" branch and thus in the "strategic" EI part of the MSCEIT remained statistically significant, whereas for all other MSCEIT branches (perceiving, using, understanding emotions) statistical significance was lost. The mediation analysis revealed that the difference between schizophrenia patients and controls regarding the MSCEIT total score was almost fully attributable to the mediating effect of non-social cognition.

Discussion: Our findings suggest that in schizophrenia patients EI is largely influenced by non-social cognitive functioning. Only the "managing emotions" branch was found to be independent of non-social cognition. Consequently, non-social cognitive performance was mainly responsible for the observed differences in EI between schizophrenia patients and controls. This has to be taken into account when interpreting MSCEIT data in this population.

M76. Working memory deficits in young adults born small for gestational age

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Background: Obstetric complications (OC) have a detrimental effect on neurodevelopment. Among OC, low weight at birth has been associated with brain morphometric abnormalities, and with greater risk to develop psychiatric disorders, including schizophrenia. Furthermore, previous studies have also indicated that low birth weight may represent a powerful predictor of cognitive functioning in adulthood. Consistently, a recent study has shown that subjects born Small for Gestational Age (SGA) have lower IQ scores in adulthood compared to subjects non-SGA (N-SGA). The aim of the present study was to evaluate the association between SGA and Working Memory (WM) performance in healthy adult subjects.

Methods: 192 Caucasians healthy individuals were recruited for the study, and underwent WM behavioral assessment with the N-Back Task. The McNeil-Sjöström Scale, administered to the mothers of participants, was used to collect obstetric complications, including weight at birth. SGA index was defined as weight at birth < 10th percentile (adjusted for gestational age, sex, and order of birth) based on the Neonatal Anthropometric Charts developed by the Italian Neonatal Study Group. On this basis, participants were grouped in SGA ($N=39$; age 27.36 ± 7.66 ; 12 males) and N-SGA ($N=153$; age: 26.30 ± 5.85 ; 73 males). Statistical analysis of socio-demographics and behavioral data was performed with ANOVAs and χ^2 .

Results: The two groups did not differ in terms of gender, age, handedness, parental socio-economic status index, and IQ (all $P>0.05$). Repeated measures ANOVA with SGA status as independent variable, WM load as a repeated measures factor and WM accuracy at 1-Back and at 2-Back as the dependent variables indicated a main effect of SGA status [$F(1,190)=4.62$; $P=0.03$], and an interaction between SGA status and WM load [$F(1,190)=4.81$; $P=0.03$]. More specifically, post hoc analysis demonstrated a statistically lower performance in SGA compared to N-SGA at 2-Back (post hoc, LSD Fisher $P=0.002$).

Discussion: Our results indicate for the first time in literature that SGA subjects have lower WM performance in adulthood. Further studies in patients with schizophrenia and their unaffected siblings will help to elucidate the relevance of SGA on WM dysfunction in schizophrenia.

M77. Jumping to conclusions predicts 4-year clinical outcome in first episode psychosis

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Background: Social cognition, which is the ability to perceive, interpret and generate responses to social interactions, is impaired in schizophrenia, and has been shown to be a stronger predictor of functional outcome than neurocognition itself or symptomatology. One of the social cognition biases is Jumping to Conclusions (JTC), defined as the proneness to require less information before forming beliefs or making a decision, and which has been related to the formation and maintenance of delusions. Using data from the GAP case-control study of first-episode psychosis (FEP), we aimed to test whether the presence of JTC would predict poor clinical outcome at 4 years in FEP.

Methods: 102 FEP patients completed assessments of clinical status (PANSS), functioning (GAF), JTC (the probabilistic reasoning "Beads" task) at the time of recruitment. The sample was split into two groups based on the presence or not of the bias (defined by making a decision after two or fewer items in the task). Follow-up data over a period of 4.1 years were obtained from the electronic psychiatric clinical records (EPCRs) in the South London and Maudsley NHS

Foundation Trust (SLaM). Data collected included several items concerning clinical course and outcome (remission, intervention of police, use of mental health act, and days of admission).

Results: Exactly half the FEP participants jumped to conclusions. There were significant differences in the Positive Scale of the PANSS (mean 14.75, SD = 5.88 vs mean 12.29, SD = 4.85; $p < 0.04$) and GAF disability scale (mean 55.42, SD 16.97 vs mean 62.58, SD = 16.74; $P = 0.02$) based on the presence or not of JTC at baseline. In terms of follow-up, days of admission (β 0.57, 95% CI 0.53- 0.62, $P < 0.001$), and mental health act intervention (OR 3.54, 95% CI 1.36- 9.19, $P < 0.001$) were significantly associated with JTC. Remission was not independently associated with JTC (OR 1.24, 95% CI 0.53 to 2.87, $P = 0.62$).

Discussion: JTC is associated with poor clinical outcomes. These results go in line with the previous considerations of JTC as a trait and with our hypothesis that it would predict a poorer clinical course. Our study raises the question of whether the implementation of specific interventions to reduce jumping to conclusions, as Metacognition Training, may be a useful addition in early psychosis intervention programs.

M78. Relationship between cognitive insight and different dimensions of social cognition in recent onset psychosis

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Background: Cognitive Insight (CI) refers to patients' capacity to distance themselves from their distorted beliefs and misinterpretations, reflect on them rationally, and recognize erroneous conclusions. CI has been found to imply two different dimensions, namely self-reflectiveness -which includes a willingness to acknowledge fallibility, corrigibility, and recognition of dysfunctional reasoning- and self certainty -tendency to be overconfident. In recent years an increasing number of studies have focused on the study of CI to better understand thinking processes implied in psychosis. CI in psychosis has adequate convergent validity with clinical measures of insight (Beck *et al.*, 2004) and seems to have a small but consistent relationship with 'total cognition' and memory (Nair, Palmer, Aleman & David, 2014). Evidence has also suggested that the two dimensions of CI may rely on different cognitive mechanisms, but this is still under research. Other processes that may be related with CI are Social Cognition (SC) deficits, since they have long been identified as aspects of the neurocognitive architecture that may contribute to aberrant thinking styles and cognitive distortions in psychosis. In this line, the aim of this study was to explore the associations between CI and different dimensions of SC.

Methods: A multicenter cross-sectional study of 9 public centers in Spain was performed, including a total of 126 patients with a diagnosis of recent onset psychosis. Symptoms were assessed with the PANSS (Kay *et al.*, 1997). Cognitive insight was measured by means of the BCIS (Beck *et al.*, 2004) and Social Cognition with tests measuring Emotional Recognition (Emotional Recognition Test, Baron-Cohen, 1997) Theory of Mind (The Hinting task, Corcoran, Mercer & Frith, 1995) and cognitive biases (JTC Garety *et al.* 1991, IPSAQ Bentall *et al.* 1991, Irrational Beliefs Test TCI, Calvete *et al.*, 2001). The relationship between CI and SC measures was examined using correlation analysis. Pearson's or Spearman's coefficients were used depending on the normality of data, as determined by the Kolmogorov-Smirnov test.

Results: Subjects with a recent onset of psychosis showed low to moderate distortions in CI as well as low impairment in most SC measures. No significant correlations were revealed between the BCIS composite score nor the self-reflectiveness subscale and any of the SC measures. The BCIS self-certainty subscale showed a weak significant correlation with the total score of the Emotional Recognition Test ($r = 0.24$, $P = 0.008$). This subscale also showed weak significant correlations with the guilt ($r = 0.19$, $P = 0.029$), emotional responsibility

($r = -0.22$, $P = 0.013$), and helplessness ($r = 0.25$, $P = 0.005$) subscales of the TCI.

Discussion: CI showed no linear relationships with most of SC measures supporting the construct validity of the BCIS as an independent measure of CI. This is in line with the scarce existing evidence on the relationship between CI and SC, which revealed no relationships between CI and the Hinting Task (Ng, Fish & Granholm, 2015). It was found that one of the most robust measures of social cognition, emotional recognition, showed a weak positive relationship with the self-certainty subscale. This may be explained by the fact that overconfidence in one's impressions may make one more prone to misattribute emotions. This may also apply to tendency to hold irrational beliefs. These results should be interpreted with caution since only small to moderate deficits were found both in CI and SC measures in this recent onset psychosis sample, and this may have limited the statistical power of the analyses.

M79. Formal thought disorder in adolescents with autism spectrum disorder: relations with executive functioning

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Background: Formal thought disorder (FTD) is a disruption in the flow of thought, as observed by disorganized speech. FTD is a hallmark feature of schizophrenia and has been associated with multiple cognitive dysfunctions, especially within the executive domain. Pragmatic language problems and executive dysfunctions are also frequently observed in autism spectrum disorder (ASD). However, only one small study (Solomon *et al.*, 2008) has previously investigated FTD in relation to executive functioning in ASD.

Methods: In the current cross-sectional study we compared 50 adolescents with high functioning ASD aged 9-18 to a group of 56 typically developing controls matched for age, sex, and IQ. Objective and subjective FTD were assessed with the Kiddie-Formal Thought Disorder Rating Scale (KFTDS) and the Odd Speech subscale of the Schizotypal Personality Questionnaire (SPQ-C-D) respectively. A cognitive test battery was administered to measure three core executive functions: working memory, inhibition, and cognitive flexibility.

Results: Adolescents with ASD displayed significantly higher levels of objective and subjective FTD, but did not differ from controls on executive functioning parameters. However, within the ASD group a higher frequency of objective FTD was associated with worse performance on verbal working memory and response inhibition.

Discussion: On a group-level adolescents with ASD show a higher frequency of FTD, despite intact executive functioning. However, relatively poor executive control may predispose individuals with ASD to idiosyncratic thought disorders.

M80. Schizophrenia and short lifetime expectancy - the importance of identifying risk factors early in the illness

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Background: Patients with schizophrenia spectrum disorder have up to twenty years shorter lifetime expectancy compared to the general population, and this difference is increasing. Recently, a study was presented that showed a significant connection between early death and low cognitive performance. Among the cognitive factors executive functioning and immediate memory differed most between patients who passed away early and those who still were alive. However, in the same study, no relationships were found between early death and symptom activity, diagnosis or age at onset. Based on the previous study, this study investigates factors known to be linked to lifetime expectancy, at patients who are in different 'cognitive risk groups' for an early death.

Methods: In the ongoing study Clinical Long-term Investigation of Psychosis in Sweden (CLIPS), 301 patients with schizophrenia spectrum disorder were analyzed according to their cognitive performance at baseline from 2001 onwards. At a follow up in 2015, 32 of those patients had died an early death. Based on the

cognitive profile of those patients who had passed away, the remaining 269 patients still alive were divided into three risk groups for an early death: 'Cognitive Low Risk' ($n = 147$), 'Cognitive Moderate Risk' ($n = 71$) and 'Cognitive High Risk' ($n = 51$). The three risk groups were then compared on weight, BMI, pulse, blood pressure, somatic signs of unknown illness, symptom activity (including symptomatic remission), and illness insight.

Results: When comparing patients from the 'Cognitive Low Risk' group with patients from both the 'Cognitive Moderate Risk' and 'Cognitive High Risk' groups, the latter groups had higher scores on PANSS negative symptoms, PANSS general symptoms, and PANSS total score. Patients in the 'Cognitive High Risk' group also had higher scores on PANSS negative symptoms than patients in the 'Cognitive Moderate Risk' group. Achieved remission were more common in the 'Cognitive Low Risk' group. No differences were found between any of the risk groups on weight, BMI, pulse, blood pressure, somatic signs of unknown illness, or illness insight (5%-level).

Discussion: The cognitive profile is important to assess early in the illness. The findings of this work also indicates that a combination of symptom control (including symptomatic remission) and control for cognitive performance could be important when identifying patients with high risk for an early death. This study shows that it is meaningful to divide patients into separate risk groups for an early death, based on their cognitive performance, and these groups will also differ in symptom activity. However, there are no differences in somatic factors or in illness insight between these cognitive risk groups.

M81. Defective translation of emotional salience into motivated behavior: a one-year follow-up study in first-episode schizophrenia

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Background: People with schizophrenia commonly suffer from anhedonia and avolition, but previous research consistently showed that they experience intact "in-the-moment" emotion. Avolition might be related to the underlying "decoupling" of emotion with behavior, within which emotional salience fail to be translated into motivated behavior (Heerey and Gold, 2007). However, previous studies seldom studied the course and progression of such emotion-behavior decoupling, in particular in people with first-episode schizophrenia.

Methods: Participants were 50 medicated patients with first-episode DSM IV schizophrenia-spectrum disorders, who were assessed at the baseline, the sixth and the twelfth month after service entry, and 48 demographically matched healthy controls. We used a laboratory-based emotion-inducing paradigm (Heerey & Gold, 2007) to measure affective experiences. This paradigm also allowed participants to expend effort in terms of pressing buttons to seek pleasurable slides or to avoid unpleasant slides, in both anticipatory and consummatory conditions. We used ANOVAs to compare the patients' baseline data with that of 48 demographically matched healthy controls. Patients' longitudinal data was analyzed using repeated measure ANOVAs for within group comparison only. We also examined the longitudinal relationship between emotion-behavior decoupling and clinical symptoms.

Results: All patients completed the follow-up. At the baseline, patients with first-episode schizophrenia-spectrum disorders and controls reported similar "in-the-moment" affective experiences. However, patients with first-episode schizophrenia-spectrum disorders exhibited emotion-behavior decoupling, which manifested as a less discriminant button-pressing effort expanded across slides of different valances, compared to controls. Patients' button pressing speed also corresponded poorly to degree of pleasantness or unpleasantness they experienced, compared to controls. Overall, the emotion-behavior decoupling in patients with first-episode schizophrenia-spectrum disorders gradually improved over twelve months. However, there was a significant anticipatory-consummatory differentiation of emotion-behavior coupling. The ability to translate emotion to motivated behavior in the anticipatory condition was relatively stable; whereas that for consummatory condition changed substantially.

During the twelve month, the PANSS positive and general symptoms changed with time, but the PANSS negative symptoms were relatively stable.

Discussion: This study provides preliminary evidence regarding the course and progression of emotion-behavior decoupling in first-episode schizophrenia spectrum, and the results suggest that the emotion-behavior decoupling in anticipatory conditions do not change with time as much as the emotion-behavior decoupling in consummatory condition. Failure of translating anticipatory emotions into effortful behavior may be a trait maker in schizophrenia.

M82. Perspective memory performance and its clinical correlates during the first year of treatment in first-episode schizophrenia: a follow-up study

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Background: PM refers to "memory for activities to be performed in the future", which is assumed to be closely related to personal and social functioning of patients with schizophrenia and other neuropsychiatric diseases. PM deficits were consistently found in both chronic and first episode schizophrenia (FES). In addition, non-psychotic first-degree relatives show similar but attenuated PM impairments with schizophrenia patients, suggesting that PM deficits may be a potential endophenotype of schizophrenia. However, so far there is only one longitudinal study that was published focusing on PM changes during clinical follow-up of FES patients. However, in that study, no follow-up was given to the control group and the practice effect in schizophrenia group could not be excluded. Therefore, the trajectory of PM changes in first-episode schizophrenia still need to be further investigated.

Methods: Thirty-five FES patients and 20 healthy controls (HCs) were recruited in a university-affiliated psychiatric hospital in Beijing and from the community through advertisements, respectively. FES patients were treated with second generation antipsychotics according to clinical guidelines. Both the FES and HCs were followed up for 1 year. Time- and event-based PM (TBPM and EBPM) performance were measured with the Chinese version of the Cambridge Prospective Memory Test (C-CAMPROMPT) at entry and the end of the study. A few cognitive functions (involving respective memory and executive functions) were also evaluated with standardized tests on the same day when PM tests were evaluated. Remission was determined at the endpoint by a PANSS score ≤ 3 for the following items: delusions (P1), unusual thought contents (G9), hallucinatory behavior (P3), conceptual disorganization (P2), mannerism/posturing (G5), blunted affect (N1), social withdrawal (N4), and lack of spontaneity (N6).

Results: Thirty-two FES patients and 17 HCs completed the follow-up study.

(1) After controlling for age, gender, and education level, repeated measures analysis of variance (ANOVA) indicated there was a significant time(baseline vs. endpoint)*group(FES vs. HCs) interaction only in EBPM ($F(1, 42) = 8.8, P = 0.005$) among all neurocognitive variables. Therefore, we further performed two paired samples t-tests in FES and HCs, respectively, regarding EBPM, which showed significant improvement in FES (13.1 ± 3.7 vs. 10.3 ± 4.8 ; $t = 3.065, P = 0.004$), rather than in HCs (15.7 ± 3.6 vs. 16.5 ± 2.3 ; $t = -1.248, P = 0.230$); (2) A remission rate of 59.4% was found. After controlling for age, gender, educational level and baseline EBPM score, remitters performed significantly better on EBPM (14.9 ± 2.6 vs. 10.4 ± 3.6 ; $F(1, 28) = 12.7, P = 0.001$) than non-remitters at endpoint of the study.

Discussion: Only EBPM showed improvement along with the clinical improvement during the first year of treatment, suggesting EBPM may represent a more sensitive neurocognitive indicator for current standard pharmacotherapy. Furthermore, our findings also imply PM is not only a trait-related endophenotype as indicated in previous studies, but also state-related.

M83. Correlations of neurocognitive functioning with negative symptoms and daily functioning in a first episode psychosis sample

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Background: Neurocognitive impairment is a key feature of schizophrenia and, along with negative symptoms, strongly predicts disability. Those who have experienced a first episode of psychosis display neurocognitive impairment that is comparable to that seen in chronic schizophrenia. As part of a pilot trial of cognitive remediation in early schizophrenia, we investigated how performance on neurocognitive tasks correlates with symptoms and real-life functioning.

Methods: Thirty-eight users of an Early Intervention in Psychosis service underwent cognitive testing using the CANTAB schizophrenia battery, prior to taking part in the cognitive remediation pilot trial. They also completed measures of everyday functioning, symptoms and quality of life using the Specific Levels of Functioning Scale, PANSS, and Manchester Short Assessment of Quality of Life respectively.

Results: A strong correlation was seen between more impaired delayed verbal memory and increased negative ($r=0.49$, $P<0.01$) and general ($r=0.46$, $P<0.01$) symptoms. Correlations were also seen between increased negative symptoms and impaired performance on tasks of visual learning and memory, attention, and problem solving. No significant correlations were seen between positive symptoms and neurocognitive functioning. More impaired real-life functioning correlated with worse performance on measures of delayed verbal memory, attention, and problem solving.

Discussion: Impaired performance on neurocognitive tasks correlated with increased negative symptoms and more impaired real-life functioning. This is consistent with previous research with first episode of psychosis patients. Delayed verbal memory strongly correlated with functioning, as seen in previous research with chronic schizophrenia patients, and also with negative symptoms. Overall, these results are consistent with other studies and highlight the need to treat neurocognitive deficits alongside symptoms.

M84. Schizotypy and neurocognitive performance in psychosis: an analysis from the first pronia sample

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Background: Schizotypy is thought to be a non-clinical manifestation of the same biological factors underlying schizophrenia and other psychosis spectrum disorders. As compared to individuals with fully blown psychotic disorders, contradictory results have been reported on cognitive processes affected in schizotypy. To clarify this aspects, we first aimed to determine whether schizotypy scores can be used to differentiate individuals with clinical high risk for psychosis (CHR) from those with recent onset psychotic (ROP) illness at the single subject level. Furthermore we aim to clarify which neuropsychological domains were related to schizotypal traits shown by our participants.

Methods: A total of 304 participants were recruited as part of an ongoing multi-national, longitudinal project named PRONIA (Personalised Prognostic Tools for Early Psychosis Management), including 70 individuals at clinical high risk for psychosis (CHR), 65 subjects with recent onset psychosis (ROP) and 169 healthy controls. Self-reported schizotypy scores using the brief form of the Wisconsin Schizotypy Scale (WSS), as well data from the PRONIA neuropsychological battery, were collected for each participant. Schizotypy scores were analyzed using a machine learning approach determine where group-belonging could be predicted based solely on WSS scores. Comparisons were performed pairwise for the three study groups. Finally a Spearman RHO correlation values were calculated between decision values of the algorithm for every subject in each two-group contrast and neuropsychological scores.

Results: Our 3-group cross-validated results showed differences in schizotypy scores in which were used to classify HC from CHR with a balanced accuracy (BAC) of 76,3%, followed by HC vs ROP (72,5% BAC), while classification of CHR vs ROP exposed the lowest performance (58,9% BAC). Mainly differences in items from the social anhedonia subscale of the WSS drove the classification results in each pairwise comparison. For the second part of the analysis, significant Spearman Rho values were found between WAIS-Vocabulary standard scores and the algorithm's decision scores of HC and CHR when contrasted against each other (HC vs. CHR: $r=0.1685$, $P<0.05$; CHR vs. HC: $r=-0.2318$, $P=0.05$). Performance in tests measuring verbal memory and processing speed showed a trend in correlation in every binary group comparison with each subject's decision scores ($P<0.1$). In addition, a trend of significance between decision scores of ROP vs HC from measures on facial emotion recognition (DANVA) could be established.

Discussion: Our unique results using a novel machine learning approach indicate that social anhedonia items separate the best between HC, CHR, and ROP individuals. This might be mediated by abnormalities in verbal and processing speed, which are required functions for proper everyday social interaction. We hypothesize a causal relationship between changes in specific verbal and cognitive abilities, and higher scores of social anhedonia, which we plan to assess using PRONIA- longitudinal follow-up data. Furthermore, impairments in facial emotional recognition indicate that aberrations in emotional processing might be relevant for predicting transition from high-risk stages to fully blown psychosis.

M85. Functional status and financial capacity in individuals with first psychosis

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Background: It has been found that individuals with first psychosis present functional and cognitive impairment that are not present in healthy adults, especially in complex financial abilities. Now a days, legal definitions of incompetence are moving away from diagnosis-based definitions toward functional definitions (Weininger and Wettstein, 1993), which require clinicians to provide evidence about the individual's knowledge and abilities essential for financial capacity. The purpose of the present study was to examine the profile of functional performance and indices of functional capacity in individuals with first psychosis. Functional status is essential for an individual to live independently in our society and comprises a broad range of conceptual and pragmatic abilities such as temporal abilities, communication, and "dealing with finances", which include talk counting coins, to more complex skills, such as paying bills and managing a checkbook.

Methods: Participants were nineteen (11 man and 8 woman) outpatients who are regularly followed-up at the Outpatient Unit of the Institute of Psychiatry, University of São Paulo, Brazil, were assessed for diagnosis, socio-demographic aspects and functional status with DAFS-Br (Direct Assessment Functional Scale- Brazilian Version) (Pereira *et al.*, 2008), diagnosis. The DAFS-BR is a standardized measure of performance in six domains of daily functioning: 1. "time orientation"; 2. "communication skills"; 3. "dealing with finances"; 4. "shopping skills"; 5. "grooming skills"; 6. "eating skills".

Results: Were observed in the scores of the DAFS-BR subdomain that "dealing with finances" were significantly more impaired with 24 (7,22) (mean; DP) from 32, in the DAFS-BR subscale.

Discussion: Financial capacity is essential for an individual to function independently in our society. Individuals with first psychosis must be assessed more detailed, with functional assessment that is sensible to identify loss of financial capacity. Occupational therapists and professionals involved with individuals with first psychosis have playing increasingly active roles in assisting patients need to focus the clinical practice to encourage these patients and families to proactively engage in financial and legal advance planning. The identification of financial impairment can help individuals with first psychosis. The present data confirm the notion that individuals with first psychosis may have subtle functional deficits affecting the ability to perform instrumental activities of the daily living.

M86. The course of neurocognitive changes in acute psychosis: relation to symptomatic change

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Background: Cognitive impairment is a core characteristic of schizophrenia and closely linked to poor functional outcome. However, there is no definitive consensus as to the course of change for cognitive functioning in psychosis after this point. There is a particular paucity of data investigating the course of cognitive changes during the acute phase of psychosis, as most longitudinal studies have focused on patients in a later phase of illness, when symptomatic fluctuations have stabilized. Therefore, this study aims to investigate the course and nature of changes in cognitive performance seen during the early acute phase of psychosis, as well as to examine any correlation between cognitive change and changes in symptom load during this stage of illness.

Methods: Participants were recruited from the acute psychiatric emergency ward of Haukeland University Hospital, Bergen, Norway, as part of the BergenPsychosis Project (BPP), including both first-episode and previously ill patients. The RBANS neuropsychological test battery was administered on admission and again at discharge from the acute ward (mean time 4.1 weeks, SD 1.86 weeks). Symptom levels were measured by PANSS.

Results: A forward multiple linear regression model (R^2 change = 0.091, $P=0.160$) with RBANS change as the dependent variable, with a first step controlling for age, gender, and baseline symptom level, adding the five PANSS composite score change variables as a measure of symptomatic change, found change in negative symptoms to be a significant predictor of improvement in total RBANS performance ($\beta = -0.358$, $P < 0.012$), with medium effect size. Forward entry multiple linear regression analyses were conducted with RBANS change scores as the dependent variable, to assess the contribution of symptom load change as measured by PANSS composite scores. The first model controlled for gender, age, and baseline PANSS composite variable scores (Positive, Negative, Depressive, Excitatory, and Disorganized), whilst the second model also included PANSS composite variable change scores.

Discussion: This study shows that short-term improvement in negative symptom load across the early acute phase of psychosis significantly predicts improvements in neuropsychological test performance, even in non-first episode patients. This supports previous findings that neurocognitive impairment is independent of positive psychotic symptoms, with fluctuation related to negative symptoms. The current findings also indicate that, contrary to previous studies concluding that cognition uniformly remains stable or even declines after the onset of psychosis, improvement in cognitive functioning may happen quite early on in the course of acute illness. Our study is among few to measure cognitive change related to symptom change at such an early stage of illness, thus revealing an effect which might have been masked by late baseline testing or long re-test intervals in previous studies.

M87. The role of disorganization symptoms in the relationship between executive functions and white matter in schizophrenia

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Background: White matter (WM) alterations have been well described in schizophrenic patients. Although their association with cognitive impairment and clinical symptoms has been separately investigated, the role of these symptoms in the relationship between WM alterations and cognition still remains unclear. Therefore, the aim of this study was to assess the role of clinical symptoms in the relationship between WM and executive functions (EFs) in patients with schizophrenia.

Methods: Thirty-nine chronic schizophrenic patients, 29 male and 10 female (mean age = 37.46), were recruited from the two sites of the Bipolar-Schizophrenia Network on Intermediate Phenotypes study

(B-SNIP). Patients were assessed with the five-factor model of the Positive and Negative Syndrome Scale (PANSS) proposed by Van der Gaag *et al.*, (2006); positive symptoms, negative symptoms, disorganization, excitement, and emotional distress. EFs were assessed with the Tower of London (ToL) test. EFs residual scores were calculated regressing ToL scores on disorganization symptoms scores and saving the standardized residual using SPSS software. In addition, the same process was performed in order to obtain the disorganization symptoms residual scores, controlling for ToL scores. Diffusion weighted images of all of the patients were acquired on a Siemens 3 T MRI scanner, in order to assess water diffusion characteristics of the WM. TBSS (Tract-Based Spatial Statistics) as implemented in FSL (Smith, 2004), was used to perform whole-brain voxel-wise regression analysis to study the relationship between WM fractional anisotropy (FA) and the five factors, the ToL scores, and the residual scores. TFCE correction for multiple comparisons was applied.

Results: A significant negative correlation ($P=0.012$) was found between disorganization symptoms and FA in some association fibers (left fornix, uncinate fasciculus bilaterally, superior (SLF) and inferior longitudinal fasciculus (ILF) bilaterally, inferior fronto-occipital fasciculus (IFOF) bilaterally, and cingulum bilaterally), commissural fibers [corpus callosum (CC)], projection fibers (corticospinal tract (CST) bilaterally and superior thalamic radiation bilaterally) and brainstem. No significant correlations were found when assessing the relationship between positive, negative, excitement or emotional distress factors and WM FA. Moreover, a significant positive correlation ($P=0.027$) was also found between ToL scores and FA in some association fibers (right IFOF and SLF bilaterally), commissural fibers (CC), and projection fibers (right CST, and right anterior thalamic radiation). However, when we controlled for disorganization symptoms in EFs scores, the correlation between these scores and WM FA did not remain significant, whereas the correlation between disorganization symptom scores and WM FA still remained significant after controlling for ToL scores.

Discussion: These results suggest that the relationship between EFs and WM FA in schizophrenic patients is influenced by disorganization symptoms, highlighting the role of these specific symptoms not only in cognitive performance but also in the neuroanatomical correlates of this performance in schizophrenic patients.

M88. It's all in the words: lexical processing is impaired in schizophrenia and bipolar mania

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Background: Verbal learning and memory difficulties are a core cognitive impairment in schizophrenia and bipolar disorder. Word recognition is a fundamental process that is influential during higher order verbal memory tasks. Despite a wealth of literature on verbal learning and memory deficits we only have a rudimentary understanding of more basic word recognition or lexical processing in these disorders. This study sought to investigate word recognition in bipolar and schizophrenia groups compared to healthy controls using a lexical decision task. The task manipulated the frequency and the imageability of stimuli.

Methods: 32 healthy controls were compared with 30 schizophrenia patients and 28 patients with bipolar mania. They were administered a computerized lexical decision task that required them to distinguish words from pseudo-words. Reaction time and accuracy were recorded.

Results: Both patient groups showed reduced overall performance on the task, that is, reduced accuracy and increased response times in deciding whether words and pseudo-words were real words. Patient's poor performance was exaggerated for low frequency word stimuli. There were no differences across the two patient groups.

Discussion: This is the first known investigation comparing word recognition in bipolar and schizophrenia. The data suggest that individuals with mania have deficits in lexical access that is comparable to that found in SZ. Further investigation of the contribution of word recognition deficits to performance on verbal learning and memory tasks in these two cohorts is necessary.

M89. The perception of intentionality in early psychosis

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Background: Paranoid delusions have been hypothesized to arise from an overattribution of meaning or malevolent intentions to others' actions. Evidence for this mechanism has been found in samples with chronic schizophrenia, but its role in the etiology of symptoms in the early stages of the illness is unclear. This study investigated whether patients with early psychosis overattribute contingency to agents' actions and whether this mechanism is associated with paranoid delusions.

Methods: 38 adolescents with early psychosis and 93 controls (age 13 to 19) watched four types of films showing two moving shapes. In the: 1) animate contingent condition one shape moved when it 'saw' the other; 2) animate non-contingent condition one shape moved independently of the other; 3) mechanistic contingent condition one shape's movement was launched by the others; and 4) mechanistic non-contingent condition one shape passed by the other without touching. Participants saw five films of each category and rated the strength of the relationship between the shapes' movements. Paranoid delusions were assessed with the PANSS. Group differences in ratings of relationship strength and associations with paranoid symptoms were analyzed with multilevel random regression analyses to account for repeated measures.

Results: Participants rated the relationship between the shapes' movements significantly stronger in the mechanistic contingent than the non-contingent condition, but perceived little difference between animate contingent and non-contingent movements. In the animate condition there was a non-significant trend effect for patients to perceive the relationship between the shapes' movements as weaker than controls ($P=0.08$). A similar trend was present in the mechanistic contingent condition ($P=0.09$), but there were no group differences in the mechanistic non-contingent condition. Patients' levels of paranoia were unrelated to their ratings of the relationship strength.

Discussion: The results show an intact perception of intentional contingency in early psychosis and demonstrate that contingency perception in the early stages of the illness is unrelated to the levels of paranoia. The findings contradict research in chronic schizophrenia samples that associated the presence of paranoid delusions with an overattribution of contingency to unrelated actions of agents. This suggests that the early illness stages might present a window of opportunity for interventions that aim to prevent the biased attribution of intent.

M90. Autobiographical memory impairment in chronic schizophrenia

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Background: Memory deficits are one of the most distinctive neuropsychological features in patients with schizophrenia. In this study, particular attention is paid to autobiographical memory as the aspect of memory that is concerned with the recollection of personally experienced past events and therefore constitutes an essential feature of our personality. Previous research on schizophrenic patients and autobiographical memory has shown that patients' memory for the past is overgeneral and lacking in detail. Until now, only a few studies (and by the majority of small sample sizes) investigated the relationship between clinical symptoms, basic cognitive functions, and self-defining memories in patients with chronic schizophrenia.

Methods: In the present study 75 patients with chronic schizophrenia (mean age 49.89 years, $sd=11.8$) and 50 healthy controls (mean age 52.3 years, $sd=11.0$) were included for comparison. For a differentiated and extended diagnosis of self-related memory performance a semi-structured interview (E-AGI, Fast *et al.*, 2007) was used. In our adapted version of the E-AGI participants were required to recall personal semantic information and autobiographical episodes from

four different life periods. The recalled episodes were first rated by their specificity level and then a detailed scoring system was applied to one single event in each of the four life periods. Additional the same single event was rated for experiential aspects of reliving (originality, vividness/visual imagery, emotional re-experiencing and emotional valence). For a better understanding of the relationship between clinical symptoms, basic cognitive functions, and self-defining memories, the E-AGI was accompanied by neuropsychological background tasks covering relevant neurocognitive domains and clinical scales assessing a broad range of psychotic and affective symptoms.

Results: Our analyses revealed significant group effects for the majority of the E-AGI main scores, with schizophrenic patients showing an impaired event recall in general, an impaired recall of personal semantic information and a reduced ability to retrieve specific memories. An analysis on the pool of recalled specific events revealed no group effect, therefore a general deficit of recalling contextual details could not be shown for the patient group. Analyses on the experiential aspects of reliving revealed significant group effects exclusively for the main auto-nostalgic markers of the E-AGI (vividness and emotional re-experiencing), but not for originality and emotional valence. Correlation analysis between psychopathology and autobiographical memory indexes revealed significant association between negative symptoms and the E-AGI retrieval measures, while no correlations were observed between negative symptoms and experiential aspects of reliving.

Discussion: Taken together, our preliminary analysis replicated the known overgenerality of autobiographical memory in schizophrenic patients, but could not show a general deficit of recalling contextual details of the recalled specific episodes. Such a preserved detail-recall in schizophrenic patients could be a consequence of a "semanticization process" and in this regard independent from the known impaired capacity for auto-nostalgic reliving during autobiographical event recall in schizophrenia.

M91. Taking it at 'face value': the use of face processing strategies in schizophrenia and bipolar disorder

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Background: The use of appropriate face processing strategies is important for facial emotion recognition, which is known to be impaired in schizophrenia (SZ) and bipolar disorder (BD). There is preliminary evidence of abnormalities in the use of certain face processing strategies in the former, but there has been no explicit attempt to assess face processing in patients with BD.

Methods: 28 individuals with BD I, 28 individuals with SZ and 28 healthy controls completed a battery of tasks assessing featural, first and second order configural face processing. The facial inversion effect was used as a proxy of second order configural face processing and compared to featural face processing performance (which is known to be relatively less affected by facial inversion).

Results: Across all conditions and tasks, accuracy and latency was reduced in the SZ group compared to controls. As expected, controls demonstrated the usual second-order inversion pattern. However, contrary to predictions the SZ patients also showed a normal second-order inversion pattern in terms of accuracy. This occurred in the context of a reverse inversion effect in terms of response latency, suggesting a speed-vs.-accuracy trade-off. In the BD group, the absence of a second-order configural inversion effect in the presence of a disproportionate reliance on featural face processing was evident. **Discussion:** To our knowledge, this is the first study to explicitly assess face processing in patients with BD, and to compare face-processing performance in BD patients to those with SZ. Our findings indicate a generalized impairment on face processing tasks in SZ, and the presence of a second-order configural face processing impairment in BD. It is possible that these face processing impairments may represent a catalyst for the facial emotion recognition deficits that are commonly reported in the BD/SZ literature.

M92. Verbal memory in first episode psychosis patients: is the hippocampus responsible for the deficit?

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Background: Verbal memory deficit has been reported by the vast majority of published research in schizophrenia. The deficits have been established in first episode psychosis (FEP), confirming they are already present at early stages of the illness. The presence of memory impairments and correlated abnormalities in hippocampal function, as revealed by a large body of neuroimaging studies, suggest a clear role for the hippocampus in the pathology of schizophrenia. Here we investigate in detail the nature of the brain structures responsible of specific verbal memory impairment in FEP patients.

Methods: The study sample comes from a large epidemiological program (PAFIP) at the University Hospital Marques de Valdecilla (Santander, Spain). Information on the Rey Auditory Verbal Learning Test (RAVLT), a widely used verbal memory measure that provides scores for different aspects of memory (i.e. acquisition, retention, susceptibility to proactive and retroactive interference), was available for 388 FEP patients and 184 healthy controls. In 218 patients and 145, structural magnetic resonance imaging data were analyzed with Voxel based morphometry (VBM), using the VBM5 toolbox.

Results: The patients group showed significantly lower results on immediate recall (Trial 1), delayed recall (Trial 7) and learning (Trial 5-Trial 1), as well as higher forgetting (Trial 6-Trial 5) scores. They also presented a significant retroactive (Trial 6-Trial 5) but proactive (list b-Trial 1) interference. Significant correlations between bilateral frontal lobe and proactive interference, as well as between right frontal lobe and retroactive interference arose. Forgetting score significantly correlated with right occipital cortex.

Discussion: These results confirm brain abnormalities responsible for verbal memory impairments in schizophrenia. FEP patients with higher scores on forgetting, proactive, and retroactive interference demonstrated further gray matter reductions in frontal and occipital brain areas. We conclude that these structures make important contributions to verbal memory, different from those made by the hippocampus.

M93. Schizophrenia & music syntactic processing- an eeg study

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Background: Constant auditory expectations are prerequisites for the interaction of human beings with their complex environment. Recent research suggested a disruption of predictive coding mechanisms in schizophrenia patients. Within electroencephalography this was shown mainly with pitch deviancy tasks resulting in a mismatch negativity (MMN). In contrast to a pitch deviancy, a harmonic deviancy in music results in an early right anterior negativity (ERAN). The ERAN is an event-related potential (ERP) reflecting processing of music-syntactic information, that is, of acoustic information structured according to abstract and complex regularities. It relies on representations of music-syntactic regularities that already exist in a memory format. The ERAN has been shown to receive its contributions from generators located in Broca's area and its right hemisphere homolog (Koelsch *et al.*, 2000; Maess *et al.*, 2001). However there is no evidence for the functionality of a bilateral network during an ERAN within schizophrenia patients.

It was the aim of the study (1) to explore the correlation of the ERAN amplitude and the clinical symptoms of the schizophrenia patients as measured by the Bernese psychopathology scale (BPS), (2) to investigate the ERAN related network activations as measured by frequency power coherence, phase amplitude coupling, and granger causality analysis (Granger 1969).

Methods: 10 patients with schizophrenia and 10 healthy controls were included in our study. They listened to chord progression either

ending on an expected or an unexpected chord. We recorded a 65 channel EEG. We computed ERPs based on the 100 expected and 100 unexpected chord trials. The ERAN amplitude was calculated as the difference between the expected and the unexpected condition. Further we used the BPS for a semi-structured interview resulting in an overall-score on the dimensions language, affective and motor symptoms (ranging from -2 till 2). We correlated the over-all score of the patients with the amplitude of the resulting ERAN of the electrodes F2 and F4. Further we calculated the phase locking factor (degree of phase locking) and spectral Granger causality (predict oscillations in one area from the past history of oscillations in another) for F2 and F4.

Results: ERAN amplitudes in the 10 patients differed from -0.3 to -3.7uv. The ERAN amplitudes of the patients were significantly smaller than those of the matched healthy controls ($P < 0.02$ for all).

We found a negative tendency between the language scale of the BPS and the ERAN amplitude of the patients ($r = -0.73$, $P = 0.059$) and a negative tendency between the ERAN amplitude of the patients and the affective score of the BPS ($r = -0.56$, $P = 0.09$). Phase locking during the unexpected condition showed a left frontal-right fronto/parietal network within alpha frequency band in the healthy controls (ANOVA: $F(1,50) = 9.3$, $P < 0.01$). Information flow was largely unidirectional, with right frontal alpha oscillations entraining parietal alpha activity. Granger causality analysis corroborated this directional coupling.

Discussion: We discuss our findings based on the neural substrates of the ERAN focusing on the areas BA 44. Here we outline the interactions between language and affective symptoms in schizophrenia and possible overlaps to music syntactic processing. Further we discuss the interaction of music induced arousal and fronto/parietal alpha frequency networks (Mikutta *et al.* 2014) and the alterations within schizophrenia. Finally we show possible ways to specify music therapy to the needs of schizophrenia patients with given symptom combinations.

M94. Preliminary evidence for the influence of working memory load on the learned predictiveness effect in schizophrenia patients

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Background: The learned predictiveness effect (LPE) is the finding that when people learn that certain cues are reliable predictors of an outcome in an initial stage of training (phase 1), they exhibit a learning bias in favor of these cues in a subsequent training involving new outcomes (phase 2) despite all cues being equally reliable in phase 2. Literature suggests that the LPE is impaired in schizophrenia patients, a disturbance probably associated with attentional deficits leading to difficulties to ignore irrelevant stimuli. It has been traditionally thought that the paradigms addressing the LPE would exclude the influence of inferential processes during the learning of contingencies. Nevertheless, recent evidence suggests that it cannot be entirely ruled out. Therefore, since the facilitation or disruption of the LPE might be controlled by cooperative or competitive interactions between both associative and propositional processes, definitive conclusions about the nature of the LPE impairment in schizophrenia cannot be clearly posited.

The purpose of the current research was to further examine the LPE in schizophrenia patients and their matched controls. If the LPE depends, at least in part, on controlled processes operating in phase 2, it should be affected by a cognitive load manipulation during this stage of learning. Consequently, we used a conventional procedure that has been proved to be useful to study the LPE in previous research, and performed two experimental conditions (with and without a secondary memory task performed during phase 2).

Methods: Thirty eight patients and thirty seven healthy controls were randomly assigned to a factorial design by 2 (groups: patients, controls) x 2 (cognitive load: no load, load), and were exposed to cues A-D ("predictive cues" of o1 or o2 outcomes) and V-Y ("nonpredictive cues" of o1 and o2 outcomes) in phase 1. In phase 2, four new compounds comprising one predictive and one nonpredictive cue were formed, and participants learned which of two new outcomes

were predicted by them. Additionally, participants in load group were asked to perform a digit-remembering task concurrently with the causal learning task during phase 2. Finally, the test phase evaluated the learning levels reached in phase 2. Ratings reflecting better O3-O4 discrimination for the "predictive compounds", AC and BD, than for the "nonpredictive compounds", VX, and WY, would be taken as evidence of LPE.

Results: The 2 (groups: patients, controls) x 2 (cognitive load: no load, load) ANOVA yielded no significant main effects of load or outcomes [$F_s(1, 71) < 1$], but there was a significant group x load interaction [$F(1, 71) = 7.707, P = .007, \eta^2_{\text{partial}} = 0.098$]. Simple effects revealed that the difference between the load and no load conditions was significant in the control group ($P = 0.031$), and marginally significant in the patient group ($P = 0.088$). Between group differences were significant for no load condition ($P = 0.016$), but not significant for load condition ($P = 0.151$).

Discussion: Our results revealed that the LPE is impaired in schizophrenia patients, and contrary to our expectations, that the cognitive load apparently enhanced the LPE in this group. Moreover, the disruption of the LPE in the cognitive load condition in healthy controls, suggests that the LPE cannot be exclusively accounted for associative processes. The findings are discussed in relationship to associative and inferential accounts.

M95. What does 2D:4D tell us about social cognition?

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Background: Several factors have been shown to be associated with the onset of schizophrenia. Hormones are one of them. Digit ratio is accepted as a sign of prenatal androgens exposure during the intrauterine period. Studies investigating fetal extremity development have reported that hormones affect bone development. It has been reported that while testosterone affects the fourth digit length, the second digit length is affected by estrogen. The hand's second and fourth digit fingers (2D:4D) are one of the new areas studied in schizophrenia, 2D:4D ratio is known to be increased in patients with schizophrenia. Moreover, studies revealed that theory of mind and empathic abilities are worse in patients with schizophrenia compared to healthy participants. It is recommended that 2D:4D correlates with sex dependent hormonally influenced variables like behavioral, cognitive traits and measures related to fertility and sexuality. Yet, these areas have not been investigated in the schizophrenic population. The aim of this study was to investigate 2D:4D, the impairments of theory of mind, empathic abilities; the relation of 2D:4D finger lengths with theory of mind and empathy in schizophrenia.

Methods: The sample consisted of 48 healthy participants (23 female, 25 male) and 48 patients (23 female, 25 male) diagnosed with schizophrenia according to DSM IV. The patients were recruited from the Schizophrenia Outpatient Unit of Psychiatry Department of Dokuz Eylül University, School of Medicine. They were assessed with the Positive and Negative Syndrome Scale (PANSS), which evaluates the severity of schizophrenia symptoms. To measure empathic abilities, Empathy Quotient (EQ) was used which included statements regarding preferences and habits. Theory of Mind abilities were evaluated using Reading Mind in the Eyes Test (RMET) that comprises eye region photographs and mental states descriptions. Index and ring finger lengths were measured using a digital vernier caliper. While for group comparison, ANOVA was used, Pearson correlation coefficient was used for correlation analysis.

Results: Statistical significance was found between patients and controls regarding empathy ($F = 4.024, df = 94, P = 0.009$) and theory of mind ($F = 3.351, df = 94, P = 0.001$) using ANOVA. When 2D:4D finger lengths were evaluated, compared to healthy participants, left digit ratio was significantly increased ($F = 3.209, df = 94, P = 0.008$) in schizophrenia patients'. However, there was not a significant relationship between 2D:4D finger lengths and theory of mind or empathy in schizophrenia ($P > 0.05$).

Discussion: These findings suggest that theory of mind and empathic abilities of schizophrenia patients show impairment when compared to healthy participants. Thus, it can be said that social cognition is

impaired in schizophrenia. Moreover, schizophrenia patients also have increased left 2D:4D finger lengths. Hox genes which regulate expression of testosterone and estrogen in utero may be the factor for this difference. Findings also support Alias' Androgen Dysgenesis notion in a way that passivity, lack of self-confidence and decrease in competition seen in schizophrenia development are related to a decrease in androgenic influence. In addition to those findings, no correlation was found between 2D:4D, theory of mind and empathy. The reasons for this may be as follows; testosterone uses different pathways in left and right hemispheres, testosterone levels differ across nations, there may be different developmental timing in the development of empathic abilities, social environment in childhood may have an effect on the development of empathic abilities.

M96. The effect of the muscarinic M1 receptor antagonist biperiden on cognition in patients with a psychotic disorder and healthy controls

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Background: The majority of the patients with a psychotic disorder report cognitive impairments in addition to positive and negative symptoms. Cognitive impairments often precede the onset of other psychotic symptoms and persist after other symptoms have been effectively treated. The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative established seven cognitive domains (processing speed, working memory, verbal- and visual learning and memory, reasoning and problem solving, attention and vigilance, and social cognition) that are fundamentally impaired in psychosis, particularly schizophrenia (Vingerhoets *et al.*, 2013). At present no effective treatment is available for these symptoms. It is well known that the neurotransmitter acetylcholine plays an important role in cognition. A post-mortem study of chronic schizophrenia patients demonstrated a reduction of up to 75% in the number of the acetylcholine muscarinic M1 receptors (Scarr *et al.*, 2009). Therefore, with this study we aimed to investigate the role of acetylcholine and the muscarinic M1 receptor in cognitive function in psychosis.

Methods: 13 patients (9 male and 4 female, mean age = 27 years) with recent onset psychosis and 19 healthy controls (11 male and 8 female, mean age = 24 years) were included. The two groups were matched for age, gender and IQ. To measure cognitive functioning, the Cambridge Neuropsychological Test Automated Battery (CANTAB) was assessed twice: once after placebo and once after oral administration of 4 mg. biperiden (a muscarinic M1 receptor antagonist). To minimize learning effects, parallel versions were used for several tasks and the time interval between test sessions was at least once week. In addition, we counterbalanced the order of placebo and biperiden. A cognition composite score was computed using standardized Z-scores as an indication of overall cognitive functioning and for all MATRICS domains separately.

Results: A repeated measures Analysis of Variance (ANOVA) showed that biperiden had no effect on cognitive function as no main ($P = 0.264$) or interaction ($P = 0.242$) effects of medication were found. However, there was a trend for group differences ($P = 0.058$) in overall cognitive function: patients had lower composite scores compared to the HC's. When looking at the separate cognitive domains, a significant main effect ($P = 0.025$) of biperiden on verbal learning and memory was found; verbal learning and memory decreased after biperiden administration. No group differences and no interaction effect were found. Moreover, no significant main or interaction effects were found for the other cognitive domains.

Discussion: These results indicate that, compared to healthy controls, patients with a psychotic perform worse on cognitive test battery. Worsening of verbal learning and memory in both the patient and the control group after M1 antagonist biperiden administration indicates a role of acetylcholine and the M1 receptor in this domain of cognition. The lack of effect of biperiden on the other cognitive domains suggest that the cholinergic muscarinic system is specifically important for verbal learning and memory. However, given the small sample size, further studies are required to replicate these findings.

M97. Cooperation and the effect of social feedback in a public goods paradigm in schizophrenia

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Background: Schizophrenia (SZ) is an illness that is related to impairments in social functioning. Research has begun to map the complex interactive social processes in SZ, however, studies on cooperation and the effect of social sensitivity are still limited. Previous studies indicate that reduced cooperation and social impairment might be due to a fundamental lack of trust in SZ. Cooperation and the ability to adapt behavior in response to social feedback from others is an essential skill underlying successful social functioning. In the current study, we employed a public goods paradigm to investigate cooperation and sensitivity to social feedback in SZ patients.

Methods: Twenty-seven patients with SZ and 28 healthy controls (HCs) were included. To investigate cooperation and social sensitivity we used the public goods game (PGG), which is an interactive paradigm that tabs into social processes directly; as participants are engaged in interpersonal decision-making in real time. Participants played 40 games in total, 20 games in a 'no fine' condition and 20 games in a 'fine' condition (social feedback). In the no fine condition, the participants had the choice of investing into the public good or not, i.e. cooperation or free-riding. In the fine condition, participants who free-rode could be punished by the other players. If participants changed their behavior after being fined, they were considered to be sensitive to social feedback. We used logistic regression and multilevel logistic regression to investigate the differences in cooperation and social sensitivity between groups, taking into account possible effects of gender, age, and IQ. In patients, symptoms were assessed PANSS. **Results:** In the no fine condition, there was a significant group effect indicating that patients were less cooperative at baseline and throughout the entire game. The effect of fine was present in both groups, patients with SZ and HCs cooperated more in the fine condition compared to the no fine condition. In the fine condition, SZ patients initially performed equal to HCs, but throughout the entire game they cooperated less compared to HCs. There were no group differences in the level of cooperation after being fined in the preceding trial; both groups showed very low cooperation after being fined. Within the SZ group, the level of cooperation and the amount of fines given to other players and the chances of cooperation after being fined were unrelated to symptoms.

Discussion: In an interactive PGG, patients with SZ are less cooperative, or free-ride more, compared to HCs. This is in line with previous research that shows that patients are inclined to distrust the cooperative nature of other individuals. This bias causes them to initiate social interaction with more negative social behavior and may therefore play a role in the social impairments that are often seen in patients with SZ. However, it also needs to be noted that both groups seemed insensitive to punishment from others, which could indicate an adverse effect of negative social feedback when it comes to promoting cooperation.

M98. Assessing change in neurocognition: reliable change indices for neurocognitive assessment in schizophrenia

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Background: A particularly important role of neurocognitive assessment is measuring change in cognitive functioning over time. The MCCB-MATRICES is the most widely used instrument to assess neurocognition in schizophrenia. Clinical efficacy of an intervention relative to a placebo or control condition is generally confirmed through statistically significant differences. However, statistical significance does not in itself provide concise information about an intervention's clinically meaningful effects. Methods for measuring

change have been discussed, with no optimal conclusion, thus researchers are using varying definitions and estimates for change scores. Examples of change score methods include the standard deviation (S.D.) method, reliable change indices (RCI), standardized-regression-based (SRB) methods, percent change, and a specified amount of domain change. As an attempt to develop a standard method of estimating significant change (statistically and clinically), we propose comparing various change score methods employed in neurocognition and comparing them to Reliable Change Index (RCI). Our aim is to provide a comparison of concepts and analyses of clinical significance with the reliable change index (RCI) using pre- and post-MCCB-MATRICES scores, in order to determine the amount of test score change that is necessary to be deemed statistically and clinically reliable.

Methods: Baseline and endpoint MCCB-MATRICES data from a parent study examining neurocognitive change following cognitive remediation therapy in patients with schizophrenia were examined. Three methods of RCI (Jacobson-Truax, Edwards-Nunnally, and Hageman-Arindell methods) were compared to published methods of neurocognitive change, SD change, effect size change, percent domain change, and SRB methods.

Results: For the three RCI methods, 40.56%, 41.23%, and 41.33% of participants showed reliable improvements in at least one domain of the MCCB-MATRICES. For SD change, 76.97% showed improvement, 69.73% improved on at least one domain looking at percent change (published method), and 68.11% showed improvement with effect size change, and 81.23% showed improvement with >20% improvement in at least one domain. When comparing RCIs with previously published change score methods, only 16.53% of improvement also resulted in RCI significant improvement. Regarding clinically meaningful improvement, the Hageman-Arindell method was most concordant with all three RCI measures as this method differentially analyzes clinically meaningful change at the individual level and at the group level (i.e., obtaining proportions of patients who have reliably changed and passed the cutoff point).

Discussion: Using different methods we find widely divergent change scores by measure and method, which can significantly affect efficacy outcomes. Hence, reporting both RCI and clinical meaningful change is warranted in neuro-cognitive intervention studies. Outcome studies often assess statistically significant change, which may not be clinically meaningful. Future research may also include the examination of cognition score change in relation to change observed on CT or MRI scans may to further assess the clinical and prognostic meaningfulness of observed changes.

M99. The experience of self-agency in children with and without familial risk for schizophrenia or bipolar disorder

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Background: Self-agency is disturbed in schizophrenia patients in that they do not consistently experience themselves as agent of their own actions and the consequences of those actions. Two models have been proposed to explain the underlying processes of experiencing agency: the motor prediction and the cognitive inference model. Motor prediction processes develop during early infancy. In contrast, it is suggested that the ability to make cognitive inferences develops later. This is not surprising as we showed that it is related to frontal lobe activation, and the frontal lobe matures until well into young adulthood. In previous research we demonstrated abnormalities in agency inferences in schizophrenia as related to frontal hypo-activation. Interestingly, there is evidence to suggest that self-disorders are predictive of psychosis onset. In line with this notion, we propose that children at risk to develop psychosis show sub-optimal development of agency inference processes.

To assess developmental aspects of self-agency experiences and the possible emergence of impairments, the current study examines the experience of self-agency in children at familial risk of developing psychosis and in a control group.

Methods: 29 children of patients with a diagnosis in the schizophrenia spectrum, 44 children of patients with bipolar disorder, and 22 children of parents without any DSM axis I disorder were included.

Age ranged between 8-21 years. All children/adolescents performed an agency-inference task while in an MRI scanner. Subjects were instructed to stop rapidly alternating letter strings when either a B (representing Blue) or R (representing Red) was visible within a letter string. After each trial they had to indicate on an 8-point scale to what extent they felt agency over a presented outcome (Blue or Red). The task was designed to match or mismatch the outcome with the participants' goal to stop at a certain color. The strength of the manipulation (i.e., matching effect) was defined as mean agency experience on matching trials minus mean on mismatching trials. Psychopathology was measured using the K-SADS-PL. fMRI-analyses were performed using the contrast between match-agency > mismatch-no agency.

Results: In the total sample we showed that experienced agency was higher on matching versus mismatching trials ($P=0.003$, $\eta^2=0.09$), replicating earlier findings in healthy adults and patients with schizophrenia. The strength of the matching effect was not related to age. Also, it did not differ between the three groups and was not related to lifetime presence of psychotic symptoms. ROI analyses showed no differential brain activation in areas that were previously found related to agency processing in adults, i.e., bilateral superior medial frontal gyrus, medial prefrontal cortex, and inferior parietal lobe. Also, at the whole brain level no significant results were found.

Discussion: This study showed that children, including children at familial or at familial and clinical risk to develop psychosis, do use goal-based inferences to guide experiences of self-agency. The results suggest that this ability is already present early in life (after 8 years of age). None of the three groups activated brain areas that were previously found to be active in adults in relation to agency experiences, which may be explained by incomplete maturation of children's brains, especially prefrontal areas. Consequently, children may use other brain areas than adults. The current study was the first to examine the developmental aspects of self-agency. Future research should focus on other contributors to (disturbances in) the development of the ability to experience agency over actions and their outcomes.

M100. Intra-individual variability across cognitive functions in first-episode schizophrenia-spectrum disorder

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Background: Accumulating evidence has suggested that intra-individual variability (IIV) across multiple cognitive domains, an index of cognitive stability, is significantly higher in schizophrenia patients than healthy controls. Nonetheless, most previous studies on IIV focused on patients with chronic illness. There is a paucity of data of IIV in the early course of illness.

Methods: Ninety-seven patients aged 18-55 years with first-episode DSM-IV schizophrenia, schizoaffective disorder or schizophreniform disorder and 51 healthy controls matched in age and gender were recruited. A brief battery of cognitive assessments including letter-number-span test, digit-symbol coding subtest of WAIS-III, logical memory subtest of WMS-III, Trail making test B (TMT-B), verbal category fluency, and Modified Wisconsin Card Sorting (MWCST) test was administered to each subject. IIV was computed according to the method adopted by Cole and colleagues (2011) using z-scores for individual cognitive tests based on healthy controls' performance.

Results: Our results showed that patients displayed a significantly higher IIV than controls ($t=2.372$, $P=0.019$). Correlation analyses revealed that TMT-B performance ($r(97)=0.513$, $P<0.001$) and perseverative errors of MWCST ($r(97)=0.486$, $P<0.001$) were significantly related to the degree of IIV in patients with first-episode schizophrenia-spectrum disorder (FES).

Discussion: We replicate and extend the findings of previous studies on chronic schizophrenia to first-episode populations who demonstrate a significantly higher degree of IIV than healthy controls. This indicates that lower stability of cognitive information processing is already observed in the early stage of illness. Significant, albeit moderate relationships between IIV on cognition and performance on MWCST and TMT-B indicate that instability of cognitive functions may

be specifically attributed to impairment in executive functioning in FES patients.

References: Cole VT, Weinberger DR, Dickinson D. Intra-individual variability across neuropsychological tasks in schizophrenia: a comparison of patients, their siblings, and healthy controls. *Schizophrenia Research* 2011;129:91-93.

M101. Hypervulnerability of the adolescent period towards the prefrontal neuronal consequences of obesity are mediated by reelin, an extracellular matrix protein linked to early onset psychiatric diseases

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Background: Overconsumption of high-calorie high-fat foods is steadily increasing year by year in developed countries and represents the major cause for the dramatic rise in obesity in the past decades. Importantly, obesity affects an alarming number of adolescents, whereby 17% were obese in the USA in 2012. These effects may be particularly dramatic for the adolescent population, given that adolescence is an essential period of maturation for late brain structures such as the prefrontal cortex (PFC). Chronic high fat intake during this period may cause particularly pronounced deficits in prefrontal cognitive functions and may be relevant for neuropsychiatric disorders with delayed onset.

Methods: We examined this hypothesis in mice fed excessive amounts of dietary fat (60% kcal from fat) throughout adolescence as a model of diet-induced obesity (postnatal day 28 onwards). In order to delineate whether the adolescent period is more vulnerable towards the negative effects of HFD, we compared prefrontal functions in periadolescent (pHFD) and adult (aHFD) cohorts receiving the same dietary regimen. Prefrontal-related cognitive tasks included two spatial working memory paradigms and a discrimination reversal learning task. We utilized immunohistochemistry, molecular biology and slice electrophysiology to identify the molecular mechanisms underlying the emergence of cognitive deficits in HFD mice. Finally, a transgenic model of forebrain-specific reelin (RELN) overexpression (RELN-OE) was utilized to assert the functional importance of the RELN protein in our model.

Results: We show for the first time that obesity induces PFC-related cognitive abnormalities in the form of deficits in working memory and behavioral flexibility. Importantly these effects emerge specifically following adolescent, but not adult, dietary treatments. Adolescence may be more vulnerable than adulthood to HFD-induced prefrontal deficits because of differences in prefrontal maturation. This differential vulnerability may be caused by the extracellular matrix (ECM) protein RELN, which is primarily expressed by a subgroup of GABA interneurons in forebrain structures, plays a crucial role in the maturation of the PFC and is involved in prefrontal-related cognitive functions. We find that pHFD induces a strong down-regulation of RELN+ cells, an effect that was valid across various PFC subregions, but not in the hippocampus or amygdala. Such deficits did not extend to other GABAergic neurons (parvalbumin or GAD67-positive). Finally, chronic HFD treatment did not cause prefrontal RELN deficits when restricted to adulthood. Based on the critical role of reelin in NMDA-dependent synaptic plasticity, we next assessed NMDA-dependent long-term depression (LTD) and long-term potentiation (LTP) and identify a marked impairment in LTD functions, while LTP remained intact, further supporting the putative importance of the RELN protein in the emergence of pHFD-induced prefrontal anomalies. We thus finally explored the functional role of RELN using RELN-OE mice. We show that RELN-OE specifically prevented the pHFD-induced deficits in working memory and cognitive flexibility. Importantly, these effects were specific for the PFC because functions associated with hippocampal and amygdala regions were not reverted.

Discussion: In conclusion, our findings highlight that adolescence is associated with an increased vulnerability for PFC-regulated cognitive deficits induced by obesogenic diets and show that the ECM protein

RELN is a critical determinant of this dissociation. Because RELN is thought to participate in the etiology of several psychiatric disorders, our findings may be relevant for such patient populations harboring metabolic comorbidities.

M102. Lower frequency of metabolic syndrome predicted by schizotypal traits in discordant siblings of patients with schizophrenia

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Background: Type 2 diabetes (T2DM) is more frequent in schizophrenia than in the general population. Several lines of evidence suggest that shared susceptibility genetic variants might be partly responsible for this association. We studied in discordant siblings of patients with schizophrenia the relationship of schizotypal features and aberrant salience with insulin resistance (IR) and metabolic syndrome (MetS). Our hypotheses were that the former two, vulnerability markers for schizophrenia, would be more common in the sibling group and that they would be associated with IR and MetS, precursors and vulnerability markers for T2DM.

Methods: This is an add-on study in a subsample of the individuals included in the project EU-GEL, Work Package 6 (Vulnerability and Severity). Fasting blood samples were collected from discordant siblings of schizophrenia patients ($n=135$) and nonclinical controls ($n=288$) who did not report a previous diagnosis of or treatment for T2DM. Insulin resistance was diagnosed with the clinical cut-off (HOMA-IR ≥ 2.7); MetS was assessed with the International Diabetes Federation (IDF) and Adult Treatment panel (ATP-III) criteria. Subjects were screened for psychopathology and assessed for schizotypy and aberrant salience with the Mini-International Neuropsychiatric Interview, the Schizotypy Interview Schedule-Revised (SIS-R) and the white noise (WN) task, respectively. Interrater reliability for the SIS-R was satisfactory (ICC: 0.79 for the positive, 0.80 for the negative subscales). Data were analyzed with univariate tests and in logistic regression models.

Results: Both IDF- and ATP-III-MetS were more frequent in controls (29.2 vs 14.1% and 34.4 vs 16.3%, respectively), controlling for age, sex and education (odds ratio [OR]=2.48, 95% confidence interval [CI]= 1.38-4.45, $P=0.002$ for IDF-MetS; OR=2.73, 95% CI=1.57-4.74, $P<0.001$ for ATP-III-MetS). ATP-III-MetS frequency was almost equal to a recently reported nation-wide figure (33.9%). The frequency of IR was similar in controls and siblings (38.5% vs 34.1%), predicted only by lower-than-high-school education in the same model (OR=1.73, 95% CI=1.16-2.59, $P=0.01$). Median values on the SIS-R positive and negative subscales for the whole sample were 1 and 0, respectively. On the WN task 39% of all subjects reported at least 1 speech illusion, yielding a median value of 0. The frequencies of above-median scores on the SIS-R subscales and aberrant salience on the WN task were higher in siblings (70.4 vs 36.5% for positive, and 67.4 vs 36.8% for negative schizotypy, $P<0.01$ for both; 48.9 vs 32.6% for aberrant salience, $P=0.01$). In the follow-up analyses, all models that predicted IR and MetS included aberrant salience and above-median scores on the SIS-R positive symptom subscale. All OR's were above 2, remaining significant after controlling for age, sex, education and group status. **Discussion:** The genetic variants possibly shared by T2DM and schizophrenia may be associated with protective as well as predisposing intermediary phenotypes, resulting in lower propensity to metabolic disorders and absence of mental disorder in the presence of schizotypal features and aberrant salience. Better metabolic profile in the sibling group might also be due to an overrepresentation of higher-functioning siblings in this sample. Negative associations of IR and MetS with both measures of psychosis-proneness (positive schizotypy and aberrant salience) lend support to hypotheses involving interactions between dopaminergic transmission and actions of insulin and insulin-like growth factor in the pathophysiology of both psychosis and metabolic abnormalities.

M103. Intervention study: the effect of an lifestyle intervention in inpatients with severe mental illness (SMI)

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Background: Lack of physical activity (PA) is an important factor in the well-known co-morbidities in this population. However, research towards the prevalence of objectively (more reliable) measured SB (SB; waking behavior in sitting/reclining posture) and PA of inpatients with SMI is limited. Therefore, in 2013 we conducted a cross-sectional study towards SB, PA and quality of life (QoL) in longstay inpatients at GGz Centraal (NL). Patients wore an accelerometer (ActiGraph GT3X+) for five days. QoL and attitude and self-efficacy towards PA were measured using questionnaires in a structured interview.

Patients ($N=184$) spend a lot of time in SB (84%) and total activity per hour (TAC/h) was positively associated with QoL (not yet published). Surprisingly, we found no associations between attitude/self-efficacy and SB/TAC. Patients who felt motivated and had the self-efficacy to be in PA, were not significantly more active compared to patients with low scores on these outcomes. This finding supported our observation that just motivating patients verbally and providing access to fitness equipment, did not led to more PA. Therefore, we started a pilot study with 16 inpatients with (morbid) obesity, by integrating a lifestyle intervention into daily treatment. This intervention consists of specific support, focussing on three (healthy) meals together with the group, an active daily schedule (e.g. joint fitness, making a walk and team sports), training in cooking meals and psychoeducation (e.g. about symptoms, side effects and quitting smoking). Based on a 'change from within-principle', it was supervised by our own psychiatrists, occupational therapists, nurse practitioner, dietician and nurses (trained as lifestyle coach). The intervention was tailored towards patients' abilities. After three months, results showed a statistically and clinically significant improvement in bodyweight, abdominal circumference, diabetes symptoms and QoL. Two patients were able to stop diabetes medications and in the vast majority, sleep medication could be reduced. In response to these findings, we would like to do further research towards this intervention in a larger and more representative sample of inpatients (not only selected by obesity) with a longer follow-up.

Methods: In a quasi experimental design, we included longstay inpatients at GGz Centraal (NL) if we had complete baseline data and excluded them if they took part in another intervention. Included inpatients ($N=137$) were assigned to the intervention ($N=66$) or treatment as usual (TAU, $N=71$). We conducted a follow-up 18 months after the start of the intervention. Disease-characteristics and metabolic health outcomes were derived retrospectively from electronic patient records.

Results: Preliminary findings towards SB and TAC/h show significant improvement in the intervention group ($N=65$) for SB (-2%, $P=0.003$) and TAC/h (+14%, $P=0.01$). The control group ($N=49$) showed no differences for SB ($P=0.68$) and TAC/h ($P=0.64$). At follow-up, the intervention group was significantly more in TAC/h compared to TAU ($P=0.02$) showing a medium effect ($d=0.45$). We do not know yet the effect of the intervention on QoL and health outcomes. Based on observations, we expect positive health outcomes. Further results can be presented in the beginning of 2016.

Discussion: Results showed a significant but small difference for SB. However, this intervention was focussed on increasing activity instead of reducing sitting behavior and therefore, TAC/h seems the most relevant outcome. The intervention group showed significant improvement in TAC/h, while there was no improvement at all for TAU. Effects on other outcomes are yet unknown. After further data-collection and -analysis, we can draw more specific conclusions.

M104. Comorbid obsessive compulsive disorder and social function in patients with chronic schizophrenia

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Background: Obsessive-compulsive disorder (OCD) is known to be common psychiatric comorbidity associated with poor prognosis in schizophrenia. Prevalence rates for OCD as high as 30% have been reported in schizophrenia populations, as compared to 1.2-2.4% in the normal population. A substantial proportion of individuals with schizophrenia reported clinically significant obsessive or compulsive symptoms, which might appear early in the developmental course of the illness. Comorbid OCD in schizophrenia can lead to a considerable psychosocial dysfunction and can influence significantly quality of life and social functioning in patients. This study aimed to evaluate the prevalence of OCD, and the relationship among obsessive-compulsive symptoms, severity of psychopathology, and social functioning in patients with chronic schizophrenia.

Methods: We interviewed 138 symptom-stable inpatients who had been on a constant dose of antipsychotics for at least 1 month prior and diagnosed as chronic schizophrenia. Subsequently, patients were classified according to the existence of OCD as evaluated using the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Demographic characteristics, the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), Korea-Positive and Negative Symptom Scale (PANSS), Korean Modification of the Scale to Measure Subjective Well-Being under Neuroleptic Treatment (SWN), the Korean Version of the Calgary Depression Scale for Schizophrenia (CDSS) and the Korean Personal and Social Performance (PSP) were performed. Comparison between two groups was done by an independent t-test and Chi-square, and regression analysis was used to evaluate association between social functioning and obsessive-compulsive symptoms in chronic schizophrenia.

Results: The prevalence of OCD in chronic schizophrenia patients was 18.1%. There was no significant difference in comparison of patients taken atypical antipsychotics between two groups ($\chi^2=2.477$, $P=0.790$). Schizophrenia with comorbid OCD showed significantly earlier onset of schizophrenia disease ($t=-2.762$, $P=0.007$), higher PANSS-general psychopathology ($t=6.340$, $P<0.001$) and total score ($t=3.614$, $P=0.001$), lower measure of PSP ($t=-8.741$, $P<0.001$) and SWN scale ($t=-2.298$, $P=0.025$) as compared to those without comorbid OCD. Social functioning (PSP) was affected with positive ($\beta=-0.339$, $P<0.001$) and negative symptoms ($\beta=-0.155$, $P=0.020$) in PANSS scale and Y-BOCS ($\beta=-0.526$, $P<0.001$).

Discussion: Comorbidity of OCD was relatively more frequent in patients with chronic schizophrenia. Obsessive compulsive symptoms might impact on personal and social performance as well psychotic symptoms. Longitudinal study will be needed to investigate relation between social functioning and obsessive compulsive symptoms in schizophrenia with large samples including acute-stage schizophrenia and outpatients.

M105. The course of diabetes in schizophrenia and bipolar disorders: an epidemiological study

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Background: People with schizophrenia are at risk of developing diabetes. However, little is known regarding the course of treatment for diabetes across psychiatric groups.

This study aims to examine the course of treatment for diabetes among groups of persons with schizophrenia disorder, bipolar disorder and diabetes only.

Methods: Using unique patient identifiers from Meuchedet, a healthcare provider to 1.2 million persons, data were linked on demographic, diabetes, pharmacological, service utilization, and psychiatric case registries. Data were extracted for the year 2014 on all persons with in the diabetes registry ($N=37,314$) who were age 18

and over. The population was disaggregated into groups with (I) schizophrenia ($N=388$, 1.04%; diabetes-schizophrenia hereafter); (II) bipolar disorders ($N=258$, 0.69%, diabetes-bipolar hereafter); and (III) a comparison group without the aforementioned disorders ($N=36,155$, 96.9%; diabetes-only). The groups were compared on SES, age, diabetic outcomes of A1C, LDL, BMI, hypertension, not psychiatric ER, general hospitalization visits and adherence to diabetic medications, antidepressants, anti-psychotics and mood stabilizers with Chi-square analyses, T-tests, Anovas and Post-hoc comparisons.

Results: Compared to diabetes-only group and diabetes-bipolar group, the diabetes-schizophrenia group was significantly ($P<0.05$) younger, and had a lower SES. The diabetes-schizophrenia group had significantly ($P<0.05$) poorer diabetes outcomes (LDL $>100=47%$; HBA1C $>9=18%$, BMI $>40=16%$), compared with the diabetes-bipolar (LDL $>100=40%$, HBA1C $>9=9%$ and BMI $>40=8%$), and the diabetes-only group (LDL $>100=41%$, HBA1C $>9=10%$ and BMI $>40=8%$). The diabetes-schizophrenia group had a significantly ($P<0.05$) higher prevalence of emergency department visits (24%) compared to the diabetes-bipolar (17%) and diabetics-only (16%) groups. The average rate of medication adherence to diabetic medications was significantly ($P<0.05$) lower for the diabetes-schizophrenia group (64%) and the diabetes-bipolar (63%) than the diabetes-only group (69%). Psychiatric medication adherence (on antipsychotics antidepressants and mood stabilizers) was significantly ($P<0.05$) lower in the diabetes-schizophrenia (62%) than the diabetes-bipolar (68%) and diabetes-only group (67%).

Discussion: Based on a large representative nationally sample of persons with diabetes, the results showed that persons with schizophrenia have poorer outcomes than those with bipolar disorder, suggesting diagnostic specificity. That suggests that comorbid schizophrenia and diabetes requires particularly careful monitoring.

M106. Neuroanatomical implications of concomitant mood disorders in subjects at clinical high risk for psychosis

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Background: Mood disorders are present in about 40% of individuals at clinical high risk (CHR) for psychosis. Such high prevalence of symptomatic concomitants raises the need to address and assess the contemporary assumption that characterizes CHR states by common neuroanatomical alterations. However, reports on the impact that mood symptoms have on CHR course trajectory remain inconsistent, with scarce and incomprehensive support from imaging literature. The present study aims to investigate the relevance of mood symptoms on the CHR neuroanatomy and symptomatology.

Methods: Magnetic resonance images from a sample of 44 CHR individuals with mood disorders (CHR-M), 30 CHR individuals without mood disorders (CHR-NM), and 34 healthy control subjects (HC) were analyzed with two complementary approaches. A surface-based morphometry analysis was used to extract cortical thickness (CT), and a voxel-based morphometry analysis was used to extract regional gray matter volumes (GMV). Ratings of clinical symptom scales and functioning between the CHR-M and CHR-NM subgroups were also investigated, as well as associations between brain structural alterations and these clinical measures. In tandem, a preliminary analysis of follow-up clinical data is provided.

Results: Preliminary results indicated different patterns of brain structural alterations and clinical symptomatology between the CHR-M and CHR-NM subgroups in comparison with the HC. Though regional GMV alterations were found in both CHR-M and CHR-NM, reduced cortical thickness was found only in CHR-NM. The CHR-M group presented with more severe clinical symptoms and impaired functioning. Preliminary analysis also showed that these differences in symptomatic and functional profiles between the subgroups become less pronounced at follow-up.

Discussion: Neuroanatomical and clinical variances were found within CHR, between the CHR-M and CHR-NM subgroups. These findings seem to suggest the impact of concomitant mood pathologies in CHR. The present study may contribute to the growing literature on "false positives" and their implications on early intervention.

M107. A network analysis on trauma, dissociation and schizophrenic symptoms in schizophrenia spectrum disorders

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Background: Schizophrenia spectrum disorders and dissociative disorders are described in the DSM-5 and ICD-10 as two categorically distinct diagnostic groups. However, several studies have shown high comorbidity between these diagnoses. In addition, symptoms typically associated with one of the two diagnostic groups have been found in the other diagnostic group (e.g. dissociation and hallucinations). It has been suggested that the overlap in dissociative symptoms might be caused by a shared causal factor, specifically trauma. The aim of the current study was to examine the relationship between trauma, dissociation and schizophrenic symptoms. The study builds on previous research by examining the data through the network model of psychopathology.

Methods: The sample consisted of 300 patients diagnosed with a schizophrenia spectrum disorder. Participants were interviewed with the Positive and Negative Syndrome Scale (PANSS). Participants also filled in the Dissociative Experiences Scale and Trauma History Questionnaire. Correlations were computed between trauma, dissociation, and schizophrenia symptoms. This was followed by a regression analysis predicting dissociation from trauma and schizophrenic symptoms. Lastly the data were analyzed through network analysis using R with the package Qgraph.

Results: Sexual and physical trauma correlated significantly with dissociation. Sexual trauma also correlated with the PANSS general symptoms scale. Crime related trauma correlated significantly with positive symptoms but trauma did not correlate with negative symptoms. Dissociative symptoms and positive symptoms correlated significantly with each other. The regression analysis showed that sexual trauma and positive symptoms explained 15% of the variance in dissociative symptoms. The network analysis showed that dissociative symptoms formed a unique symptom cluster. Individual dissociative symptoms were strongly related to each other but loosely with schizophrenic symptoms and trauma.

Discussion: The results are in line with previous research showing relations between trauma dissociation and positive symptoms. However, this study also shows these relations explain only a small part of the dissociation in this patient group. In addition, the results indicate that, although dissociation is related to positive symptoms, it should be treated as an individual symptom of interest.

M108. Pharmacologic management in cases of dual diagnosis-schizophrenia and alcohol use disorder

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Background: Data from literature suggest that lifetime prevalence of alcohol use disorder in individuals with schizophrenia reaches 50% [1]. The presence of documented medication compliance substance abuse stands as a major factor contributing towards relapse [2]. Also, patients with treatment-resistant schizophrenia have high rates of alcohol abuse (51%) and substance abuse (51%) according to a systematic literature review that included 65 studies [3]. Slight advantages were found for second-generation antipsychotic agents over conventional antipsychotics regarding the improvement of distinct psychopathological symptoms, reduced craving, and greater reduction of substance use [4]. Anti-craving agents like naltrexone, nalmefene, and acamprosate, or aversive agents like disulfiram, could also be used for the treatment of alcohol use disorder in patients with schizophrenia.

Methods: A group of 22 patients, 16 male and 6 female, diagnosed with schizophrenia and alcohol use disorder (both according to DSM 5 criteria), admitted in our department for psychotic episodes, were initiated on naltrexone ($n = 12$) or nalmefene ($n = 10$), after treatment for alcohol withdrawal and stabilization of psychotic symptoms. Naltrexone was administered daily 50 mg QD, while nalmefene 18 mg was administered prn, according to the summary of product characteristics. All patients were stabilized on an atypical antipsychotic

(olanzapine $n = 8$, risperidone $n = 6$, amisulpride $n = 4$, aripiprazol $n = 4$) during hospitalization. The evolution of psychotic and addiction-related symptoms were evaluated for 24 weeks (baseline, week 1, week 2, week 4, week 8, week 12, week 20, week 24) using Positive and Negative Syndrome Scale (PANSS), Severity of Alcohol Dependence Questionnaire (SADQ), Clinical Global Impression –Severity (CGI-S), and Global Assessment of Functioning (GAF). Laboratory analyses, including GOT, GPT, and gamma-GT, were collected at every visit. Inclusion criteria: age 18-65, using of two contraception methods during treatment, ability to sign informed consent, SADQ score over 15, PANSS under 90. Exclusion criteria: other psychiatric comorbidities, unstable organic conditions, suicidal ideation or/and behavior, treatment resistant schizophrenia. Last observation carried forward and intent-to-treat analysis were used for statistic interpretation of data.

Results: After 24 weeks, 45.4% of all the treated patients registered a significant decrease ($P < 0.01$) in SADQ score (-65.7% compared to baseline), with paralleled improvements in CGI-S (-50.8%) and GAF (+62.2%), while PANSS score improved with 11.2% compared to baseline. Naltrexone treated patients improved slightly better than nalmefene treated subjects, but differences didn't reach statistical differences on PANSS ($P = 0.332$), CGI-S ($P = 0.410$) or GAF ($P = 0.221$). Gamma-GT values reached a mean level of 44.7 U/l at end-of-treatment visit, compared to 120.5 U/l at baseline, with no significant differences between the two groups.

Discussion: Anti-craving agents that interact with opioid receptors are efficient in dual diagnosed patients- schizophrenia and alcohol use disorder, with an important percentage of cases recording improvements after 24 weeks.

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M109. The adverse effect of nicotine dependence and cannabis use on outcome of first episode psychosis is mediated by poor medication adherence

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Background: Both substance use and poor medication adherence are associated with poor outcome in psychosis. Two major limitations of the published data on substance use and poor medication adherence are the small sample size of most studies and the narrow focus, usually on use of only one substance. In addition, the relation of poor medication adherence to tobacco smoking has not to date been investigated.

Methods: To clarify the contributions of substance use and poor medication adherence to poor outcome in the year following a first episode of psychosis, 205 patients were evaluated for use of tobacco, alcohol, cannabis and stimulants at their psychosis onset, and in a 1-year follow-up. Data on medication adherence and symptom remission were also collected.

Results: First episode psychosis patients had high rates of overall substance use before (37-65%) and after psychosis onset (45-66%). 44% showed poor medication adherence and 55% did not reach remission from psychosis.

No single substance use before the first episode of psychosis reached significance for an association with medication adherence during the follow-up. Similarly, substance use before the psychosis onset was not

associated with remission status at follow-up. Substance use in the year after psychosis onset was associated with increased probability of poor medication adherence during the follow-up. In particular, the analysis showed significant main effects of nicotine dependence (OR=2.18), cannabis use (OR=2.86), and stimulant use (OR=2.63) on the odds of being non-adherent to treatment. In contrast, the OR failed to reach significance for an association between problem drinking and poor medication adherence.

Substance use in the first year after psychosis onset was associated with increased probability of non-remission during the one year follow-up. In particular, the analysis showed significant main effects of nicotine dependence (OR=2.13) and cannabis use (OR=2.60) on probability of not achieving remission. In contrast, the ORs failed to reach significance for an association between problem drinking and non-remission as well as between stimulant use and non-remission. Medication adherence significantly predicted remission during the one year follow-up. In particular, patients with poor medication adherence showed a six-fold increased probability of non-remission of their psychosis when compared with patients with good medication adherence. When substance use in the one year follow-up period was added in to this model, the association between medication adherence and remission was still significant. Following Baron and Kenny's approach to mediation, criteria were satisfied only for nicotine dependence and cannabis use post onset. In order to test for mediation, the associations between nicotine dependence after psychosis onset and non-remission as well as between cannabis use and non-remission were adjusted for medication adherence. When medication adherence was added in to the model, even if increased, the ORs failed to reach significance. Sobel tests for mediation showed that medication adherence was a significant mediator of the relationship between nicotine dependence and remission ($z=2.02$, $P=0.04$) as well as that between cannabis use and remission ($z=2.12$, $P=0.03$).

Discussion: In conclusion, medication adherence lies on the causal pathway between nicotine dependence and cannabis on the one hand and non-remission on the other. As cannabis and tobacco are often consumed together in the same joint and there is accumulating evidence of a common underlying vulnerability to both substances, further research is needed to definitively disentangle their independent contribution on patients' clinical outcome.

M110. 36 Month results of a smoking and healthy lifestyles intervention among people with a psychotic disorder

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Background: People with schizophrenia have a life expectancy 15 years less than the general community, and much higher rates of chronic diseases such as cardiovascular disease, diabetes and obesity. In response to this disproportionately high burden of illness the first Australian National Report Card on Mental Health stated "the reduced life expectancies and poor health of people with the most severe mental illnesses...is a national disgrace and it should be a major public health concern". Telephone interventions for health behaviors (such as smoking, alcohol use, low fruit and vegetable consumption and high levels of sedentary activity) as well as for psychotic symptomatology and also smartphone applications have been evaluated with promising results. This is the first randomized controlled trial to evaluate a cognitive-behavioral intervention addressing smoking and other health behaviors among people with psychotic disorders.

Methods: Study participants were randomly assigned to receive a single face to face session consisting of feedback and motivational interviewing and nicotine replacement therapy, plus either: (i) a face-to-face intervention targeting multiple health risk behaviors; or (ii) a predominantly telephone delivered intervention involving monitoring. Follow-up surveys were completed at 15 weeks ($n=165$, 70.2%),

12 months ($n=139$, 59%), 18 months ($n=132$, 56.2%), 24 months ($n=133$, 56.6%), 30 months ($n=129$, 54.9%) and 36 months ($n=134$, 57%). ITT analysis was used for primary outcomes and mixed models were used for both primary and secondary modeling, so all study participants were included in analyses.

Results: At baseline, participants ($N=235$, Age, $M=41.6$ years, 59% male) were smoking on average 28.6 (SD= 15.3) CPD. There were no significant overall differences between the telephone and face-to-face conditions in the primary smoking outcome of biochemically confirmed point-prevalence abstinence rates (8% and 11% respectively) at 36 months. There were no significant differences between groups in most measures of exercise, diet and body measures (total minutes walking per week, total minutes sitting per week, BMI, waist circumference, weight, waist-to-hip ratios).

Discussion: Face-to-face and telephone-delivered interventions are feasible and effective among people with severe mental disorders for smoking. Interventions for multiple health behavior change appear worthy of further research among people with psychotic disorders.

M111. Impact of cannabis use on clinical outcomes and treatment failure in first episode psychosis

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Background: Cannabis is frequently used by people with first episode psychosis (FEP), though its effect on clinical outcome is less clear. We investigated whether cannabis use may be associated with increased risk of hospitalization and whether antipsychotic treatment failure, as indexed by number of unique antipsychotics prescribed, may mediate this effect in a large dataset of patients with FEP.

Methods: Data were obtained from electronic health records of 2,026 people with FEP in the South London and Maudsley NHS Foundation Trust (SLaM) using the Clinical Record Interactive Search tool (CRIS). Cannabis use was identified using natural language processing. Data on subsequent hospital admission and the number of unique antipsychotics prescribed (a marker of treatment failure) were obtained and analyzed using multivariable regression and mediation analyses with age, gender, ethnicity, marital status and diagnosis as covariates.

Results: Cannabis use was present in 46.3% of the sample at first presentation and was particularly common in patients who were 16-25, male and single. It was associated with increased frequency of hospital admission (incidence rate ratio 1.50, 95% CI 1.25 to 1.80), increased likelihood of compulsory admission (odds ratio 1.55, 1.16 to 2.08) and greater number of inpatient days (B coefficient 35.1 days, 12.1 to 58.1). Antipsychotic treatment failure mediated increased frequency of hospital admission (natural indirect effect: 1.09, 95% CI 1.01 to 1.18; total effect: 1.50, 1.21 to 1.87), increased likelihood of compulsory admission (NIE: 1.27, 1.03 to 1.58; TE: 1.76, 0.81 to 3.84) and greater number of inpatient days (NIE: 17.9, 2.4 to 33.4; TE: 34.8, 11.6 to 58.1).

Discussion: Cannabis use in patients with FEP was associated with increased likelihood and duration of hospital admission. This was linked to the prescription of several different antipsychotic drugs, indicating clinical judgement of antipsychotic treatment failure. This suggests that cannabis use might be associated with worse clinical outcomes in psychosis by contributing towards failure of antipsychotic treatment.

M112. Better social but worse academic premorbid adjustment in cannabis-users psychotic patients across Europe

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Background: Several studies report that patients with psychosis who used cannabis have a better cognitive performance than those who

did not (Rabin *et al.* 2011). In a previous study we found out a higher premorbid IQ, and a better IQ in psychotic patients who smoked cannabis in their lifetime, and our findings were consistent with the idea that this association is due to a better premorbid functioning rather than to an ameliorative effect of cannabis use on cognitive performance (Ferraro *et al.*, 2013). A number of authors have hypothesized that psychotic patients who consume cannabis constitute a differentiated subgroup of patients that have better cognitive and social skills, necessary to engage in illegal drug consumption, than non-using patients (Compton *et al.*, 2011; Løberg *et al.*, 2014; Arnold *et al.*, 2015). Given that the prevalence, and patterns, of cannabis use are culturally driven, we wanted to test the hypothesis of a better premorbid functioning in First Episode Psychosis (FEP) cannabis-using and non-using patients coming from different European countries (England, Italy, Spain, France, the Netherlands) as part of the EUGEI-STUDY.

Methods: 1,745 people (746 cases; 999 controls) completed the assessment for Intellectual Quotient (IQ) (WAIS-brief version) premorbid adjustment (Premorbid Adjustment Scale – PAS) and cannabis use (CEQ-Revised). We first performed a factor analysis on PAS components, by obtaining two main factors: “Premorbid Social Adjustment” (PSA) and “Premorbid Academic Adjustment” (PAA). We therefore performed linear mixed models with IQ, PSA, and PAA as dependent variables and cannabis lifetime (Yes/No), subject status (Cases/Controls), gender and age as independent variables.

Results: Across all countries, IQ was higher in those patients who smoked cannabis in their lifetime compared to those who did not ($P=0.027$). This IQ difference was only 3 points and was the same for cases and healthy controls ($P=0.949$). Similarly, patients who had smoked cannabis in their lifetime showed better PSA scores than non users ($P=0.009$). The difference in PSA score between cannabis-users and non-users was significantly greater in cases than controls ($P=0.038$). Conversely, across all countries, PAA resulted worst in patients who smoked cannabis lifetime than patients who did not ($P<0.001$) and this PAA score difference was the same for cases and controls ($P=0.693$).

Discussion: Our cannabis-using FEP patients have higher IQ, better PSA and lower PAA than non user patients across 5 different European countries. Starting from these preliminary results, we can conclude that a better PSA is significantly associated with cannabis use in FEP patients. Nevertheless, in an exploratory analysis, a better IQ resulted related to a better PAA (<0.001) but not to PSA ($P=0.260$); thus indicating an independent relationship of IQ and PSA with cannabis use. Further analysis are required in order to model these multivariate relationships.

M113. Comparison of CHR risk symptoms in the pronia population - first results from the PRONIA study

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Background: In Europe schizophrenia is among the leading causes of years lost to disability (YLDs) in adults (Wittchen *et al.*, 2011). Consequently, a special interest in the prevention of schizophrenia and psychotic disorders exists (Solis *et al.*, 2014). For the aim of early detection different clinical high risk criteria (CHR) have been developed. The currently most widespread criteria are the ultra-high risk (UHR), and the basic symptom approach. UHR criteria were developed to detect an imminent risk for a transition to psychosis. They comprise the attenuated psychotic symptom criterion (APS), the brief limited psychotic symptom criterion (BLIPS) and the genetic risk and functional decline criterion. Under the umbrella of the UHR concept, different assessment concepts have been developed, resulting into two dominating scales, the Comprehensive Assessment of the At Risk Mental State (CAARMS) (Yung *et al.*, 2005) and the Structured Interview of Prodromal Syndroms (SIPS) (McGlashan *et al.*,

2010). One major difference between these scales is the obligatory requirement of a considerable functional deterioration as part of all three UHR criteria in the CAARMS. Basic symptoms are conceptualized as earliest, therefore mostly subjective disturbances of several domains. With regard to the prediction of psychosis the cluster ‘Cognitive Disturbances’ (COGDIS) is currently the most used Basic symptom criterion (Schultze-Lutter *et al.*, 2007). The co-occurrence of both UHR and COGDIS criteria, was associated with a higher risk for a transition to psychosis than one of the criteria alone (Ruhrman *et al.*, 2010; Schultze-Lutter *et al.* 2014). In PRONIA, a modified version of the SIPS UHR criteria as well as COGDIS are used as alternative inclusion criteria.

Methods: PRONIA (‘Personalized Prognostic Tools for Early Psychosis Management’) 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 $n=1700$. To elucidate the effects of different CHR criteria, PRONIA performs additional assessments of the original SIPS 5.0 and the CAARMS criteria in all CHR participants included by the PRONIA criteria.

Results: The first 76 CHR subjects included into PRONIA were considered for a first analysis of the distribution of inclusion criteria. 82.9% were included by the PRONIA UHR criteria, 17.1% by the COGDIS criteria. SIPS 5.0 criteria were met by 81.4%. However, only 42.1% of the included individuals fulfilled any of the CAARMS definition of UHR criteria.

Discussion: Our preliminary analysis demonstrated a high correspondence between the PRONIA and the SIPS 5.0 definitions of UHR criteria. The proportion of individuals meeting the CAARMS criteria was considerably lower, which may indicate a lower sensitivity for at-risk states. The prospective follow-up design of PRONIA will reveal the impact of these differences on the 18-month risk of transition to psychosis.

M114. Addressing the risks of being ‘at risk’: the effects of labeling versus symptom severity on public attitudes toward individuals at risk for psychosis

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Background: While there is a wide consensus regarding the potential benefits that early detection and intervention in clinical high-risk states for psychosis might offer, inclusion of an official psychosis risk diagnosis in the DSM raises serious concerns regarding the iatrogenic stigmatizing effect that a diagnostic label of this kind might have on patients, families and institutions. Based on examples from other areas in medicine (e.g., ‘hearing loss’ as opposed to ‘attenuated deafness’), and recent proposals within psychiatry to replace ‘schizophrenia’ with a diagnostic label that relates to aspects of human mentation that are universal (Sato, 2006; van Os, 2009), we have recently hypothesized (Koren, 2013) that reframing the psychosis risk syndrome as ‘endangered reality-testing syndrome’ has the potential to address these concerns. The goal of this presentation is to introduce this notion and present pilot data that provide preliminary support for its validity.

Methods: A random sample of 125 adults from the general population read an experimental vignette describing a young adolescent experiencing either mild or severe prodromal symptoms who was randomly assigned a ‘psychosis-risk’ or ‘high-risk reality testing’ diagnostic label, and answered questions about stigma, hope, and need for care toward the individual in the vignette.

Results: Compared with the ‘psychosis risk’ label, ‘high-risk reality testing’ elicited significantly higher appraisals of self-image, hope,

likelihood of seeking help, and need for care. No similar effects were found for symptom severity.

Discussion: These pilot results provide first empirical support for the social and clinical potential of 'high-risk health' formulations in minimizing the potential stigmatizing harms of 'at-risk' diagnostic labels and improving help-seeking behaviors. As a result, they lay the theoretical and methodological foundation for future studies that will replicate and extend the above findings among individuals at high risk and their families.

M115. At risk for psychosis or bipolar disorder? evaluation of bipolar at-risk (BAR) criteria in a UK sample

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Background: Schizophrenia (SZ) and bipolar disorder (BD) are chronic and typically recurring disorders with significant psychosocial morbidity and high premature mortality. In the last 10-15 years much research attention has been devoted to developing prodromal criteria to identify individuals at 'ultra high risk' (UHR) for developing schizophrenia and, more recently, for bipolar disorder ("Bipolar at-risk criteria", BAR; Bechdolf *et al.* 2010). The aim of the present study was to evaluate the predictive validity of the BAR criteria in an independent cohort from the OASIS clinic (Outreach and Support in South London) in the United Kingdom.

Methods: A medical file-audit study was conducted at OASIS, a clinical service located in Lambeth, Southwark and Lewisham, South London, offering treatment to people at UHR for psychosis for between 14 and 35 years of age. BAR criteria were applied to the initial assessment reports of all help-seeking individuals treated at OASIS between 2001 and 2011 (N=204). All entries were then checked for criteria indicating transition to BD.

Results: BAR criteria were fulfilled in 15% of the sample (N=31). Transition to Bipolar I or II disorder occurred in 7,7% (N=16) of the sample. There were significantly more cases in the non-BAR group (75%) than in the BAR group (25%; $P=0.004$).

Discussion: Predictive validity of BAR criteria in this independent sample was poorer than in the original sample. Extension of existing BAR criteria and their evaluation in prospective studies with larger sample sizes may provide further validity of these criteria.

M116. Effectivity of a digital panss-training

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Background: The Positive and Negative syndrome Scale (PANSS; Kay *et al.*, 1987) is a semi-structured clinical scale that is used to assess the severity of symptoms of schizophrenia. It is frequently used in a multitude of studies world-wide. Adequate training of raters is crucial for reliable scoring (Lewis *et al.*, 1998). Therefore, a standardized digital training that is readily available for training and knowledge maintenance may prove useful and cost-effective. However, despite the importance of a high quality digital PANSS assessment training, not many studies have been done on this subject. In this study, we compared the effectivity and usefulness of a newly developed short theoretical digital PANSS training with a traditional, more extensive practice-oriented training.

Methods: Thirty-four higher education students were invited to participate in a PANSS-training. Sixteen of them were allocated to follow the digital training and 18 were allocated to a traditional practice-based training. The groups were matched on sex, age, level of education, and clinical experience. The digital training was developed by an independent consultancy bureau (CROnos CCS) and consisted of an online module which the trainee could go through individually in 3 hours. It contained extensive explanation of scoring and footage of a case as illustration. The traditional practice-based training was provided by an experienced trainer at the Rob Giel Research Center

(RGOc) and lasted 2 days. After the training, both groups rated two patient video's and were tested on their theoretical knowledge. Ratings on the items were compared to expert ratings according to the Kay criteria (1991) and were compared between the groups. Group total scores on the subscales, inter-rater reliability, degree of theoretical knowledge, and subjective feeling of preparedness to conduct a PANSS interview were compared between the groups.

Results: Preliminary results showed that the participants that followed the traditional training scored more reliably than the group that followed the digital training, based on the Kay criteria for both test interviews. However, none of these differences were significant.

The positive and general subscale ratings did not differ significantly between the groups. On the negative subscale, ratings in the traditional training group ($\mu=19.37$ [2.12]) were lower than those in the digital training group ($\mu=22.66$ [4.37], $P=0.009$), and closer to the expert rating. Moreover, more students felt prepared to administer a PANSS interview after the traditional (68.8%) than the digital training (27.8%).

Inter-rater reliability was high and comparable between the groups (.978 and .972).

Discussion: Participants in the traditional training group seemed to score more reliably, even though the scores are close. Especially the negative symptoms seem to be scored less reliably after the digital training, compared to the traditional training. The short duration and the lack of feedback and interaction during the digital training may play a role in the differences in effectivity. Therefore, further research on the possible influence of these factors is needed. Additionally, the limited amount of people that felt confident administering a PANSS interview after the digital training gives rise to the question whether a rating training is enough to administer the PANSS reliably. After the necessary improvements this digital training could be a useful and cost-effective addition to the current PANSS training.

M117. Venous compared to capillary blood sampling with a point-of-care device in clozapine treatment: patients' preferences

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Background: White blood cell (WBC) monitoring, initially weekly, later monthly, is obligatory in clozapine treatment, because clozapine, drug of last resort in therapy-resistant schizophrenia, can induce potentially fatal leukopenia and agranulocytosis. Probably both the increased risk and obligatory WBC-monitoring contributes to the current low clozapine prescription rates.

Recently a point of care device (POCD) for WBC-count plus differentiation from capillary blood has become available. If acceptable to and preferred by the patients, it could form a breakthrough in blood sampling methods in clozapine therapy and positively contribute to motivation for clozapine therapy. Therefore the preference of patients on clozapine therapy for conventional sampling or for blood sampling with a POCD, and the influence of the method on motivation for clozapine therapy were investigated.

Methods: Patients on clozapine maintenance therapy were asked to fill a visual analog scale (VAS) ranging from 0-10, right after monthly blood sampling, 2 times after conventional blood sampling and 2 times after testing with a POCD. Patients were asked about domains as pain perception, worries, nasty feelings and anxiety around the sampling, and psychotic experiences ('feeling sucked out'). The total burden was calculated by adding all outcomes. Two additional questions were asked: What they preferred, either venous or capillary sampling; and whether their experience influenced their motivation for clozapine use.

Results: 31 outpatients and 39 inpatients agreed to give their informed consent. In all domains separately, and on the composite item total-burden, capillary point-of-care sampling was favorite. Patients preferred point-of-care sampling, inpatients even more than outpatients.

The method of sampling moderately influenced patients' motivation for clozapine therapy.

Discussion: Capillary blood sampling in clozapine maintenance therapy is feasible and preferred by the patients. The method could influence

motivation for clozapine therapy and by this clozapine prescription numbers.

M118. Insight and suicidality in psychosis: a cross-sectional study

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Background: As many as half of patients with schizophrenia have had lifetime suicidal thoughts or attempted suicide. Approximately 2-5% of these patients die from suicide. Suicide in schizophrenia has been linked with some classic general risk factors for suicide such as depression, impulsive personality traits, longer duration of untreated psychosis (DUP) or early phases of the illness. However, mixed results have been reported regarding the relationship between insight and suicide risk in psychosis. We aimed to test whether specific insight dimensions are associated with suicidality in patients with psychotic disorders as this could have implications for developing suicide prevention strategies in psychosis.

Methods: 143 patients were recruited. Suicidality was assessed by using the item of the Calgary Depression Scale for Schizophrenia. Insight was measured by the Scale of Unawareness of Mental Disorder (SUMD), including awareness of mental illness, awareness of the need of pharmacological treatment and awareness of the social consequences of the illness.

Results: The sample was mixed (mean age at first contact: 38.4 ± 11.9 years and just 14 patients (9.8%) with a course of illness lower than one year). 64.3% of them had a schizophrenia diagnosis. 38 patients (26.6%) had attempted suicide before the assessment. Being unemployed, being single, having depression or hopelessness, having negative symptoms and having attempted suicide previously in the past were found to be associated with suicidal ideation in bivariate analyses. Considering insight, awareness of having a mental illness (0.7 ± 1.1 vs 0.4 ± 0.7 , $P=0.001$) and better awareness of the social consequences of it (0.6 ± 0.9 vs 0.4 ± 0.8 , $P=0.039$) were found to be associated with suicidality, while no differences between groups were found when considering awareness of the need for treatment. No insight dimensions remained significant in the linear regression model, while depression ($P < 0.005$) and previous suicidal behavior ($P=0.018$) did survive as significant predictors of suicidality, thus mediating the above associations.

Discussion: Suicidality in patients psychosis seems to be associated with some insight dimensions, although depression and previous suicidal behavior might mediate these relationships. Our results appear to be consistent with previous studies, on which our hypotheses were based. Of note, most of previous studies included first episode samples and different measures of insight such as the Birchwood Insight Scale (BIS) or the item 12 of PANSS scale. Further replication studies with greater samples, comprehensive psychopathological assessments (including the use of a multidimensional insight scale) and more prolonged follow-up periods are needed to clarify the role of insight in suicidality over the course of the psychotic illness. Findings from such a research project may also lead to the development and implementation of suicide prevention strategies in psychosis focused on the management of insight over the illness.

M119. Associations between paranoia and levels of depression and anxiety in the general population: two meta-analyses

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Background: Psychosis has been suggested to lie on a continuum across clinical and non-clinical groups. Research on the phenomenal continuum of psychosis has yielded robust evidence for experiences of paranoid ideation in the general population. Research on the etiological continuum of psychosis, however, is discovering mechanisms that may associate with clinical and non-clinical paranoia. Building on the clinical studies where level of paranoia was associated

with levels of depression and anxiety, this study aimed to investigate the respective associations of levels of depression and anxiety with paranoia in the general population. Using a meta-analytic approach, we hypothesized that the two negative emotions correlate positively with paranoia in the general population.

Methods: A total of 6214 studies published in 1999-2015 were examined, among which 31 studies were eligible for the meta-analyses. Twenty-four studies (24 effect sizes) were included in the first meta-analysis for studying the association between levels of depression and paranoia. Twenty-three studies (25 effect sizes) were included in the second meta-analysis for studying the association between levels of anxiety and paranoia.

We followed the PRISMA guidelines for reporting of this meta-analytic study. All data were converted to Pearson's r correlations for generating a summary effect size of correlation for each factor with paranoia. Heterogeneity, publication bias and risk of bias were formally tested for the respective meta-analysis.

Results: There was a significant and positive correlation between levels of paranoia and depression, with a summary correlation of 0.375 for the random-effects model. There was a significant and positive correlation between levels of paranoia and anxiety, with a summary correlation of 0.404 for the random-effects model. The aggregated correlations fell within a small to moderate range. The heterogeneity levels for both associations were high, with an I^2 of 98.371% for the correlation between depression and paranoia, and an I^2 of 91.537% for that between anxiety and paranoia. However, no publication bias was found in both meta-analyses.

Discussion: Our hypothesis that levels of depression and anxiety were associated with non-clinical paranoia was supported, with comparable effect sizes for both depression and anxiety. Despite high levels of heterogeneity, the results remained unchanged after extreme outliers were removed. Therefore, we conclude that members of the general public who have a higher paranoia level were also more depressed and anxious.

This was the first meta-analytic study investigating the association between non-clinical paranoia and levels of depression and anxiety. However, the design of the included studies did not allow us to delineate the direction of the associations, and correlational findings do not imply causality. Clinical studies have stipulated the role of depression and anxiety as both antecedents and consequences of paranoia. Future studies could look further into the direction of association between non-clinical paranoia and negative emotions. Since many studies measured both depression and anxiety within the same sample, there is a possibility that both emotions may relate to paranoia in interaction rather than separately.

M120. The schizotypy factors are a suitable model for the symptoms of schizophrenia

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Background: It is believed that the personality characteristics and symptoms observed in schizophrenia lie on a continuum, with subclinical symptoms. This is referred to as schizotypy and is observed in the non-clinical population. High levels of schizotypy are associated with similar cognitive, behavioral, genetic and brain function patterns to schizophrenia, albeit in a more subtle manner. While schizotypy is interesting in its own right as a personality dimension, the continuum theory of schizophrenia also recognizes schizotypy as a suitable model for investigating schizophrenia, free from the confounding influences. Like schizophrenia, factor analytic studies have described schizotypy symptoms to fall into three main categories: positive, negative and cognitive schizotypy (thought to reflect positive symptoms, negative symptoms and cognitive deficits associated with schizophrenia). As very few studies have investigated the expression of schizotypy across the schizophrenia continuum, the aim of this study was to explore the manifestation of schizotypy symptoms in non-clinical individuals, first-degree biological relatives of patients with psychosis and patients with schizophrenia.

Methods: 349 adults (144 patients with schizophrenia or related psychosis, 40 first-degree relatives and 165 healthy controls) were assessed for schizotypy factors using the Oxford-Liverpool Inventory of Feelings and Experience (O-LIFE). The O-LIFE primarily measures three factors of schizotypy: unusual experiences (UnEx) scale containing items related to hallucinations and magical thinking; introverted anhedonia (InAn) scale containing items relating to lack of enjoyment from sources of pleasure and cognitive disorganization scale (CogDis) containing items relating to social anxiety, poor attention and poor decision making. A MANOVA exploring the relationship between schizotypy scores and group was conducted with age and gender controlled for as covariates. Of the 144 patients, 92 were assessed for positive, negative and cognitive symptoms using the Positive and Negative Syndrome Scale (PANSS). Pearson's correlations were conducted between schizotypy factors and PANSS subscales, as well as individual items.

Results: Our results revealed that overall schizotypy scores were significantly higher in the patient group as compared to first-degree relatives and controls ($P < 0.001$). Post-hoc analysis showed that between-subject effects for each O-LIFE factor was also significant ($P < 0.001$). Significant correlations were found between UnEx and overall PANSS positive score ($P < 0.001$), as well as individual items 'delusions' ($P = 0.001$), 'unusual thought content' ($P = 0.002$), 'grandiosity' ($P = 0.010$) and 'hallucinatory behavior' ($P < 0.001$). Significant correlations were also found between InAn and individual items 'passive/apathetic social withdrawal' ($P = 0.043$) and 'emotional withdrawal' ($P = 0.019$) and between CogDis and the individual item 'tension' ($P = 0.004$).

Discussion: This is the first study to demonstrate the dimensional nature of schizotypy across the psychosis continuum using the O-LIFE, supporting the use of schizotypy as a model for schizophrenia. Our significant correlations between UnEx and individual PANSS positive symptom items as well as total positive symptom score confirms that the UnEx factor of schizotypy relates to positive symptoms of schizophrenia. Overall, the multidimensional nature of schizotypy traits, as measured in the O-LIFE, resemble the factors of schizophrenia symptoms and these findings provide further support for a dimensional model of psychosis.

M121. Clinical insight in non-affective psychosis and psychiatric hospital readmission: a systematic review

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Background: Although poor insight into illness affects a majority of the patients with psychosis, making it one of the main features of schizophrenia, it is still poorly understood. While poor insight has been associated with reduced adherence to medication and increased depressive symptoms, its impact on subsequent psychiatric hospitalizations is still unclear. Considering the current annual financial cost of schizophrenia is estimated to be £2 billion of which 61% accounts for readmission, understanding the effect of insight on relapse is therefore clinically and economically important.

Methods: Systematic search incorporated four databases: PsychINFO, Medline, Ovid MEDLINE(R) and EMBASE in order to find relevant, available articles investigating clinical insight and its relationship to psychiatric rehospitalization in a non-affective sample.

Results: A systematic search identified six suitable manuscripts. One retrospective, one prospective and one observational study found clinical insight to be significantly associated with readmission. A further two prospective studies found some dimensions of insight to have an impact on subsequent psychiatric hospitalization and one recent prospective article found no such association.

Discussion: Heterogeneity of outcome measure could be accounted for the limited available literature. Notwithstanding the limitations of the included studies and discrepancy in their results, on balance the majority of studies suggest that poor insight or low score on certain dimensions of insight may be associated with an increased risk of subsequent psychiatric hospitalization. However, more rigorous longer follow-up studies with larger samples are needed in order to clarify the findings.

M122. Reported childhood abuse and stress reactivity in psychosis: a replication attempt

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Background: In 2011, Lardinois and colleagues reported a relationship between reported childhood abuse and an increased sensitivity to stress in patients with a psychotic disorder. Given the increased sensitivity to the replicability of findings in psychological research, we examined whether we would obtain similar results in a different sample by assessing childhood abuse with a semi-structured interview.

Methods: Fifty three patients with non-affective psychotic disorder, recruited from Rivierduinen mental health care institute, were examined during 5 days using an intensive diary method to assess levels of negative affect and minor psychotic experiences in relation to event stress and activity stress. Patients filled out a minimum of 20 diary questionnaires. Reported childhood abuse was assessed using the semistructured 'childhood experience of care and abuse' interview.

Results: There were main effects of activity stress ($b = 0.17$; $P < 0.001$) and event stress ($b = 0.09$; $P < 0.05$) on negative affect. However, different from previous findings, the relationships between activity stress/event stress and negative affect were not significantly modified by the severity of reported childhood abuse ($b = .003$; $P = 0.25$ and $b = 0.003$; $P = 0.22$, respectively). Furthermore, activity stress significantly predicted minor psychotic experiences ($b = .5$; $P < 0.05$) but event stress did not ($b = .09$; $P > 0.5$). Replicating previous findings, the relationship between activity stress and minor psychotic experiences was significantly modified by the severity of reported childhood abuse ($b = .04$; $P = 0.01$) and analogously for event stress ($b = 0.03$; $P < 0.03$). The positive relation between activity stress and minor psychotic experiences and between event stress and minor psychotic experiences was stronger in those reporting more severe childhood abuse.

Discussion: The results of Lardinois *et al.* (2011) were partially replicated. Significant interaction effects between the stress measures and reported childhood abuse on minor psychotic experiences were found, but no significant interaction effects on negative affect were found, although the direction of found effects were similar to previous findings. Several reasons could account for this discrepancy. First, a different, arguably more objective measure for reported childhood abuse was used. The current assessment used a semi-structured interview, whereas the previously used instrument was a self-report questionnaire. Second, although the number of participants was similar to the original study, the study may have lacked the power necessary to find existing effects.

M123. Is simple schizophrenia that simple? an observational study

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Background: Although simple schizophrenia (SS) was defined by Bleuler (1911), Otto Diem firstly (1903) described a schizophrenia's subtype characterized by insidious onset, negative symptoms, intelligence and affective deterioration, loss of self-care as well as decrease in social and occupational functioning without hallucinations, delusions, catatonia or formal thought disorders. Controversially, SS was included in DSM-I (1952), removed (DSM-III), added (DSM-IV) as simple deteriorative disorder and removed again in DSM-5. Despite ambiguous definitions, low prevalence and scarce research interest, clinicians are still using this category in daily practice. An operational definition with a dimensional description, as well as complementary test results could be useful to homogenize the dysfunctional pattern and pathophysiology underlying SS.

Methods: All patients clinically diagnosed of SS (fulfilling DSM-IV-TR and ICD-10 criteria) for the last 10 years (2006-2015) and admitted to our inpatient units (both adult and children and adolescent wards)

were reviewed. An analysis was conducted to characterize this population socio-demographically and clinically and to determine the diagnosis stability.

Results: 21 subjects (13 adolescents and 8 adults) were included. They were mainly Caucasian (61.9%), single (100%), male (90.5%) and 21.7 (SD=2.5) years old with Cluster-A personality traits (47.6%), and occasional drug abuse (14.3%; mainly tobacco (9.5%) and cannabis (9.5%)). They were admitted an average of 19.3 (SD=2.3, range: 13.7-55.3) days, usually referred by their family (71.4%) from the outpatient unit (42.9%), emergency room (23.9%) or day hospital (19.1%). The reasons for referral used to be multiple: social isolation or home confinement (76.2%), lack of motivation (42.9%), school absenteeism (42.9%), aggressiveness (28.6%), bizarre behavior (14.3%) and rarely depressive symptoms (4.8%). Youth were admitted shorter than adults (15.1 ± 1.9 vs 26.1 ± 4.3; $P=0.0146$) but adults got better improvement measured by EEAG rising (18 vs 42.5; $P=0.0122$) although there were no differences at initial assessment (EEAG=30 vs 25; $P=0.6312$). The majority (95.2%) received antipsychotic treatment: mainly aripiprazole (38.1%), paliperidone (19.1%), risperidone (14.3%) and clozapine (14.3%). At mental state examination they presented flat affect (76.2%), apathy (71.4%), sleep disturbances (61.9%), functioning impairment (61.9%), abulia (57.1%), poor eye contact (57.1%), poor speech (55%), loss of self-care (42.9%), anhedonia (38.1%), aggressiveness (38.1%), bizarre ideas or behavior (29.7%), suspiciousness (23.8%), anxiety (15%) and depression (9.5%). Impairments were found in neuropsychological test in these areas: executive functions (76.5%), cognitive flexibility (57.1%), verbal fluency (42.9%), verbal memory (58.3%), and visual memory (41.7%); although IQ estimations were in the average. 12 patients had follow-up information for 5,2 (SD=3.5) years whose readmission rate was 1.1 (SD=0.4)

Discussion: The majority (83.3%) kept the same diagnosis and only one patient change the diagnosis to another form of schizophrenia; so in our sample SS was a consistent diagnosis defining a nosological entity characterized by flat affect, apathy and social and functioning impairment, with altered executive functions without positive psychotic symptoms. Although it is a retrospective observational study, to our knowledge this is the largest sample encompassing youth and adults diagnosed of SS (Serra-Mestres *et al.* 2000). However, further research is needed to identify markers and predictors of prognosis and to test safe and effective interventions to improve overall outcomes.

M124. Comparison of factor structure of the positive and negative syndrome scale (PANSS) in patients with refractory versus and non-refractory schizophrenia in a large Brazilian sample

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Background: The Positive and Negative Syndrome Scale (PANSS) is the most widely known and used scale for the evaluation of symptom severity in schizophrenia. Several reviews of PANSS Factor Analyses (FA) showed that the best solution is the five-factor model (generally Positive, Negative, Disorganized/Cognitive, Excited/Hostility, Anxiety-Depression). We have previously compared patients with Treatment Resistant Schizophrenia (TRS) ($N=141$) with patients with non TRS (NTRS) ($N=150$) and we found that FA of patients with NRS yielded a five factor model: Negative (1), Positive (2), Excitement (3), Motor (4), Anxious/Depression (5) while FA in patients with RS yielded a six-factor solution with the following factors: Positive (1), Negative (2), Disorganized/ Cognitive (3), Hostility (4), Excitement (5) and Depression (6).

The aim of the present study is to replicate our previous findings now with a much larger sample ($N=681$).

Methods: We conducted an exploratory FA with PANSS data of 681 patients with schizophrenia (285 RS and 396 NRS) of the database of the Projesq-Schizophrenia Research Program of the Institute of Psychiatry of University of Sao Paulo Medical School and Proesq -

Schizophrenia Research Program of Federal University of São Paulo. Patients were defined as having Treatment Resistant Schizophrenia based on Kane *et al.* historical criteria. Two FA models with principal component extraction and Varimax rotation were applied to the complete items set of the PANSS. Number of factors was chosen by Kaiser's criterion and loading cut-off was set at 0.5.

Results: The comparison between patients with TRS and NTRS in terms of demographic variables and PANSS subscales showed: NTRS sample was composed by 63% males, with mean age of 35.97 years old (11.3), they have 5.25 (1.73) years of schooling, they became ill at 22.75(8.52) and had been ill for 13.41(10.13). TRS sample was composed by 65% males, with mean age of 34.73 years old (9.93), they have 5.13 (1.53) years of schooling, they became ill at 20.02(6.45) and had been ill for 14.5(8.27). The first group had a total PANSS of 64.03 (18.58) with subscales: Positive of 13.67 (5.5), Negative 18.54 (6.87), General Psychopathology of 31.88 (9.47). TRS patients had a total PANSS of 72.62 (20.65) with subscales: Positive 15.89 (5.73), Negative 21.33 (7.37), and General Psychopathology 35.34 (10.48).

FA of patients with NTRS yielded a five factor model, which accounted for 56.09% of the total variance, with the following factors: Negative (1), Positive (2), Cognitive (3), Excitement (4), Anxious/Depression (5). FA in patients with TRS yielded a five factor solution which explained 59.76% of the variance, with the following factors: Cognitive (1), Negative (2), Positive (3), Excitement/Anxious (4) and Depression (5). **Discussion:** The present EFA comparing patients with TRS versus patients with non TRS was unable to replicate our previous findings in terms of the factor structure of patients with TRS. However, in patients with non TRS showed the same factor structure previously obtained with a smaller sample, particularly in terms of structure of the negative factor.

M125. A systematic review exploring negative symptoms and depression in schizophrenia – an update of the literature

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Background: The centrality of negative symptoms were emphasized in the early descriptions of schizophrenia by both Bleuler and Kraepelin. Negative symptoms have been further operationalized in accordance with their assumed causation; primary negative symptoms being a product of the disease process and secondary negative symptoms being caused by side effects of medication, social deprivation or depression. Previously under-recognized, depressive features are now considered a common occurrence in schizophrenia with up to 50% of patients experiencing depression at any one point. The exact nature of the relationship between negative symptoms and depression remains unclear. However increased clarity is important for both depressive and negative symptom dimensions as this may enable the development of more targeted treatments and improved outcomes. Therefore, the aim of this systematic review was to examine the relationship between depressive and negative symptoms in schizophrenia.

Methods: A systematic review following PRISMA guidelines reviewing 1621 articles were identified from EMBASE, PsychInfo and Medline and a further 2 articles were hand searched from references. 27 met inclusion criteria and were included in the review.

Results: Symptoms such as subjective sadness and pessimism are reported to have more specificity for depression whereas alogia and blunted affect are mainly seen as negative symptoms. Anergia and avolition are seen in both. Emotional blunting, a feature of anhedonia, appears to be specific to depression whereas the social withdrawal aspect of anhedonia appears to closely align with negative symptoms. Furthermore, negative symptoms appear to be a trait symptom whereas depression appears to be a state symptom in schizophrenia. **Discussion:** Studies suggest that a depressive dimension can be identified separate to negative symptoms in schizophrenia; however certain symptoms have clear overlap. The nature of anhedonia may provide an area of focus for future research. In depression anhedonia may reflect a diminished capacity for pleasure, conversely as a negative symptoms may reflect a reduction in our natural tendency to overestimate past and future pleasure.

M126. Development and psychometric validation of the questionnaire of stressful life events (QSLE). Spanish version

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Background: Currently, there are few instruments to assess stressful life events (SLE) available in Spanish. In adults, there is only an adaptation of the questionnaire of life events, PERI-modified (Dohrenwend *et al.*, 1978) adapted by Vizcarro (1984). The youth population have a scale of SLE for children (6 to 11 years) and adolescents (12 to 18) reported in Mardomingo (1992). Instruments that evaluate SLE over the entire life span and frequency and stress levels have not been studied yet. Therefore, the aim of this study is to validate a new questionnaire about stressful life events (QSLE) in patients with first-episode psychosis (FEP) and healthy controls. The QSLE proposes to measure the emotional impact -level of stress- and age when the life event occurred.

Methods: Participants were 207 people with FEP ($n=102$) and healthy controls ($n=105$), ages 11-47 years, recruited from the Parc Sanitari Sant Joan de Déu, or child-adolescent mental health center in the Sant Joan de Déu Hospital and clinic network. The QSLE was administered assessing SLE before FEP. Four additional measures were included to characterize the sample and using in convergent/discriminant validity analyses: the Scale of Life Events (PERI-Modified; (Dohrenwend *et al.*, 1978); the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein & Opler, 1987); the Clinical Global Impression- Schizophrenia scale (ICG-ESQ; Haro *et al.*, 2003); and the Global Assessment of Functioning Scale (GAF; Hall, 1995).

Results: The Cronbach's alpha of total score was 0.79. The QSLE total scores strongly correlated with the PERI-Modified global score ($r=0.52$, $P<0.001$). The QSLE demonstrated good discriminant validity because the QSLE total score was not correlated with positive, negative and general symptoms, negative symptoms severity or functioning. The QSLE had only small correlations with positive symptoms severity ($r=0.39$; $P<0.05$).

Discussion: Analyses indicated that the QSLE is a valid measure to capture SLE in patients with psychotic disorder, including measures of frequency and distress. The next step is to demonstrate that the assessment of LEs over the life-time including levels of frequency and distress is more strongly associated with psychotic symptoms and clinical outcome, thus improving prevention and prediction.

M127. Psychometric schizotypy predicts prodromal and schizophrenia-spectrum symptoms, psychological measures, and functional adaptation: a 4-year longitudinal study

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Background: Current approaches conceptualize schizotypy as the underlying developmental vulnerability for schizophrenia-spectrum psychopathology. The positive and negative schizotypy dimensions are differentially associated with measures of personality, psychopathology, and impairment. Nevertheless, longitudinal studies remain scarce. The present study aimed to extend our previous findings by examining whether psychometrically assessed positive and negative schizotypy predict prodromal symptoms, schizophrenia-spectrum personality disorder (PD) traits, psychological measures, and functional adaptation in a 4-year follow-up assessment of a nonclinically ascertained sample.

Methods: This study is part of an ongoing longitudinal project examining psychosis risk and resilience. At the first assessment, 547 nonclinical Spanish young adults completed the Wisconsin Schizotypy Scales. At the fourth assessment, approximately 4 years later, a selected subset of these participants ($n=89$), oversampled for high schizotypy, were interviewed for schizophrenia-spectrum PDs, positive and negative subclinical symptoms, and functioning. Participants also

completed questionnaire measures of suspiciousness, affective symptoms, self-esteem, and cognitive schemas.

Results: Negative schizotypy uniquely predicted schizoid PD traits, negative symptoms, impaired functioning, and diminished positive self-schemas. Positive schizotypy uniquely predicted avoidant PD traits and negative other-schemas. Both dimensions predicted schizotypal and paranoid PD traits, suspiciousness, depression, low self-esteem, and negative self-schemas. In addition, the two dimensions predicted positive symptoms (the effect size was larger for positive schizotypy) and diminished positive other-schemas (the effect size was larger for negative schizotypy).

Discussion: The results extend our previous findings and demonstrate that positive and negative schizotypy longitudinally predict differential and overlapping patterns of symptoms, personality, maladaptive schemas, and functioning. These data lend further cross-cultural evidence of the predictive validity of the schizotypy dimensions. Furthermore, the findings support that schizotypy provides a useful model for understanding risk and resilience factors for the development of schizophrenia-spectrum psychopathology.

M128. Autism traits and positive psychotic experiences in adolescents from the general population: associations with theory of mind

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Background: Autism spectrum disorders (ASD) and schizophrenia spectrum disorders (SSD) share multiple phenotypic similarities and risk factors, and co-occur at a higher rate than would be expected. One similarity between these disorders is that are associated with deficits in theory of mind (ToM). Because these disorders are hypothesized to exist on extended continua, one would expect lower ToM in individuals from the general population who exhibit traits of autism and/or report psychotic experiences. In this study we explored these traits and experiences in relation to ToM in a large sample of adolescents from the general population. We will consider findings in relation to a diametrical model, which has been proposed to explain the co-occurrence of ASD and SSD. In a diametrical model, one would expect that having high levels of autism traits AND psychotic experience would result in better ToM than having EITHER high autism traits OR psychotic experiences because the diametrical nature of the disorders will ameliorate any ToM difficulties.

Methods: Participants were 244 (54.5% Female) adolescents recruited from secondary schools in the West Midlands region of the United Kingdom. Mean age was 15.60 years ($SD=1.56$). Participants completed the Autism Quotient (AQ) and the Community Assessment of Psychic Experiences (CAPE; positive subscale) to assess autism traits and psychotic experiences, respectively. ToM was measured on the Reading the Mind in the Eyes Task (RMET) and the YONI task. The YONI tasks has subscales for first- vs second-order ToM, and cognitive vs affective ToM.

Results: High levels of autism traits showed an inverse association of small effect size with second-order ToM ($r=-0.18$, $P=0.007$), but not first-order ToM, as indexed by the YONI task. The inverse association between AQ and ToM was evident for cognitive ($r=-0.18$, $P=0.006$) and affective ($r=-0.15$, $P=0.02$) aspects of ToM. There was a medium size effect for the inverse association between AQ and ToM measured on the RMET ($r=-0.22$, $P=0.001$). High levels of positive psychotic experiences on the CAPE were inversely associated with second-order ToM only ($r=-0.14$, $P=0.03$), and the effect size for this association was small. There were no significant correlations between CAPE and other aspects of ToM.

There was a small but significant association between AQ and CAPE scores ($r=0.17$, $P=0.01$). To examine the overlap between autism traits and psychotic experiences, cluster analysis was conducted on AQ and CAPE scores. The three clusters were described as "high AQ/high CAPE" ($n=49$, 19.7%); "low AQ/high CAPE" ($n=61$, 24.5%); and "low AQ/low CAPE" ($n=113$, 45.4%). When these three groups were compared on indices of ToM, there were no significant group differences.

Discussion: In adolescents from the general population, higher levels of autism traits are associated with poorer performance on tasks measuring ToM. This association holds for cognitive and affective aspects of ToM, but is only evident in more complex (second-order) ToM. Higher positive psychotic experiences were associated with second-order ToM only. Second-order ToM relates one's ability to infer what one person thinks about another person's thoughts, rather than the more simple ability to understand another person's thoughts. In clinical populations of ASD and SSD, both are impaired. The findings provide evidence that similar (but less severe and less diffuse) deficits in ToM exist at lower ends of the continua of autism and psychosis. We did not find support for the diametrical model of the co-occurrence between ASD and SSD when examining ToM in this general population sample.

M129. Theory of mind and attempts of suicide after first episode of psychosis

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Background: Theory of mind (ToM) is "the ability to infer intentions, dispositions and beliefs of others". This ability to understand the mental states of others is important for a variety of social functions, including understanding pragmatic speech, pretending deception, imagining, understanding jokes, and empathy. Several studies have found ToM deficits in individuals with chronic schizophrenia. As well severity of ToM deficits was found in first episode of psychosis. The objective of this study is analyzing the differences in ToM deficits between patients with attempts of suicide after FEP and those without attempts of suicide. Also we pretend analyze relationship between ToM deficits with attempts of suicide after FEP.

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 after FEP was collected using Schedules for Clinical Assessment in Neuropsychiatry SCAN. This clinical interview contains a question about attempted suicide. False beliefs tasks were used to evaluate ToM. First-order false belief tasks measure the recognition of a story character's false belief about the world whereas second order false belief tasks assess the understanding of the beliefs of a story character about another story character's thoughts. The stories were read individually to the subjects. To examine first-order stories we used the Cigarettes story (Happé, 1994). Second-order stories we used the following task: Ice-cream Van Story (Baron-Cohen, 1989).

Results: Bivariate analysis found relationship between first order false beliefs and attempts of suicide after FEP ($P < 0.005$). As well second order and suicide attempts correlated ($P < 0.005$). Those results formed the basis for more multivariable regression model. Binary logistic regression models were built to test the real influence of first and second false beliefs on suicide attempts. Second false beliefs are related with attempts of suicide in the regression model (OR = 0.21, 95% CI = 0.058-0.752).

Discussion: As a conclusion, ToM is impaired in who realized attempts of suicide after FEP. Attempts of suicide is associated with substantial ToM deficit. ToM impairment could be a trait marker of attempts of suicide after first episode of psychosis, however, further work is necessary to examine the specificity of these findings in people at risk of suicide in first episode of psychosis.

M130. Insight and theory of mind

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Background: Theory of mind (ToM) impairment is common in patients with schizophrenia. ToM is "the ability to infer intentions, dispositions and beliefs of others". Poor insight has also been linked to poor outcome in schizophrenia. Clinical insight refers to one's awareness of having a mental illness that requires treatment and includes dimensions of Awareness of Illness, Relabeling of Symptoms and Need for Treatment.

Methods: Sixty-five patients in their first episode of non-affective or affective psychosis participated in this study. Subjects were recruited during their first contact with any of the mental outpatient or inpatient health services. All patients were initially screened by psychiatrist for the presence of psychotic symptoms, and were subsequently diagnosed using an SCID structured interview. We excluded patients with a previous diagnosis of neurological disease or a history of head trauma with loss of consciousness. All the participants gave their written informed consent, and the research protocol was approved by local Ethics Committees. Scale of Unawareness of Mental Disorder (SUMD) was used to evaluate insight. This scale consists of three general items: awareness of mental disorder, awareness of the effects of medication and awareness of the social consequences of the disorder. Furthermore, the SUMD accounts for 17 items related to specific symptoms, which are divided into two subscales, awareness and attribution. Theory of mind was evaluated using Hiting task adapted for Corcoran *et al.* (1995). Five of the original ten vignettes were used. Each vignette described an interaction between two characters along with an extract of their dialog and ended with one character dropping a hint to the other. Participants were required to state what the character really meant by their utterance. A correct response is therefore scored as 2 or 1 depending on when the response was given.

Results: Significant relationship ($P \leq 0.05$) was found between impairment in ToM with awareness of mental disorder ($r = 0.28$). No significant relationships were found between impairment in ToM and others dimensions of insight or total score.

Discussion: These results suggested that treatments targeting meta-ization abilities that contribute to representations of self and others may improve insight deficits associated with poor outcome in schizophrenia.

M131. Parental psychosis and early developmental vulnerability in offspring

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Background: Children of parents with mental illness are well known to be at increased risk of developing the same or concordant disorders in adulthood. Early in life, such at-risk offspring are also known to demonstrate a range of potential antecedents of later mental ill-health, including problems with emotional and behavioral development. We present findings in 5-year old children of parents with a wide variety of mental disorders, including schizophrenia and related disorders, and compare patterns of offspring psychosocial vulnerability across diagnostic groups.

Methods: Data from an Australian population cohort were used to investigate the pattern of associations between exposure to various parental mental disorders (considered in broad diagnostic categories from administrative inpatient and outpatient data collections) and vulnerable emotional and behavioral developmental outcomes in their offspring as measured in the Australian Early Development Census conducted during the children's first year of formal schooling.

Results: Positive associations between parental mental illness and vulnerability in the childhood externalizing and internalizing domains

were seen across the full spectrum of parental mental health diagnoses, with the strengths of association greater for the childhood externalizing than the internalizing domain. The strongest associations were found for parental disorders with childhood onset, and the associations for parental psychoses were less than those found for parental substance abuse or personality disorders. Parental depression and anxiety disorders had the smallest associations with childhood developmental vulnerability.

Discussion: Emerging emotional and behavioral difficulties apparent early in child development are associated with parental mental ill-health, and apply to varying degrees to all parental psychiatric diagnoses. A substantial number of parental psychiatric diagnoses are more strongly associated with higher developmental risks for offspring than parental schizophrenia and related disorders.

M132. Antipsychotic medication and remission of psychotic symptoms 10 years after a first-episode psychosis

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Background: Several national guidelines recommend continuous use of antipsychotic medication after a psychotic episode in order to minimize the risk of relapse. However some studies have identified a subgroup of patients who can obtain remission of psychotic symptoms while not being on antipsychotic medication for a long period of time. This study investigated the long-term outcome and characteristics of patients in remission of psychotic symptoms with no use of antipsychotic medication at the 10-year follow-up

Methods: The study was a cohort study including 496 patients diagnosed with schizophrenia spectrum disorders (ICD 10: F20 and F22-29). Patients were included in the Danish OPUS Trial and followed up 10 years after inclusion, where patient data was collected on socio-demographic factors, psychopathology, level of functioning and medication

Results: A total of 30% of the patients had remission of psychotic symptoms at the time of the 10-year follow up with no current use of antipsychotic medication. This favorable outcome was associated with female gender, high GAF-F score, participation in the labor market and absence of substance abuse.

Discussion: Results from several RCTs advise against discontinuation of antipsychotic medication, but our results from the 10-year follow-up indicate that a subgroup do obtain long-term remission while not being on antipsychotic medication. Hence, guidelines on antipsychotic medication do not pay sufficient attention to patients who discontinue antipsychotic medication and are still able to obtain remission of psychotic symptoms.

M133. Association of white blood cell count and C-reactive protein level with symptoms of psychotic disorders: findings from a large cohort

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Background: Immunological mechanisms may play a role in symptomatology of patients with a psychotic disorder. Besides inflammatory processes that occur due to the disorder, metabolic problems and medication use may cause increased inflammatory markers and concurrent psychiatric symptoms. The aim of this study is to investigate whether levels of C-reactive protein (CRP) and white blood cell count (WBC) are related to positive and negative symptoms of psychotic disorders, and whether age, gender, duration of illness, smoking behavior, body mass, and metabolic syndrome affect this relation.

Methods: CRP and WBC values of 1123 patients with a psychotic disorder were related to positive and negative symptoms measured with the Positive and Negative Syndrome Scale. CRP was analyzed by survival analysis correcting for detection limit and logistic regression

(CRP > 5.0 mg/L as cutoff), WBC by linear regression. In case of a significant association, the confounding factors were added to the model.

Results: Both positive and symptoms were positively related to WBC, but not after correction for confounders. Due to a large number of cases of CRP measures below the detection limit, CRP only showed a significant association with negative symptoms in the logistic regression with dichotomized values, which remained significant after correction. Metabolic problems showed a strong association with both CRP and WBC.

Discussion: Inflammatory markers were indeed related to psychotic disorders and their symptoms, particularly negative symptoms. Future studies could use more precise measures of inflammatory markers and measure symptomatic state at specific moments in illness progression.

M134. Symptomatic, functional and personal remission in schizophrenia and related psychotic disorders: persistent patterns in a large naturalistic cohort study

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Background: A good approach to studying the outcome of schizophrenia and related psychotic disorders is to measure the three types of remission i.e. symptomatic, functional and personal in a longitudinal study. So far, most studies have follow up periods of one year, include only one or two types of remission and, have no large sample size. Our primary aims were (a) to identify the proportion of individuals with schizophrenia and related psychoses, who met remission criteria based on clinical, social and personal domains and (b) to examine if the proportions of patients who met a definition of remission had changed over time.

Methods: In the Northern Netherlands, an extensive Routine Outcome Monitoring (ROM) protocol for patients with psychotic disorders is implemented. Out of this ROM database, data from 2012 to 2014 were included. Symptomatic remission was assessed using the Positive and Negative Syndrome Scale Remission Criteria. A score of 4 or higher (indicating a clinically relevant problem) on at least one of these items was defined as no remission.

Functional remission was assessed using the new functional remission tool (FRT, Wiersma *et al*, 2015) for people with serious mental illness (SMI). The FRT involves an assessment by a mental health professional, who conducted a semi-structured interview with the patient and his or her family, and/or uses patient files relating to the three areas of functioning (i.e. daily living and self-care, work, study and house-keeping, and social contacts). These areas are rated on a three-point scale with 0 = independent, 1 = partially independent, and 2 = dependent. A score of 1 or higher was defined as no remission.

Personal recovery was not included in our ROM system, therefore the Happiness Index is defined as a proxy of personal recovery. A score of 5 or lower is defined as no recovery.

Results: This is an ongoing cohort study, still including patients within the ROM-procedure (from $n=813$ in 2012 to $n=1489$ in 2014). The mean age was 44.8 years with a mean duration of illness of 17 years and 65% being male. Since this is a naturalistic study, numbers varied for the different rating scales ($n=598-1489$). On average 45% of the patients live alone, with 31% living in supported housing or in a long-stay department of a mental health organization. Symptomatic remission ranged from 48.5% to 55.2%, functional remission was completed in 13.5-15.7% of the patients and partial remission was shown in 12.4-15.8%. However, functional remission was absent in >70%. Personal recovery as expressed by the Happiness Index was achieved by 73.4-79.9%.

Discussion: This large naturalistic cohort demonstrated various, but persistent patterns of three types of remission over three year period of time in persons with SMI. Symptomatic and personal remission rates are hopeful with relatively high scores of well-being. In contrast, functional recovery is still not obtained in a large part of these patients. Negative symptoms are implicated as a major barrier in obtaining functional remission, and should be given more attention during treatment. Programs to lead people with SMI to work and other activities might help in breaking these persistent patterns.

M135. Association between schizophrenia and dementia: does schizophrenia in offspring increase the risk of developing dementia? A Danish population-based study

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Background: Individuals who suffer from schizophrenia are more likely to develop dementia than people in general. Some authors have hypothesized that the increased risk is due to comorbid factors such as substance abuse, whereas other authors have suggested a shared etiology between the two disorders. A recent Danish nationwide register-based study has found a higher risk of dementia in patients with schizophrenia even after adjustment for substance use and medical comorbidity, and thus, indicating a link between the two disorders. In agreement, studies have suggested shared genetic risk factors for schizophrenia and Alzheimer's disease (AD) and hence disease mechanisms, such as hyper-phosphorylation of tau, that could play a role in both disorders. This indicates a shared etiology between the two disorders, which may result in familial co-aggregation, but nevertheless, only few studies of limited size that were based on interviews have investigated this hypothesis. We therefore conducted a nationwide register based study to examine whether the risk of AD was increased in subjects whose offspring suffered from schizophrenia. We also investigated whether a potential elevated risk was specific to families with schizophrenia or whether a risk increase was also observed in families with other types of psychiatric contact.

Methods: A population-based cohort of 1.4 million parents who were born in Denmark between January 1, 1930 and December 31, 1953, and who were living in Denmark at their fifties birthday, was selected. This cohort was followed from the subjects fifties birthday and until emigration, death, end of study (December 31, 2013), or the onset of dementia, whichever comes first. Incidence rate ratios for AD were calculated using Poisson regression.

Results: The incidence rate ratio of AD in individuals with offspring with schizophrenia compared to individuals with offspring without psychiatric contact was only slightly increased, at 1.10 (95% CI: 1.00-1.21). When adjusting for the individuals own psychiatric history, the increased risk for AD decreased to 0.97 (95% CI: 0.88-1.07). Similar results were found for offspring with other psychiatric disorders, such as bipolar disorder, other affective disorders and personality disorders. When only including individuals without psychiatric history, offspring with schizophrenia only resulted in a small non-significantly increased risk for AD, at 1.09(95% CI: 0.97-1.21). No dose response effect was observed, as individuals with either two or three offspring with psychiatric contact only had a slightly increased risk for AD, with IRR at 1.16 (95% CI: 1.04-1.29) and 1.14 (95% CI: 0.86-1.46) respectively.

Discussion: We found no evidence of increased risk for AD among persons with offspring with schizophrenia. These results may suggest that there is no familial co-aggregation of disease, and therefore indicate that schizophrenia and AD do not share common genetic risk factors. Our results are at odds with a recent Danish study that found an increased risk for dementia in schizophrenic patients.

M136. General fertility rate in non-affective psychosis: routine data-linkage using maternity and psychiatric data

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Background: Evidence suggests that women with non-affective psychosis and schizophrenia have lower fertility than other women. However, much of this research was conducted on historical datasets, therefore the impact of improvements in pharmacological and community-based management of psychosis remains under-examined. Our data report on General Fertility Rate (GFR) analyses, stratified by age for both linked datasets. We hypothesized that the GFR would be lower for women with a diagnosis of psychosis than for women without a psychosis.

Methods: We used routine psychiatric and maternity data using a repeated cross-sectional design to report on birth rates from 2000–2013 in two geographical areas of Scotland (Glasgow and Aberdeen). Cases were identified from all women presenting with an ICD-10 F20–29 diagnosis of non-affective psychosis, presenting to Community Mental Health Teams in the two areas. These data were matched with maternity datasets for the two areas (SMR-02 and Aberdeen Maternity and Neonatal Databank). Each case was matched with 3 controls without psychosis drawn from the maternity datasets and matched for age, parity and deprivation. GFR rates were calculated per annum from the data by dividing the total number of live births in each year, multiplied by 1000 and then divided by the total number of women aged 15–49 in that year. This was repeated for women both with and without a diagnosis of non-affective psychosis.

Results: We report data from the initial extraction from the Glasgow dataset. For all years we generated a GFR of 71.32 for women with a non-affective psychosis, compared with a GFR of 86.85 for control women. The GFR range for cases varied from 51.47 to 113.33; and from 58.08–155.50 for controls. Maternal age at birth of first child was significantly older for cases compared to controls. (29.3 yrs vs. 26.6 ($P=0.008$)). We also report comparison data from the Aberdeen dataset and further analyses stratified by age.

Discussion: These data are consistent with existing studies, confirming the hypothesis that women with a non-affective psychosis had a lower GFR than controls without a psychosis. This was consistent across all years studied. We note that the data are limited by the reliance on community mental health data, but also highlight that this captures all women receiving treatment for psychosis, rather than relying on hospital admission data. Our findings support moves towards developing more responsive healthcare approaches to management of pregnancy for women with non-affective psychosis.

M137. Prospective and cross-sectional associations between theory of mind, social functioning, and psychotic experiences in adolescents in the general population

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Background: Theory of Mind (ToM) is significantly impaired in acute psychosis, first episode psychosis, individuals at risk of psychosis, and first-degree relatives of individuals with schizophrenia. Findings suggest that a deficit in social cognition may be a trait marker for psychosis, yet it is unclear when this deficit first emerges. The aim of this study was to examine in a non-clinical sample of adolescents whether ToM abilities during early and late adolescence are predictive of psychotic experiences (PE) over time, and whether this relation is (partly) mediated by social functioning (SF).

Methods: A sample of 293 now 18- and 19-year-old adolescents, stemming from a case-control sample (T0) from the general population with and without auditory vocal hallucinations (AVH), were assessed after five years (T1) on ToM (The Story Book Frank Task), and after eleven years (T2) on PE (Community Assessment of Psychic Experiences (CAPE)), ToM domains (Conflicting Beliefs and Emotions task (CBE); first-order and second-order beliefs and emotions), and SF (The Groninger Questionnaire about Social Behaviour (GSVG-45); school, parents, job, hobbies, friends, romantic partners and chores). It was examined whether ToM abilities at age 12–13 are predictive of PE at age 18–19, and whether SF is a mediator of this relationship. The mediation model will also be tested cross-sectionally at T2.

Results: ToM ability at T1 did not significantly predict T2 frequency ($B=0.04$, $P>0.05$) and distress ($B=-0.04$, $P>0.05$) of PE, or SF ($B=0$, $P>0.05$). Cross-sectionally (T2), first-order emotion skills were significantly related to frequency of PE ($\beta=-0.28$, $P<0.05$) and second-order emotion skills were significantly related to distress of PE ($B=-0.49$, $P<0.05$). As these relationships were very weak, they disappeared when SF was added to the model and significantly predicted both frequency ($B=-2.95$, $P<0.00$) and distress ($B=-3.28$, $P<0.00$) of psychotic experiences. Specifically, job functioning ($B=3.26$, $P<0.01$) was significantly related to frequency of PE, whereas school ($B=-1.86$, $P<0.05$) and job functioning ($B=-1.94$,

$P < 0.05$) were significantly related to distress of PE. No domains of ToM were related to SF at T2.

Discussion: The present findings suggest that ToM ability during early adolescence is not predictive of PE or SF at late adolescence in a non-clinical sample. Cross-sectionally during late adolescence, both ToM emotional skills and SF were related to PE, yet they were not related to each other. This was contrary to our mediation hypothesis. Importantly, SF influences frequencies and distress of PE rather than ToM ability, as the weak association between ToM ability and PE at T2 disappeared when SF was accounted for. It is likely that ToM skills are still developing from early to late adolescence, making it unfeasible to use ToM as a precursor for PE during adolescence. Moreover, as ToM abilities were quite good in this non-clinical sample and possibly above a certain threshold, other factors could be of greater importance to influence SF. All symptomatology in this sample was highly interrelated cross-sectionally during late adolescence (PE and SF), supportive of a general staging model of psychopathology.

M138. Compulsory admission during first episode of psychosis: does ethnicity still matter?

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Background: Many studies have reported that black African and black Caribbean patients are more likely than white British patients to come into contact with mental health services compulsorily and via adversarial routes, such as those involving the police and other criminal justice agencies.

Aims: To re-examine the relationship between ethnicity compulsory admission at first episode, comparing data from a recent study to data from the AESOP (Aetiology and Ethnicity of Schizophrenia and Other Psychoses) study, completed around 15 years ago. The AESOP study found significant differences in the proportion of compulsory admission among black Caribbean (Adj. OR = 2.30; CI = 2.30–4.32) and black African (Adj. OR = 4.33; CI = 1.88–9.99) compared to white British patients.

Methods: A retrospective incidence study design was employed, using the Biomedical Research Centre (BRC) clinical record interactive search (CRIS) system. In brief, CRIS is a regional case register based in South London containing a large dataset of anonymous clinical data of over 250,000 patient records derived from the South London and Maudsley NHS Foundation Trust (SLaM) electronic health record system. All patients presenting to SLaM adult mental health services for the first time with a psychotic disorder between May 2010 and April 2012 and in the catchment area served by SLaM were screened using the Item Group Checklist of SCAN diagnostic measure. Data relating to socio-demographic characteristics, mode of contact, and source of referral were collected from clinical records. Individuals were included as cases if they were: resident in the London boroughs of Lambeth or Southwark (served by SLaM); aged 18–64 years (inclusive) and experiencing psychotic symptoms of at least one day duration.

Results: We identified 348 individuals with first episode psychosis from the on-going cohort study described above and preliminary data from May 2010–Jan 2012 were included in the analysis. In contrast to the AESOP study, which found higher rates of compulsory admissions and adverse pathways to care in black African and black Caribbean groups, we found no evidence of marked differences between these groups and white British patients for compulsory admission (Adj. OR = 1.68; CI = 0.93–3.04 and Adj. OR = 0.82; CI = 0.40–1.67 for black African and black Caribbean patients respectively). The preliminary findings from the current data suggest that the discrepancy between White British and minority groups are narrowing. Particularly black Caribbean patients (15.7%) were less likely to be detained compulsorily ($\chi^2 = 8.26$ df = 3 $P = 0.04$) compared to white British (23.2%). However, a further exploration of gender differences revealed that Black African men (Adj. OR = 2.21; CI = 1.01–4.85) were more likely to be detained compulsorily compared to white British, but no difference was observed in the black Caribbean men (Adj. OR = 1.12; CI = 0.44–2.85).

Discussion: The evidence from the present study suggests that ethnicity may not, any longer, be strongly or straightforwardly associated with more compulsory admissions at first contact. New illness-phase specific treatments (such as early intervention of

psychosis) may have contributed to changes in patterns of compulsory admission by ethnic group.

M139. Prevalence of deficit syndrome in schizophrenia: an updated meta-analysis

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Background: Schizophrenia (SZ) is a heterogeneous disorder that currently is conceptualized as a syndrome with a polyhedral, dimensional, and multifactorial nature. Such complexity provides debates about whether this heterogeneity is due to individual variations in the effects of a single illness, or reflects multiple diseases under a same construct. A stable presence, often progressive, of a cognitive, motivational, and emotional impairment in a subgroup of patients with SZ led to the concept of deficit schizophrenia (DS) twenty years ago. Some authors support the hypothesis that DS is a separate disease, and therefore, involves special approaches. The Schedule for the Deficit Syndrome (SDS), a semi-structured interview, is considered to be the “gold standard” instrument to assess DS, whose prevalence has been estimated to be around 25–30%. Notwithstanding, this reference data precede the new model of early intervention in psychosis. Our study aims to determine an updated prevalence of DS.

Methods: Articles reporting the prevalence of DS, or the studies in any field of SZ with a deficit subtype categorization were identified for this purpose. The use of SDS instrument was required to include any study in the meta-analysis segment, in order to standardize the criteria. Computerized search was performed in MEDLINE/PubMed and EMBASE, using the terms: 'deficit schizophrenia', or 'negative schizophrenia', or 'negative symptoms', or 'deficit syndrome', and 'schedule for the deficit syndrome'. Search was restricted to the works published between 1990 and 2015. Opinion articles, individual case reports, studies with purposive sampling or less than ten subjects, and the researches based on the first psychotic episodes or treatment-refractory schizophrenia were excluded. Data analysis was conducted, using MedCalc software, version 15.8. Statistical procedure was calculated for the meta-analysis of proportions.

Results: Fifty-six studies met the inclusion criteria ($N = 5270$). Overall prevalence was 29.80% for fixed effects model (95%CI: 28.58–31.05) and 35.61% for random effects (95%CI: 31.71–39.61). Cochran's heterogeneity statistic was $Q = 462.43$, $I^2 = 88.11\%$, and P -value < 0.0001 .

Discussion: Results obtained in this update go in line with the previous literature. Prevalence of DS seems to be a stable phenomenon, for which enough effective therapeutic tools are not yet available. It is why that the development of new treatments for negative symptoms remain one of the great pending challenges in the SZ research.

M140. Association between polygenic risk scores and treatment resistance in schizophrenia: results from the crestar collaboration

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Background: Treatment-resistant schizophrenia (TRS) affects around 30% of all who suffer from schizophrenia. Socio-demographic and clinical predictors of TRS have been suggested in the literature. Ideally in addition to these factors the prediction of TRS may also include genetic data. However, the access to genetic data is limited, and no clear evidence for genetic predisposition for TRS is known. A polygenic risk score associated with the risk of schizophrenia has been developed by the Psychiatric Genetics Consortium. We aim to investigate the association between the polygenic risk score for schizophrenia and treatment resistance in patients with schizophrenia.

Methods: We identified all cases with schizophrenia diagnosed between 1999 and 2007 using Danish population-based registers.

Genome-wide data were obtained from the Danish Neonatal Screening Biobank started in 1981, and information on age, sex, psychiatric contacts and place of residence were obtained from National Registers. Cases were followed from their first diagnosis of schizophrenia until TRS, and were censored at emigration, death or at end of follow-up, December 31, 2010. The polygenic risk score was calculated based on 24,755 SNPs identified from the Psychiatric Genomics Consortium meta-analysis (34,600 cases and 45,968 controls). A proxy for treatment resistance was based on information on antipsychotic prescriptions and psychiatric hospitalization, and was defined as either clozapine initiation and/or hospitalization after at least two subsequent periods of antipsychotic monotherapy. A narrow definition of TRS was restricted to only patients who initiated clozapine. We estimated hazard rate ratios (HR) adjusted for population stratification, and despite the limited sample size, we in addition included the following predictors for TRS: age, sex, born in the capital, psychiatric in-patient hospitalization in the previous year, admitted to psychiatric hospital, and calendar year.

Results: We identified 862 schizophrenia cases with genome-wide data. Of these, 182 (21.1%) met the TRS definition during follow-up of a total of 4,691 person-years. The cohort consisted of 391 (45.4%) females and 471 (54.6%) males, and median age at first schizophrenia diagnosis was 19 years (inter-quartile range: 17-21 years). A higher polygenic risk score was associated with a slightly increased rate of TRS, HR = 1.13 (95% CI: 0.95-1.35). Using the alternative TRS definition of clozapine initiation only (105 patients), the estimate was slightly higher, HR = 1.23 (95% CI: 0.97-1.55).

Discussion: This study did not provide statistically significant evidence for an association between an increased genetic liability for schizophrenia and treatment-resistant schizophrenia. However, the direction of estimates indicates a tendency for this association in line with other studies on clozapine and the polygenic risk score. The estimated effects were more pronounced when restricting the outcome to clozapine initiation only. The predictive power of polygenic risk score in identifying TRS patients is at present inadequate to be of clinical utility. For future research on genetic prediction for TRS and potential implementation in clinical practice larger genetic samples and possible combination with non-genetic markers is needed.

M141. Parental somatic illness' effect on prodromal symptoms of children – northern Finland birth cohort 1986 study

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Background: The prediction and prevention of psychosis are of major interest in the schizophrenia research. Until today, however, it has remained unclear how parental somatic illness affects children's mental health. Severe somatic illness of a parent has considerable effects on family life. Parental illness reduces the attention towards children and, hence, the illness's long-term consequences for the children remain unknown. There is a lack of research-based knowledge on whether the children of parents with somatic illness have an increased risk for psychiatric disorders or psychosis. Existing studies reporting a decrease in children's psychological wellbeing due to parental somatic illness have generally been based on limited data and various study design. The limitations of previous studies are often small sample sizes and short follow-up times. We investigate parental somatic illnesses and their relation to children's mental health. The aim is to study whether parental somatic illness increases children's prodromal symptoms of psychosis.

Methods: This study is a prospective population-based survey. The Northern Finland Birth Cohort 1986 (NFBC 1986) covers all children (9,432 in total) born alive in Northern Finland. The NFBC 1986 members' expected date of birth fell between 1 July 1985 and 30 June 1986. The general population-based cohort data have been collected since pregnancy up to the present date. At the age of 16, the cohort members completed the PROD-screen questionnaire, which is a screening instrument for prodromal symptoms of psychosis with 21 questions. Parental somatic illnesses were collected from different registers including both inpatient and outpatient treatments. The illnesses were subsumed in 19 different categories using the

International Classification of Diseases (ICD) Coding. Independent samples t-test was used to define the associations between parental somatic illness and children's prodromal symptoms at age 16.

Results: In total, 6682 children were included in the analysis. This study found that children with mother's musculoskeletal disorders had statistically significantly higher PROD-screen scores (mean 3.9, SD 3.6) compared to their peers (mean 3.5, SD 3.5), $P=0.004$. A total of 8.9% of children ($N=597$) had a mother with musculoskeletal disorder. In addition, an increased children's PROD-screen score was observed if the mother had suffered from violent injury and intoxication (mean 4.0, SD 4.0) compared to other children (mean 3.5, SD 3.4), $P=0.016$. A total of 4.5% ($N=302$) of children had a mother with diagnosis of violence and intoxication. In other disease classes statistically significant differences were not found. Similarly, children's father's disease did not produce statistically significant differences.

Discussion: In this general population based sample mother's musculoskeletal disorders as well as violence and intoxication stand out as potential risk factors for children's prodromal symptoms, while father's disease did not play such an important role. In general, the effect of maternal somatic illness on the psychotic-like symptoms of the children was not strong. The results suggest that parental diseases may lead more significantly to other children's mental diseases than psychosis. However, children's needs should be taken into account when treating and rehabilitating a parent, specifically mother, suffering from somatic illness. The early support could lead to prevention of children's mental problems. Further research is needed to investigate the benefits of interventions. The major strength of the study is that it utilizes an extensive and reliable sample, a complete census of all infants born during a year in Northern Finland (NFBC 1986).

M142. Monitoring of risk of violence and patients' clinical characteristics: a prospective cohort study

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Background: The majority of people with mental disorders does not commit violent acts, and the majority of violent acts is not committed by people with diagnosed mental disorders. However the lack of specific studies in this area in Italy and the recent radical change that occurred in the Italian forensic system has prompted a more detailed investigation in this field. The aims of this study are to compare the socio-demographic, clinical, and treatment-related characteristics of long-term inpatients with a lifetime history of serious violence with age-, sex- and diagnosis-matched controls with no history of violence; to identify the predictors of aggressive and violent behavior during a one-year follow-up.

Methods: This is a prospective cohort study, involving patients staying in long-term residential facilities in Northern Italy. Patients with or without a lifetime history of serious violence were assessed with a comprehensive set of standardized assessment instruments covering psychopathology and psychosocial functioning (e.g., SCID-I and II, FPS, SLOF, BPRS, Insight Scale), aggressiveness and impulsivity (e.g., BDHI, STAXI 2, BIS-11), personality traits (e.g., MCMI-III), neuropsychology (e.g., WCST, GO-NOGO, IGT, BACS), emotion recognition assessment (e.g., FEEL), and the Theory of Mind (e.g., IVAM). Patients were reassessed with a selected set of instruments at the one-year follow-up, and were evaluated bimonthly with the MOAS to monitor the occurrence of any aggressive and violent behavior, for a total of 24 MOAS evaluations for each patient.

Results: The sample includes 139 inpatients, 82 (mean age 44.9±11.4 years) with a history of serious violence and 57 (mean age 46.7±9.5 years) controls; most patients were of male gender. The mean total BPRS score for the violent group was 50.2 (+24.1), while for the control group was 57 (+19.1), indicating a moderate level of symptomatology; the large majority had a diagnosis of schizophrenia. The total FPS mean score was 44.5 (+17.3) for violent patients and 38.5 (+15.0) for controls. We will also report detailed data about personality, impulsivity, neuropsychology and emotion recognition skills. With regard to the bimonthly monitoring of aggressive and violent behavior, there were some limited differences between the two

groups only in the first 2 months, while in the other 10 months there was no difference in the incidence of aggressive and violent behavior. *Discussion:* Patients with a history of serious violence staying in residential facilities, where treatment and clinical supervision are granted, do not show higher rates of aggressive and violent behavior as compared to patients never violent; this is an important finding in a country (Italy) where all Forensic Mental Hospitals have been closed and small residential facilities have been set up for patients with an history of violence. However, this finding does not necessarily translate to patients living in the community, where treatment and clinical supervision are more difficult to provide.

M143. Neighborhood characteristics and the incidence of first episode psychosis (FEP) and duration of untreated psychosis (DUP)

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Background: The incidence of psychotic disorders varies between geographical areas and it has been hypothesized that neighborhood level factors may influence this variation. It is also plausible that the DUP is also associated with neighborhood characteristics. The aims of this study are to determine whether the incidence of FEP and the DUP are associated with the level of social deprivation, fragmentation, social capital and population density at a neighborhood level.

Methods: All individuals with a FEP from a geographical defined catchment area over a five year period were included. Social deprivation was measured using the Pobal Haase-Pratschke Deprivation Index (HP Index). Social fragmentation reflected the level of social mobility in the neighborhood and was measured using the same construct from previous studies, namely Allardyce *et al* (2005). The proportion of individuals engaged in voluntary work in each electoral division was taken as proxy measure of social capital. Age standardized incidence rates were calculated for each neighborhood factor and zero inflated Poisson regression models were performed that included all of the neighborhood factors collectively.

Results: A total of 292 cases of FEP were included in the study, of whom 45% had a diagnosis of a schizophrenia-spectrum disorder. The age standardized incidence rate of FEP in the most deprived area was 72.4 (95% C.I. 26.4–162.7) per 100,000 person years compared to 21.5 (95% C.I. 17.6–26.0) per 100,000 person years in the most affluent areas. This represents a 3.4 fold increase in FEP incidence in the most deprived areas. The incidence of FEP was also increased in neighborhoods that were more socially fragmented (IRR=2.40, 95% C.I. 1.05 to 5.51, $P=0.04$) and there was a trend for the incidence to be increased in neighborhoods with lower social capital (IRR=1.43, 95% CI 0.99–2.06, $P=0.05$). The median DUP was 4 months and was higher in more socially fragmented neighborhoods.

Discussion: The incidence of psychotic disorders is related to neighborhood factors and it may be useful to consider neighborhood factors when allocating resources for early intervention services.

M144. Serum C-reactive protein in adolescence and subsequent schizophrenia in adulthood: a population-based prospective birth cohort study

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Background: Meta-analyses of cross-sectional studies confirm increased circulating inflammatory marker levels in acutely unwell patients with schizophrenia and related psychotic disorders but longitudinal studies are needed to understand the direction of this association. We report a longitudinal study of serum C-reactive protein

(CRP) level in adolescence and subsequent risk of psychotic disorders in adulthood in the Northern Finland birth cohort 1986.

Methods: Serum high-sensitivity CRP levels were measured using a quantitative, immunofluorometric method in fasting blood samples collected at age 16 years. No other acute phase proteins or inflammatory cytokines were measured. ICD-10 diagnoses of non-affective psychosis including schizophrenia were obtained from centralized hospital inpatient and outpatient registers at follow-up until end of age 27 years. Logistic regression was used to calculate the odds ratio (OR) for psychotic outcomes associated with baseline CRP levels, which was analyzed as both continuous and categorical variable using American Heart Association criteria. Age, sex, body mass index, and maternal education were included as potential confounders.

Results: The sample comprised 6362 participants with data on serum CRP levels at 16 years. At follow-up until end of age 27 years 88 cases of non-affective psychosis were identified (includes 22 cases of schizophrenia). Baseline CRP levels were associated with risk of schizophrenia at follow-up. Using CRP as a continuous measure, the adjusted OR for schizophrenia by age 27 years for each SD increase in CRP levels at 16 years was 1.24 (95% CI, 1.07-1.44). Using CRP as a categorical variable, those with high (>3 mg/L) compared with low (<1 mg/L) CRP levels at baseline were more likely to develop schizophrenia; adjusted OR 3.87 (95% CI, 1.20-12.49). However, there was no evidence for an association between CRP and the broader category of non-affective psychosis (which includes schizophrenia); the OR for non-affective psychosis for each SD increase in CRP was 1.11 (95% CI, 0.97-1.26). Using CRP as a categorical variable there was a nearly two-fold increase in the odds of non-affective psychosis for participants with high CRP at baseline compared with low CRP; however, this was not statistically significant; adjusted OR 1.96 (95% CI, 0.91-4.23).

Discussion: A longitudinal association between adolescent CRP levels and adult schizophrenia diagnosis indicates potentially important role for systemic inflammation in the pathogenesis of the illness, although the findings, based on a small number of cases, need to be interpreted with caution and require replication in other samples.

M145. High prevalence rate of agitation in the Chinese population with newly hospitalized patients suffering from schizophrenia: results from an observational survey in China

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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 of agitation among Chinese newly hospitalized patients suffering from schizophrenia, and to explore possible risk factors related to agitation.

Methods: We conducted a large, multicenter, observational study in fourteen psychiatry hospitals throughout China. Patients aged ≥ 18 years, newly hospitalized (admission within 24 hours) with a diagnosis of schizophrenia or hallucinatory paranoid state according to International Classification of Diseases, Tenth Revision criteria were included in the study. Information about agitation and correlative factors of all enrolled patients were investigated including general demographic data, disease characteristics, Clinical Global Impression-Severity (CGI-S), Behavioral Activity Rating Scale (BARS), Positive and Negative Syndrome Scale-Excited Component (PANSS-EC) and Modified Overt Aggression Scale (MOAS). Two weeks later, psychiatrists re-made a diagnosis of all the enrolled patients, excluding non-schizophrenic patients.

Results: Of 1512 patients enrolled in the study, 1400 (92.6%) were eligible. Of these patients, 853 (60.9%) met the criteria for agitation according to PANSS-EC, 826 (59.0%) met the criteria for agitation according to BARS, 665 (47.5%) met both criteria for agitation. The most important factor contributing to agitation was aggression (OR=7.941, 95% CL 6.151-10.252), other risk factors associated with agitation were north region (OR=1.791, 95% CL 1.356-2.367), involuntary hospitalization (OR=1.611, 95% CL 1.181-2.197) and higher CGI score (OR=1.518, 95% CL 1.289-1.789).

Discussion: To our knowledge, this is the first study to investigate the prevalence rate of agitation among Chinese newly hospitalized patients suffering from schizophrenia, and to explore possible risk factors related to agitation. Since the study exclusively included the yellow race, of which more than 90 percent were the Han nationality, there was no an ethnic impact. Using BARS and PANSS-EC, the prevalence of agitation in the sample was 59.0%, 60.9%, respectively. To make the sample more representative, we used two agitation rating scales to explore possible risk factors related to agitation. 47.5% ($n=665$) were included in the agitation group. The most important factor contributing to agitation was aggression (OR=7.941, 95% CL6.151-10.252). To conclude, A high prevalence rate of agitation among newly hospitalized schizophrenic patients exists in China. Agitation is associated with aggression and therefore requires pay abundant attention and prompt intervention for prevention in patients with schizophrenia.

M146. Effect of wider social environment on relapses in schizophrenia: a six-year follow-up study

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Background: There is substantial amount of evidence that the wider social environment is associated with risk of schizophrenia and other psychotic disorders. However, there is little information about the effect of social environment on the prognosis and relapses of schizophrenia. The concept of social capital -broadly defined as the glue that holds a community together in social networks, with community cohesion, and participation- has been proposed as a social risk factor for health disparities and the high rates of schizophrenia in urban areas. Neighborhood-level social capital and disadvantages, as measures of wider social environment, may also effect the symptomatic remission and relapses in schizophrenia.

Methods: In a registry-based longitudinal study, 112 schizophrenia and 35 schizoaffective disorder patients were followed with six-months period from January 2009 to December 2013. Each assessment involved screening of each patient for hospitalization, total dosage of antipsychotic treatment, need for change in treatment, suicide attempt, emergency admission, and current address (neighbourhood) in each six-months period by using the hospital case registry and the interviews with patients and their relative(s). The wider social environment were defined as neighborhood-level social capital (informal social control, social cohesion and trust, social dysorganization, and vote turnout), and social disadvantage (unemployment and poverty). Variables of wider social environment were based on a general population study which assessed mean level of social capital in urban neighborhoods of Izmir in 2008, and on vote turnout of general elections in 2009, 2010, 2011.

Results: Symptomatic relapses in six-year follow-up were associated with residential instability. Higher the number of intracity moving, higher the risk of relapses during the follow-up period (adjusted β : 0.05; 95% CI: 0.02-0.09; $P < 0,05$). There was no association between relapses and indicators of wider social environment including neighborhood-level social capital (informal social control, social cohesion and trust, social dysorganization, and vote turnout), and social disadvantage (unemployment and poverty). Symptomatic relapses were associated with usage of higher doses of antipsychotics.

Discussion: Our findings may indicate that residential mobility can be associated with relapses in schizophrenia. A change in location of residence may be a stressful life event for patients and as well, residential mobility may lead to increased social isolation and lack of support because of severance of contacts with neighbors, relatives and friends. Furthermore, not the wider social environment but the narrow social environment may be more important for schizophrenia patients.

M147. Sub-clinical psychotic experiences increase rate of contact with mental health services

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Background: Psychotic experiences (PEs), without psychotic disorder, overlap with other psychiatric problems, and predict later diagnosis of psychosis, but their relevance for mental health services as a whole is incompletely characterized in longitudinal data. Aims: To investigate the association between PEs (binary), ascertained in a community survey, and later contact with local mental health services. Objectives: To report the overall rate of contact with mental health services in the sample, to assess the association between this outcome and PEs, and to evaluate the effect of alternative explanations for mental health service contact.

Methods: SELCoH ($n=1698$) was a representative household survey carried out in 2008-2010 in South East London, with a 71.9% household participation rate. Anonymized survey data for participating individuals was linked with the South London and Maudsley NHS Trust Clinical Record Interactive Search (SLaM-CRIS) system. This system contains clinical records on all individuals accessing SLaM care from 2006 to the present day. Linkage was carried out on routine personal identifiers, generating survival data for time to first contact with MHS. Cox regression in STATA version 14 was used to assess associations between PEs (assessed using the Psychosis Screening Questionnaire, generating a binary variable) and time to first contact, crudely and accounting for potential confounders.

Results: Among 1455 subjects consenting to linkage, person-time for 103 participants was ignored as they made contact with mental health services prior to the SELCoH interview. Remaining were 1352 subjects, among which there were 73 contacts. The overall median observation time across all subjects was 5.26 years, and it was 5.28 years among those without PEs and 5.21 years in those with PEs. Observation times did not differ significantly between these groups (Wilcoxon rank sum $P=0.312$). The overall rate was 11.19 contacts per 1000 person-years of observation. The rate in men was 7.94 contacts per 1000 person-years, and in females 14.17 contacts per 1000 person-years. In those without PEs the crude rate was 9.54 contacts per 1000pyrs, in those with PEs it was 19.4 contacts per 1000 person-years, giving a crude rate ratio (RR) of 2.03. Graphical and inferential evaluation of the proportionality assumption did not suggest that proportional hazards assumptions had not been violated. The RR for contact with mental health services comparing PEs to no PEs, after adjusting for age, gender, ethnic group and educational attainment, was 2.1(95%CI: 1.16,3.79, $P=0.014$). After removing subjects who were diagnosed with psychosis ($n=2$), the estimate for the association was unchanged.

Discussion: PEs in a community survey were associated with a shorter time to first contact with mental health services for any problem, after adjusting for sociodemographic confounders, and persisted after removing people diagnosed with psychosis. Future work should consider the explanatory role of depressive and anxiety symptoms for this association, for example in data with information on timing of PE onset. Acknowledgments: The first author was funded by a Wellcome Trust Clinical Research Training Fellowship(WT101681AIA). This abstract represents independent research funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

M148. Psychotic-like experiences and violence among young Chinese men

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Background: Recent research has highlighted the importance of paranoid delusions/ paranoid ideation as risk factors for violent behavior in both clinical and community samples. Most of the studies, however, have been carried out in high-income Western countries and

it remains to be determined whether this association is generalizable across different cultures.

Methods: We carried out a representative survey of young men age 18 to 34 ($N=4.238$) residing in Chengdu, Sichuan province, China. We employed a standardized self-report questionnaire developed/administered in a similar survey of British young men which was translated into Mandarin and back-translated into English to guarantee equivalence with the original version. Respondents self-reported on demographic characteristics, violent behavior, psychotic-like-experiences (Psychosis Screening Questionnaire) and psychiatric comorbidity measure using standardized instruments.

Results: Of the five psychotic-like-experiences under study, only paranoid ideation demonstrated a significant association with violence (OR 2.62, 95% CI 1.33-5.13, $P < 0.01$). Violence occurred in the context of intoxication, was severe as indicated by victim injury and police involvement, directed toward partners/family members/friends, and independent of psychiatric comorbidity. A putative categorical diagnosis of psychosis demonstrated a unique association with violence toward strangers and victim versatility but only in the absence of anxiety disorder or in the presence of antisocial personality disorder or drug abuse.

Discussion: These findings are in accordance with studies of clinical and community samples in Western countries, and indicate cross-cultural generalizability of the association between paranoid ideation/delusions and violence. Moreover, our findings point to a high level of hidden psychiatric morbidity in young Chinese men associated with violence which could be explained by severe stigma of mental illness in Chinese societies.

M149. Prevalence of non-response and non-remission in schizophrenia

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Background: Clinicians and researchers in the field of schizophrenia are becoming increasingly aware that a considerable number of patients do not improve with standard antipsychotic treatment. Nevertheless, the estimates regarding the percentage of patients that do not respond or respond partially to treatment vary a lot. An important reason for the uncertainty about the prevalence of non-response and non-remission in schizophrenia, regardless adequate antipsychotic treatment, is the lack of consensus on how response and remission should be defined.

Methods: We used individual patient data from 16 randomized trials; 6221 patients assigned to 7 different antipsychotics (amisulpride, flupenthixol, haloperidol, olanzapine, quetiapine, risperidone, and ziprasidone) were included in the analysis. We defined a period of 4 to 6 weeks (preferably 6) as follow-up time to assess non-response and non-remission, and we excluded patients who received placebo or an antipsychotic drug at an ineffective dose (2010). As various definitions of non-response have been used in the literature, we applied four different cut-offs covering the whole range of percentage PANSS/BPRS reduction (≤ 0 , < 25 , < 50 , and $< 75\%$). For symptomatic remission from psychosis, we used the consensus criteria proposed by Andreasen *et al* (2005) without employing the time criterion. We synthesized the rates of each study using the weighted average of their logit transformations; weights were assigned according to the inverse of their variance. In addition, we examined clinically useful baseline variables for predicting later non-response defined as $\leq 0\%$ PANSS/BPRS reduction (i.e. no improvement or symptom worsening) and later non-remission.

Results: When non-response was defined as $\leq 0\%$ PANSS/BPRS reduction, 19.8% (CI: 18.8-20.8%) of patients did not respond to treatment; for the cut-off of less than 25% reduction, the prevalence was 43% (CI: 41.7-44.3%); for the cut-off of 50% reduction, it was 66.5% (CI: 65.3-67.8%); and for the cut-off of 75% reduction, it was 87% (CI: 86-87.9%). As for no symptomatic remission, the prevalence was 66.9% (CI: 65.7-68.1%). Earlier onset of illness, lower baseline severity and treatment with haloperidol or ziprasidone predicted non-response defined as $\leq 0\%$ PANSS/BPRS reduction. Male gender, longer duration of illness, higher baseline severity, higher baseline positive and negative sub-score, and treatment with haloperidol or ziprasidone

predicted no symptomatic remission as defined by Andreasen *et al* (2005).

Discussion: The results of our study are striking; the prevalence of non-response and non-remission rates was markedly high. The main strength of our analysis is the inclusion of individual patient data from several thousand participants that enabled us to apply uniform definitions of non-response and non-remission. On the other hand, the data came from randomized controlled trials with strict inclusion and exclusion criteria. Moreover, the heterogeneity among single studies was considerable. Notwithstanding these limitations, our results provide a unique insight into the question how many patients do not respond to antipsychotic treatment. Future studies should systematically present non-response rates in 25 percentile steps together with non-remission rates in order soon to have estimates based on larger sample sizes. In addition, studies on patients treated under naturalistic conditions resembling everyday clinical practice are warranted in order to enhance the generalizability of the results.

M150. Shift in positive and negative psychotic symptoms and violence

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Background: Investigations into associations between psychotic symptoms and violent behavior using methods which allow causal inference have begun to yield new and important findings. Mediation analyses have demonstrated that delusions of threat and persecution result in violence if the patient is angry due to delusions. Negative symptoms are thought to be protective. Methods investigating shifts of intensity, which can occur during relapse of illness, may be a new way of identifying causal associations.

Methods: We carried out a prospective cohort follow-up study of 409 forensic patients discharged from secure units across England and Wales to the community. Symptoms were measured using the Positive and Negative Syndrome Scale (PANSS), violence using the MacArthur Violence Instrument (MVI). Temporal associations were tested between each symptom and violence co-occurring during six and 12 month time periods.

Results: At 6 months 54 (14%), and at 12 months 43 (12.5%) participants were violent. All positive and most negative symptoms were associated with violence. After inclusion of all items in the statistical model, only hostility (+ve) and poor rapport (-ve) were associated. Hostility was identified as explanatory variable in the association between excitement, suspiciousness/persecution and violence. Shift towards positive symptoms was associated with increase in violence, shift towards negative symptoms showed no association. A protective effect of negative symptoms was shown only when adjusting for positive symptoms.

Discussion: Hostile affect was the main driver in the association between psychotic symptoms and violence, specifically when associated with excitement and suspiciousness/persecution. Although negative symptoms exert a protective effect, this is overwhelmed by the effect of positive symptoms and hostile affect. When a patient shows a high level of PANSS symptoms or a shift in symptoms from a low to a high level the risk of violence is increased. Further shift from an already high level results in a three-fold increase in risk of violence. The findings confirm the importance of affect, specifically anger and hostility, in the causal link between psychotic symptoms and violence.

M151. Metabolic screening and status among newly diagnosed patients with schizophrenia: a population-based cross-sectional study

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Background: Schizophrenia is associated with metabolic abnormalities, which are partly attributable to antipsychotic drug use. Screening and

routine monitoring for metabolic abnormalities is recommended; however, knowledge of screening and metabolic status in early phases of schizophrenia is sparse. We aimed to evaluate the extent of screening and to characterize metabolic status (blood levels of glucose and lipids) in patients newly diagnosed with schizophrenia with focus on effects of previous antipsychotic drug use and possible gender differences.

Methods: A population-based cross-sectional study in the Central Denmark Region including all adults (≥ 18 years) born in Denmark after January 1, 1955, and with a first-time schizophrenia diagnosis during the period April 1, 2000, to September 30, 2012. Metabolic measures at baseline (± 90 days from first-time schizophrenia diagnosis) were obtained from the clinical laboratory information system. We applied descriptive statistics using Wilcoxon rank-sum tests and chi-square tests as appropriate. Correlations between the metabolic parameters and extent of antipsychotic treatment, as well as time since first psychiatric diagnosis, were tested by Spearman's correlation coefficient.

Results: We identified a total of 2,452 patients with a first-time schizophrenia diagnosis. Screening for metabolic abnormalities at baseline were carried out in 1,040 (42.4%) of these patients (455 women, 43.8%; median age 25.7 (IQR: 21.9–33.6) years). The extent of screening ranged from 19.2% tested in 2001 to 70.7% tested in 2011. Blood tests showed that 58.4% had an abnormal lipid profile (either increased total cholesterol, increased LDL, increased triglycerides, or decreased HDL) with 53.6% having abnormal profiles on two or more lipid measures. A total of 13.8% had increased blood glucose (10.4% in the prediabetes range, and 3.4% in the diabetes range) at baseline. Patients with previous prescription of antipsychotic drugs ($n=615$) were more likely to have blood glucose values in the prediabetic and diabetic range (16.4% vs. 10.1%, $P=0.01$), and an abnormal lipid measure (65.7% vs. 46.8%, $P < 0.001$), than individuals with no prior prescription of antipsychotics ($n=425$). We found no gender differences with regard to the proportion with increased blood glucose. More women than men showed abnormal lipid profiles (63.3% vs. 54.7%, $P=0.03$), with 50.5% vs. 44.2% among patients with no prior antipsychotic prescriptions ($P=0.33$), and 70.9% vs. 61.7% among patients with prior antipsychotic drug use ($P=0.06$). The amount of antipsychotic treatment prior to schizophrenia diagnosis correlated significantly with blood levels of hemoglobin A1c, non-fasting and fasting glucose, total cholesterol, high-density lipoprotein cholesterol (inverse), and triglycerides. Total duration of psychiatric illness correlated significantly with non-fasting and fasting glucose, and triglycerides (all $P < 0.05$).

Discussion: Despite guidelines, less than half of the patients with a first-time schizophrenia diagnosis were screened for abnormal baseline metabolic parameters, although the proportion increased throughout the study period. Abnormal lipid profiles were found in more than half of the persons tested, and they were more common among persons already redeeming prescriptions for antipsychotics. The increased metabolic abnormalities already present in the early phase of illness emphasize the need for screening and monitoring of this group of patients.

M152. Longitudinal epigenetic analysis of clozapine use in treatment-resistant schizophrenia: data from the Crestar Consortium

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Background: Approximately one-third of patients with schizophrenia are considered treatment-resistant. For these patients, the atypical antipsychotic drug clozapine is recommended as the only evidence-based treatment available. However, there is still significant variability in treatment-response and many patients suffer side-effects (including some rare but severe adverse reactions such as agranulocytosis). Animal studies have demonstrated that clozapine influences histone modification and DNA methylation, and a recent EWAS study in humans identified multiple differentially methylated positions (DMPs)

and differentially methylated regions (DMRs) in clozapine-exposed samples. We used a longitudinal, within-participant design to conduct genome-wide analysis of DNA methylation changes in treatment-resistant patients over 6 months of clozapine use.

Methods: We recruited 11 participants with a diagnosis of treatment-resistant schizophrenia, before they were prescribed clozapine. We then collected whole-blood samples at baseline and follow-up (6 weeks, 12 weeks and 6 months after clozapine start date), alongside clinical assessments. We quantified DNA methylation at $\sim 480,000$ sites across the genome using the Illumina 450 K HumanMethylation array and following pre-processing, normalization and quality control, an epigenome-wide association study was performed comparing DNA methylation at each time point.

Results: Multiple CpG sites showed changes in DNA methylation that were found to be significantly associated with length of time exposed to clozapine. The most significant CpG site was located in the gene body of CRB1; CRB1 is expressed exclusively in the eye, and the central nervous system, and has been previously associated with Lever's congenital amaurosis and retinitis pigmentosa.

Discussion: This is the first study to identify longitudinal epigenetic changes following clozapine exposure in human subjects. Recruitment is ongoing and further analysis will look at whether epigenetic changes are associated with treatment-response/adverse reactions. Ultimately, these data will help us understand the mechanisms involved in clozapine, potentially providing biomarkers to predict clozapine response.

M153. Stimulus repetition effects on neurophysiological correlates of mental workload in psychotic patients

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Background: The present study proposes to refine our understanding of cognitive deficits in patients suffering of psychosis. We focused on electrophysiological measurements of mental workload in psychopathological context using a new electrophysiological method based on intra-block averaging of ERP amplitudes. Specifically, the allocation of attentional resources is dependent on both the mental workload and the time-course of a task. Because attention and the capacity to store information in short-term registers are impaired in psychosis, it is of great interest to detail their disease-specific neurophysiological correlates.

Methods: 16 healthy, cognitively intact adults (age-range 18–35) and 16 patients diagnosed with a psychotic episode were recruited. They had neither history of sustained head injury, nor neurological disorders.

The participants were confronted with an auditory oddball paradigm in three different conditions:

- no task (detection of rare stimuli; control condition)
- a weak constraining task: counting forward condition (counting rare stimuli)
- a strong constraining task: counting backward condition

Continuous EEG was recorded using twenty-three surface electrodes placed over the scalp according to the 10–20 international electrode placement system. The ERP components of interest were: P2, P3a, and P3b components. All components were identified on frontal (F3, Fz, F4 electrodes combined) electrode locations in the grand-average waveforms. We performed an ERP waveform averaging in a sequence block containing 5 rare stimuli, so that a total of 8 consecutive blocks were obtained for each task (passive followed by weak and strong workload tasks). Secondly, the amplitude of each block was compared to the first block, and expressed as a percentage (i.e., magnitude) of variation. This procedure allowed the quantification of the attentional resource used during the test for each task and consequently represents an index of the variability of their intensity.

Results: In the weak constraining task, P3a and P3b amplitude remained relatively stable throughout the target stimulus-repetition in healthy subjects although they decreased in psychotic patients. In the strong constraining task, the amplitudes of P3a–P3b linearly decreased following the repetition of the target stimulus in healthy subjects. In contrast, stimulus-repetition led to only a weaker decrease with transitory increase in amplitude of P3a and a tendency toward an increase of the P3b amplitude in the patient group.

Discussion: This individual electrophysiological index to measure mental workload might prove to be particularly valuable to evaluate the processing of mental workload on psychotic diseases. During the strong constraining task, the first few stimuli appearing during a sequence of repetitive stimuli are treated with much more attention because of their psychological importance in healthy subjects. Yet, with stimulus repetition less attentional resources are engaged and can therefore be reallocated to supplementary processes required for mental effort enhancement. This is clearly not the case in patients suffering of psychosis. The results suggest that psychotic patients fail to attribute as much attention to the first stimuli as the healthy subjects did. This suggests that the attentional resources are somehow already allocated to other processes during the tasks. Altogether, these findings support the concept of a blunted EEG response in psychotic patients who recruit the maximum neural generators in simple attention conditions without being able to modulate their brain activation facing the complexity of increasing working memory needs.

M154. Separation of recent-onset psychosis patients from healthy controls based on resting-state functional connectivity pattern classification

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Background: Multivariate pattern recognition analyses (MVPA) have the potential to identify brain pattern alterations across the entire brain due to their capacity to extract the innate inter-regional dependencies of distributed brain pathologies from high-dimensional training data and generalize the learned discriminative rules to unseen patient cohorts. While MVPA applied on structural data has been confirmed to be a valuable biomarker for patients with psychosis, the MVPA classification based on functional connectivity (FC) alterations might be promising better sensitivity. In this study we investigated whether multivariate pattern classification using whole-brain resting-state FC facilitates the identification of individuals experiencing recent onset psychosis (ROP), as well as how these alterations relate to memory performance.

Methods: We used rsfMRI images from 19 sex and gender matched healthy controls (HC) and 19 ROP patients obtained from PRONIA. Correlation matrices between brain regions were used as features for multivariate analysis. The support vector machine pipeline wrapped into repeated nested cross-validation was used to train a multi-modal diagnostic system and evaluate its generalization capacity in new subjects. Ultimately, the predictions of the different training partitions were combined into classifier ensembles, which provided a final group membership prediction through averaging. The top features were extracted in order to determine the regions of FC that were most discriminative for the classification. The same participants have undergone the neuropsychological testing of verbal and working memory functions: Rey Auditory Verbal Learning Test, Auditory digit span (forward and backward), verbal fluency (semantic and phonetic). We correlated the decisions scores provided by the classification algorithm with the participants' memory performance.

Results: We found an overall classification accuracy, sensitivity, and specificity of 86.8%, 78.9%, and 94.7%. We found an overall alteration of whole-brain FC involving both inter- and intrahemispheric brain connections. Marked long-range alterations that were driving the classification of ROPs and HCs occurred between the fronto-temporal and fronto-parietal regions, along with short range connections between the frontal lobe and both right posterior cingulate gyrus and right thalamus. The decision scores from the SVM classification correlated significantly with the forward digit span scores.

Discussion: We were able to show that the separation of ROP patients from HCs based on rsFC pattern classification is possible with an accuracy of 86.8%. Our further goal to show a relationship between memory performance and decision scores of the classifier was supported by the forward digit span. Long range connections between the fronto-parietal regions complement previous findings indicating activations in these regions during this task. Resting-state

biomarkers could be used to predict schizophrenia at the single-subject level in not only chronic patients, but also patients experiencing a recent onset psychosis.

M155. Lower hippocampal muscarinic M1 receptor expression is related to visual spatial learning and memory deficits in first episode psychosis patients

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Background: Many patients report cognitive deficits in learning and memory prior to, and after first onset of a psychotic episode. There are longstanding implications that the muscarinic cholinergic system, plays a critical role in cognition [1]. A hallmark post mortem study found 75% reduction in M1 receptor density in a subgroup of patients with schizophrenia compared to healthy controls, which they termed muscarinic receptor deficiency schizophrenia or MRDS[2]. It is unknown whether this MRDS group suffered from cognitive deficits. Recent clinical pilot studies examining effects of M1 agonists and positive allosteric modulators show improved learning and memory [3,4] in schizophrenia patients. The aim of the present study was to assess M1 expression at illness onset, and whether it is associated with deficits in learning and memory.

Methods: M1 receptor subtype expression was measured using single photon emission computed tomography (SPECT) with a M1 specific radiopharmaceutical 123I-Iododexetimide on a high resolution scanner with 72 gamma cameras. M1 receptor expression was quantified as binding potential. Additionally, a structural T1 weighted magnetic resonance image was made to co-register the M1 SPECT scan for anatomical identification of the hippocampus, our region of interest. Twelve medication free recent onset psychotic patients were assessed. (mean age: 27.42; 9 male and 3 female subjects) The Cambridge Neuropsychological Test Automated Battery (CANTAB) validated for psychotic disorders was used to assess working memory, visual spatial - and verbal learning and memory.

Results: A one sampled t-test was employed to test whether within group hippocampal binding potentials differed from 0. Hippocampal binding differed significant from 0 ($t = 3.196$ (11), $P < 0.009$) showing a within group main effect for hippocampal M1 binding potential. Regression analysis showed that this lower hippocampal M1 binding potential trend significantly predicted lower scores on visual spatial learning and memory ($F = 0.206$ (1), $P = 0.06$), but no effect was found for working memory, and verbal learning.

Discussion: Preliminary findings seem to show lower hippocampal M1 receptor expression may be related to deficits in visual spatial memory and learning aptitude at onset of psychotic disorders, and thus may be a promising clinical marker. M1 agonist antipsychotic treatment may be effective in treating patients experiencing deterioration in visual learning and memory. Further analysis should be done to compare patient hippocampal M1 receptor expression to typically developing subjects to discern degree of pathology.

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M156. Cortical hierarchy underlies preferential connectivity disturbances in schizophrenia

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Background: Schizophrenia is a disorder hypothesized to arise from global excitation/inhibition (E/I) imbalance, yet is associated with focal deficits in neuroimaging studies. Using computational modeling and clinical fMRI, we propose a mechanism reconciling global deficits with focal imaging findings.

Methods: We implemented in silico E/I perturbations within a biophysical model of brain activity, which produced alterations in resulting simulated fMRI signals. To assess predicted changes in connectivity and variance, we conducted resting-state fMRI in 161 schizophrenic and 164 matched healthy subjects. Voxel-wise and network-level connectivity, and variance analyses were performed.

Results: As predicted by our model, schizophrenia patients showed elevated covariance connectivity and signal variance. Intriguingly, effects localized to associative networks such as default mode network (DMN) and fronto-parietal control network (FPCN). FPCN-DMN covariance was significantly increased in schizophrenia, correlated with symptoms, and was absent in a comparison group of bipolar patients ($N=73$). To investigate how such preferential deficits could arise from global disinhibition, we extended our model to reflect biologically plausible differences in associative vs. sensory network dynamics. This in silico cortical hierarchy revealed emergent, preferential vulnerability of higher-level networks to global disinhibition, suggesting a mechanism for heterogeneous functional dysconnectivity in schizophrenia.

Discussion: The elevated covariance connectivity in chronic schizophrenia can be reconciled with hypoconnectivity seen in previous studies by observing that this elevated covariance occurs in a setting of elevated signal variance, which reduces connectivity inferred by correlational measures. Furthermore, our model suggests a plausible mechanism by which global disinhibition can produce preferential deficits in associative regions.

M157. Abnormal brain activity in the left prefrontal cortex is related to deficit in using semantic encoding strategies in schizophrenia

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Background: Individuals with schizophrenia have impaired episodic memory and have difficulties when encoding associations between different items. Specifically, patients do not formulate efficient encoding strategies and do not spontaneously use the semantic information underlying two linked items to facilitate their memorization. While the impairment in self-initiation of semantic encoding strategies (SES) in schizophrenia is well documented, little is known about the underlying neural correlates and whether individual differences exist in the patient group.

Methods: Fifty-eight participants (35 schizophrenia patients and 23 matched healthy controls) took part in the study. To isolate the brain activation related to the self-initiation of SES, we developed a memory task involving 128 object pairs to memorize that could either be from the same category or not. For half of the trials, participants were asked whether both objects were from the same or different categories, and for the other half of the trials, which object was bigger in real life. We expected that healthy participants would spontaneously self-initiate SES when the orienting question asked about object size, and both objects were semantically related. Participants subsequently performed a recognition task outside the magnetic resonance imaging (MRI) scanner. Functional MRI data were preprocessed and analyzed using SPM8. To isolate the neural activity related to the self-initiation of SES, we performed the contrast (related pairs – unrelated pairs) for the encoding question 'Bigger?'. After fitting a fixed effects model for each participant, we performed a

random effect analysis across participants to produce a group t-map. Between-group effects were then examined with a two-sample t-test. We also performed post-hoc analyses to separate the patients into two subgroups: those with a clear deficit of self-initiation of SES, and those without.

Results: Significant lower performance in patients compared to healthy controls was observed in the condition where the participants needed to self-initiate SES ($P < 0.05$). Between-group brain activation differences were also observed in this condition ($P < 0.001$, monte-carlo corrected). Significant lower activation was observed in the left prefrontal cortex, the left inferior temporal gyrus, and in the cerebellum of patients when both objects were semantically related compared to when they were not. Patients presenting greater deficit in self-initiation of SES also demonstrated more abnormal brain activation in the left prefrontal cortex compared to patients without such a deficit and to healthy controls.

Discussion: These results support previous evidence that the left prefrontal cortex is important in the self-initiation of SES. Abnormal brain activity in prefrontal cortex in schizophrenia patients is also related to their deficit of self-initiation of SES. This abnormality is greater in patients who demonstrate a deficit in SES. This highlights the importance of considering how heterogeneity of neuroimaging findings in schizophrenia may be related to cognitive style and to patient-specific cognitive deficits. Furthermore, our findings encourage interventions aimed at improving SES in patients showing this deficit, which may potentially improve episodic memory and overall cognition.

M158. Altered cortico-limbic connectivity during the facial perception in individuals with social anhedonia

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Background: Deficit in the facial emotion processing has been identified as one of the most consistent findings in patients with schizophrenia. However, it is still unclear whether similar facial perception deficit would also be found in at-risk individuals with social anhedonia. The present study aimed to examine the neural mechanism of facial emotion perception in individuals with social anhedonia.

Methods: Eighteen individuals with social anhedonia (mean age = 19.2 years; SD = 1.1) and 26 controls (mean age = 19.3 years; SD = 0.9) were recruited from a large scale college student sample. No significant differences were found between two groups on age, gender proportion, and IQ estimates. A facial emotion recognition task (including angry, fear, happy, and neutral facial expressions) consisting of two sessions were adopted during the fMRI scan in a Siemens 3 T scanner. Individuals' images were preprocessed using SPM8. Dynamic causal modeling (DCM) analysis was conducted to analyze the functional connectivity. We extracted bold signals of three ROIs (amygdala, ventral lateral prefrontal cortex (vlPFC), dorsal lateral prefrontal cortex (dlPFC)) in the right hemisphere and constructed four models to be estimated and selected using DCM10. The parameters including intrinsic connectivity and modulatory effects of facial expressions were compared between two groups.

Results: Compared to controls, individuals with social anhedonia showed hyper-activation in right posterior insula (angry condition) and reduced activation in the ACC and the caudate (fear condition) during the presentation of the negative facial expressions ($P < 0.001$, $k > 100$ voxels). Using the DCM, we found a weaker modulatory effect of the facial expression stimuli on the effective connectivity from amygdala to vlPFC in individuals with social anhedonia ($t = 2.2$, $P < 0.05$).

Discussion: These results suggested that individuals with social anhedonia have already demonstrated altered cortico-limbic connectivity as compared to those individuals without social anhedonia.

M159. Functional connectivity and striatal dopamine synthesis in schizophrenia treated with antipsychotic drugs: multimodal imaging study using [18F]DOPA PET and resting MRI

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Background: Schizophrenia is one of the most debilitating mental illness characterized by psychotic symptoms like hallucinations and delusions often coupled with cognitive and social impairments. The first antipsychotic drug, chlorpromazine, enabled to treat patient with schizophrenia though the mechanism of action was not known at the moment. After the discovery of dopamine as a neurotransmitter, the findings that all the antipsychotic drugs, which were developed structurally similar to chlorpromazine, block the dopamine receptors and that their affinity for dopamine receptors is closely associated with their clinical effectiveness provided indirect evidence that dopamine dysfunction contributed to schizophrenia. This is showing that researches into the mechanism of antipsychotic action informed understanding of the pathophysiology of schizophrenia. However, it was not until the application of molecular imaging to schizophrenia research that it became possible to investigate dopamine dysfunction in the living human brain. A recent meta-analysis regarding molecular imaging studies of the dopaminergic dysfunction in schizophrenia revealed that the primary locus of dopaminergic abnormality in schizophrenia is presynaptic, which is related with dopamine synthesis capacity, baseline synaptic dopamine levels, and dopamine release.

As mentioned earlier, all the antipsychotic drugs currently available are acting on the postsynaptic dopamine receptors and the antipsychotic drugs may exert antipsychotic effect by blocking the receptor and reducing the elevated dopaminergic neurotransmission from presynaptic to postsynaptic area. However, all the antipsychotic drugs with the same mechanism of action are not all the same in the aspects of clinical efficacy. For example, clozapine shares its pharmacological characteristics with other antipsychotic drugs as a dopamine blocker. However, clozapine is the only antipsychotic drug with proven efficacy in refractory patients with schizophrenia. This could be associated with the unique pharmacological characteristics of clozapine that affects glutamatergic system, interacting with dopamine system in a co-modulatory manner. Furthermore, clozapine seems to affect functional connectivity between the frontal lobe and the striatum in a different manner influencing presynaptic dopamine synthesis. In the present study, we sought to evaluate the antipsychotic effect on functional connectivity and presynaptic dopamine capacity and compare the effect between first-line antipsychotic drugs and clozapine.

Methods: We measured functional connectivity between the frontal lobe and the striatum by using resting MRI and presynaptic dopamine capacity by using [18 F]DOPA PET in healthy volunteers and patients with schizophrenia who were treated with first-line antipsychotic drugs and clozapine.

Results: Clozapine group showed lower k_i values from [18 F]DOPA than other groups (Group: $df=2$, $95.303 F=12.156$, $P<0.001$; Region: $df=2$, 60.184 , $F=34.104$, $P<0.001$) and functional connectivity from resting MRI was negatively correlated with k_i values ($r=-0.360$, $P=0.03$).

Discussion: This might suggest that clozapine might make the functional connectivity stronger, leading to reduced presynaptic dopamine synthesis.

M160. Adjunctive selective estrogen receptor modulator increases neural activity in the hippocampus and inferior frontal gyrus during emotional face recognition in schizophrenia

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Background: Estrogen has been implicated in the development and course of schizophrenia with most evidence suggesting a neuro-

protective effect. Treatment with raloxifene, a selective estrogen receptor modulator, can reduce symptom severity, improve cognition and normalize brain activity during learning in schizophrenia. People with schizophrenia are especially impaired in the identification of negative facial emotions. The present study was designed to determine the extent to which adjunctive raloxifene treatment would alter abnormal neural activity during angry facial emotion recognition in schizophrenia.

Methods: Twenty people with schizophrenia (12 men, 8 women) participated in a thirteen-week, randomized, double-blind, placebo-controlled, crossover trial of adjunctive raloxifene treatment (120 mg/day orally) and performed a facial emotion recognition task during fMRI after each treatment phase. Two-sample t-tests in regions of interest selected a priori were performed to assess activation differences between raloxifene and placebo conditions during recognition of angry faces.

Results: Adjunctive raloxifene significantly increased activation in the right hippocampus and left inferior frontal gyrus compared to the placebo condition (FWE $P<0.05$). There was no significant difference in performance accuracy or reaction time between active and placebo conditions.

Discussion: This study provides the first evidence suggesting that adjunctive raloxifene treatment changes neural activity in brain regions associated with facial emotion recognition in schizophrenia. These findings support the hypothesis that estrogen plays a modifying role in schizophrenia and shows that adjunctive raloxifene treatment may reverse abnormal neural activity during facial emotion recognition, which is relevant to impaired social functioning in men and women with schizophrenia.

M161. Brain activation findings from a family study of emotional and non-emotional face recognition in schizophrenia

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Background: A robust finding in schizophrenia is the presence of deficits in the ability to accurately perceive and recognize emotions from faces. These deficits have been directly linked to functional outcome, such as community and social functioning. Furthermore, behavioral and neuroimaging research also indicates similar dysfunction in nonpsychotic relatives of individuals with schizophrenia, suggesting that these deficits may represent a marker of genetic liability to schizophrenia. However, an area of debate concerns whether deficits are specific to recognizing facial emotions or instead reflect more generalized perceptual and cognitive dysfunction. The current study aimed to distinguish between specific and generalized neural dysfunction underlying impaired facial emotion recognition in schizophrenia and to examine associations with the genetic liability to the disorder.

Methods: Twenty-eight individuals with schizophrenia, 27 nonpsychotic first-degree biological relatives, and 27 healthy controls underwent functional magnetic resonance imaging (fMRI) while performing a facial recognition task in which they had to make judgments about either the emotion or age of the face presented. Behavioral performance (accuracy and reaction times) and functional activation (BOLD signal change) data were analyzed to examine differences between participant groups and between the emotional and non-emotional (age) face recognition conditions.

Results: Schizophrenia patients had lower accuracy and longer reaction times compared to controls and relatives for both emotion recognition and age recognition conditions, while relatives had intact performance across both conditions. Patients had similar patterns of hypoactivation compared to controls during emotion and age recognition, particularly in medial and lateral prefrontal cortex and striatal regions. Relatives had similar hypoactivation as patients, and additionally displayed increased deactivation compared to controls and patients in regions associated with the default-mode network. Few regions were uniquely activated during emotion recognition, but in schizophrenia patients, emotion recognition compared to age recognition was associated with greater activation in right temporoparietal cortex and the anterior cingulate cortex.

Discussion: The similar pattern of brain activation abnormalities during facial emotion and age recognition suggests that deficits in facial

emotion recognition in schizophrenia are associated with more generalized neurocognitive functioning that is not specific to evaluating facial emotions per se. Furthermore, the similar activation abnormalities in nonpsychotic relatives despite intact recognition accuracy suggests that functional brain activation may be a more nuanced marker of disorder liability than behavioral performance. Additionally, the unique deactivation findings in relatives may represent compensatory mechanisms that preserve intact performance. Continued research into common mechanisms of impairment in schizophrenia and potential compensatory mechanisms in relatives may help to identify new targets for cognitive remediation in schizophrenia.

M162. Brains of first-episode psychosis patients do not synchronize with others during movie viewing conditions

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Background: Patients with psychotic disorders have problems in separating reality from imagination. A common feature in prevailing theories is that the psychotic brain responds less reliably to external and internal stimuli, which might contribute to the distortion of reality. It remains unresolved, however, whether such impaired reliability can be demonstrated during processing of complex naturalistic information.

Methods: Fifty-one first-episode psychosis patients and 32 community-based control subjects were included from the Helsinki Early Psychosis Study. We used a naturalistic audio-visual stimulus—a 7 min 20 s clip from the fantasy movie *Alice in Wonderland* (Tim Burton, 2010; Walt Disney Pictures)—during 3-tesla functional magnetic resonance imaging to quantify real life-like information processing in the brain. We used intersubject correlation (ISC) technique to provide markers for brain-response reliability during movie viewing (Hasson *et al.*, 2010, *Trends Cogn Sci*). We computed voxelwise ISCs for each patient within the patient group, for each control subject within the control group, as well as for each patient with respect to the control groups (i.e. similarity between patients' and controls' voxel time-series). Participants' age and sex were included as nuisance covariates in comparisons of ISC maps between groups. To assess the psychological functions related to statistically significant clusters in the ISC maps, we modeled brain activity with regressors varying with the fantasy content and salience of the movie events, as evaluated by separate control groups ($n=17$ for fantasy, $n=15$ for salience) outside the scanner.

Results: Patient-to-control and patient-to-patient ISCs were significantly lower than control-to-control ISCs in the right ventral precuneus, right anterior insula and left middle frontal gyrus ($P < 0.05$ small volume corrected for multiple comparisons). Activity in the precuneal cluster correlated with the fantasy (for patients: $P < 0.001$; for controls: $P < 0.001$) and salience (for patients: $P = 0.011$; for controls: $P < 0.001$) ratings of the movie, each controlled for the other, in patients and control subjects. Activity in insula correlated ($P = 0.019$) with the salience content of the movie in control subjects.

Discussion: We found that first-episode psychosis patients' brains synchronize less (i) with each other and (ii) with healthy control subjects than the brains of control subjects with each other during movie viewing. The group differences were observed in regions related to default-mode, executive, and salience networks, implicated in models of psychosis. Association of precuneus and insula signal with fantasy and salience further support the relevance of the findings for understanding the brain basis of psychosis. These findings are the first to suggest that natural information is processed unreliably in the key networks of patients with early psychosis.

M163. Association of genetic variants with the brain activity during emotional processing: a multivariate study

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Background: Anomalies in emotional responses and processing are crucial phenotypes of schizophrenia, whose risk is mainly explained by genetic components. Furthermore, previous neuroimaging studies in healthy subjects have suggested that inter-individual variability of the cerebral response to emotional, especially threatening stimuli are associated with genetic variation. In the present study, our aim was to identify a top-set of single-nucleotide polymorphisms (SNPs) contributing to explain the genetic component of brain response to threatening stimuli. With this aim, we first identified the brain region whose activity is mainly under genetic control using a sample of healthy twins. Then, we investigated in healthy non-twins the multivariate contribution and ranking of specific SNPs in explaining the variance in activity of those previously located areas.

Methods: 28 healthy twin pairs (16 monozygotic and 12 dizygotic) and 191 healthy non-twins participated to the study. Both groups performed a task requiring processing of emotional threatening faces during fMRI. Zygosity in twins was inferred using a standardized questionnaire. Non-twins were genotyped using whole genome microarrays. Thereafter, the following steps were performed: 1) ICC Matlab Toolbox implemented in SPM8 was used in order to identify brain areas in which the activity during emotion processing was correlated between monozygotic twins ($ICC > 0.6$; $P < 0.001$); 2) BOLD-fMRI parameter estimates of areas resulting by ICC analysis were entered in an ACE model in order to estimate the weight of genetic contributions with respect to the total phenotypic variance; 3) BrainSpan Atlas was used in order to identify the genes with the greatest mRNA expression in the area associated with the greatest genetic component; 4) SVS toolbox was used to select genetic variants spanning 100 kb upstream and downstream the selected genes; 5) these genetic variants were then entered in an univariate association analysis using a sample of healthy non-twins in order to investigate their association with activity of the brain region with the greatest genetic contribution during processing of threatening stimuli (Filters: $MAF > 0.1$, $HWE < 0.003$, $r^2 < 0.1$, Genotype Call Rate ($< 95\%$); Association- $P < 0.005$); 6) the resulting genetic variants were entered in a Random Forests analysis to assess their multivariate contribution and ranking in explaining the variance of the target phenotype.

Results: The ACE model indicated that the amygdala was the brain region whose activity during processing of threatening stimuli is mainly explained by genetic factors ($a^2 = 0.57$). Furthermore, the univariate association analysis indicated that 82 out of 6935 genetic variants of 4007 genes expressed in amygdala (as indicated by BrainSpan) were significantly associated with emotion-related amygdala activity of non-twins subjects. Finally, the multivariate analysis revealed that these 82 SNPs explained 30% of the total phenotypic variance. Eight of these SNPs were the main contributors in explaining this variance ($P < 0.05$): rs231395, rs9393735, rs6849514, rs3095749, rs4802761, rs10897445, rs501908, rs17499486.

Discussion: Our findings suggests that multiple genetic variations are implicated in modulating the activity of the amygdala, which is the brain region associated with the greatest genetic control in the present study. Among the 8 most relevant SNPs, rs17499486 (NPAS3) has been already associated with risk of schizophrenia and bipolar disorder. Given that emotional abnormalities and genetic risk are crucial aspects of schizophrenia, these findings call for further investigation of their relevance in this brain disorder.

M164. Hyperactivation of salience network during eye gaze perception in schizophrenia

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Background: The ability to process social information accurately and effectively is disrupted in schizophrenia (SZ), severely affecting social

functioning. Abnormal processing of eye gaze direction—a ubiquitous social cue—significantly accounts for deficits in broader social functioning in SZ. Few studies have examined the neural mechanisms underlying altered gaze perception in SZ. This study aims to identify altered neural circuitry of gaze perception in SZ, which may provide useful treatment targets for future therapeutic strategies.

Methods: Twenty-one individuals with SZ (age: 31.9 ± 10.4 ; 10M/11 F) and 20 healthy controls (HC) (age: 32.2 ± 14.0 ; 10M/10 F) completed the study. Gaze perception was probed with a psychophysics eye-contact perception task during BOLD fMRI. The task was presented in a blocked-event-related design, with stimuli of faces with 9 varying gaze directions (from averted to direct in gradual increments). Participants had to indicate by pressing a button whether they feel the face is looking at them (eyes: yes/no), or the gender of the face (gender: male/female). Trial types (eyes, gender) were modeled as regressors to identify the brain regions recruited in gaze processing. All *P* values for fMRI results were FWE-corrected.

Results: HC and SZ were well matched for age, sex, and parental education. The two groups performed similarly on gender identification, $t(39) = 1.10$, $P = 0.28$. Participants endorsed eye contact in a linear fashion relative to eye-contact signal strength: 12%, 14%, 21%, 32%, 44%, 52%, 66%, 80%, and 89%, $F(4.6, 181.1) = 180.0$, $P < 0.001$. No significant group effect, $F(1,39) = 1.86$, $P = 0.18$, or Group X Signal Strength interaction, $F(4.6, 181.1) = 1.43$, $P = 0.22$, was observed. Eyes trials, relative to gender trials, elicited increased BOLD signals in numerous brain regions, most prominently in posterior medial frontal cortex (pmFC), bilateral inferior frontal gyrus/anterior insula, supra-marginal gyrus/superior temporal gyrus, precentral gyrus, precuneus, and superior/mid/inferior occipital gyrus, all P 's < 0.001 . For eyes trials, SZ (relative to HC) showed increased activation in pmFC ($x, y, z = [-9, 8, 52]$, $k = 3104$, $P < 0.001$) and right insula ($x, y, z = [39, 5, 4]$, $k = 457$, $P = 0.005$). For gender trials, SZ (relative to HC) showed increased activation in left pre- and post-central gyrus ($k = 656$, $P = 0.001$). Group comparison for the Eyes-Gender contrast yielded marginally higher activation in pmFC ($x, y, z = [0, 2, 64]$, $k = 282$, $P = 0.091$) in SZ compared with HC.

Discussion: Gaze perception, relative to gender identification, activated distributed brain regions associated with salience processing. Hyperactivation was observed in pmFC and insula in SZ during gaze perception, supporting aberrant affective processing of social information in the disorder. Future analyses will compare the SZ and HC for brain activation as well as functional and effective connectivities to identify specific neural mechanisms underlying altered social cognition in schizophrenia.

M165. Neuroimaging of appraisals of psychotic experiences: an experimental investigation of symptomatic and non-need-for-care individuals

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Background: Using experimental analogs of anomalous experiences, it has been shown that threatening appraisals help differentiate individuals with psychotic experiences (PEs) with and without a need for care. An experimental analog adapted for use with functional magnetic resonance imaging (fMRI) was used to investigate appraisals at the neural level. It was predicted that differences in threatening appraisals between clinical (symptomatic) and non-clinical (non-need-for care) participants would correspond to differences in neural activation. A secondary prediction was that there would be a significant correlation between fMRI signal change and threatening appraisal scores for observed group differences.

Methods: Appraisals following an anomalous experience-inducing task (the Cards task) were examined in clinical ($n = 16$) and non-clinical ($n = 16$) participants with PEs, and controls ($n = 16$), while being scanned.

Results: Behaviorally, the clinical group endorsed significantly higher threatening appraisal scores than the non-clinical and control groups, who did not differ from one another. Additionally, non-clinical participants with PEs responded to the tasks in a similar manner to controls at the neural level. The clinical group, however, displayed heightened activation in a range of frontal, occipital, parietal, and subcortical regions, compared to the other groups, suggestive of

affective and cognitive processing deficits and/or biases. These differences in activation showed a modest correlation with threatening appraisal scores.

Discussion: Despite ongoing PEs, individuals without a need for care appear to process anomalous experiences in a manner similar to controls, while clinical participants show evidence of biased or deficient affective and cognitive processing, hypothesized to contribute to appraisals of PEs as threatening.

M166. Thalamic medio-dorsal connectivity during attentional control measured with independent component analysis is associated with familiar risk for schizophrenia and with a polygenic risk score

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Background: Several studies have demonstrated that attentional abnormalities are present in patients with schizophrenia as well as in subjects at risk for this brain disorder. Furthermore, imaging results indicate that cortical and subcortical brain regions supporting attentional processing are abnormally activated in patients with schizophrenia and in their relatives. However, it is not known whether functional connectivity between cortical and subcortical areas during attentional processing is a key feature of schizophrenia and whether it is associated with genetic risk for the disease. Here, we investigated with Independent Component Analysis (ICA) patterns of functional connectivity during attentional control in healthy controls (NC), patients with schizophrenia (SCZ) and unaffected siblings of patients (SIB) (Aim1). Then, we tested if altered connectivity in SCZ and SIB is modulated by a PolyGenic Risk Score (PGRS) for schizophrenia as computed in the PGC2 cohorts (Ripke *et al.*, 2014) in a sample of healthy subjects (Aim2).

Methods: Subjects performed the Variable Attentional Control task (VAC) during fMRI, allowing to investigate brain activity associated with increasing demands of attentional control. Aim1: One group spatial ICA was performed on VAC data of 356 NC, 55 SCZ and 40 SIB through the Group ICA of fMRI toolbox implemented in SPM8. A screening for the reliability of every IC was conducted through spatial correlations with templates of gray matter, white matter, cerebrospinal fluid and Attentional Control Network (ACN) in order to identify the Components of Interest (COIs). Thus, a full factorial analysis was performed on COI spatial maps, with diagnosis as categorical predictor. Results were thresholded at $P < 0.05$ FWE corrected for whole brain. Pearson's correlation between significant connectivity strength within the Components of Interest (COIs) and accuracy rate during VAC was performed. Aim2: A PGRS was calculated for 175 NC on the basis of the 108 loci (128 SNPs) reaching GWAS significance in a previous work for their association with diagnosis of schizophrenia (Ripke *et al.*, 2014), following published procedures (Purcell *et al.*, 2009). VAC imaging data were processed as described for Aim1. A multiple regression on COI spatial maps was then performed using PGRS as covariate of interest using the Medial Dorsal nucleus (MD) of the thalamus as the volume of interest based on results obtained investigating Aim 1. Results were thresholded at $P < 0.05$ FWE corrected for the volume of interest (i.e., MD), at $P < 0.05$.

Results: Aim1: ICA identified one COI (correlation with ACN, $r^2 = 0.04$). ANOVA identified a main effect of diagnosis in MD ($x = -6, y = -20, z = 0$, Z -value = 5.99). In particular, SCZ had lower connectivity strength than SIB and NC, and SIB had intermediate connectivity strength between SCZ and NC (all $P < 0.02$). Pearson's correlation analysis indicated a positive correlation between connectivity strength in the significant cluster and VAC behavioral accuracy ($r = 0.18$, $P = 0.0001$). Aim2: we focused our attention on the COI associated with the greater correlation with the spatial template of the significant COI within Aim1 ($r^2 = 0.01$). Multiple regression analysis on this COI identified in the negative contrast a significant cluster located in MD.

Discussion: Our results indicate that impaired thalamic MD functional connectivity is present in both SCZ and SIB, and correlates with behavioral accuracy. Moreover, MD connectivity strength is associated with a PGRS for schizophrenia. Taken together, these findings suggest

that MD patterns of functional connections may be considered an intermediate phenotype for schizophrenia.

M167. Association of the *bdnf* Val66Met polymorphism with negative symptoms severity, but not cognitive function, in first-episode schizophrenia spectrum disorders

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Background: A functional polymorphism of the brain-derived neurotrophic factor gene (BDNF) Val66Met has been associated with cognitive function and symptom severity in patients with schizophrenia. It has been suggested that the Val66Met polymorphism has a role as a modulator in a range of clinical features of the illness, including symptoms severity, therapeutic responsiveness, age of onset, brain morphology and cognitive function. However, little work has been done in first-episode schizophrenia (FES) spectrum disorders. The objective of this study is to investigate the association of the BDNF Val66Met polymorphism on cognitive function and clinical symptomatology in FES patients.

Methods: Using a cross-sectional design in a cohort of 204 patients with FES or a schizophrenia spectrum disorder and 204 healthy matched controls, we performed BDNF Val66Met genotyping and tested its relationship with cognitive testing (attention, working memory, learning/verbal memory and reasoning/problem solving) and assessment of clinical symptom severity.

Results: There was no significant influence of the BDNF genotype on cognitive factor scores in either patients or controls. An augmented severity of negative symptoms was found in FES patients that carried the Met allele, in comparison to non-Met carriers ($F = 5.05$, $P < 0.026$). No differences were found in positive symptomatology ($F = 0.23$, $P = 0.63$).

Discussion: The results of this study suggest that in patients with a first-episode of schizophrenia or a schizophrenia spectrum disorder, the BDNF Val66Met polymorphism does not exert an influence on cognitive functioning, but is associated with negative symptoms severity. BDNF may serve as suitable marker of negative symptomatology severity in FES patients within the schizophrenia spectrum.

M168. Differential consistency of subcortico-cortical intrinsic connectivity patterns in schizophrenia

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Background: Brain architecture can be divided into a cortico-thalamic and so-called 'modulatory' systems. Intrinsic functional brain connectivity (iFC) between these systems is altered in schizophrenia. Affected modulatory systems concern key structures of pathophysiological hypotheses such as striatum, medial temporal lobes (MTLs), amygdala, and cerebellum. While altered connectivity is known for each modulatory system separately, it is unknown whether modulatory systems' connectivity patterns with the cortic-thalamic system are comparably altered across systems, i.e. if separate modulatory systems' connectivity patterns are consistent across patients.

Methods: To investigate this question, patients with schizophrenia and healthy controls were assessed by resting-state fMRI. Independent component analysis of fMRI data revealed cortical intrinsic brain networks (NWs) with time courses representing proxies for cortico-thalamic system activity. Modulatory system activity was represented by fMRI-based time courses of selected regions-of-interest (ROIs), such as hippocampus and parahippocampus for MTLs or ventral and dorsal striatum for striatum. Correlation (Pearson) of ROI- and NWs-time courses yielded individual connectivity matrices (all-ROIs-NWs, NWs-

NWs, ROIs-ROIs, modulatory-system-ROIs-NWs) as main outcome measures, which were classified by support-vector-machine-based leave-one-out cross-validation. Differences in classification accuracy were statistically evaluated for consistency across subjects and systems.

Results: Correlation matrices based on all-ROIs-NWs yielded 91% classification accuracy, which was significantly superior to ROIs-ROIs and NWs-NWs (56% and 74%, respectively). Considering separate modulatory systems, cerebellum-NWs and MTL-NWs reached highest accuracy values with 91% and 85%, respectively, while those of striatum-NW and amygdala-NW were significantly lower with about 65% classification accuracy.

Discussion: Results provide initial evidence for differential consistency of intrinsic connectivity patterns between modulatory systems and the cortico-thalamic system. Data suggest that differential dysconnectivity patterns between modulatory and cortical systems might reflect different disease states or patient subgroups.

M169. Deficits in context-dependent adaptive coding of reward in schizophrenia

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Background: In schizophrenia, reward processing is impaired in various ways. However, the neural mechanisms underlying these deficits are still largely unknown. Here, we focus on the efficiency of neural reward representations. We ask how the brain of patients with schizophrenia deals with the problem that there are unlimited reward levels to represent but only limited activation levels to code them. Theoretical principles of information processing and empirical findings suggest that in order to efficiently represent all possible rewards, reward sensitive neurons have to adapt their coding range dynamically to the current reward context. Adaptation ensures that the reward system is most sensitive for the most likely rewards. Reduced neural adaptation would prevent precise reward representations and could potentially lie at the root of many dysfunctional reward processes in schizophrenia.

Methods: To investigate adaptive coding in patients with schizophrenia ($n = 27$) and healthy controls ($n = 25$), we used fMRI in combination with a variant of the monetary incentive delay task. The task involved two reward contexts, one in which small rewards were most likely and one in which large rewards were most likely. This design allowed us to study the neural adaptation of reward representations to different contexts.

Results: Compared to healthy controls, patients with schizophrenia showed less efficient neural adaptation to the current reward context, which led to diminished discriminability and, hence, imprecise neural representation particularly of small rewards. Importantly, the deficit correlated with general symptom severity and occurred primarily in two reward sensitive regions, the right caudate and the right anterior insula/inferior frontal gyrus.

Discussion: Our results suggest that some of the deficits in reward processing in schizophrenia might be due to inefficient neural adaptation to the current reward context. Furthermore, because adaptive coding is a ubiquitous feature of the brain, we believe that our findings provide an avenue to defining a general impairment in neural information processing underlying this debilitating disorder.

M170. Ventral striatal activation during reward processing in psychosis: a neurofunctional meta-analysis

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Background: Deficits in reward processing are proposed to underlie the formation of psychotic symptoms, likely mediated by elevated dopamine levels in the ventral striatal (VS) dopamine levels. Functional

magnetic resonance imaging studies showed alterations of VS activity during reward processing in chronic and first-episode patients, as well as high-risk subjects for psychosis. However, findings are inconclusive, conflicting, and difficult to subject to meta-analysis without introducing bias because several studies reported that findings were not statistically significant but did not report statistics. In this paper, we present a novel innovative approach to meta-analyze differences in VS activity during reward processing between subjects with schizophrenia spectrum disorders or clinical or genetic high-risk state for psychosis and healthy controls.

Methods: Effect size of the group differences in VS activity, and correlation between VS activity and negative and positive symptom scores in patients were analyzed using MetaNSUE, a random-effects method that enables the unbiased inclusion of non-statistically significant unreported effects.

Results: The meta-analysis included 23 studies (917 patients) for reward anticipation, 9 studies (358 patients) for reward feedback, and 8 studies (314 patients) for reward prediction error. We found significantly reduced bilateral VS activity during reward anticipation (23 studies, $n=917$) in patients compared with healthy controls (left/right Cohen $D=-0.50/-0.70$; $P<0.001$). Left VS abnormality was more severe in patients with high scores of negative symptoms during reward anticipation ($r=-0.41$; $P<0.001$). Patients also showed bilateral VS hypoactivation during reward feedback (left/right $d=-0.57/-0.56$; $P<0.001$) and right VS hypoactivation during prediction error processing at trend level ($d=-0.53$, $P=0.01$, uncorrected for multiple comparisons). Simulations showed that exclusion of studies with non-statistically significant unreported effects was associated with a strong bias (d bias=0.22), whereas estimations using MetaNSUE were unbiased even when statistics were seldom reported (d -bias <0.001).

Discussion: This meta-analysis provides robust evidence that patients with psychosis reveal VS hypoactivation during reward anticipation. The assessment of VS prediction errors seems to be promising but more studies are needed to draw valid conclusions.

M171. Neural correlates of trust in health, psychosis and in patients at ultra-high risk for psychosis

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Background: Psychosis is a disorder that is characterized by social dysfunction. It has been shown that in patients with chronic psychosis reduced trust in others impairs their social interactions. Neuroimaging research has indicated that this could be due to a reduced sensitivity to social reward and an impaired theory of mind, as reflected in reduced caudate activation and also reduced activation in mentalizing networks. While these mechanisms could be underlying the formation of social difficulties they could also be due to negative social experiences or illness chronicity. To date little is known about potential deficits in trust and their underlying neural mechanisms in the early stages of the illness. Here we investigate the development of trust and its associated brain mechanisms in individuals in the early stages of a psychotic illness and those at UHR, to identify whether reduced trust could be a marker of an increased vulnerability for psychosis.

Methods: To measure trust and the responsiveness to social feedback of others, we used two interactive repeated trust games, with a trustworthy (returning more) and an unfair partner (returning less than invested). We explored basic trust, the development of trust, and the underlying neural mechanisms in 22 patients with early psychosis (16-21 years), 17 UHR (16-31 years) and 44 healthy controls (16-31 years). Whole brain and region of interest (ROI) analyses, based on social decision making paradigms and previous trust game research in the field in chronic psychosis were conducted in SPM.

Results: Behaviorally, patients had lower basic trust (first investment) towards unknown others than controls, but towards the end of the social interaction their investments did not differ from the other two groups. UHR's levels of trust were in between patients and controls, not differing significantly from either group.

At a neural level, ROI analysis showed, when investing in a trustworthy partner, more medial prefrontal cortex (mPFC) activation in controls

than the two other groups. Patients activated the temporo parietal junction (TPJ) significantly less than controls and UHRs. When investing in an unfair partner significantly higher medial prefrontal cortex (mPFC) activation in UHRs than in the other two groups was found. In addition, ROI analysis also revealed more TPJ activity in UHR than the other groups. Whole brain analyses showed that investing in an unfair partner activated the caudate in all three groups.

Discussion: Behaviorally, patients showed less basic trust towards others, but like the other groups they adjusted their behavior to the trustworthy or unfair feedback of the second player over repeated interactions, showing that their social learning mechanisms are intact. The fact that all three groups activated the caudate in the unfair condition might also be an indication for intact social learning. Reduced frontal and TPJ activation in patients could point towards impaired mentalizing as a possible underlying mechanisms of the reduced levels of basic trust.

UHR performed in between patients and controls, indicating that the problems with trust in psychosis are related to the illness and also to the risk of psychosis, i.e. the prodromal phase. UHR activated the TPJ throughout the two games more than the other groups, suggesting that they might engage in compensatory mentalizing processes to a higher degree. In conclusion, the current findings suggest that the prodromal phase might represent a time window during which guided social intervention might prevent further reductions in trust towards others. Patients might also profit most from targeted social interventions in the early illness stages as they are still able to learn trusting behavior during repeated social interactions.

M172. Suicide attempt in schizophrenia and first-episode psychosis: clinical and biological associations

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Background: People with schizophrenia are known to die much earlier than expected. Up to 40% of this excess premature mortality can be attributed to suicide and unnatural deaths (Bushe *et al.*, 2010). A review (Palmer *et al.*, 2005) estimated the lifetime suicide risk at 4.9% for people with schizophrenia. Detection of those at risk patients is important; however, risk prediction is known to be imprecise.

The aim of the study was to compare the clinical and biological features in a population of patients with schizophrenia or first-episode psychosis according to the presence or absence of a history of suicide attempt.

Methods: It was a comparative study carried out about 81 male patients with schizophrenia or schizophreniform disorder according to DSM-IV criteria. All patients were enrolled in the study at the psychiatry department of the university hospital of Monastir (Tunisia) and were evaluated by the following psychometric scales: PANSS (Positive and Negative Symptom scale), CGI (Clinical Global Impressions), GAF (Global Assessment of Functioning), BPRS (Brief Psychiatric Rating Scale) and Calgary depression scale (CDS). Plasma concentrations of biological parameters (lipid profile, liver, renal and pancreatic functions) were determined by colorimetric enzymatic methods.

Results: Patients with suicide attempt history ($n=27$; 33.33%) had higher PANSS positive scores ($P=0.02$), higher CGI gravity scores ($P=0.05$), lower GAF scores ($P<10^{-3}$) and higher BPRS scores ($P=0.046$), there was no association between suicide attempt and the CDS scores.

Concerning the biological parameters, the plasma concentrations of bilirubin, hepatic transaminases (ALT and AST) were significantly higher in patients with suicide attempt history ($P<10^{-3}$, $P=0.012$ and $P<10^{-3}$, respectively).

Discussion: In our study population, suicide attempt history was associated with the severity of psychotic symptoms as evidenced by significantly higher scores in PANSS, BPRS, CGI, and GAF but not with the depressive dimension as evaluated by the CDS. We have also established that psychotic patients with a history of suicide attempt were more exposed to liver malfunctioning; this result can be explained by a higher use of antidepressants in this patients.

Other risk factors have been reported in the literature like the family history of suicide attempt, the period of hospitalization in psychiatry

unit or soon after discharge, substance misuse and the non adherence to treatment.

M173. Childhood trauma moderates the effects of common variants of the FKBP5 binding protein 5 (FKBP5) gene on right hippocampal volume in schizophrenia

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Background: Early life stress may interact with certain genetic vulnerabilities to confer susceptibility to psychiatric illnesses such as schizophrenia (SZ), via long-lasting effects on hypothalamic-pituitary-adrenal (HPA) axis. With this system, the FKBP5 binding protein 5 (FKBP5) gene has regulatory effects on glucocorticoid receptor function, and common variation in this gene has shown interactive effects with childhood trauma to confer greater risk for psychotic experiences and cognitive deficits in SZ. This study set out to investigate the effects of four FKBP5 single-nucleotide polymorphisms (SNPs) and their potential interaction with childhood maltreatment on the structure of the hippocampus, as a well established stress-sensitive region, in SZ and healthy controls (HC).

Methods: Genotyping was performed for FKBP5 rs1360780, rs4713902, rs9394309 and rs9470080 for 145 SZ and 65 HC available cases from the Australian Schizophrenia Research Bank. Due to low frequencies of minor allele homozygotes for all SNPs, the minor allele homozygotes were paired with heterozygotes to form a (genotype) group of minor allele carriers for comparison to major allele homozygotes. All participants completed the Childhood Adversity Questionnaire to index exposure to childhood maltreatment (defined by exposure to physical, emotional, sexual abuse, and/or neglect). High resolution T1-weighted structural brain scans (MPRAGE) were acquired using Siemens Avanto 1.5 T scanners and preprocessed using Freesurfer v5.1. Hippocampal and amygdala volumes were extracted from the automated parcellation using the Destrieux atlas. Controlling for sex and total intracranial volume, hierarchical regressions were performed to test the main effects of (1) genotype, (2) childhood maltreatment and (3) the interaction between these variables on right and left hippocampal volumes in SZ and HC separately; subsequent ANCOVAs were used to determine differences in brain volume between cases of the same genotype, in the context of childhood maltreatment exposure, for SNPs showing significant interactions in regression models.

Results: There was a significant main effect of genotype on hippocampal volume for three SNPs (rs1360780, rs9394309, and rs9470080) in SZ only, with major allele homozygotes showing greater volume loss in the right hippocampus than minor allele carriers; there were no main effects of trauma on hippocampal volume. Two of these SNPs (rs9394309 and rs9470080) showed significant interaction effects with childhood trauma exposure: post-hoc analyses suggest that these interaction effects were driven by the effect of trauma on minor allele carriers. There were no significant effects for any SNPs in the left hippocampus, and no significant effects in HCs.

Discussion: These findings suggest that common FKBP5 variants impact hippocampal volume in SZ, with some of these effects being moderated by childhood trauma exposure. Further investigation of the complex interplay between genetic and environment factors involved in altering hemisphere-specific neurobiological stress systems of the brain may aid the development of novel stress-targeted pharmacological and therapeutic treatments for SZ.

M174. Connectomics in schizophrenia: from early pioneers to recent brain network findings

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Background: Schizophrenia has long since been conceptualized as a disorder of brain connectivity. The historical roots of this hypothesis

can be traced back to the late 19th century when influential scholars such as Meynert, Wernicke, Kraepelin and Bleuler worked on a theoretical understanding of the multifaceted syndrome that is currently referred to as schizophrenia.

Methods: Using original papers, reviews and biographies of early connectionists, the roots of the disconnectivity theory of schizophrenia are traced throughout recent history. Covering the works of connectionists from the late 19th century onwards, it is examined how their pioneering hypotheses hold up in light of current evidence.

Results: From a modern-day perspective, Meynert's and Wernicke's theories on association fiber pathology are supported by findings from diffusion-weighted imaging studies, while Bleuler's notion of conduction pathology can be linked to observed disruptions in functional connectivity. Kraepelin hypothesis of a disruption of the 'inner harmony of all parts of the psychic workshop' is now corroborated by findings of a disproportionate disruption of brain hubs and 'rich club' organization of the brain's network. Each from a different perspective, and thus not always in agreement, these visionary scholars already identified 'malintegration' of neural information due to disruptions in the association fibers linking brain hubs as a potential mechanism underlying symptoms such as psychosis and cognitive disorganization.

Discussion: From early connectionists to recent findings, considerable conceptual and empirical evidence suggests that schizophrenia might best be understood as a brain network disorder, affecting the brain's central communication infrastructure for whole brain integration. As the field continues to develop, novel directions in connectomics may contribute to pressing issues in schizophrenia research, including early recognition and treatment of the emerging illness.

M175. Childhood trauma in young adults at ultra high risk for psychosis is associated to lower fractional anisotropy in the left uncinate fasciculus and parahippocampal cingulum

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Background: Childhood trauma is highly prevalent in adolescents who later develop psychiatric conditions. Nevertheless, no study has assessed the impact of abuse/neglect on brain white-matter (WM) in populations at-risk for psychosis. We tested the hypothesis that lower WM-integrity is associated with early-trauma and subclinical psychotic symptoms in adolescents at-risk for psychosis (UHR).

Methods: Eighty-seven UHR and thirty-seven healthy controls (HC) - aged 14-29 - were recruited from the community and assessed by Structured Clinical Interview for DSM-IV Axis-I disorders and Comprehensive Assessment of At-Risk Mental State (CAARMS). UHR participants were further assessed by Positive and Negative Syndrome Scale, Calgary Depression Scale for Schizophrenia, Beck Anxiety Inventory and Child Trauma Questionnaire. Participants were followed-up for two years and nine UHR participants (10.3%) converted to psychosis. Diffusion-weighted images were acquired on all the participants to derive region-wise mean fractional anisotropy values of 20 WM tracts. MANCOVA and stepwise regression models were computed to probe for WM-integrity disruption in UHR and explore its association with trauma, subclinical psychotic symptoms, and non-psychotic psychopathology. Significant threshold was set to $P \leq 0.05$ after Bonferroni correction.

Results: Compared to HC, UHR participants showed lower anisotropy in the left uncinate fasciculus (LUF) ($P=0.020$) and (right) parahippocampal cingulum (PC) ($P=0.015$) after controlling for age, gender, and ethnicity differences.

Within the UHR sample, those participants diagnosed with a non-psychotic disorder at any time in their life showed lower anisotropy in the same tracts when compared with UHR with no SCID diagnosis (LUF: $P=0.013$; right PC: $P=0.029$). In these participants, a lower anisotropy in the parahippocampal cingulum was associated with more severe at-risk mental state (right PC) ($P=0.005$) and general psychopathology symptoms (left PC) ($P=0.031$); while lower anisotropy in the LUF was associated with more severe anxiety symptoms ($P=0.029$) and more severe reported emotional childhood abuse ($P=0.038$). Higher emotional abuse was also associated with significantly higher general psychopathology symptoms ($P=0.009$).

Finally, reported sexual abuse in the UHR sample was significantly associated with more severe at-risk mental state and a significant predictor of psychotic conversion.

Discussion: Our findings suggest that the clinical impact of early trauma in individuals at risk for psychosis may be mediated by WM-integrity disruption of the uncinate fasciculus and parahippocampal cingulum: tracts connecting limbic structures involved in memory and emotional processing.

M176. Ketamine induced nmda-receptor blockade and hippocampal glutamate in healthy volunteers

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Background: Aberrant hippocampal glutamatergic signaling has been postulated as a disease mechanism in schizophrenia (1). Magnetic Resonance Spectroscopy (MRS) studies found elevated Glx (glutamate +glutamine) in unmedicated patients with schizophrenia in vivo in different areas of the brain, including the hippocampus, which may be secondary to N-methyl-d-aspartate receptor (NMDAR) hypofunction (2). To test the hypothesis that NMDAR blockade would result in increased hippocampal Glx, we measured ketamine induced Glx changes in healthy volunteers.

Methods: We conducted a Magnetic Resonance Spectroscopy (MRS) study to evaluate changes in hippocampal Glx during a ketamine challenge (0.27 mg/kg over 10 minutes, then 0.25 mg/kg/hour for 50 minutes, 0.01 ml/s) in a group of 19 healthy volunteers. Psychotomimetic effects were assessed with the Brief Psychiatric Rating Scale (BPRS) and the Clinician Administered Dissociative States Scale (CADSS). Imaging was performed on a 3 T head-only scanner (Magnetom Allegra, Siemens Medical Solutions, Erlangen, Germany), equipped with a circularly polarized transmit/receive head coil. MRS data were collected from a voxel in the left hippocampus (2.7x 1.5x 1cm). A series of sagittal, coronal, and axial T1-weighted anatomical scans (gradient-recalled echo sequence, TR/TE=250/ 3.48ms, flip angle= 70°, 5mm slice thickness, 1.5mm gap, 512x 512 matrix) were acquired for voxel placement. Following manual shimming, water-suppressed spectra were acquired using the point-resolved spectroscopy sequence (PRESS; TR/TE=2000/ 80ms; 1200 Hz spectral bandwidth; 1024 points; number of averages= 640 (21 min 20 s)). MRS data were analyzed in jMRUI. Spectra were quantified with respect to creatine in the time domain using the AMARES algorithm. For statistical analyses, we used a mixed repeated measures design with neurometabolites as dependent variables, experimental condition as fixed factor, and voxel gray matter fraction as covariate.

Results: Subjects reported a significant increase in both BPRS and CADSS scores during the ketamine challenge. We found an increase in Glx with ketamine compared to saline (saline: 0.62±/ 0.13; ketamine: 0.69 ±/0.08; F= 3.756; P= 0.04), even after excluding statistical outliers (F= 9.408; P< 0.01). We found no correlations between clinical symptoms and Glx (all p >.05).

Discussion: Here, we describe an increase of hippocampal Glx during a ketamine challenge in healthy volunteers that is similar in extent to our previous report of elevated hippocampal Glx in unmedicated patients with schizophrenia. This is consistent with a study revealing hippocampal hypermetabolism and structural deficits in patients transitioning from a prodromal state to syndromal psychosis, and reporting that ketamine causes increased extracellular glutamate, hippocampal hypermetabolism, and atrophy in a mouse model, suggesting that glutamate acts as driver of hippocampal pathology (3). Because hypermetabolism and glutamate excess may antedate structural changes, development of drugs designed to modulate NMDAR function could be promising in the quest of arresting disease progression in schizophrenia or even in efforts of preventing the emergence of the full clinical picture.

M177. A TSPO blocking study to determine the specific binding of [11C]-PBR28 in patients with schizophrenia

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Background: Epidemiological, genetic, and clinical evidence all indicates that inflammation plays a role in schizophrenia. When microglia are activated, they express high levels of the 18-kDa translocator protein (TSPO). TSPO can be measured in vivo with Positron Emission Tomography (PET) radiotracers, such as [11C]-PBR28, and an increase in [11C]-PBR28 binding ratio has been shown in patients with schizophrenia relative to healthy controls. The main outcome measure in studies using TSPO tracers is the total volume of distribution (Vt), creating some difficulties in the direct estimation of specific binding. Our research group has already shown that in healthy volunteers a significant proportion of Vt is specific to TSPO, but this has never been addressed in schizophrenia. In this study we have used a TSPO agonist to block the binding of [11C]-PBR28 in order to estimate the TSPO specific binding in schizophrenia.

Methods: Six patients with schizophrenia were recruited from South London and Maudsley (SLaM) NHS Foundation Trust. All subjects were genotyped for the rs6971 polymorphism using a Taqman SNP Genotyping Assay and were homozygote high-affinity binders (HABs). Subjects received a baseline bolus injection of [11C]-PBR28 followed by a 90-minute emission scan. PET data were co-registered with whole brain structural images acquired with a 3 T magnetic resonance imaging (MRI) scanner. During the PET acquisition, arterial blood data were sampled via the radial artery using a combined automatic-manual approach. In a follow-up visit patients received a selective TSPO blocker followed 2 hours later by a repeat [11C]-PBR28 scan. Quantification of [11C]-PBR28 tissue distribution was performed using the two tissue compartmental model accounting for endothelial vascular TSPO binding (2TCM-1 K). A logan plot analysis will also be conducted in both schizophrenia patients and healthy volunteers.

Results: Following blockade with XBD173 all six patients with schizophrenia showed a significant reduction in TSPO specific binding across different brain regions. Mean reduction of distribution volume were 57% for the whole brain (baseline Vt: 4.27 ± 0.59; after blocking Vt: 1.79 ± 0.44), 57% for the gray matter (baseline Vt: 4.37 ± 0.60; after blocking Vt: 1.82 ± 0.48) and 55% for the frontal lobe (baseline Vt: 4.31 ± 0.58; after blocking Vt: 1.85 ± 0.46).

Discussion: Using this approach we have found that in schizophrenia patients there is a substantial, more than 50%, component of [11C]-PBR28 volume of distribution that represents TSPO specific binding. Further work is currently being conducted to determine if there are differences in the percentage of specific binding between schizophrenia patients and healthy volunteers.

M178. White matter integrity in treatment-refractory schizophrenia: a diffusion tensor imaging study

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Background: We are yet to understand the mechanisms that contribute to treatment-resistance in schizophrenia. Reduced white matter fractional anisotropy - a marker of disrupted microstructural integrity is a well-established finding in schizophrenia.

Methods: This study examines whether treatment resistance in schizophrenia is associated with a distinctive pattern of white matter integrity compared to a non-refractory group. We applied tract-based spatial statistics (TBSS) to diffusion tensor imaging data from 34 patients with refractory schizophrenia and 44 non-refractory patients. **Results:** There were no significant differences in fractional anisotropy between the refractory and non-refractory groups. This is the first study to compare white matter integrity between these two schizophrenia subtypes using TBSS.

Discussion: These results need to be replicated to verify our findings, with a particular emphasis on developing a robust dimensional criterion definition of treatment resistance for future investigations. NB: This work is still in progress and is currently being finalized. Details will be amended to this abstract shortly.

M179. Increased glutamate in prefrontal cortex of patients with psychotic disorders and auditory verbal hallucinations

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Background: Auditory verbal hallucinations (AVH), have been linked to deficiencies in fronto-temporal and inter-hemispheric white matter tracts (Allen *et al.* 2012). Specifically, abnormalities in tracts connecting either the prefrontal cortices of both hemispheres or frontal and temporal areas within the left hemisphere have often been associated with AVH (Curcic-Blake *et al.* 2015). Proton magnetic resonance spectroscopy (1H MRS) is a novel technique for determining the levels of specific neurochemical components in a given area. Of specific interest is the neurotransmitter glutamate, a major excitatory neurotransmitter. In this study we investigated the levels of glutamate in the white matter of a tract belonging to above mentioned pathways in the dorso-lateral prefrontal cortex (DLPFC).

Methods: Sixty-seven patients and thirty healthy controls (HC) underwent magnetic resonance spectroscopy (MRS) to estimate levels of glutamate+glutamine (Glx) in the DLPFC. The severity of symptoms was assessed using the positive and negative syndrome scale (PANSS). Patients either had AVH (AVH group; $n = 45$) or had never experienced them (NeverAVH group; $n = 22$). In addition, Glx levels were estimated relative to creatinine (Glx/Cr). The spectrum was estimated from a voxel (of volume 8 cm³) placed in the left DLPFC, belonging to both the cingulum and forceps major.

Results: We found no difference in age, gender, medication, negative PANSS score or general symptom severity among 3 groups of participants (healthy controls, schizophrenia patients with and without current hallucinations). Patients had generally lower levels of Glx as compared to HC ($t = 2.09$, $P = 0.04$). Among patients, those with lifetime AVH had higher levels of Glx than the patients who had never experienced AVH ($t = 2.25$, $P = 0.025$). The results stayed the same after corrections for the duration of illness and levels of gray matter, levels of creatinine and cerebrospinal fluid in the voxel ($t = 2.4$, $P = 0.02$). We found no evidence for an association of the severity of symptoms (measured using the P3 hallucinations item of the PANSS or PANSS positive subscale) with Glx levels.

Discussion: Increased Glx levels in patients with AVH as compared to the group who had never experienced AVH is in line with suggestion that glutamate might be a mediating factor in AVH and glutamate hypothesis of schizophrenia (Coyle 2006). Moreover, our results are largely consistent with a previous study of Hugdahl *et al.* (Hugdahl *et al.* 2015), who found similar decreased levels of Glx in a patient group and increased levels in an AVH group as compared to a No AVH group.

M180. The effect of cigarette smoking on brain structure in patients with schizophrenia and healthy subjects: a systematic review and meta-analysis

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Background: Smoking rate in schizophrenia is significantly higher than in the general population. In fact, 70-80% of schizophrenia patients use tobacco and more than 50% of them are heavy smokers (Ziedonis *et al.*, 2008). There is a growing consensus that cigarette smoking is associated with a range of brain abnormalities, including alterations in gray matter (GM) volume and in white matter (WM) integrity (Azizian *et al.*, 2009). This study aimed to examine the main findings of structural neuroimaging studies on smokers without psychosis and in

schizophrenia smokers, to establish if cigarettes smoking contributes to the structural abnormalities observed in schizophrenia.

Methods: We searched the literature for studies that examined structural magnetic resonance imaging (MRI) measures in patients with a diagnosis of schizophrenia and/or in healthy controls in relation to their status of smokers. PubMed and Ovid databases were searched for eligible studies published up to September 2014, and references were also examined for relevance and included if appropriate. There was insufficient homogeneity across studies to allow a meta-analytic approach of region of interest (ROI) studies. Therefore, data were used for a systematic review. Nevertheless, a subset of seven VBM studies on healthy smokers were subjected to signed differential mapping (SDM), a meta-analytic technique for voxel-wise neuroimaging data (Radua *et al.*, 2013).

Results: Sixteen studies comparing healthy subjects smokers (HS) and non-smokers (HNS), and 5 studies comparing patients with schizophrenia smokers (PS) and non-smokers (PNS) with HS and HNS met the inclusion criteria. Our meta-analysis included 543 HS and 880 HNS. The findings showed that HS had a significantly smaller ($P < 0.05$) GM volume of bilateral insula, subcallosal cingulate, right medium prefrontal cortex and right superior temporal gyrus. Studies not included in the meta-analysis reported smaller GM volume also in the cerebellum and in hippocampus. Findings on the relationship between smoking and WM were inconsistent. Results from studies on GM changes in patients are inconsistent, with two studies reporting smaller volumes of prefrontal areas and one showing larger volumes of different regions. Two studies evaluated WM and reported a significant reduction of anterior thalamic radiation and frontal lobe tracts in patients smokers.

Discussion: Tobacco smoking seem to contributes to decrease GM volume in areas of the brain that have been consistently been reported as altered in patients with schizophrenia. However, only few studies examined populations of patients smokers, with substantial methodological differences, which make it difficult to draw any conclusion. Given the overrepresentation of smokers among patients with schizophrenia and the findings in non-patient smokers, we can hypothesize that the brain alterations seen in psychosis may be at least partly influenced by the excessive use of tobacco. More studies are needed to determine the real effect of tobacco smoking in patients and future research should consider smoking as an important variable when studying brain structural changes in schizophrenia.

M181. The effect of manual editing in freesurfer

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Background: FreeSurfer is a fully automated surface-based procedure, which provides measurements of cortical thickness and surface area and is an important tool to study structural changes in patients with schizophrenia. Manual editing is often recommended but the effect is poorly investigated. In the present pilot study, we wish to compare ten healthy individuals, with and without editing. It is assumed that the cortical structure is unchanged over a six-week period in healthy individuals. Thus, it was hypothesized that the overall repeatability between baseline and follow-up results would improve after manual editing.

Methods: As part of a larger longitudinal cohort, investigating structural changes in antipsychotic-naive schizophrenia patients and healthy controls, a randomly selected sample of ten healthy individuals were scanned at baseline and at six-week follow-up. The T1-weighted structural images were acquired on a 3 T MR scanner and underwent the standard FreeSurfer longitudinal pipeline with a specific 3 T option enabled. The reconstructed surfaces were visually inspected and manually edited separately by two raters (i.e. R1 and R2). A paired t-test was used to compare the overall difference in correlations before and after manual editing. For the individual regions of interest (ROI) an F-test was used to compare the precision with and without manual editing. The intraclass correlation coefficient (ICC) between the raters was analyzed for absolute and change in thickness and surface area.

Results: The segmentations visually improved after manual editing. The difference in correlations after manual editing significantly improved the consistency for overall cortical thickness for both the left ($t=6.469$, $P=0.000$ (R1) and $t=2.927$, $P=0.006$ (R2)) and right hemisphere ($t=2.675$, $P=0.012$ (R1) and $t=3.819$, $P=0.001$ (R2)). The results for overall surface area remained non-significant for both the left ($t=1.430$, $P=0.162$ (R1) and $t=0.535$, $P=0.596$ (R2)) and right hemisphere ($t=1.381$, $P=0.176$ (R1) and $t=0.803$, $P=0.428$ (R2)). For the ROI's, both significant increases and decreases in precision was found, but with minor consistency and overlap between the two raters. For cortical thickness, the largest increase and decrease in correlation was found in the left frontal pole (0.345 to 0.713) and left temporal pole (0.855 to 0.729), respectively. For surface area, the largest increase and decrease in correlation was found in the right frontal pole (0.836 to 0.947) and left medialorbitofrontal (0.968 to 0.908), respectively. The ICC (left hemisphere) was 0.969 for overall thickness and 0.584 for change in overall thickness; and 0.915 for overall area and 0.440 for change in overall area. The ICC (right hemisphere) was 0.958 for overall thickness and 0.526 for change in overall thickness; and 0.935 for overall area and 0.501 for change in overall area.

Discussion: It was hypothesized that the segmentations would improve after manual editing, which was found, as an overall improvement of cortical thickness, but not of surface area. It is important to stress that the present results can only be interpreted for this particular dataset with a longitudinal setup. It was also observed that editing does not only have a local effect. The small sample size may be a limitation for the present pilot study. General recommendations on how to edit errors do exist, but there is no unequivocal description. This could result in an individual subjectivity in deciding what is needed to edit - here reflected by the moderate agreement between the two raters.

M182. Gray matter volume patterns in thalamic nuclei predict genetic risk for schizophrenia and symptoms severity

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Background: Post-mortem and neuroimaging studies consistently indicate neuronal loss in the thalamus of patients with schizophrenia (SCZ) [1]. Other studies in non-affected siblings of SCZ (SIB) suggest a shared genetic risk for alterations in the thalamus. However, gray matter volume (GM) decrease in the thalamus does not unequivocally qualify as an intermediate phenotype. We hypothesized that a structural intermediate phenotype could be found at the level of GM patterns in thalamic subregions rather than considering the whole thalamus. Using voxel-based morphometry we aimed to differentiate between SCZ, SIB, and healthy controls (HC) to obtain a multivariate thalamic intermediate phenotype. Moreover, we stratified SCZ and HC based on thalamic GM patterns to investigate the association between thalamic GM patterns and symptoms severity.

Methods: We recruited 96 clinically stable SCZ (29 females, mean age \pm SD: 33 ± 7.7 years), 55 SIB (22 females, 35 ± 8.8 years), and 249 HC (111 females, 30 ± 8.4 years). Groups were matched for socio-economic status index and handedness (all $p > .05$), but not for gender and age (all $P < 0.05$), therefore included as covariates in all subsequent analyses. Symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS). HC were evaluated with the Schizotypal Personality Questionnaire (SPQ). We evaluated premorbid intelligence by means of Kaufman Brief Intelligence Test (KBIT). Structural scans were segmented and spatially normalized in SPM8 using DARTEL. We parceled the thalamus into seven regions of interest using a published cytoarchitectonic atlas [2]: anterior/midline nuclei (AT); mediodorsal nucleus; intralaminar nuclei; ventrolateral region; ventral anterior region; geniculate nuclei; pulvinar. We computed the first principal component of GM values in each region and used these variables together with demographic and KBIT information [3] as predictors of diagnosis (HC, SIB, SCZ) using random

forests. We permuted results 10 000 times to compute a Misclassification Index (MI) for each individual. We clustered SCZ and HC based on MI values into correctly and incorrectly classified groups. We tested differences in PANSS total score (mean $76 \pm$ standard deviation 21) and chlorpromazine equivalents (mean 561 mg/day \pm standard deviation 303 mg/day) in SCZ; we tested SPQ score differences in HC (Mann-Whitney U).

Results: Random forests discriminated SCZ from HC (accuracy: 81%) and SIB from HC (accuracy: 80%). The most important variables to discriminate SIB from HC were KBIT scores and left AT volumes ($P < 0.05$). Misclassified SCZ received lower doses of antipsychotics ($U=221$, $P=0.004$) and had milder symptoms compared to correctly classified patients ($U=85$, $P=0.01$), even when pharmacological treatment was factored out ($U=71$, $P=0.03$). On the other hand, misclassified HC had marginally greater SPQ scores (subscale "disorganized behavior"; $U=533$, $P=0.08$).

Discussion: Machine learning reveals a multivariate thalamic intermediate phenotype of schizophrenia, giving the greatest weight in this classification to KBIT and left AT volumes. The involvement of the AT in genetic risk for schizophrenia is consistent with prior reports [4]. Additionally, we found that SCZ with thalamic GM patterns closer to HC had milder symptoms and were treated with lower doses of antipsychotics. Together, these findings suggest a genetic background of thalamic GM decreases in SCZ and an association between these brain alterations and symptoms severity.

M183. White matter microstructure and phospholipase A2 activity in drug-naïve patients with first-episode psychosis: a state-dependent study

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Background: Several theoretical models consider that white matter (WM) abnormalities have a central role in the pathophysiology of schizophrenia. Brain imaging studies have found WM microstructure abnormalities in individuals with psychosis, and a few studies have shown that such abnormalities may vary after some weeks of antipsychotics (AP) intake. Phospholipase A2 (PLA2) is an enzyme involved in cell membrane homeostasis and remodeling, and it has been implicated in demyelination. PLA2 activity seems to be elevated in the acute phase of schizophrenia, and AP may normalize such abnormality. We sought to examine whether WM microstructure abnormalities and PLA2 activity would vary depending on the phase of the disorder (acute vs. stable phase) in a group of drug-naïve FEP. Also, we aim to evaluate whether PLA2 and WM microstructure variations over time would be correlated.

Methods: Twenty-five FEP and 69 healthy controls (HC) underwent MRI scanning and blood collection at study entrance. After one month of sustained symptomatic remission (mean follow up time = 12.7 weeks), 20 FEP underwent a second MRI scanning and blood collection; after a similar period of time, 36 HC also underwent the second MRI acquisition and blood collection. An automated, tract-based, segmentation approach was employed for the extraction of fractional anisotropy (FA) of regions-of-interest (ROIs). Based in previous studies with psychotic patients, we selected 44 ROIs which have showed abnormal FA in such investigations. We used a radio-enzymatic method to measure PLA2 (total and subtypes) activity.

Results: At baseline, in comparison to HC, FEP presented reduced FA in 20 of the ROIs ($P < 0.05$, uncorrected). No difference in PLA2 activity reached statistical significance. Following remission of acute psychotic symptoms, no difference in FA emerged in the between-group comparison; and FEP presented higher total and secreted PLA2 (sPLA2) activity than HC ($P < 0.05$, uncorrected). As complimentary analyses for the FEP group, we conducted an intra-group comparison for the ROIs which had presented reduced FA at baseline; we found significant increases of FA in left cingulum, frontal WM and splenium of corpus callosum ($P < 0.05$, uncorrected). We could not find any correlation between the rate of change of FA over time for such ROIs and for sPLA2 activity.

Discussion: Some studies have found that AP intake can favor myelination, promote FA changes and decrease PLA2 activity in schizophrenia. In some animal studies, sPLA2 activity have been particularly associated to demyelination and oligodendrocyte injury. Our results suggest that, as symptoms are mitigated, WM abnormalities present in the acute phase of FEP could reverse, as well as sPLA2 activity may be related to such recovery. However, such changes were not correlated in our study; perhaps such changes may underlie different biological mechanism of acute phase recovery. Also, the reduced number of subjects evaluated at follow-up may have impacted our results.

M184. A comprehensive and systematic review of the structural neuroimaging underpinnings of thought disorder in schizophrenia

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Background: Research into the etiology of schizophrenia has increasingly become focused on symptom-based, syndromal and/or pathogenic subgroups and dimensions. One such syndrome is thought disorder (TD), which refers to abnormalities in the amount and form of speech production. These abnormalities impair communication and presumably reflect disorganized thought processes. The aim of the present review was to comprehensively and systematically summarize our current understanding of the neurobiology of TD in schizophrenia by examining structural neuroimaging data.

Methods: The review was conducted in accordance with the PRISMA guidelines and undertaken using three search engines: PubMed, Scopus, and Web of Science. Exploratory and confirmatory studies were included. Studies that did not employ structural neuroimaging, did not investigate TD, or analyzed TD in samples comprising individuals without schizophrenia, schizoaffective disorder, or schizophreniform disorder were excluded.

Results: A total of 4707 articles were identified from the search process and a further 8 were found manually (e.g. from citation and reference lists). 94 structural neuroimaging studies were included. A number of types of structural measurements have been used, though the majority involve regional volumetry or water diffusivity/anisotropy, and derived indices such as asymmetry or gyrification. A fairly diffuse array of regions was identified that play a role in TD, including areas within the temporal, limbic and prefrontal cortices, as well as the nucleus accumbens, the cerebellum, and the corpus callosum. However, the vast majority of analyses have been general and exploratory (i.e. correlations were investigated between neuroimaging measures and all symptoms of schizophrenia), and many of the results are inconsistent across the literature. As such, some of these findings may be accounted for by inflated type II error due to multiple comparisons. The most frequently replicated finding has been a reduction in left posterior superior temporal gyrus gray matter volume in conjunction with a greater severity of positive TD.

Discussion: The structural correlates of TD in schizophrenia suggest the involvement of brain regions that relate to linguistic and other cognitive deficits. However, despite the large number of studies that have conducted exploratory research in the field, there has been little hypothesis-driven research using reliable and comprehensive measures of TD.

M185. Brain subtyping enhances neuroimaging predictions of schizophrenia group membership

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Background: Global initiatives currently aim to predict psychosis on the basis of neuroimaging data using machine learning. However, these predictions are limited by heterogeneity within canonical categories, such as schizophrenia, first-episode psychosis, or high-risk groups. We conducted a proof-of-concept study aiming to enhance machine learning predictions by finding hidden subgroups

of individuals with chronic schizophrenia using structural brain imaging data (i.e., brain subtypes). It was hypothesized that reducing heterogeneity with brain subtyping would result in an increase in power when predicting membership of an individual into a schizophrenia or control group.

Methods: A total of 145 3 T structural magnetic resonance imaging volumes were used from a publicly available database (the Mind Research Network Center of Biomedical Research Excellence; COBRE), including 71 patients with chronic schizophrenia (age(SD) = 38.1(13.9); 57 female) and 74 healthy control subjects (age(SD) = 35.8(11.5); 51 female). Preprocessing involved a standard voxel-based morphometry (VBM8) pipeline in addition to the control of age, sex, and global gray matter volume. Unsupervised clustering techniques were employed to decompose the schizophrenia gray matter images into two subgroups comprised of brains that were more similar to each other than to brains the other group. Equally sized control subgroups were created by selecting age- and sex-matched individuals from the larger control cohort. For each pair of subgroups, each individual's group membership was predicted using support vector machines wrapped in nested, cross-validation frameworks. Predictive accuracy was compared to the results for the entire cohort of schizophrenia patients versus controls.

Results: Two subgroups were separated with unsupervised clustering (S1: $n = 40$; age(SD) = 29.9(10.39); 1 female; S2: $n = 31$; age(SD) = 47.63; 13 female). Differences were found for age ($P < 0.001$), sex ($P < 0.001$), duration of illness ($P < 0.001$), age at first psychiatric illness ($P < 0.05$), and chlorpromazine equivalent antipsychotic dose ($P < 0.05$). Single-subject predictive accuracy of group membership was substantially higher in S2 (80% balanced accuracy; BAC) compared to predictions from the entire sample (BAC = 66%) and S1 (BAC = 63%). Comparison of the brain map signatures involved in subgroup prediction indicated differences in fronto-parietal areas.

Discussion: This study supported the hypothesis that brain subtyping enhances machine learning predictions. The results indicated that subgroups were associated with illness onset, illness severity, and also residual effects of age and sex. While the study provides proof-of-concept evidence that brain subtyping can enhance predictions, it also highlights the importance of controlling for heterogeneity introduced by basic demographic factors. Future research will address these limitations and extend the research in longitudinal samples of first-episode and high-risk individuals.

M186. Identification of two clusters within schizophrenia diagnosis with different structural, functional and clinical characteristics

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Background: The possible existence of different subgroups of patients within the schizophrenia diagnosis might contribute to the lack of replication of the structural alterations reported in for this syndrome.

Methods: We analyzed magnetic resonance studies from 121 schizophrenia patients (64 first episodes), 22 patients with bipolar disorder and 60 healthy subjects. Regional cortical thickness, curvature and area values, and subcortical volumes were assessed. Principal component analyses and canonical discriminant function were planned to identify subject subgroups. Glucose metabolism data using FDG-PET, amplitude of P300 event-related potential and PANSS scores at inclusion and after 6 months of follow-up were compared between the subgroups based on structural data in order to validate these subgroups.

Results: A function mostly contributed by cortical curvature discriminated groups A (healthy controls, bipolar patients and the most of the schizophrenia patients) and B, composed of 24 patients with schizophrenia (of them 12 first episodes). Group B but not group A schizophrenia patients showed larger mean regional curvature values as well as lack of improvement in negative symptoms after follow-up and lack of glucose metabolism increase in putamen. Moreover, schizophrenia group B patients showed significantly lower thalamic and cingulate glucose metabolism as compared to healthy controls.

Discussion: Cortical curvature may be useful to discriminate biologically distinct schizophrenia subgroups. Previous treatment or chronicity may not contribute to these subgroups.

M187. Abnormalities of language pathways in patients with schizophrenia with and without auditory hallucinations: a DTI-based tractography study

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Background: Auditory verbal hallucinations (AVH) are frequently observed in patients with schizophrenia (SZ) and could be the result of white matter (WM) fiber abnormalities that connect the frontal and/or temporo-parietal regions involved in speech production and perception. Nevertheless, studies evaluating these fasciculi are inconsistent. Thus, we studied WM integrity changes both within intra- and interhemispheric fasciculi in SZ with AVH (SZ+) and without AVH (SZ-) compared to healthy controls (HC), using diffusion tensor imaging-based tractography.

Methods: Thirty four patients with schizophrenia (DSM-IV) (11 SZ- and 23 SZ+) and 34 HC were included in the study. Diffusion-weighted images (MRI-3 T) were acquired. Maps of diffusion and fiber tracts, connecting the frontal and temporal regions, were generated in each participant then transferred in the MNI (Montreal Neurological Institute) space. Fractional anisotropy (FA), mean and radial diffusivities (MD and RD) were individually extracted in the left arcuate (AFL) and inferior fronto-occipital (IFOFL) fasciculi and the interhemispheric auditory pathway (IAP) in order to test integrity differences between the three groups.

Results: SZ- and SZ+ presented increased diffusivities (MD and/or RD) in AFL and IFOFL compared to HC suggesting an integrity loss, due to a demyelination. However, these changes were more pronounced in SZ+, who also showed decreased FA suggesting a neuronal loss. Regarding IAP, a significant decreased FA was only observed in SZ+ compared to HC suggesting a neuronal loss in SZ+.

Discussion: This study is the first to compare integrity changes within intra- and interhemispheric fasciculi. On one hand, abnormalities in intrahemispheric fasciculi related to language in schizophrenia were observed whatever the hallucinatory trait (SZ+ and SZ-). On the other hand, abnormalities in interhemispheric auditory pathway were observed only regarded SZ+ suggesting that this interhemispheric connection could be particularly involved in the occurrence of AVH.

M188. Schizophrenia and psychotic bipolar I disorder: cortical gyrification and brainage scores differences

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Background: Several studies have addressed differences and overlap in brain structural changes between schizophrenia and bipolar disorder. Most of these studies have utilized voxel-based morphometry or volumetry, which are indicators of (current) brain structure. Novel emerging morphometric techniques, however, allow the analysis of facets of brain structure, which reflect (subtle) neurodevelopmental disturbances, like cortical gyrification. In addition, the BrainAGE scores (Brain age estimation gap score) is a unidimensional score derived from multi-variate VBM analysis, which provides information on deviation of a single subject's brain from physiological aging or developmental trajectories.

Methods: We analyzed $n=34$ schizophrenia patients, $n=19$ bipolar I disorder patients (currently euthymic) with previous psychotic symptoms, and $n=34$ healthy control subjects (with no psychiatric history or first-degree relatives with a psychotic or mood disorder). All subjects underwent MRI scanning on a 3 T system, acquiring high-resolution T1-weighted MPRAGE sequences with 1x1x1mm voxel resolutions. First, we analyzed the MRIs for gyrification differences, using a mean curvature approach (see Luders *et al.*, 2006), focusing on

differences in prefrontal gyrification. Second, we computed the BrainAGE score (Franke,... Gaser, 2010) for each subject.

Results: Schizophrenia and bipolar groups both showed altered gyrification in prefrontal areas, albeit in markedly different locations: while the former showed change in frontopolar and orbitofrontal cortices, the bipolar group showed differences in anterior cingulate cortices, including subgenual portions. For BrainAGE score, schizophrenia patients showed higher scores compared to either healthy controls or bipolar patients (which did not differ from healthy subjects).

Discussion: Our BrainAGE score findings indicate accelerated age-related changes in brain structure in schizophrenia, but not (psychotic) bipolar I disorder patients. This suggests that only schizophrenia might be associated with steeper age-related decline. The gyrification analyses, in turn, suggest that both disorders might have a neurodevelopmental component, with changes manifesting in different areas of the prefrontal cortex. While differences in medication are a limitation of both analyses, our findings provide further insight in the problem of biological overlap and differences between these two conditions, esp. by extending brain structural findings to those parameters reflecting neurodevelopmental and accelerated aging.

M189. Heterogeneity of brain structural endophenotypes of schizophrenia

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Background: Although schizophrenia is a clinically highly heterogeneous disorder with a variable disease phenotype, there is very little research on the biological correlates on this heterogeneity. Based on previous studies using voxel-based morphometry (VBM) in schizophrenia (Nenadic *et al.*, NeuroImage 2010; Koutsouleris *et al.*, NeuroImage 2008), we present analyses on novel alternative brain structural markers and investigate the relation in different subgroups of schizophrenia.

Methods: We analyzed high-resolution T1-weighted MRI scans of $n=87$ schizophrenia patients and $n=99$ healthy control subjects. Patients were divided in three subgroups based on their symptoms profiles (factor analysis on SANS and SAPS items). This resulted in three groups with predominantly negative, disorganized and paranoid symptoms (which did not differ for age and gender). We then used a spherical harmonics approach (Luders *et al.*, 2006) to analyze cortical complexity, and Freesurfer software to analyze cortical thickness, comparing each subgroup with healthy controls.

Results: We found considerable heterogeneity in both cortical thickness and complexity measures across the three schizophrenia groups. A common overlap in left lateral prefrontal cortex emerged. However, the distribution in other areas was highly heterogeneous. Overall, patients with a negative symptom profile showed most extensive deficits in both brain structural parameters.

Discussion: Our findings provide additional support on the heterogeneity of putative biological markers of schizophrenia. They emphasize the neglect of previous studies to acknowledge the possibility of schizophrenia reflecting different biological entities, which would be highly relevant for subsequent studies, both on imaging as well as the genetic underpinnings. The overlap in lateral prefrontal cortex (among others), however, might also suggest some mutual changes present in all (or most) patients within the diagnostic category.

M190. The influence of AH11 variants on the diagnosis and treatment outcome in schizophrenia

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Background: Family, twin and adoption studies show evidence for a strong genetic component in schizophrenia. Genetic contribution for

treatment outcome in schizophrenia has been continuously suggested. The Abelson helper integration site-1 (AH1) locus, which is located on chromosome 6q23 and has a genomic size of 213,792 bp, encodes the protein, Jouberin, and is widely expressed in the brain. The association of AH1 with SCZ was first reported in family sample with high incidence of schizophrenia through a genome-wide linkage scan. This result was subsequently replicated in a linkage analysis of a linkage peak on 6q and in a fine-mapping study that identified seven markers significantly associated with schizophrenia. The present study aimed to explore whether four single nucleotide polymorphisms (SNPs) within the AH1 gene could be associated with schizophrenia and whether they could predict the clinical outcomes in patients with schizophrenia treated with antipsychotics.

Methods: Four hundred twenty-six in-patients with schizophrenia and 345 controls were genotyped for four AH1 SNPs (rs11154801, rs7750586, rs9647635, and rs9321501). Genomic DNA was extracted from blood by standard methods and quantified. High-throughput genotyping using a pyrosequencer (Biotage AB, Uppsala, Sweden) was used for genotyping the four SNPs of AH1 under investigation. PCR primers and sequencing primers used for the pyrosequencing assay were designed by using the Pyrosequencing Assay Design Software v.1. Baseline and clinical measures for patients with schizophrenia were assessed through the Positive and Negative Syndrome Scale (PANSS). Haploview 4.2 (Daly Lab at the Broad Institute, Cambridge, MA, USA) was used to generate a linkage disequilibrium (LD) map and to test for Hardy-Weinberg equilibrium. Allelic and genotypic frequencies in schizophrenia subjects were compared with those of controls using the χ^2 statistics. The repeated-measure ANOVA was used for the assessment of treatment outcomes measured by PANSS changes.

Results: The case-control analysis did not show any difference in the genotypic distribution of the SNPs, while in the allelic analysis, a weak association was found between the rs9647635 A allele and schizophrenia. Furthermore, in the haplotype analysis, three haplotypes resulted in being associated with schizophrenia (A-C-C-C, A-T-A-C, A-C-A-C for rs11154801, rs7750586, rs9647635, and rs9321501). With regard to the influence of the investigated polymorphisms on clinical improvement, in the genotype analyses, repeated-measures ANOVA did not show any association. On the other hand, in the allelic analyses, two SNPs (rs7750586 and rs9647635) were found to be associated with improvement at the negative subscale of the PANSS (respectively $P=0.033$ and $P=0.029$).

Discussion: Our findings suggest a possible influence of AH1 variants on schizophrenia susceptibility and antipsychotic response, particularly concerning negative symptomatology. Subsequent well-designed studies would be mandatory to confirm our results due to the methodological shortcomings of the present study.

M191. White matter related genes: association study in both schizophrenia and autism spectrum disorders

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Background: Compelling evidence supports the existence of clinical and neurobiological links between Schizophrenia (SZ) and Autism Spectrum Disorders (ASD) (Rapoport *et al.*, 2009). To this respect, SZ and ASD have shown to share common deficits in connectivity and synaptic plasticity (de Lacy and King, 2013), which could be related to the white matter abnormalities also observed in both disorders (Dennis and Thompson, 2013, Wheeler and Voineskos, 2014). The aim of this study was to analyze the sequence variability of a set

of white matter related genes in a group of SZ and ASD patients and healthy subjects in order to: i) explore whether these genetic variants are associated with the risk for these disorders, ii) test the diagnosis specificity of these genetic variants across the SZ-ASD continuum.

Methods: A case-control genetic association study was conducted in a sample of 883 Caucasian subjects from the AUSZ Consortium: 326 SZ and 136 ASD patients (DSM-IV), and 421 healthy subjects. DNA from all subjects was extracted from saliva or blood samples using standard methods. Sixty-five SNPs in 9 genes were genotyped using a customized OpenArray® Real-Time PCR System (Applied Biosystems). The genes were selected taking into account their involvement in a candidate gene network related to myelin structure and oligodendrocyte development (MAG, MBP, MOG, CNP, PTEN, QKI, OMG, FYN, and OLIG2). Hardy-Weinberg Equilibrium (HWE) and Linkage Disequilibrium (LD) were tested with HAPLOVIEW v4.1. Single Genetic association analyses were conducted using PLINK and were adjusted for multiple testing.

Results: Significant association was observed between haplotypes in CNP gene (2',3'-Cyclic Nucleotide 3' Phosphodiesterase, 17q21) and SZ (corrected P -values <0.04), and also between haplotypes in MAG (Myelin Associated Glycoprotein, 19q13.1) and ASD (corrected P -values <0.05). Moreover, haplotypes in MBP (Myelin Basic Protein, 18q23) and MOG (Myelin Oligodendrocyte Glycoprotein, 6p22.1) genes were nominally associated with both diagnoses

Discussion: Our findings seem to indicate the implication of myelin/oligodendrocyte genes in the risk for both SZ and ASD. These results are in line with other studies (Vourc'h *et al.*, 2003, Voineskos *et al.*, 2008) and add evidence to the suggested link between these genetic variants and white matter alterations described in both disorders. Moreover, our study shows that within the analyzed candidate gene network some of the genetic risk variants seem to be shared across the SZ-ASD continuum while others would be disease specific. This highlights the interest of conducting studies on more specific phenotypes across the SZ-ASD continuum.

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M192. Expression of GRM3 and of the splicing isoform GRM3Δ4 in human post-mortem hippocampal tissue across the lifespan: relevance to schizophrenia

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Background: Recently, the PGC has reported GWAS significant association of the metabotropic glutamate receptor 3 encoding gene (GRM3) with schizophrenia, confirming the role of GRM3 as a candidate gene for this disorder. Also, a splice variant, GRM3Δ4, has been found and it encodes a truncated form of the receptor expressed in human prefrontal cortex and hippocampus. Finally, age-related changes in the expression of GRM3 in human prefrontal cortex have been found, but hippocampal data are still few.

In this study, we determined the hippocampal expression of GRM3 and GRM3Δ4 in healthy subjects and schizophrenia individuals. Then, we investigated whether the expression of GRM3 and GRM3Δ4 is affected by selected risk associated genotypes, (SNPs rs12704290 and rs11982256) recently reported to be associated with schizophrenia. Finally, we investigated the possible correlation between gene expression and age in both populations

Methods: RNA sequencing data were available from the Brain Tissue Collection of the Lieber Institute for Brain Development for 79 Caucasian and African American individuals that met DSM-IV criteria for schizophrenia and for 182 controls matched for age (age range 17-70) from post-mortem hippocampus. Analyses of covariance were conducted with age, sex, and RNA integrity number as basic covariates for gene expression and genotype associations. Pearson's linear correlation coefficient was used to analyze the significance and

the direction of the association between gene expression and age. Fisher's r -to- z transformation was applied to assess the significance of the difference between the correlation coefficients found in controls and schizophrenia patients. All data processing was performed using R statistical language.

Results: Schizophrenia patients showed lower expression of GRM3 ($P=0.03$) and Exon1 ($P=0.03$), Exon3 ($P=0.02$), Exon4 ($P=0.01$), and Exon5 ($P=0.002$) compared to matched controls. No genotype association was found with the SNPs considered in this study with gene or exons expression in both populations. GRM3Δ4 expression did not reach significant difference between cases and controls, nor was affected by the selected SNPs.

Increases in age significantly predicted lower GRM3 expression in both controls ($r=-0.18$, $P=0.01$) and schizophrenia patients ($r=-0.37$, $P=0.0008$). All exons showed an inverse correlation with age in schizophrenia patients ($P < 0.05$) while only Exon2, Exon4, Exon5, and Exon6 were inversely correlated with age in controls ($P < 0.05$).

Discussion: Glutamatergic dysfunctions are believed to be key players in schizophrenia pathophysiology and future treatment strategies. In this study, we have reported a lower expression of GRM3 in schizophrenia patients hippocampal brain tissue compared to matched controls and the existence of an inverse correlation of GRM3 expression with age, that tends to be more prominent in schizophrenia patients. Therefore, further studies are required in order to explore the biological and functional correlates of these expression analyses in the context of schizophrenia pathophysiology and therapy.

M193. Different multilevel phenotypes for schizophrenia based on disrupted signaling genes

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Background: GWAS studies in schizophrenia have not yielded targets for person-specific interventions. Alternatively, studies can focus on genes that were initially identified as harboring disruptive de novo mutations in sporadic cases. We examined the impact of four such genes on illness phenotypes.

Methods: Structured interviews (DIGS), cognition (WAIS III), symptoms (PANSS) were examined in 48 genotyped cases finding that over 30% of the sample carried a rare/missense mutations in any of 4 genes. Gene carrier groups were compared to cases without any of these mutations and healthy controls.

Results: Carriers of different disrupted genes showed significant differences, as follows. SLC39A13 (zinc transporter) ($n=4$) greatest psychopathology and severe cognitive deficits; TGM5 ($n=4$) less symptoms but specifically slower processing speed; PTPRG ($n=5$); prematurity and childhood psychosis, good cognition except poor working memory ARMS/KIDINS220 ($n=5$): comparable severe pathology in all symptom factors and cognitive scores, degeneration is suggested in light of their early accomplishments. Individual case vignettes highlighted familial psychosis, learning disorders, substance abuse, traumatic brain injuries, and medical comorbidity in all 4 subgroups.

Discussion: The results suggest that genes prone to de novo mutations in sporadic cases may provide missing leverage to resolve the complexity of schizophrenia. A differential focus on working memory, processing speed, neuroprotection, and zinc treatment should be pursued for these newly identified conditions. Other findings are that ethnicity may not limit genetic research when the focus is gene function rather than particular sequence variations and that pre-morbid exposures may sometimes reflect pleiotrophic effects of psychosis vulnerability genes rather exposures producing nongenetic phenocopies. This novel approach may be applicable to other complex disorders.

M194. Genome-wide expression and DNA methylation analysis in a Brazilian cohort of antipsychotic-naïve first episode of psychosis patients

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Background: The investigation of individuals during their first-episode psychosis (FEP), before the progression and the treatment with antipsychotic medications, is helpful for understanding the complexity of schizophrenia. Considering that schizophrenia is a chronic condition, disease progression, and use of antipsychotic medication can confound results on gene expression and DNA methylation. Our main aim of this study is to identify genetic markers using transcriptomic and methylomic approaches in a cohort of FEP.

Methods: For this study we selected 60 controls and 60 FEP patients at first onset (antipsychotic-naïve patients) with confirmed diagnosis of schizophrenia after 2 months of follow-up. All patients are between the ages of 18-40 fulfilling criteria for psychotic diagnoses according to the DSM-IV. Blood was collected for DNA and RNA extraction. We generated gene expression data (Illumina HT-12 BeadChip), DNA methylation data (Illumina HumanMethylation 450 BeadChip) and genotype data (Illumina Psych Array). We applied careful quality control for all datatypes and investigate changes in expression and methylation using linear models, and gene co-expression network based approaches (WGCNA). For all analyses sex, age, and smoking data were used as covariables. In addition, we studied this in the context of genotypes by generating polygenic risk scores and expression quantitative trait loci.

Results: For now, we found 24 genes upregulated and 16 down-regulated in FEP when compared to controls (Bonferroni P -value < 0.05 and [fold change] > 0.2). Moreover, the WGCNA analysis identified 5 modules significantly correlated to the phenotype and the Gene Ontology Enrichment analysis showed many biological processes enriched for these modules, including inflammatory response, RNA processing, and translational elongation and termination. Besides, by the date of the conference, we will present differential methylation results between cases and controls, and the correlation between gene expression and methylation results. We will place them into a biological context by applying network based co-expression and enrichment analyses. Inclusion of genotype-based results will reveal the relationship between overall genetic risk for schizophrenia and treatment as well as a genetic basis of individual and network expression, and methylation results.

Discussion: These patients are all antipsychotic-naïve, received the same treatment protocol with risperidone and have multiple layers of genetic information collected at different timepoints. Here, we found not only genes already studied in schizophrenia, but also novel genes that might be related to the onset of disease and are not detectable after drug treatment. To our knowledge, this sample is unique and it will reveal detailed genetic signatures associated with schizophrenia, treatment duration, and treatment response. We expect these findings will provide a singular resource to help understand the biological processes of schizophrenia before and right after treatment intervention.

M195. Brain asymmetry and schizophrenia in the postgenomic age – how a symptom-based approach might help uncovering the genetic link

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Background: Most people are right-handed and show left-hemispheric language lateralization, but a minority exhibits left-handedness and right-hemispheric language lateralization. This atypical laterality pattern is observed significantly more often in schizophrenia patients than in the general population, which led several authors to conclude that there is a genetic link between laterality and schizophrenia. It has

even been suggested that a failure in the lateralization process, orchestrated by genes, could be the primary cause of schizophrenia. However, the molecular genetic evidence for a link between laterality and schizophrenia is weak.

Methods: Recent genetic evidence indicates that schizophrenia is not a single disorder but a group of heritable disorders caused by different genotypic networks leading to distinct clinical symptoms. To uncover the link between schizophrenia and laterality, we therefore suggest a paradigm shift where genetics are not mapped on schizophrenia as a whole but on discrete schizophrenia symptoms. For instance, some lateralized functions, like language, can be directly linked to certain symptoms (e.g., auditory verbal hallucinations, disorganized speech) because both pertain to the same cognitive system (i.e., language). Other symptoms, such as catatonic behavior, for example, may not show such a clear-cut association with atypical laterality.

Results: Specifically, we propose that each major schizophrenia symptom should be assessed with detailed and specialized questionnaires such as the Psychotic Symptom Rating Scales or the Auditory Hallucinations Rating Scale for hallucinations and the Scale for the Assessment of Negative Symptoms, the Negative Symptoms Assessment, or the Clinical Assessment Interview for Negative Symptoms for negative symptoms, for example. Moreover, since different lateralized functions seem to have partly independent genetic determinants, we would suggest to always assessing hand preference, hand skill, and a behavioral measure of language lateralization (e.g., the dichotic listening task) as basic asymmetry phenotypes. In addition, behavioral markers of other lateralized functions (e.g., emotional or spatial processing) and markers of structural brain asymmetries (e.g., measured with voxel-based morphometry of diffusion tensor imaging) might be of interest. The same phenotypes need to be examined in patients with schizophrenia and healthy controls.

Discussion: Taken together, we hope that such a symptom-driven approach, in which specific symptoms are associated with specific lateralized functions, can help to stimulate new research that might help to finally disentangle the riddle of how laterality is related to schizophrenia.

M196. Lack of association and linkage of schizophrenia to chromosome 22q11 in Korean population

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Background: Chromosome 22q11 has been reported to be a susceptibility locus of schizophrenia. It also contains various candidate genes for which evidence of association with schizophrenia has been reported. However, negative results were also generated from both linkage and association analyses. To determine whether genetic variations in chromosome 22q11 are associated with schizophrenia in the Korean population, we performed linkage analysis and case-control association study.

Methods: Three microsatellite markers within a region of 4.35 Mb on 22q11 were genotyped for 47 multiplex schizophrenia families, and a non-parametric linkage analysis was applied. The association analysis was done with 227 unrelated patients and 292 normal controls. For 39 SNPs spanning 1.4 Mb region (33 kb interval) which contains four candidate genes of schizophrenia, i.e., DGCR, COMT, PRODH, and ZDHHC8, allele frequencies were estimated in pooled DNA samples.

Results: Five SNPs showed suggestive evidence of association ($P < 0.05$) and two more SNPs showed a trend for association ($P < 0.1$). Individual genotyping was performed for those seven SNPs and four more intragenic SNPs. In this second analysis, all of the eleven SNPs individually genotyped did not show significant association.

Discussion: The present study suggests that genetic variations on chromosome 22q11 may not play a major role in the genesis of schizophrenia in Korea.

M197. Disturbance of metabotropic glutamate receptor-mediated long-term depression (mGlu-LTD) of excitatory synaptic transmission in the rat hippocampus after prenatal immune challenge

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Background: Prenatal immune challenge has proved to induce moderate to severe behavioral disabilities in the offspring. These defects are underlined by changes in synaptic plasticity especially in the hippocampus. In this line we have previously reported that prenatal exposure to bacterial LPS could induce inhibition of long-term potentiation in the CA1 area of the male offspring associated with spatial learning inabilities. Nevertheless, these changes were observed in juvenile/adult rat. We have recently reported that deficits of synaptic plasticity could be observed in immature animals as shown by the early loss of the ability of synapses to undergo long-term depression. Moreover, aberrant forms of plasticity were also evidenced such as the transient occurrence of LTP instead of LTD in 15-25 day-old animals. Interestingly this switch from LTD to LTP seemed to involve the activation of metabotropic glutamate receptor subtype 1 and 5 (mGlu1/5). We have thus investigated whether the long-term depression elicited by the direct activation of these receptors (mGlu-LTD) which a selective agonist (DHPG) was also disturbed after prenatal stress.

Methods: Experiments were conducted on hippocampal slices obtained from 4-70 day-old rats born from stressed dams. For this, maternal immune challenge was performed by injecting (ip) LPS (500 µg.kg⁻¹) at E19. Synaptic transmission was evoked in the CA1 subfield by stimulating afferent fibers (Schaffer collaterals/commissural fibers) at 0.066 Hz. Field excitatory postsynaptic potentials (fEPSPs) were recorded microelectrode arrays (MEAs). Slices were perfused with extracellular medium at 37 °C and drugs were directly applied to the perfusate.

Results: We find that in prenatally stressed rats, DHPG elicits long-term potentiation (DHPG-LTP) independently of N-methyl-D-aspartate receptors. Further pharmacological characterization with selective antagonists LY367385 and MPEP of mGlu1, and mGlu5, respectively, indicates that mGlu5 and, to some extent mGlu1 receptors, are involved in this switch of plasticity. Moreover, this DHPG-LTP is observed at later developmental stages than previously observed, i.e. after 25 day-old. The long-term depression associated with the activation of CB1 cannabinoid receptor is unaffected by prenatal stress.

Discussion: Our data show that prenatal stress drastically alters mGlu1/5-associated plasticity throughout development. These findings are in full agreement with our previous contribution (Escobar *et al.*, 2011, Biological Psychiatry) showing that prenatal stress profoundly altered excitatory synaptic transmission not only by decreasing NMDA receptors expression but also by modifying mGlu action on synaptic plasticity. Indeed, prenatal stress changed completely the outcome of afferent stimulation converting LTD to LTP. The direct activation of these receptors can thus reproduce such changes. However, the alterations of mGlu-mediated plasticity are observed on a longer time-scale than those obtained when triggering plasticity with electrical stimulation. This suggests that mGlu-mediated plasticity is good index of the long-lasting deficits reported in this model. Behavioral experiments will be undertaken to assess the relevance of this switch in plasticity in the cognitive deficits elicited by prenatal stress.

M198. ErbB signaling inhibition ameliorate behavioral deficit induced by phencyclidine (PCP) in mice

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Background: The ErbB signaling pathway has been genetically and functionally implicated in schizophrenia. Numerous findings support the dysregulation of neuregulin (NRG) and epidermal growth factor

(EGF) signaling pathway in schizophrenia. Higher NRG1, ErbB1, and ErbB4 expression levels were reported in postmortem dorsolateral prefrontal cortex of schizophrenia patients. In addition, perinatal administration of EGF or NRG to neonatal mice, or overexpressing the NRG1 type I isoform resulted in schizophrenia-like behavior as abnormal social behavior, spatial working memory, and sensorimotor gating. Moreover, infusion of NRG1 to adult mice into the hippocampus increases levels of extracellular dopamine (DA), while perinatal exposure to EGF or NRG evokes overflow of extracellular striatal DA. Taken together, these data support the idea that hyperactivation of the ErbB signaling which probably triggers changes in the dopaminergic system may underlie the role of the pathway in the etiology of schizophrenia, and suggesting that inhibition of the pathway might serve as a novel candidate as drug development for schizophrenia. Herein, we studied, in mice, the capability of blocking the ErbB signaling, in comparison with the atypical antipsychotic drug clozapine, to counter schizophrenia-like behavior induced by administration of the psychostimulant phencyclidine (PCP).

Methods: ICR mice were treated acutely or sub-chronically with either saline or 5 mg/kg or 10 mg/kg PCP, respectively. 30 min before the behavioral testing mice were injected with either 5 mg/kg, 10 mg/kg JNJ-28871063 (JNJ), a potent pan-ErbB kinase inhibitor that crosses the blood brain barrier, or 2 mg/kg clozapine, while the control group was injected with saline. Acute PCP-treated mice were subjected to the open field task, while sub-chronic PCP-treated mice were tested in novel object recognition and sociability tasks.

Results: We demonstrated that administration of 5 mg/kg JNJ, but not 10 mg/kg, significantly reduced the mice hyperactivity that was induced by an acute injection of PCP as measured in the open field. Moreover, the ability of 5 mg/kg JNJ to attenuate the effect of PCP found to be as effective as 2 mg/kg clozapine. In addition, we showed that, like clozapine, both 5 mg/kg and 10 mg/kg JNJ ameliorated the social deficit induced by sub-chronic administration of PCP. Administration of JNJ did not alter spontaneous activity in the open field, and has no effect on social recognition.

Discussion: Our preliminary data suggest that treatment with JNJ attenuate abnormal behaviors induced by PCP, and has similar effects as the antipsychotic drug clozapine. Thus, the ErbB signaling pathway, a modulator of the dopaminergic systems, can be a novel candidate and a new starting point for drug development for schizophrenia.

M199. Glutamate dehydrogenase-deficient mice: a novel mouse model of schizophrenia-like phenotypes

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Background: Glutamatergic abnormalities are commonly observed in schizophrenia (SZ), but all current medications for SZ symptoms target monoaminergic neurotransmitter systems, and are inefficient in treating all symptom clusters. Animal models that capture glutamatergic abnormalities in SZ and mimic its behavioral and neurochemical attributes are critical for better understanding of the neurobiology of the disorder and for the development of new pharmacological treatments. Recent findings indicate that expression of glutamate dehydrogenase (Glud1) mRNA is reduced in the hippocampus of patients with SZ, particularly in the CA1 subregion. Glud1 encodes the GDH protein, a mitochondrial enzyme that converts glutamate to alpha-ketoglutarate. Aim: To assess whether a dose-dependent genetic alteration in CNS Glud1 expression in mice affects glutamate levels, and alters behavioral and gene expression patterns relevant to SZ, alone or with added social isolation stress in adolescence.

Methods: Male and female CND-Glud1 deficient (CND-Glud1^{+/-} and CND-Glud1^{-/-}) or control (CND-Glud1^{+/+}) mice were divided into social isolation or group-housing conditions from postnatal day (PND) 38 to PND60 and then tested for SZ-relevant behavior. Our behavioral battery included nesting behavior, locomotor activity, and anxiety-like behavior in open field, social preference and social recognition in the three chambers paradigm, wet T-maze for reversal learning and extra-

dimensional set shifting and amphetamine-induced locomotor activity (2 mg/kg). Hippocampal samples from behaviorally naïve CND-Glud1^{-/-} and control group housed mice were analyzed for glutamate content and for mRNA gene expression of excitatory (glutamatergic) and inhibitory (GABAergic) markers.

Results: CNS-Glud1-deficient mice show elevated glutamate levels in the right hippocampus. Behaviorally, CNS-Glud1-deficient mice exhibit impaired nesting behavior, baseline, and amphetamine-induced hyperactivity in the open field, and deficits in reversal learning and extra-dimensional set shifting. Social Isolation in adolescence induced hyperlocomotion at baseline in all mice, increased amphetamine-induced locomotor activity in control mice, and triggered reversal and extra-dimensional set shifting deficits in CND-Glud1^{+/-} mice. Expression of GAD1 mRNA was reduced in the right hippocampus of CNS-Glud1^{-/-} mice, and there was an overall reduction in the expression of inhibitory markers, consistent with commonly observed reductions in markers of hippocampal GABA interneurons in SZ.

Discussion: Collectively, these studies show that Glud1 deficiency phenocopies key features of SZ in mice. Thus, Glud1 may play a critical role in SZ-related pathology and moreover, glutamate metabolism in the hippocampus may drive SZ-related pathology. These findings could lead to better understanding of SZ etiology and provide new treatment venues for its symptoms.

M200. Deficits in neuronal and gabaergic markers in the frontal cortex following sub-chronic phencyclidine treatment in the rat – correlates with schizophrenia

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Background: Cognitive impairment associated with schizophrenia is now recognized as a potential psychopharmacological target for treatment. To better understand the factors and mechanisms underlying cognitive deficits, reliable pre-clinical models that mimic the underlying pathology observed in schizophrenia are needed. Deficits in cognition and social behavior induced by sub-chronic (sc) treatment with the N-methyl-D-aspartate receptor antagonist phencyclidine (PCP) along with reduced levels of the Ca²⁺ binding protein parvalbumin, located in fast spiking GABA interneurons, have reliably been demonstrated in our laboratory (Neill *et al.*, 2010, PMID: 20705091; Harte *et al.*, 2014, Schizophrenia Research, Volume 153 - page 282).

Magnetic resonance spectroscopy (MRS) has been used to study possible neuronal abnormalities in vivo in schizophrenia. One of the most consistent MRS findings in schizophrenia is reduced levels of the neuronal marker N-acetylaspartate (NAA) in the frontal lobe [2]. Another aspect of pathology of relevance to the observed cognitive deficits concerns the downregulation of GABAergic neurotransmission, manifested as reduced expression of glutamic acid decarboxylase 67 (GAD67), a key synthesizing enzyme for GABA (Brugger *et al.*, 2011, PMID: 21145039). In the present study we examined the influence of our scPCP treatment regime on in vivo and subsequent ex vivo post-mortem levels of NAA and on the expression of GAD67 in the frontal cortex (FC).

Methods: 40 adult female hooded-Lister rats, received vehicle or sub-chronic PCP (2 mg/kg) i.p. twice daily for 7 days, followed by 7 days washout ($n=20$ per group). Following conformation of behavioral deficits analyze the effect of scPCP on NAA levels we employed in vivo MRS and ex vivo post-mortem HPLC detection respectively and a quantitative western blotting strategy for GAD67.

Results: In vivo MRS studies demonstrated a significant reduction of NAA levels in the FC following scPCP treatment (~35-40%, $P < 0.05$ vs Vehicle). In support of the MRS data we also found similar deficits in NAA in the FC following HPLC analysis in the same cohort of rats ($P < 0.001$ vs Vehicle). We found significant deficits in GAD67 expression following scPCP treatment (22%, $P < 0.05$ vs Vehicle) in synaptic fractions from the FC, a principal site of GABA production and function.

Discussion: These data represent further validation of our scPCP model to reproduce different pathological deficits observed in schizophrenia. We recently showed that chronic treatment with AUT00206, a novel Kv3.1 channel modulator, has efficacy to reverse a scPCP-induced cognitive deficit and the accompanying reduction in parvalbumin

interneurons (Harte *et al.*, 2014, Schizophrenia Research, Volume 153 - page 282). Moreover, it has been reported that these voltage-gated Kv3.1 potassium channels are responsible for rapid repolarization of the action potential in these interneurons (Johnston *et al.*, 2010, PMID: 20519310). Our next aim is to explore the efficacy of AUT00206 to restore neuronal functioning essential for normal cognitive processing in the scPCP model.

M201. Constitutive loss of ERBB4 signaling does not affect attention and inhibitory control in mice

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Background: The receptor tyrosine kinase ErbB4 and its ligand trophic factors of the neuregulin (NRG) family have been associated with schizophrenia and other mental disorders in human genetic studies. At the molecular level Nrg-ErbB4 signaling has been implicated in neural development and synaptic plasticity, whereas at the behavioral level this pathway seems to contribute to positive and cognitive symptoms of schizophrenia. In-vivo studies in mice have shown how abnormal Nrg-ErbB4 signaling leads to deviant behaviors relevant to distinct aspects of schizophrenia, including hyperactivity, sensorimotor deficits in pre-pulse inhibition, impaired nest-construction capacity, working and spatial memory deficits, and impaired social behavior. However, no studies have so far shown the direct involvement of ErbB4 in cognitive tasks measuring attention and inhibitory control, two aspects of executive function impaired in schizophrenia.

Methods: We investigated the effects of constitutive loss of ErbB4 in the central nervous system of mice on performance in a 5-choice serial reaction time task (5CSRTT) assessing attention and inhibitory control, as well as the effect on several other behavioral tests relevant to schizophrenia. Male ErbB4^{+/+} ($n = 14$) vs. ErbB4^{-/-} ($n = 15$) mice were tested between 8 and 12 weeks of age in a battery of tests that targeted specific domains: general health assessment (spontaneous behaviors, vision test, and grip strength meter test), motor function (activity in the open field, OF), anxiety-like behavior (elevated plus maze, EPM; dark-light box, DLB; novel cage-induced hypophagia), spatial and working memory (T-maze; Barnes maze, BM), contextual and cued fear learning and memory (fear conditioning, FC), sensorimotor gating (pre-pulse inhibition, PPI), and nesting behavior.

Results: In contrast to our hypothesis, ErbB4^{-/-} mice did not show deficits in attention and inhibitory control in the 5CSRTT. In line with previous reports of impairments in hippocampal function, ErbB4^{-/-} mutants showed deficits in nest building and impaired performance in the probe trial of the BM. ErbB4^{-/-} mice displayed no differences in spontaneous behavior in a habituated environment, in contrast with activity in novel situations, such as on the EPM and in the OF, where ErbB4^{-/-} mice displayed higher activity, without a clear anxiety-related phenotype. In FC, we observed reduced freezing levels 24 h after shock, potentially linked to hippocampal function deficits or to an increase of general activity of ErbB4^{-/-} mice in novel conditions. Moreover, ErbB4^{-/-} mice displayed impaired startle response and reduced PPI at a 30-ms interval.

Discussion: In contrast to our hypothesis, the specific endophenotypes related to schizophrenia in the domain of cognitive control, i.e., attention and inhibitory control, were spared in ErbB4^{-/-} mice. Nonetheless, our data suggest that ErbB4^{-/-} mice recapitulated most of the behavioral phenotypes associated with schizophrenia, further confirming the role of Nrg-ErbB4 signaling in this disorder.

M202. Multimodal brain analysis in psychosis risk – the Oulu brain and mind study

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Background: Severe psychiatric disorders like schizophrenia typically have their onset in adolescence or early adulthood. The detection of

people who are at highest risk of developing schizophrenia has been challenging. Currently there are no biological tests to predict onset of schizophrenia before psychotic symptoms have already been developed. Recently a number of studies on brain have shown promising results, but no guidelines have been able to form for clinical work. We were able to conduct a multimodal brain analysis relatively large sample of people in young adulthood. The aim was to find out most significant abnormalities in brain function in people at risk for developing psychosis.

Methods: The Oulu Brain and Mind study sample consisted of 329 members of the Northern Finland 1986 Birth Cohort at age 21-24 years. Their mental health was assessed comprehensively by interviews and questionnaires. We were able to form two psychosis risk groups: Symptomatic Risk for Psychosis and Familial Risk for Psychosis. The MRI scanning methods included structural MRI, Diffusion Tensor Imaging (DTI), Resting state functional MRI (R-fMRI) and fMRI with three different tasks (Sternberg test, facial recognition task and prediction error task). Additionally a battery of cognitive test was used. The scanner was a GE Signa 1.5 Tesla MRI.

Results: The two psychosis risk group did not differ from control group or each other in cognitive profile. In the structural analysis we found gray matter volume reduction in a small area covering both cerebellar hemispheres and the vermis in subjects who had both symptomatic and familial risk for psychosis compared to control subjects. In the R-fMRI we found lower activation in familial risk group compared to control group in the posterior cingulate cortex, right inferior frontal gyrus and anterior lobe of the right cerebellum. In the facial recognition test we found FR subjects increased activity in premotor cortex and under-deactivation of prefrontal cortex structures during happy facial expression. In the white matter analysis (DTI) no differences were found.

Discussion: We had multiple gray matter findings both in structural and functional analysis, but none in white matter analysis. The study suggests that gray matter networks lie behind psychosis risk; and white matter integrity deficits may develop later on in psychosis.

M203. The effect of deviance predictability on mismatch negativity in schizophrenia patients

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Background: Mismatch Negativity (MMN) is an electrophysiological index of prediction error processing and has been considered an endophenotype marker in schizophrenia. While the prediction error is a core concept in the MMN generation, predictability of deviance occurrence has rarely been assessed in MMN research and in schizophrenia patients.

Methods: We investigated the MMN to 12% temporally predictable or unpredictable duration decrement deviant stimuli in two runs in 29 healthy controls and 31 schizophrenia patients. We analyzed MMN amplitudes and latencies, and its associations with clinical symptoms at electrode Fz. With a stimulus onset asynchronicity of 500 ms in the regular predictable condition, a deviant occurred every 4 seconds while it varied randomly in the unpredictable condition.

Results: In the random condition we found diminished MMN amplitudes in patients which normalized in the regular deviance condition, resulting in an analysis of variance main effect of predictability and a predictability × group interaction. Deviance predictability did not affect the MMN of control subjects and we found no relevant results with regard to MMN latencies.

Discussion: Our results indicate that MMN amplitudes in patients normalize to the level of control subjects in the case of a temporally fixed regular deviant. In schizophrenia patients the detection of deviance is basically intact. However, the temporal uncertainty of deviance occurrence may be of substantial relevance to the highly replicated MMN deficit in schizophrenia patients.

M204. Developmental molecular profiles of human choroid plexus epithelial cells determined by whole transcriptome RNA sequencing

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Background: Increasing evidence from rodent studies has implicated the homeobox protein orthodenticle homeobox 2 (OTX2) as playing a critical role in orchestrating the postnatal maturation of neural circuitry of the cerebral cortex. The choroid plexus (CP) appears express a major supply of OTX2 in the postnatal brain. Recent evidence suggests that the CP might also play a role in the developmental pathophysiology of schizophrenia (SZ). In this study, we use whole transcriptome RNA sequencing (RNA-Seq) to determine the molecular profiles associated with human CP epithelial cells during postnatal development.

Findings of this study will provide insight into the molecular underpinnings of the regulation of OTX2 production in the CP during postnatal human development. In this context, OTX2 deficit has recently been observed in subjects with SZ and developmental events that are regulated by OTX2 also appear to be disturbed in this illness. **Methods:** Using the Arcturus XT[®] Laser Capture Microdissection (LCM), CP ependymal cells were captured individually from each sample using a developmental cohort of control subjects age ranging from 92 days to 26 years ($N=21$). Total RNA was then isolated using the Picopure[®] mRNA Isolation Kit from Arcturus[®], and amplified. Expression profiling experiments were conducted by Life Technologies in San Francisco, CA. Libraries were constructed using the Ion Ampliseq Human Transcriptome kit, templated using Ion Chef, and sequenced on Ion Torrent Proton instruments using PI chips. Sequences are aligned using Ion Torrent Suite algorithms. Transcript abundance is analyzed by normalizing to reads per million reads using the Ampliseq RNA analysis plug-in available in the Torrent Suite software. A quartile normalization of the geomean of the top 1500 genes ranked by average expression was performed, followed by a normalization to transthyretin (TTR), a known human post-mortem transcript highly expressed in the CP, to determine age-related clusters. Additional quartile normalization was performed within the distributed data to illustrate genetic differences within the sample group.

Results: Preliminary results of the mRNA expression analysis show which genes are modified from infancy to early-adulthood. Further analysis will shed light on the potential developmental nuances of the CP in subjects with SZ.

Discussion: Our results contribute to the limited data set of sequenced CP transcriptomes, and is novel in its survey of the developmental genome. Our results show that ribosomal-encoding transcripts, transcripts involved in signal transduction, cytoskeletal organization and neuronal development are developmentally regulated. These results give insight into the CP genetic development and regulation from infancy to early-adulthood; a period of time during which deviations of brain circuitry formation are thought to occur in SZ. The brain undergoes extensive developmental changes during adolescence, including the remodeling and pruning of circuitry in neuronal networks that eventually lead to cognitive maturation in adulthood. Recent data suggests that OTX2, which is transcribed, translated, and secreted by the CP in the postnatal brain, might play a critical role in the regulation of these developmental processes, raising the possibility that functional dysregulation of the CP may contribute to SZ disease onset by disturbing the supply of OTX2. As such, comparison of findings of this study and possible alteration in the molecular signature of CP epithelial cells in SZ may shed light onto the pathophysiology of this illness and potential corrective strategies.

M205. Augmentation of human neocortical gamma oscillations with a novel Kv3 positive modulator *in vitro*

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Background: The failure of translation of biological effects from preclinical animal models to humans is a major barrier to the development of new and effective medicines for CNS disorders, particularly in psychiatry. One reason for this failure may be that human cortical microcircuits are likely to be more complex and exhibit different physiology and pharmacology to rodent neuronal circuits. As such, performing research in rodent systems has significant limitations and to reduce the risk of failure in the clinic it would be highly preferable to perform basic research in adult human brain tissue to eliminate species difference confounds and validate the efficacy of medicines in assays that are directly derived from the target organ that they are intended to treat. Synchronous gamma frequency oscillations (30-80 Hz) are critical for processing and integrating cognitive modalities. Previous studies in patients suffering from schizophrenia¹ condition demonstrate an inability of neocortical networks to generate coherent gamma frequency oscillations. Kv3-family potassium channels such as Kv3.1 are selectively expressed in PV+ interneurons in the neocortex. Kv3 channels allow fast-spiking PV + interneurons to fire accurately at high frequencies to orchestrate the activity of neocortical networks. Such high rates of firing, with high temporal accuracy, are required for the generation of neocortical gamma rhythms. In addition, 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: Targeting Kv3 channels, and enhancing the activity of PV+ interneurons, has potential as a pharmacological treatment for patients suffering from schizophrenia. We have, therefore, examined the effect of a novel Kv3 modulator (AUT00206) in slices of resected human neocortical tissue. These samples were obtained from patient undergoing elective neurosurgery for the removal of brain tumors. Non-epileptic comparison tissue overlying the tumor was obtained during the debulking procedure. Persistent gamma frequency oscillations were elicited by the bath application of kainate (400-600 nM).

Results: *In vitro* human gamma oscillations were not altered by the application of AUT00206 (10 microM; $n=3$ slices). In order to acutely model network alterations associated with schizophrenia we then tested the impact of the psychotomimetic agent PCP on human cortical gamma activity. Following application of PCP, we then tested the impact of AUT00206 on human cortical gamma oscillations. In the slices that had undergone acute treatment of PCP, AUT00206 (10 microM) we observed a significant increase (50%) in gamma oscillation power ($n=6$ slices). In addition, we have also been able to record activity in frontal cortical slices obtained from a patient undergoing neurosurgery who suffered from chronic schizophrenia. In that instance, AUT00206 alone was able to significantly increase (47%) the power of kainate induced oscillations ($n=3$ slices).

Discussion: In summary these results demonstrate, for the first time using ex vivo live human brain tissue, that AUT00206 significantly increases the power of network oscillations in human neocortical networks only in slices that been exposed to PCP. Moreover, we show that in slices obtained from a patient with chronic schizophrenia, gamma oscillation can be augmented by AUT00206. 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.

M206. Fragmentation of the presynaptic protein SNAP-25 is reduced in the orbitofrontal cortex of subjects with schizophrenia: a possible mechanism enhancing snare function

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Background: In the presynaptic terminals, Ca²⁺ influx rapidly triggers SNARE (N-ethylmaleimide-sensitive factor attachment protein receptor)-mediated vesicle fusion and neurotransmitter release. When micromolar Ca²⁺ concentrations are achieved and sustained in certain microdomains, a plethora of downstream pathways are additionally activated, including several proteolytic enzymes such as calpains. Beyond metabolism, proteolysis may serve as a negative feedback to tone down or switch off specific cellular functions, with potential roles in neuromodulation and synaptic plasticity. Using postmortem human brain tissue, we previously showed that schizophrenia (SCZ) was associated with enhanced SNARE complex assembly in the orbitofrontal cortex (OFC). Here, we surveyed for proteolytic fragments (PFs) of SNARE core proteins SNAP-25 (S25), syntaxin-1 (STX), and VAMP, along with key binding partners Munc18-1 (M18) and synaptotagmin (STG). Further, we quantified full-length (FL) and PFs of these presynaptic targets in the OFC of SCZ cases and matched controls, and investigated their potential relation with SNARE dysfunction.

Methods: OFC (Brodmann's area 10/47) samples from 20 SCZ and 13 control subjects were collected at the Macedonian/New York State Psychiatric Institute Brain Collection. Total homogenates and syntaxin-1-immunoprecipitation (IP) products were run in SDS and/or blue-native (BN) gels, and resolved by immunoblotting with specific antibodies. Criterion for PF identification included the detection of sharply defined bands below FL target-specific molecular weight, with at least 2 different antibodies. Additionally, alkaline phosphatase (AP) was used to fully dephosphorylate brain samples and study functional binding properties of PFs to STX, possibly interfering with SNARE assembly.

Results: We identified PFs for S25 at ~15 kDa, M18 at ~50 kDa, and STG at ~42 and ~35 kDa, but none for STX1 or VAMP. In STX co-IP extractions, S25 and M18, but not STG, PFs were further immunodetected, suggesting a functional role for these PFs in the SNARE cycle. Furthermore, S25 PF interaction with STX was threefold lower in AP-treated brain homogenates. In the OFC of SCZ subjects, S25 PF (but not FL) immunodensity was significantly reduced (50%, $P=0.005$) compared to healthy controls. Including sex, age, brain pH, antipsychotic medication intake, and β -actin levels as covariates in the model ($F(6,26)=4.82$, $P=0.002$) the significance of clinical diagnosis (β -coefficient=0.22; $P=0.009$) was not altered, although a pronounced age-dependent effect was unmasked (β -coefficient=0.01; $P=0.009$). We could not covary for postmortem interval (PMI) because it significantly differed between SCZ and control groups. However, using an independent human postmortem brain cohort, we did not observe significant PMI effects on S25 PF. Interestingly, S25 PF and FL S25 immunodensities showed respectively negative ($i=-0.386$; $P=0.026$) and positive ($r=0.297$; $P=0.093$) associations when correlated with 150-kDa SNARE complexes, as previously quantified by BN-PAGE in the same OFC samples. M18 and STG PFs did not show significant associations with SNARE complex density, and were not altered in SCZ OFC compared to controls.

Discussion: These results indicate that the proteolytic fragmentation of S25 may be a novel physiological mechanism modulating SNARE activity by sequestering STX into a nonfunctional complex. Disturbed proteolytic processing of S25 may facilitate the enhanced SNARE function observed in SCZ brain. Future studies should address the identification of proteolytic enzymes responsible for S25 cleavage.

M207. Glutamate decarboxylase, somatostatin and parvalbumin expression in the thalamic reticular nucleus in patients with schizophrenia and mood disorders

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Background: The thalamus plays a key role in facilitating sensory discrimination and cognitive processes through its connections with all cortical regions. Located between the dorsal thalamus and the cortex is the thalamic reticular nucleus (TRN), a thin sheet of GABAergic neurons. This nucleus sends inhibitory projections to other thalamic nuclei, modulating the flow of information from the thalamus to the cortex. The TRN is involved in sensory gating, attentional modulation, sleep spindles, γ oscillations, emotional salience and cognitive flexibility. These aspects of neural function are all disrupted in patients with schizophrenia. However, to our knowledge, there has been little characterization of the TRN in patients with schizophrenia. We aimed to characterize the TRN by examining expression of mRNA for GABAergic markers glutamate decarboxylase (GAD67), somatostatin (SST), and parvalbumin (PV).

Methods: Tissue was sourced from the Stanley Foundation Neuropathology Consortium consisting of 15 subjects in each of four groups (schizophrenia, bipolar disorder, major depression without psychotic features, unaffected controls). All groups were matched for age, race, sex, RNA Integrity Number, brain pH, and post-mortem interval. To determine the extent to which the TRN may be affected in schizophrenia, we measured GAD67, SST, and PV mRNAs in TRN using in situ hybridization. For comparison, we also measured GAD67 and PV mRNA in the medial dorsal and anterior nuclei.

Results: Comparing GABAergic markers, the level of GAD67 and SST mRNA were similar in the TRN in each group. PV mRNA was significantly lower in each group than the other GABAergic markers in the TRN. Comparing groups, there was a trend toward reduced SST expression in the TRN in schizophrenia compared with controls ($P=0.08$). We also found a ~30% reduction in PV mRNA in medial dorsal nucleus in schizophrenia compared to the control group ($P < 0.01$) as well as a ~30% reduction in PV mRNA in anterior nucleus in schizophrenia compared to the control group ($P < 0.05$).

Discussion: Neurons of the TRN express GABAergic markers GAD67, SST, and PV. These preliminary results suggest there may be a difference in the expression of somatostatin mRNA in the TRN of individuals with schizophrenia. Furthermore, there were differences in the expression of PV mRNA in higher-order thalamic nuclei, specifically the medial dorsal and anterior thalamic nuclei. These differences in GABAergic marker expression in the thalamus may contribute to impaired sensory and cognitive function in individuals with schizophrenia.

M208. Obstetric complications and neurocognition in early-onset schizophrenia

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Background: According to neurodevelopmental models, schizophrenia is the behavioral outcome of deviations in early neurodevelopment, including prenatal insults such as obstetric complications (OC). Several studies and meta-analyses indicate an association between OC and later development of schizophrenia. However, little is known about the role of prenatal insults on early-onset schizophrenia (EOS), which defines adolescents with onset of schizophrenia symptoms between 12 and 18 years of age. A central feature of schizophrenia is neurocognitive deficits. No study has investigated the relationship between OC and neuropsychological functioning in EOS. The aim of this study was to examine whether there is a higher frequency of OC in early-onset schizophrenia compared to controls, and to investigate the relationship between OC and neurocognitive dysfunction in the two groups.

Methods: Nineteen early-onset schizophrenia patients and 53 matched healthy controls were tested with the MATRICS Consensus Cognitive Battery (MCCB). MCCB is considered to be the gold standard test battery in neuropsychological assessment of schizophrenia patients. The test battery consists of ten tests and cover seven domains: Speed of Processing, Attention/Vigilance, Working Memory, Verbal Learning, Visual Learning, Reasoning/Problem Solving, and Social Cognition. The neurocognitive measures were combined with OC data from the Norwegian Birth Registry. The registry includes information about medication during pregnancy, labor interventions, birth complications, maternal complications after birth, whether this was a live birth, any diagnoses in the child or evidence of congenital abnormalities. Complications were grouped into four categories: Baby's health, Complications of pregnancy, Interventions during labor, and Complications of delivery.

Results: We found no group differences in OC between early-onset schizophrenia and healthy controls. In order to identify possible group differences in the OC - neurocognition relationship we performed correlation analyses in each group separately. Results showed that in early-onset schizophrenia, shorter gestational length was significantly correlated with the overall neurocognitive composite score, and with speed of processing. There were no statistically significant correlations in the control group.

Discussion: The present study supported the hypothesis of a relationship between OC and neurocognitive deficits in early-onset schizophrenia. In particular, gestational length was related to processing speed. The worsened neurocognitive functioning did not appear among controls, which indicated a different impact of gestational length in the two groups. The findings implied that some of the poorer neuropsychological performances commonly found in early-onset schizophrenia may be partly attributable to length of gestation. We found no higher frequency of OC in early-onset schizophrenia, suggesting that shorter gestational length did not increase the risk for developing early-onset schizophrenia, but significantly affected the neurocognitive difficulties seen among cases.

A major limitation of this study is the modest sample size. Strengths of the study are the use of a comprehensive neurocognitive test battery, and the collection of data from medical records with a large number of objective measures of obstetric complications.

M209. N-acetylcysteine prevents the emergence of schizophrenia-like behaviors in an environmental two-hit mouse model

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Background: Therapeutic interventions during critical periods of neurodevelopmental vulnerability before the onset of behavioral symptoms have the potential to prevent conversion to psychosis in at-risk subjects. A growing body of evidence implicates oxidative stress and inflammation in the early maturational deficits observed in the brains of people with schizophrenia. N-acetylcysteine (NAC), a glutathione precursor with antioxidant, anti-inflammatory, and glutamate-modulating properties, is a promising drug in the treatment of various psychiatric disorders. After showing that NAC protects against isolation rearing-induced amphetamine hypersensitivity, the purpose of this study was to evaluate the effects of NAC in a novel two-hit mouse model of schizophrenia. This model combines prenatal immune challenge and peripubertal stress exposure to induce abnormalities on adult behavior.

Methods: Prenatal immune activation was induced by a low dose (1 mg/kg, i.v.) of the synthetic viral mimic poly(I:C) on gestation day 9. The peripubertal stress protocol included five distinct stressors applied on alternate days between postnatal days 30 and 40. NAC was administered through the drinking water (1 g/L) during the period of stress exposure; control animals received tap water only. The behavioral effects of the environmental manipulations were assessed in adult animals (postnatal days 70-100), and included elevated plus maze (EPM), prepulse inhibition (PPI) and locomotor response to amphetamine (AMPH; 2.5 mg/kg, i.p.).

Results: Replicating previous findings, peripubertal stress increased anxiety-like behavior in the elevated plus maze test regardless of the

prenatal history. NAC failed to prevent the stress-induced changes in anxiety-like behavior. The combination of prenatal immune activation and peripubertal stress induced significant sensorimotor gating deficiency and amphetamine hypersensitivity, both of which were fully prevented by NAC treatment.

Discussion: The peripubertal period is a critical developmental stage in which pathophysiological conditions can negatively affect the developing brain, but also represents a window of opportunity for therapeutic intervention. Our findings indicate that NAC prevents the pathological consequences of the interaction between prenatal immune activation and peripubertal stress exposure, rather than counteracting general stress-induced behavioral abnormalities. These beneficial effects of NAC warrant further mechanistic investigation, including its effects on neuroinflammation and oxidative stress in relevant brain areas of animals submitted to this two-hit model. In conclusion, our preclinical data support the potential of NAC as a useful pharmacological strategy for preventing the progression to full-blown pathology in individuals at risk to develop schizophrenia. Clinical trials are necessary to evaluate the safety and efficacy of NAC in prodromal and first-episode subjects.

M210. Risk factors moderating the relationship between childhood trauma and premorbid adjustment in first-episode schizophrenia (FES) patients

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Background: The neurodevelopmental model is the most widely accepted explanation for the pathogenesis of schizophrenia (1). Poor premorbid adjustment (PA) has been cited as supporting evidence for neurodevelopmental disorders (2). Childhood trauma (CT) is recognized as a risk factor for Sz and for poor outcome (3). The relationship between CT and PA has not been extensively researched, and particularly the moderating effects of other risk factors. In this study we aimed to assess the rate of CT in FES patients compared with healthy controls, study the relationships between CT and PA, and explore whether other factors moderate the relationships between CT and PA.

Methods: This cross-sectional exploratory study was conducted at Stellenbosch University, South Africa. Participants were minimally treated, diagnosed with Sz, schizoaffective disorder, or schizophreniform, and experiencing a first-episode of psychosis. We used the Childhood Trauma Questionnaire (CTQ) (4) and the Premorbid Adjustment Scale (PAS) (5). We used chi-squared tests, independent sample T-tests, and bivariate correlations. ANOVA was used to analyze interaction effects.

Results: The sample consisted of 129 participants (52 controls and 77 patients). Participants had a mean age of 24.8 years and the majority participants were male (70.5%), of a Colored ethnicity (48.1%), with a secondary education or lower (91.5%). We found no significant differences between patients and controls in terms of CTQ subscale and total scores. High physical neglect was most frequently reported amongst both patients (42.9%) and controls (42.3%). We found a strong association between sexual and physical abuse and PA. Sexual abuse was significantly associated with academic adjustment in childhood ($r=0.273$, $P=0.019$), and with social adjustment in early ($r=0.275$, $P=0.018$) and late adolescence ($r=0.352$, $P=0.002$). Physical abuse was significantly associated with academic adjustment in childhood ($r=0.299$, $P=0.010$), early adolescence ($r=0.259$, $P=0.031$) and late adolescence ($r=0.251$, $P=0.044$). Emotional abuse was significantly associated with academic adjustment in childhood ($r=0.274$, $P=0.018$). Physical neglect correlated significantly with academic adjustment in childhood ($r=0.306$, $P=0.007$) and early adolescence ($r=0.356$, $P=0.002$), and with social adjustment in early adolescence ($r=0.292$, $P=0.010$). Emotional neglect correlated significantly with academic adjustment in early adolescence ($r=0.271$, $P=0.022$) and late adolescence ($r=0.262$, $P=0.034$). Interactions between moderators and independent variables that reached statistical significance were: obstetric complications, neurological abnormalities, and substance abuse.

Discussion: High NES motor coordination was a protective factor that reduced the influence of emotional and physical abuse and physical neglect on PA social and academic domains from childhood through to late adolescence. Other factors that reduced the influence of emotional and physical abuse on PA were substance abuse and obstetric complications. Our results strongly suggest a risk factor strengthening the relationship between CT and PA is sequencing of motor acts. More severe abnormalities in sequencing of motor acts enhanced the influence of sexual abuse on PAS academic adjustment in childhood. Although our findings require replication it suggests that more severe abnormalities in sequencing of motor acts may lead to more severe premorbid academic adjustment problems in childhood for individuals with a history of sexual abuse.

M211. Autism – schizophrenia continuum hypothesis in the light of social cognition

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Background: Schizophrenia and autism are two neurodevelopmental disorders with some shared genetic background (Rapoport 2009, Crespi 2012) and clinical/cognitive features, especially in social cognition (Couture 2010, Sasson 2010). The few studies directly comparing the two disorders lead to discordant results. The Movie for the Assessment of Social Cognition (MASC, Dziobek 2006, Montag 2010) is a new video-based instrument designed for the evaluation of subtle mindreading difficulties. This test requires subjects to make inferences about video characters' mental states. We recently validated the French version of the MASC in healthy controls and subjects with schizophrenia. Under the assumption of the autism-schizophrenia continuum, our hypothesis is that subjects with early prodromal symptoms of schizophrenia have an intermediate profile between subjects with autism and subjects with usual onset schizophrenia, in terms of social cognition abilities.

Methods: Nineteen subjects with early-prodrome schizophrenia (EP-SCZ, i.e. prodromal symptoms before the age of 15), nineteen subjects with usual onset schizophrenia (U-SCZ, i.e. prodromal symptoms after the age of 15), nineteen subjects with high functioning Autism Spectrum Disorder (ASD) and twenty healthy controls (HC) were included. Diagnoses were confirmed using the Diagnostic Interview for Genetic Studies (DIGS-3) and Autism Diagnostic Interview - Revised (ADI-R, Lord 1994). Intellectual efficiency was evaluated with WAIS-III, 9 subtests. The French version of the MASC was administered to all subjects, and they were also examined for neurological soft signs (NSS), reflecting abnormal brain development (Krebs, 2007).

Results: The four groups did not differ in age, gender and global Intellectual Quotient. In the MASC task, there were differences in correct mental state inferences (total score) between ASD (24.2 ± 6.6), EP-SCZ (27.0 ± 4.2), U-SCZ (29.1 ± 3.6) and HC (33.1 ± 2.9) ($F = 13.27$; $P < 0.001$). Furthermore, the difference was significant between each group of patients and HC ($P < 0.01$), and between ASD and U-SCZ ($P < 0.01$). EP-SCZ were intermediate and not significantly different from ASD and U-SCZ for the total score. Nevertheless, EP-SCZ subjects, as ASD, made significantly more 'exceeding ToM' errors than U-SCZ ($P < 0.01$). ASD patients made also more 'under-mentalizing' errors, reflecting deficit of 'theory of mind'. There was a negative correlation between MASC and NSS scores ($r = -0.253$, $P = 0.039$).

Discussion: The MASC test proved to be sensitive in detecting mindreading difficulties in ASD and in the two schizophrenia subgroups, versus healthy controls. Our results support the hypothesis of a continuum between Autism Spectrum Disorders and schizophrenia, with a higher developmental burden and social cognition impairment in individuals with early-prodrome SCZ. However, the precise mechanisms leading to social cognition deficit could be slightly different and need further exploration. This study was part of the AUSZ program, supported by ERANET Neuron grant (ANR-2010-NEUR-002-01), and Fondation de France.

M212. Acute or chronic treatment with the antioxidant N-acetylcysteine (NAC) restores behavior deficits in male rats of an animal model of schizophrenia based on neurodevelopment

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Background: The hypothesis of poor neurodevelopment in schizophrenia has led to the use of animal models based on interventions at this stage. The model used in this study consists of the injection of metilazoximetanol acetate (MAM) on the 17th day of gestation in Wistar rats. The offspring of rats exposed to this treatment present, in early adulthood, a variety of behavioral and neurochemical impairments consistent with schizophrenia, including deficiency in glutathione (GSH), a major free radical scavenger, poor social interaction, and high responsiveness to psychostimulants. Objectives: The present study evaluated if acute or chronic treatment with the GSH precursor and antioxidant, N-acetylcysteine (NAC), was able to reduce behavior deficits in adult male MAM offspring.

Methods: All procedures were approved by our Ethic Committee in the use of animals of Universidade Federal do ABC (CEUA-UFABC, 007/2014). Pregnant Wistar rats were treated with an ip injection of MAM (25 mg/kg) or saline (control group) on the 17th day of gestation. In the acute experiment, on the 90th postnatal day (PND) male pups received a systemic injection of saline or NAC (150 mg, 250 mg or 500 mg/kg) and were evaluated with the behavioral tests: social interaction and hyperlocomotion (induced by the NMDA antagonist MK801, 0.5 mg/kg). In the chronic experiment, animals were received chronic treatment with the dose of 250 mg/kg of NAC, for 15 days (from 75th to 90th PND) and were subjected to the same tests of acute experiment.

Results: All Statistical analyses were done using SPSS software with one or two-way ANOVA followed by Duncan post-hoc when necessary. Frequency of social interaction was analyzed with factors Treatment1 (MAM or saline) and Treatment2 (saline, NAC150, NAC250, NAC500), revealing significant effects for both factors and interaction between them. Post-hoc test showed that NAC, at doses 250 mg and 500 mg, significantly reduced deficits in social interaction caused by MAM (Duncan, $P < 0.05$). Three-way ANOVA of hyperlocomotion (traveled distance) with factors Treatment1, Treatment2 and Treatment3 (MK or saline) detected significant effects for the three treatments and interactions between them. Duncan post-hoc tests showed that MAM rats treated with MK presented a pronounced increase in locomotor activity compared to all groups. NAC250 and NAC500 significantly reduced this hyperlocomotion (Duncan, $P < 0.05$). In the chronic experiment frequency of social interaction was analyzed with factors Treatment1 (MAM or saline) and Treatment2 (saline or NAC), revealing significant effects for both factors and interaction between them. Post-hoc test showed que NAC significantly reduced deficits in social interaction caused by MAM (Duncan, $P < 0.05$). Two-way ANOVA of hyperlocomotion (traveled distance) with the same factors detected significant effects for the two treatments and interactions between them. Duncan post-hoc tests showed that MAM rats treated with MK presented a pronounced increase in locomotor activity compared to all groups and NAC significantly reduced this hyperlocomotion (Duncan, $P < 0.05$).

Discussion: Results indicated that the antioxidant NAC was effective in improving or abolishing behavior deficits observed in MAM model. These results corroborate the hypothesis that oxidative stress may have an important contribution for deficits observed in MAM model. Additionally, our data give support to a potential antipsychotic effect of that antioxidant NAC.

M213. Functional analysis of schizophrenia-associated genes during zebrafish development

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Background: Recent large-scale genome-wide association studies have begun to uncover numerous genes potentially linked to

schizophrenia, yet it is unclear how these genes function in vivo and if they are part of underlying common molecular and cellular pathways that contribute to schizophrenia. While these studies have begun to converge on some common targets, such as glutamate transmission and neuron excitation, the functions of many of the linked genes are not well understood. Determining the role of these genes in the vertebrate nervous system can help define the pathways disrupted in schizophrenia.

Methods: Recent technological breakthroughs in zebrafish – targeted genome editing, whole-brain activity imaging, brain atlas registration, behavioral profiling – combined with the ease of studying large numbers of animals make it an ideal system for analyzing these genes during vertebrate neurodevelopment. The nearly transparent tissue of the zebrafish brain provides direct optical access to all neurons, and the small size of the organism at approximately one week of age allows for quantitative high-throughput analysis of behavior. Using Cas9 genome editing, with the approach optimized for conducting a large-scale reverse genetic screen, I have generated zebrafish loss-of-function mutants. I have established a pipeline for analysis of these mutants, characterizing differences in behavior with movement and startle assays and imaging their brains for altered neural activity, synaptic density, and structural changes. To assay these mutants for functionally altered brains I am using a recently published technique, pioneered by members of the Schier and Engert labs, that reports integrated neuronal activity in freely-swimming larvae. Analysis of the resulting activity maps and brain structural changes is done with the context of the new Z-Brain neuroanatomy atlas, developed in conjunction with the activity monitoring technique.

Results: Combining these cutting edge technologies for the first time, I have generated zebrafish mutants for mutants for over 150 schizophrenia-associated genes and begun to analyze them with my established pipeline. Screening of these mutants is ongoing. As of November 2015, I have screened over 30 mutants and over one third display differences in neural activity and structure. For example, one mutant in a conserved transcription factor has increased neural activity levels and loss of synaptic vesicle density in the forebrain (telencephalon) and cerebellum. This mutant additionally shows behavioral differences, moving more than wild-type larvae. Differences observed in other mutants include reduced activity and synapses in the hypothalamus and reduced activity in the specific subregions of the forebrain.

Discussion: The most exciting outcome of this work would be the finding that several of the mutants in schizophrenia-associated genes share behavioral and neuroanatomical phenotypes, indicating that they are involved in the same or similar underlying pathways. The cerebellum and structures in the mammalian forebrain (hippocampus, thalamus, cortex, striatum, and basal ganglia), which I found altered in zebrafish loss-of-function mutants, have been implicated in schizophrenia. It would also be exciting if the altered behavior in mutants were reminiscent of abnormal behaviors in human schizophrenics, such as reduced prepulse inhibition or catatonia. If mutants with abnormal behavior are identified, the high-throughput nature of zebrafish larvae can be further exploited in future behavioral-based drug screens. Understanding the molecular causes of schizophrenia has the potential to uncover underlying pathways and is an essential step in developing new therapies and diagnostics.

M214. Combination of maintenance electroconvulsive therapy (ECT) and clozapine in patient with refractory schizophrenia: a case report

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Background: In theory 25% of all patients suffering from schizophrenia cannot be treated adequately with either antipsychotics or with clozapine. Adjunctive treatment with ECT is one of the treatment options for clozapine non-responders. This case report describes the efficacy and tolerability of maintenance electroconvulsive therapy (ECT) as combination treatment with clozapine in treating patient with refractory schizophrenia.

Methods: Ms L. is a 35-year old, college-educated woman with schizophrenia. She had no family history of psychosis. She first exhibited delusions of reference and functional hallucinations at age 18. She was

diagnosed with schizophrenia, paranoid type according to the criteria of the Diagnostic and statistical manual of mental disorders 4th edition (DSM-IV)(American Psychiatric Association 1994), and admitted to the hospital for 1 month. After discharge she graduated from junior college and worked as aid-nurse for a while. At age 21, she readmitted because of exacerbated auditory hallucinations and persecutory delusions. Prior to most recent hospitalization, she had been marginally adapted but unstable with repeated hospitalization, aggressive behavior, and suicidal idea. On most recent admission, at age 35, she was treated with clozapine, aripiprazole, and amisulpride, unfortunately her symptoms did not respond to clozapine up to 500 mg/day combined with aripiprazole 10 mg/day and amisulpride 800 mg/day, during 2 months of treatment. To improve her psychotic symptoms modified ECT was performed in an operating room using MECTA-SR-1 device. The first series of acute ECT, 3 times a week for 4 weeks, was done and her pharmacologic treatment was tailed down to clozapine 300 mg/day. Her symptoms were markedly improved and she discharged after 2-months hospitalization. A decision was made to continue the administration of bilateral modified ECT once weekly as an out-patient. **Results:** Then, the following continuation ECT (once a month) resulted in continued improvement and could reduce her clozapine dosage to 200 mg/day, which has been continued until now. Her CGI-S score decreased from 6 to 3(mildly ill), and Global assessment of functioning (GAF) score increased from 21 to 68.

Discussion: This case report suggests that combining ECT to clozapine in patients with refractory schizophrenia seems effective and well tolerated.

M215. Group cognitive-behavioral therapy for Korean patients with early psychosis

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Background: The efficacy of cognitive-behavioral therapy (CBT) for schizophrenia has been well established. However, there is less evidence regarding group CBT for people in the early stages of psychosis, particularly in Asian countries. This study aimed to develop a Korean model of group CBT for early psychosis and to evaluate the effectiveness of this model.

Methods: We developed a Korean version of group CBT consisting of metacognitive training, cognitive restructuring, stress management, and psychoeducation. The Subjective Wellbeing under Neuroleptics (SWN-K) scale, Ambiguous Intentions Hostility Questionnaire (AIHQ), Drug Attitude Inventory (DAI), Beck Depression Inventory (BDI), and Perceived Stress Scale (PSS) were administered before and after 13 sessions. Changes in the scores on these self-rated scales were analyzed with paired t-tests.

Results: A total of 40 patients with early psychosis participated in group CBT between September 2012 and July 2015. Of the 32 patients who completed more than 70% of the total sessions, 29 completed scales both before and after group CBT. Scores on the SWN and DAI increased significantly (P -value = 0.001 and 0.011, respectively) and those on the AIHQ decreased significantly (P -value = 0.002) after group CBT. Scores on the BDI and PSS did not change significantly.

Discussion: Group CBT had a positive effect on the quality of life, insight, suspiciousness, and perceived stress of patients with early psychosis in Korea. Controlled trials with larger samples are warranted.

M216. Peer support groups in the community as an evolution from a psychoeducation program: the experience from Rio de Janeiro

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Background: Self-help and peer support groups, in expansion in several countries, offer mutual support, hope, empowerment and

recovery to people undergoing situations similar to mental illness, particularly schizophrenia, and provide a wider coverage than psychoeducational programs from psychiatric services. In Brazil, this is a distant reality. Self-help groups for schizophrenic patients and their relatives still develop restrict activities and there is little experience with peer support groups in the community.

Methods: 108 individuals were selected among relatives and patients for a multi-family psychoeducational program at the Institute of Psychiatry of the Federal University of Rio de Janeiro from 2011 to 2014. The program encompasses a first step for assessment (1 month-duration), a second step for information (8 weekly seminars – 2 month-duration), and a third step for discussion and reflection (1 to 2 years-duration). It intends to train them to identify the problems, to carry out a joint search of the relevant solutions, to develop coping skills, to manage crisis, to face stigma and to expand a social network, aiming at the empowerment and recovery of the persons affected. For one to two years, 4 groups held biweekly 2 hour-meetings with professionals. By the end of this step, participants were encouraged to proceed with the meetings within the community, on an autonomous basis (outside the psychiatric institution).

Results: All the groups decided to keep holding the meetings within the community. Each group opted for a name (“Open your Mind” since August/2013; “Exchanging ideas” since November/2013; “Minds in action” and “It’s possible” since February/2015), and undertook to search and organize its own space within the community (churches and commercial buildings). The “Open your Mind” created two banner materials with 14 strategic topics for treatment and recovery of schizophrenic patients and relatives thereof; said materials to be exposed at the meeting room were also incorporated by the other groups. The “Exchanging Ideas” decided to join the “Minds in Action”, by the date of foundation of this latter. Once set up, all the groups agreed to admit new members, upon free request from individuals who took knowledge of the program through Internet and personal references. All the groups stay active, hold either monthly or biweekly meetings and operate on an autonomous basis, without need of professionals. They already organized open seminars for the community to discuss the recovery from mental disturbances as well as social events, and planned supportive actions for the management of crisis affecting their members.

Discussion: These are the first community-oriented and independent peer support groups one has ever heard about in Brazil so far, and a leading initiative from a psychoeducational program developed inside a psychiatric institution. This kind of approach to schizophrenia and others severe mental illness through seminars, by providing to relatives and patients a more optimistic view under the recovery paradigm, as well as the meetings held with multi-family groups allowed a collective empowerment. All the individuals, former passive receptors of knowledge and directives from professionals, became active agents in creating autonomous and independent peer support community-based tools. Such empowerment is demonstrated by initiatives, such as the creation of an own identity, search of a space and implementation of programs with own financial resources. This work primarily focuses on a clinical perspective through the transformation of all the individuals into active agents of their own recovery, being able to expand their social action field.

M217. Baseline tone matching ability facilitates personalization of cognitive remediation approach

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Background: While the aggregate literature on cognitive remediation (CR) for schizophrenia indicates that low moderate effect sizes can be obtained for cognitive and functional outcomes, questions about essential training elements remain. These shortcomings have constrained the translation of CR research into practical application. Personalized CR approaches offer the promise of enhancing cognitive and functional outcomes in people with schizophrenia spectrum disorders.

Methods: Baseline auditory processing impairment was used as the tailoring variable to inform treatment strategy because it identifies a sizeable subgroup of the population, and there is a conceptual basis for using sensory/perceptual problems as a marker for personalizing

cognitive treatment. Using a 2x2 factorial design, subjects were first stratified according to intact/impaired status on Tone Matching (TM), an easily administered 5 minute measure of auditory processing, and then randomized to receive either CR that includes computer-based sensory processing training (Brain Basics; BB) before moving to attention and higher level cognitive tasks, or CR that starts directly with training of attention and then higher level cognitive tasks (Brain Training; BT). Both BB and BT sessions included 15 minutes Bridging group discussion, and were attended 3 times a week for 30 sessions. MCCB and UPSA-B were administered prior to randomization, at the end of treatment, and 3 months later.

Results: 34 adult outpatients with schizophrenia or schizoaffective disorder completed BB (N=17) or BT (N=17). TM status significantly interacted with treatment group as predictors of change on MCCB ($P < 0.05$) and UPSA-B ($P < 0.01$). Patients with baseline impaired auditory processing improved significantly more on cognitive and functional outcomes when CR included auditory processing training. 86% of TM impaired subjects in BB showed a positive treatment response on the MCCB compared to 20% positive response to BT. Further, sensory processing improvement was associated with cognitive improvement. On the other hand, there was no added benefit to giving sensory processing training to subjects with baseline intact auditory processing, who responded similarly to the two CR approaches.

Discussion: Baseline auditory processing ability as measured by the Tone Matching Test served well as a tailoring variable, and facilitated positive CR outcomes by guiding the match between patients and appropriate treatment. Many CR programs include a restorative approach with hierarchically organized cognitive training exercises, but there are differences in the range of cognitive skills included in the hierarchy. Some emphasize training in the early processing of sensory information and never train more complex cognitive skills such as problem solving, whereas others begin training at the level of attention and proceed to train problem solving and other higher order cognitive abilities. This data suggests that patients with impaired auditory processing benefit from training in basic perceptual processing but those with intact auditory processing do not. Tailoring treatment to baseline deficits in sensory processing provides a systematic, evidence based method of personalizing CR treatment.

M218. Environmental enrichment prevents the contextual fear conditioning deficit in an animal model of schizophrenia: possible role of BDNF

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Background: Schizophrenia is a highly disabling mental disorder. Its pathophysiology is not completely elucidated, but changes in brain-derived neurotrophic factor (BDNF) appear to be associated. Environmental enrichment has been suggested to increase BDNF levels and to improve some cognitive deficits. In this study, we aimed to evaluate a possible beneficial effect of early and long-term exposure to Enriched Environment (EE) on the fear conditioning deficit displayed by the SHR (Spontaneously Hypertensive Rats) strain – a new animal model of schizophrenia recently characterized by our group – and the involvement of BDNF.

Methods: Young male Wistar rats (WR) and SHR (21 PND) were housed for 6 weeks in two different conditions: in large cages (10 animals/cage) containing objects of different colors, forms and materials that was changed 3 times/week (EE condition) or in standard cages (5 animals per cage – Control condition). Fear conditioning test was performed after 6 weeks of the end of EE. Brain of animals that weren't exposed to behavioral test was collected. One hemisphere was dissected to collect hippocampus to quantify BDNF and the other was sectioned to perform immunohistochemistry for NeuN to quantify neurons.

Results: As previously shown, SHR presented deficit in fear conditioning. Environmental enrichment was able to prevent this deficit in SHRs and increased neurons counting in hippocampus. BDNF levels were increased in EE animals of both strains immediately after the end of

the period of enrichment. After 6 weeks of the end of EE exposition, there was an increase of BDNF in hippocampus only in SHR animals not exposed to EE.

Discussion: In conclusion, environmental enrichment can be a potential non-pharmacological strategy to prevent some cognitive deficits associated with schizophrenia and it's possible that BDNF is related to this benefit. As next steps, we want to investigate the cascade of signaling that BDNF is activating to reverse the deficits of the SHR strain.

M219. Cognitive behavioral therapy focusing on social functioning in adolescents with recent onset schizophrenia

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Background: Targeting negative symptoms such as social withdrawal is essential to preserve social participation in patients with schizophrenia. Recently, a new Cognitive Behavioural Therapy (CBT) approach targeting inactivity in a schizophrenia population showed promising results (Grant *et al* 2012). The therapy is based on accumulating evidence that dysfunctional beliefs in conjunction with neurocognitive impairments can impede social functioning. However, this therapy has not yet been investigated in a recent-onset population. We investigate the applicability and effectiveness of a shortened, partly group based, Cognitive Behavioural Therapy focussing on social activation (CBTsa) in patients with recent onset schizophrenia. We hypothesize that CBTsa in a recent-onset population will result in a substantial reduction in severity of negative symptoms, in particular social withdrawal; also we expect that CBTsa will lead to an improvement in terms of Quality of Life and overall functioning.

Methods: This is a multicenter single blind randomized controlled trial with 6 month-follow up.

Study population: patients between 18 and 35 years old with negative symptoms of at least moderate severity, and who have been recently (<4 yrs) diagnosed with schizophrenia. The CBTsa intervention includes both a group-based (8 sessions) and an individual (6 sessions) part. Main study parameters comprise: negative symptoms, social functioning, and quality of life.

Results: 85 participants (age 19-35) are currently enrolled in the study; 5 CBTsa intervention groups have been completed. Post- and follow-up assessments are currently being administered.

Preliminary study results will be presented.

Discussion: Results of the study will be discussed and compared with those of other studies investigating psychological interventions focusing on negative symptoms and social functioning in patients with schizophrenia.

M220. A smartphone application approach to support treatment of (attenuated) psychotic symptoms in adolescents

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Background: The use of mobile technologies has increased in mental health services. Primarily, mobile technologies were utilized to collect research data. Recently, first research projects have examined the feasibility and validity of mobile technologies supporting therapy. Preliminary evidence indicates that mobile-based interventions may improve psychotic symptoms.

Especially young patients seem to be interested in mobile technologies and may benefit of the use of smartphone applications within treatment settings. We aimed to develop a smartphone application to support the therapy of adolescents with psychotic or attenuated symptoms and to test feasibility in this group of patients. The

smartphone application targets medication adherence, real-time symptom assessment, and supports coping with symptoms and stressful situations in daily life.

Methods: Adolescent patients (age range 13-18 years) who have been intensively assessed in a specialized center for early recognition of schizophrenia spectrum disorders and fulfill attenuated psychotic symptoms syndrome according to the Structured Interview of Prodromal Syndromes or meet criteria for a schizophrenia spectrum disorder are asked to participate in this study. The application is only used in combination with a therapy in our university clinics for child and adolescent psychiatry. Two questionnaires were developed to assess usability and subjectively perceived benefit of the smartphone application. We will analyze the data from the participants after using the application for two months.

Results: The development of the smartphone application will be finalized in December 2015. Inclusion of potential participants and usage of the application will start in January 2016.

Discussion: First research results using mobile technologies in the treatment of psychotic disorders are promising. While especially young people seem to be interested in mobile technologies, there is a lack of investigations in this population. Furthermore, there is little evidence about therapeutical use of mobile technologies in adolescents with attenuated psychotic symptoms. We will provide first data about feasibility, usability, and acceptance of a specific application developed for adolescents with psychotic and with attenuated psychotic symptoms.

M221. Transcranial magnetic stimulation, transcranial direct current stimulation and electroconvulsive therapy for medication-resistant psychosis of schizophrenia

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Background: In schizophrenia, 20-30% of patients fail to obtain remission from psychosis despite having received adequate anti-psychotic treatment. Brain stimulation techniques that do not require invasive surgery such as repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS) and electroconvulsive therapy (ECT) are often suggested as alternative treatment options for medication-resistant psychosis in schizophrenia. We investigate relevant existing findings in this field, to provide an overview of the current status of these treatments and elucidate gaps in the existing literature that require attention.

Methods: PubMed, Embase and the Cochrane library were searched for articles on rTMS, tDCS and ECT in medication-resistant psychosis or schizophrenia, using the following search terms; medication resistant, treatment resistant, refractory, resistance, intractable, schizophrenia, psychosis, psychotic, hallucinations, delusions, ECT, electroconvulsive therapy, electroshock therapy, TMS, transcranial magnetic stimulation, rTMS, tDCS, transcranial direct current stimulation. A total of 105 articles were screened for inclusion in a qualitative synthesis, mostly focusing on sham-controlled RCT's dating from 2013 to 2015 with exclusion of case reports. This resulted in a total of 20 studies that were eligible for inclusion in the current overview.

Results: Up till now, results on stimulation techniques in the treatment of medication-resistant psychosis are inconsistent. rTMS showed promising initial results for auditory verbal hallucinations (AVH), but three recent large RCT's indicate effects may mostly be due to placebo. tDCS has shown promise as a treatment for AVH, but only in case studies and two small RCT's. To further define its efficacy for AVH treatment, tDCS requires larger RCT's confirming positive results. Concerning ECT, psychotic symptoms generally decrease, but more importantly, its efficacy should yet be demonstrated in a double-blind placebo controlled trial.

Discussion: The evidence for brain stimulation techniques to relieve medication-resistant psychosis is currently still weak. Although previous meta-analyses indicate significant mean effect sizes for rTMS as a treatment for AVH, recent large RCT's indicate no effect compared with placebo. The use of tDCS for refractory AVH and ECT for intractable psychosis show some initial promise, but require

adequately sized placebo-controlled RCTs to confirm efficacy of these treatments. Currently, we are halfway at running such an RCT on tDCS at our study center, some interim results of which will be known at SIRS 2016 and added to this presentation.

M222. Stem cell derived interneuron transplants as a treatment for schizophrenia: preclinical validation in a rodent model

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Background: Schizophrenia is characterized by positive symptoms, like delusions and hallucinations, and negative symptoms, like social withdrawal and cognitive deficits. Schizophrenia has been associated with hyperactivity in the ventral hippocampus (vHipp), a brain region that can both regulate activity of the mesolimbic dopamine system and sends direct projections to the prefrontal cortex. Previously, we demonstrated that hyperactivity in the vHipp underlies increased dopamine cell activity and positive symptoms in the methylazoxymethanol acetate (MAM) model of schizophrenia. The increase in vHipp activity is thought to be caused by a deficit in inhibitory interneurons. Indeed, schizophrenia patients show reductions in interneuron markers in the vHipp, an effect that is primarily limited to parvalbumin (PV) and somatostatin (SST) interneuron subtypes. Therefore, in the current experiments, we tested the hypothesis that restoring PV- or SST- interneuron function in the vHipp would reverse behavioral and physiological deficits in the MAM model of schizophrenia.

Methods: To produce a schizophrenia-like phenotype in male offspring, pregnant rats were injected with MAM (22 mg/kg, i.p.) on gestational day 17. To generate enriched populations of PV- or SST-positive interneurons, we used a mouse embryonic stem cell line containing dual reporters (Lhx6::GFP and Nkx2.1::mCherry). Cells were grown in culture, sorted by flow cytometry, then injected into the vHipp of MAM or saline control rats on postnatal day 40-45. Thirty days after transplantation, we measured latent inhibition, social interaction, and attentional set-shifting to model positive, negative, and cognitive symptoms, respectively. A subset of animals were used for ex vivo patch clamp recordings to measure spontaneous inhibitory post-synaptic potentials (sIPSC) in endogenous pyramidal cells in the vHipp. With the remaining rats, we performed in vivo extracellular recordings to determine firing rate of putative pyramidal cells in the vHipp and spontaneous activity of dopamine cells in the ventral tegmental area (VTA). After recording, all animals were perfused and dual-fluorescence immunohistochemistry was used to confirm that transplanted cells survived and differentiated into PV- or SST-positive interneurons.

Results: We found that both the PV- and SST-positive transplants integrated into the existing circuitry, as evidenced by an increase sIPSC amplitude and frequency in vHipp pyramidal cells. Further, both cell transplants reduced pyramidal cell firing rate in the vHipp, and normalized dopamine population activity in the VTA. Despite their similar physiological effects, the PV- and SST-enriched transplants had dramatically different effects on behavior. Although both cell types attenuated deficits in reversal learning and restored latent inhibition, only the PV-positive transplants were able to reverse deficits in extradimensional set-shifting and social interaction.

Discussion: Our results suggest that PV- and SST-positive interneurons in the vHipp differentially regulate schizophrenia-like behaviors. The SST-positive transplants appear to have beneficial effects on behaviors that rely on dopamine signaling, including latent inhibition and reversal learning. PV-positive transplants improved performance in these behavioral tasks, but were also able to normalize behaviors that involve the prefrontal cortex, including social interaction and extradimensional set-shifting. These results suggest that restoring PV interneuron function in the vHipp may be an effective treatment strategy for schizophrenia to improve not only positive, but also negative and cognitive symptoms of the disease.

M223. Capturing the individual environment of patients. basis for targeted psychotherapy

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Background: Assessing variation of psychotic symptoms and the determinants thereof at the level of the individual patient, may be crucially important for the diagnosis and treatment, as well as for the assessment of treatment efficacy.

Methods: Using experience sampling methodology (ESM), we investigated 60 patients with non-affective psychosis in order to determine temporal dynamic patterns between mood states and paranoia in each individual. Furthermore, we used ESM to assess the efficacy of mindfulness based cognitive therapy (MBCT) in 130 patients with residual affective problems at risk to experience paranoia.

Results: Huge variation was found in the temporal association between mood states and paranoia at the level of the individual. E.g. for some people, anxiety would precede paranoia whereas for others, relaxation preceded paranoia. In the MBCT study, momentary paranoia levels in the intervention group were significantly reduced and feelings of social acceptance significantly increased compared to control.

Discussion: Real-life ambulatory assessment may substantially improve our understanding of symptom patterns at the level of the individual patient, making patients active partners in the therapeutic process. Furthermore, real-time monitoring may be pivotal in illuminating mechanisms of change.

M224. Climb: a mobile app intervention to treat social cognition impairments and improve social functioning in chronic psychosis

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Background: Recent evidence indicates that social cognitive deficits and social marginalization affect functional disability and quality of life in chronic psychosis. While group therapy and social cognition training target effectively these domains, access and engagement to these interventions in the U.S. remain outstanding challenges that limit their widespread and optimal utilization. Advances in software development and mobile technology can help bridge the gap between mental health clinics and individuals with chronic psychosis by: 1) making treatment available cost-effectively and in a non-stigmatizing manner 2) optimizing user experience to sustain engagement 3) supporting real-time analysis of user performance and progress. In particular, remote digital interventions can be offered and tailored to individuals with chronic psychosis who live in under-resourced areas geographically distant from mental health clinics, and/or by those who do not approach conventional treatment settings because of mental health stigma. This presentation discusses a personalized digital health approach called CLIMB. CLIMB is a package of diagnostic and treatment tools specifically designed for individuals with chronic psychosis that includes computerized social cognitive assessments, personalized computerized social cognition training, a HIPAA-compliant videoconferencing tool used for remote clinical assessments and CBT-based group tele-therapy, and a peer-to-peer secure social network. In CLIMB, recruitment, screening, enrollment, assessments, and intervention all take place remotely.

Methods: The single-arm, exploratory study is ongoing. We field test CLIMB for 8 weeks by providing iPads to 36 participants with a DSM-V diagnosis of schizophrenia or schizoaffective disorder, who participate in the study remotely. We investigate the feasibility and acceptability of this approach, evaluate retention, and explore effects on social cognition, clinical symptoms, and quality of life. Clinical and cognitive assessments are conducted before and after the intervention. Social cognition is evaluated by administering iPad versions of the Bell-Lysaker Emotion Recognition Task and the Prosody Identification Task.

Symptoms severity is assessed using the PANSS interview. Participants are asked to complete the Schizophrenia Quality of Life self-report.

Results: We present results from the first 15 participants with pre- and post-treatment data. Preliminary findings suggest that delivering CLIMB remotely to individuals with chronic psychosis is feasible and acceptable. Study procedures were conducted successfully, and all iPads have been returned fully undamaged. We present results from group and individual interviews conducted with participants during the iterative design phase of the study. In addition, CLIMB appears to improve aspects of social cognition ($t=4.11$, $P < 0.05$), negative symptoms ($t=4$, $P < 0.05$), and quality of life ($t=4.21$, $P < 0.05$).

Discussion: To the best of our knowledge, this is the first study to demonstrate the feasibility of delivering an entirely remote intervention targeting social cognition and social functioning in people with chronic psychosis. We plan to recruit an age-matched Treatment As Usual comparison group to investigate the extent to which CLIMB improves social cognition, negative symptoms, and quality of life. If successful, this type of approach can enhance the delivery of mental healthcare services to underserved clinical populations including individuals with psychosis, and have significant public-health relevance.

M225. Harnessing the power of latent profile analysis to classify nonclinical adolescents using psychometric indicators of risk

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Background: To date, most of the studies of prodromal symptoms and clinical indicators of incipient psychosis have been based upon studies of clinic-referred, help-seeking individuals. The eventual goal is to develop applicable measures for use in general population samples. Relatively little is known regarding the frequencies of these symptoms and indicators in the general adolescent population. Latent profile analysis is a special form of latent class analysis (LCA) that uses continuous indicators. Using a community-derived nonclinical sample of adolescents, we sought to determine whether we could apply this relatively novel statistical technique to identify different classes of individuals at varying degrees of relative risk.

Methods: Four hundred and forty-nine high-school students between the ages of 12 and 19 were administered a battery of self-report measures in order to assess risk for the later development of psychosis-spectrum disorders. The following measures were included: the Prodromal Questionnaire-Brief (PQ-B), Oviedo Schizotypy Assessment Questionnaire (ESQUIZO-Q), Anticipatory and Consummatory Interpersonal Pleasure Scale-Adolescent version (ACIPS-A), and General Health Questionnaire 12 (GHQ-12).

Results: A four-class model was the best fitting model for our data. The latent profile analysis identified four distinct classes who varied in terms of their relative risk. Participants in class 1 (LC1) accounted for 54% of the sample and showed a relatively low level of symptoms. Class 2 (LC2, 29% of the sample) had higher scores on all measures compared to LC1. LC3 (6% of the sample), with higher score profiles, could be characterized as a schizotypal symptom group. LC4 (12% of the sample), showed the highest score pattern and were characterized as a very high distress, prodromal symptom group. The average class membership for class 1, class 2, class 3, and class 4 were 0.97, 0.94, 0.95, and 0.96, respectively, indicating good overall discrimination.

Discussion: The present study demonstrates that LCA may be used with psychometric indicators for the purpose of classifying adolescents in terms of the presence of risk indicators for psychosis-spectrum disorders. These results are consistent with findings from other investigations that have identified several distinct risk groups who display different clusters of deficits associated with adverse psychiatric outcomes, including a clinical high-risk group without attenuated psychotic-like symptoms. The findings also buttress support for use of this statistical technique for the identification of groups of individuals in the general community who may be at heightened risk for psychosis-spectrum disorders and would benefit from further screening efforts.

M226. Longitudinal changes in auditory verbal hallucinations in schizophrenia

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Background: Auditory verbal hallucinations (AVHs) are one of the most frequent and distressing symptoms of schizophrenia but studies have rarely examined which dimensions should be the primary target of treatment. Various dimensions of AVH have been suggested to respond differentially to antipsychotic treatments and clinicians and patients may differ in their views on how symptoms relate to subjective distress. Hence the present study is a longitudinal examination of patients with persistent AVHs to uncover which dimensions improve over the course of 1 year treatment and how physical symptom domains are related with subjective stress separately from the clinician and patient perspectives.

Methods: A total of 87 patients with schizophrenia presenting persistent AVHs were assessed at 6-month and 1-year from the baseline using both the clinician-rated Psychotic Symptom Rating Scales-Auditory Hallucination Subscale (PSYRATS-AH) and self-reported Hamilton Program for Schizophrenia Voices Questionnaire (HPSVQ).

Results: The baseline sex ratio, age, duration of illness, and total scores on PSYRATS-AH and HPSVQ between the completers and non-completers at 6-month and 1-year assessments did not significantly differ. The prevalence of AVHs was significantly decrease among 68 patients followed at the 6-month (T1) with 8 no longer showing the symptoms of AVHs (McNemer X², $P=0.008$). At 1-year assessment (T2), significant decrease in the prevalence of AVHs from 6-month was not observed among 49 patients. The decrease in the prevalence of AVHs over 1-year period (T3) for 51 patients was significant with 8 no longer showing the symptoms of AVHs (McNemer X², $P=0.008$). From the clinician perspective, PSYRAT-AH showed significant improvements in frequency, duration, degree of negative content, amount of distress, and disruption to life at T1. At T2, no significant changes were observed. Over the course of year (T3), duration of illness, belief re origin of voices, degree of negative content, amount of distress, and intensity of distress improved. In contrast, from the patient perspective as based on the HVSPQ, significant decrease in only frequency and distress occurred at T1, no significant changes followed at T2, and duration, distress, how bad they make you feel, and clarity improved in T3. In addition, different patterns of cross-sectional associations between distress and disruption to life and other aspects of AVH's were found for clinicians and patients.

Discussion: Our results demonstrated that significant disagreement exists between clinician and patient evaluations of improvement in symptoms and their relationships with distress and interference with life. Clinicians should consider such discrepancies in order to improve treatment adherence and satisfaction of patients.

M227. Cognitive biases moderate paranoia and subjective distress in response to social stress

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Background: Recent sociodevelopmental models of psychosis postulate that cognitive biases play an important role in the development of psychosis. Experiences of social adversity alter cognitive schemas and sensitize the dopamine system, leading to aberrant processing of stimuli, which may eventually develop into psychotic symptoms in the context of biased cognitive schemas and social stress. This study aimed to test whether cognitive biases in individuals with different psychosis liability moderate levels of paranoia and distress in response to social stress, using Virtual Reality (VR) experiments.

Methods: Fifty-five patients with recent onset psychotic disorder (FEP), 20 patients at ultra-high risk for psychosis (UHR), 42 siblings of patients with psychosis and 53 controls walked five times in a virtual

bar with different levels of environmental social stress. Virtual social stressors were population density, ethnic density, and hostility. Paranoia and subjective distress in response to virtual social stress were measured throughout the experiments, cognitive biases were assessed at baseline. Multilevel random intercept regression analyses were used to test cognitive biases as predictor and moderator of paranoia and subjective distress.

Results: Cognitive biases were higher in FEP and UHR compared to siblings and controls. Paranoia and subjective distress were predicted by cognitive biases in all groups, most strongly by problems with social cognition, selective attention to threat and cognitive inflexibility. Interaction effects were found between degree of environmental social stress and cognitive biases on paranoia and distress. External attribution bias also moderated the effect of psychosis liability on paranoia and distress.

Discussion: Cognitive biases are stronger in individuals with high psychosis liability, and are associated with more paranoia and distress in response to social stress. The effect of cognitive biases increases with degree of social stress in the environment.

M228. Associations between acoustically measured tongue and jaw movements and negative symptom severity in patients with schizophrenia in Italy and the United States

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Background: The negative symptoms of schizophrenia are very impairing to patients' lives and functioning and are a focus of considerable empirical and clinical attention. Computerized acoustic analysis of patients' speech is a sophisticated and promising approach for measuring two cardinal negative symptoms of schizophrenia: blunted affect, and alogia. This is the first cross-language study of the effect of schizophrenia on speech as measured by analyzing phonetic parameters with sound spectrography. We hypothesized that reduced movement of the tongue and jaw would be correlated with negative symptom severity in two samples of patients with schizophrenia, one from Italy, and one from the United States.

Methods: Audio recordings of spontaneous speech were available from 40 schizophrenia patients. WaveSurfer 1.8.8 was used to create, from each speech sample, a file of formant values (F0, F1, and F2; where F0 is the fundamental frequency (pitch) and F1 and F2 are resonance bands indicating the moment-by-moment shape of the oral cavity). We also measured the portion of the recording in which there was speaking, as opposed to pauses ("fraction voiced," FV). Correlations between variability in the three phonetic indices (and FV) and negative symptom severity scored with Scale for the Assessment of Negative Symptoms (SANS) and Positive and Negative Syndrome Scale (PANSS) was tested.

Results: Meaningful correlations (i.e., $r > |.25|$) between SANS total score and variability of tongue front-to-back position (the standard deviation (SD) of F2; $r = -.33$), as well as variability in pitch (SD of F0; $r = -.30$) were observed in the Italian sample. We also found a significant and meaningful association between SANS avolition/apathy subscale score and SD of F2 ($r = -.49$) in the Italian sample. We did not find these correlations in the U.S. sample. In both the Italian and US samples, FV was meaningfully correlated with: SANS total score ($-.34$ and $-.35$), SANS avolition/apathy ($-.42$ and $-.38$), and SANS anhedonia/asociality ($-.45$ and $-.33$)

Discussion: Although the development of automated, objective bi-behavioral tools for symptom assessment in psychiatry has been slow, the field of computational linguistics and acoustic analysis have shown recent technological advances, suggesting that such methods could represent a reliable and valid assessment approach. The findings of our study suggest a need for additional research on phonetic indices as correlates of the severity of negative symptoms for the possible future development of tools for symptom monitoring/tracking over time. Doing so would allow for potential improvement in the reliability of assessment of negative symptoms, and for the

eventual development of predictive tools for early detection of symptoms in youth at high risk for developing a psychotic disorder. Our unique findings also suggest that such research should be done in different samples and settings, and with patients who speak different languages.

M229. The chicken or the egg? Whether resilience precede or follow recovery in schizophrenia

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Background: Even if we at present have valuable information about the heterogeneity both in course and outcome of this mental disorder, schizophrenia today too often defines a person rather than describing the illness.

Results from previous studies on recovery and sustained recovery in schizophrenia using operational consensus based criteria show that personal resources (resilience) play a significant role in attaining normal real life functioning (Torgalsbøen, 2001; Torgalsbøen and Rund, 2010; Torgalsbøen, 2012). Main characteristics of recovered subjects were in addition to high resilience, no use of any neuroleptic medication for an average of 17 years, indicating that resilience might be a determining factor in a sustained recovery from schizophrenia. These results made it necessary to investigate prospectively how variables such as hope, self-efficacy, and resilience influence real life functioning of people with first-episode schizophrenia. This approach is in line with the increasing interest among researchers to identify factors promoting recovery. Personal resources such as self-efficacy, hope and resilience may account for the unexplained variance in outcome. Enhanced understanding of putative protective factors in the individual with schizophrenia is vital for understanding and predicting recovery. As part of The Oslo schizophrenia recovery study we aim to investigate the longitudinal relationship between schizophrenia and resilience as a personality trait.

Methods: The study is ongoing and here we present the preliminary results from the 4-year follow-up.

During this time period, all participants are assessed every year at five time points. Thus it is possible to assess sustained remission and full recovery over time as well as studying personality traits in a sample not narrowed to the relapsing patients most often seen in hospital/inpatient settings.

Twenty eight first-episode schizophrenia patients at average 21 years of age were recruited to the study and assessed at multiple follow-up points with a clinical interview, an inventory of social and role functioning (Global Functioning: Social; Global Functioning: Role) and measures of self-efficacy, hope, resilience, and neurocognition (MCCB). Operational criteria of remission and full recovery are applied as well. Diagnoses were established using the Structural Clinical Interview for DSM-IV.

A healthy control group consisting of 28 participants is included in the study and matched pairwise on variables such as gender, age, and closely on education. They are assessed at admission, after two, six and ten years.

Results: 63% of the participants fulfill (all or partly) the criteria of full recovery and the retention rate is high (78.6). Preliminary results show that at the group mean level, increases in reported resilience were observed both before and after improvements in functional levels of the participants. Hope and Self-efficacy increased most from baseline to six months, and subsequently continued to rise steadily until the end of the follow-up. At an individual level, preliminary crossed lag analyses are most in accordance with bidirectional influences between the three measures of resilience and functional outcome.

Discussion: At this point in the course of illness the results indicate that at an individual level changes in pathology have preceded increased levels of reported resilience. Based on the preliminary analyses it is on an individual level difficult to conclude on causal direction. This will be further explored in partial least squares, an analysis better suited for small samples. The increase in self-efficacy and hope during the very early course indicates that this period is an important window of opportunity to personalize further treatment.

M230. Comparing the lived-experiences of first-episode psychosis service-users with differing early negative symptom trajectories: a mixed methods study

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Background: Negative symptoms are common and disabling features of schizophrenia and other psychotic disorders. However effective treatments for negative symptoms have proved elusive, making them an important target for treatment development. Whilst some recent progress has been made in understanding negative symptomatology, the lived-experiences of those presenting with negative symptoms remains a largely untapped resource for achieving this aim. This paper will describe a mixed methods study which identified distinct trajectories of negative symptom severity in a large first-episode psychosis cohort using longitudinal modeling techniques before exploring the lived-experiences of members of the identified trajectory classes using qualitative methods. **Methods:** 1006 participants in the EDEN study – an evaluation of the impact and cost-effectiveness of Early Intervention in Psychosis (EIP) Services in the UK – were followed up for 12 months following acceptance into EIP. Negative symptom severity data was modeled using latent class growth analysis, allowing latent trajectory classes to be identified. Participants were later invited to take part in a series of semi-structured interviews about their experience of psychosis. A purposive sample of 24 interview participants from across the identified latent trajectory classes was selected. Verbatim transcripts of the selected participants' interviews were analyzed thematically and comparisons made between the experiences of those with differing negative symptom severity and course.

Results: Four negative symptom trajectories were identified: 63.9% of the sample presented with consistently minimal negative symptoms, 13.5% with persistent mild negative symptoms, 5.4% with persistently high levels of negative symptoms and 17.1% with initially elevated negative symptoms which remitted within 12 months. Participants across trajectory classes included descriptions of diminished expression, lack of motivation, and social withdrawal in their accounts of the experience of psychosis. Some participants put these symptoms down to a decrease in their capacity for emotion, cognition or motivation, however most participants explained the negative symptoms they described as resulting from medication side-effects, lack of confidence or avoidant coping strategies. There were notable contrasts between the way in which members of different negative symptom trajectory classes understood their experiences, described the treatment they had received and their approaches to recovery.

Discussion: It is possible to identify distinct latent classes with similar trajectories of negative symptom severity within a first-episode psychosis cohort. The majority of EIP service-users present with consistently minimal negative symptoms, and a substantial proportion of those who present with elevated negative symptoms on entry to EIP experience a remission of these symptoms within 12 months. Only a relatively small subgroup of EIP service-users present with persistently elevated negative symptoms throughout the first 12 months. Participants' descriptions of the experience of negative symptoms and differences between the accounts of those with differing negative symptom trajectories suggest a number of hypotheses about the mechanisms underlying these symptoms. Investigation of these hypotheses may contribute to the development of an evidence-based biopsychosocial model of negative symptoms.

M231. The cascade of stress: a network approach to explore differential dynamics in populations varying in familial risk for psychosis

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Background: The experience sampling method (ESM) allows for the prospective examination of individuals' affective states and other

experiences from moment to moment in their daily life. A network visualization hereof may help to reveal the potential impact that affective states, contexts and other experiences have on one another over time. Such cascades of effects at the micro-level may play an important role in the eventual development of psychopathology. As minor daily stress plays a central role in the development and persistence of psychotic symptoms, it is especially important to understand the role of minor daily stress in the dynamic network of experiences. The current study examined dynamic longitudinal networks of the relations between minor daily stress, affect, and behavior. Furthermore, networks of individuals with differing familial risk for psychosis were compared.

Methods: Time-series data were obtained through six ESM-studies. The sample consisted of 654 individuals varying in familial risk for psychosis: healthy controls ($n=244$), siblings of psychotic patients ($n=165$) and psychotic patients ($n=245$). Using multiple multilevel models, group specific mental state networks were created based on significant regression coefficients. Corresponding P -values were calculated employing a novel permutation procedure. The resulting networks were analyzed and compared. This was done by comparing structural network parameters as well as specific network paths between the three groups.

Results: Populations varying in familial risk of psychosis show differences in their mental state networks. In all three populations, stress had a central position in the network, however, the persistence of stress was highest in patients. In comparison to the two other groups, in patients, experiences of stress led to more feelings of loss of control and more feelings of suspiciousness, and suspiciousness in its turn was stronger connected to feeling anxious the next moment. There was a linear dose response association of familial risk of psychosis and instrength ('incoming connections') of feeling anxious and loss of control, of outstrength ('outgoing connections') of feeling irritated. Patients showed a self-reinforcing loop between feeling down and feeling insecure, that was not present in the two other groups.

Discussion: These findings support the idea that minor daily stress may indeed play an important role in the induction of a cascade of effects that eventually is responsible for the experience of psychotic symptoms. Populations varying in familial risk of psychosis differ in their connections between mental states. The network approach facilitates a thorough insight into the complex dynamic structure between minor daily stress, emotions, and experiences in psychotic disorder. This knowledge may prove relevant for the improvement of personalized treatment strategies.

M232. A provisional qualitative analysis of the meaning of and influences on recovery according to people diagnosed with a first episode psychosis 20 years ago and their family members/partners

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Background: Although recent years have seen a burgeoning of qualitative research in First Episode Psychosis (FEP), few studies have explored long term recovery. Qualitative research is vital to explain recovery in psychosis. It can explore the meaning, contexts, and determinants of recovery; examine the interlocking pharmacological, personal, social, and economic contributions to recovery and specify the complex processes involved in recovery. Little is known about how people with a diagnosis of a FEP and their family members/partners conceptualize recovery in later life and what they perceive as facilitating and hindering their recovery over the long term. The in-depth exploration of recovery from the differing perspectives of service users and their family members and partners is a prerequisite to recovery orientated service provision.

Methods: Our presentation reports on the qualitative component of a mixed methods 20 year follow up study. Semi-structured interviews were conducted with service user participants ($n=20$) and the family members/partners of these service user participants ($n=7$). Service

user participants are members of a representative epidemiological cohort of people diagnosed with a FEP between 1995 and 1999 in Dublin, Ireland. Constant comparative analysis, as described in Grounded Theory, will be used to explore participants' definitions of recovery and to identify the key influences they perceived on their recovery.

Results: Results will be available for the conference.

Discussion: Findings provide service user, family member, and partner perspectives which can inform the education of mental health professionals, clinical practice, and the concept and operational criteria of recovery in psychosis. They may facilitate the recovery orientation of mental health services by guiding clinical practice to aid the achievement of recovery goals that matter to service users and their family members/partners. Results may facilitate the development of new treatment strategies to promote recovery and enhance and optimize mental health service provision for those who experience psychosis.

M233. A systematic review and meta-synthesis of service users' perceptions of the meaning of and influences on recovery in psychosis

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Background: Orientating mental health services to the recovery oriented approach requires the exploration and integration of service user perspectives in order to optimize mental health service delivery and recovery outcomes. To facilitate this paradigm shift, a synthesis of qualitative studies exploring the meaning of recovery and influences on recovery from the viewpoint of the service user is warranted. Due to the substantive difference between what is termed 'psychotic illness' and other types of 'mental illness', there is a clear rationale for examining recovery in psychosis as a separate entity. In addition, a review of this nature could not be located in the literature.

Methods: A systematic review and meta-synthesis were undertaken to synthesize the findings of qualitative studies exploring the meaning of recovery and factors that influence recovery from the perspective of adults aged 18+ diagnosed with 'psychotic illness'. We adopted a pre-planned comprehensive search strategy to identify all available studies that answered our research questions. Searches of PubMed, PsycINFO, CINAHL Plus, Psychology and Behavioral Sciences Collection, and Web of Science were conducted by two librarians and the lead author (AK, CS, & DOK), using both relevant control language search terms and free-text search strings. We also hand searched reference lists of included articles and the tables of contents of journals which published seminal articles. Three authors (DOK, AH, & BK) independently screened articles by title, by abstract, and then by full text. A quality assessment was conducted on all articles that met eligibility criteria using a tool devised by Walsh and Downe (2005). We completed a meta-synthesis of included articles guided by the method of analysis detailed by Walsh and Downe (2005). ENTREQ and PRISMA statements were adhered to.

Results: Articles which met criteria for this review were included in the meta-synthesis. A number of overarching themes emerged across both research questions. Themes identified for Meaning of Recovery include: the absence of symptoms or episodes, accepting, understanding, and managing the illness; regaining control and autonomy; maintaining wellbeing; taking responsibility; functioning effectively; having structure and routine; having a positive identity, and having a meaningful and valued role in society. Themes identified for Influences on Recovery include: positive and negative aspects of medication, lifestyle modification, individual willpower and determination, positive and negative qualities of mental health professionals, social and peer support, having material resources and basic needs met (food, clothing, and shelter), social acceptance and stigma, spirituality, and cultural factors.

Discussion: Findings show a disparity between service user defined recovery and recovery as conceptualized by mental health professionals. Mental health services may be enhanced by the adoption of a holistic approach which takes into account the spiritual needs of the

service user, recognizes the influence of culture on the recovery process, focuses on building psychological resilience, and promotes well-being and physical health in addition to managing crisis and setbacks. By providing person centered, strength based, collaborative care, service users can be enabled to exercise autonomy and agency and take responsibility for their life and recovery. Findings provide an understanding of the needs of people with psychosis which may guide service provision, provide new ideas for future research, and enable the development of innovative strategies and interventions to support recovery. Themes identified contribute to the conceptual clarity of recovery in 'psychotic illness'.

M234. Clozapine therapeutic drug monitoring from capillary blood using the dried blood spots technique

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Background: Clozapine is the drug of last resort in treatment-resistant schizophrenia. However, the relation between clozapine dosage and plasma levels vary greatly which could easily result in pseudo-clozapine non-response when too low plasma levels are reached which remains undetected if not measured. As many developed (Israel, Russia, Serbia) and underdeveloped (African) countries lack the facility of clozapine therapeutic drug monitoring (TDM), this is not a theoretic possibility but a common reality. The challenge was to develop a technique that enables clozapine TDM for clinical use in these countries. We decided to apply the technique of dried blood spots (DBS), that has been validated in TDM of tuberculosis, for clozapine.

Methods: Patients on stable clozapine treatment, in whom the clozapine dosage had remained unchanged for at least two weeks, were asked to participate. Bloods sampling took place at baseline, 2, 4, 6, and 8 hours after clozapine intake. At each of the 4 blood samplings, 3 samples were taken at the same time: regular venous samples, dried blood spot samples from regular venously sampled blood and dried blood spot samples from capillary sampled bloods.

Results: The results from the DBS analysis showed good linearity over the concentration time curve measured. The accuracy and between- and within-day precision variation values, validated three times, were within accepted ranges. Different blood spot volumes and hematocrit values had no significant influence on the results. DBS samples were stable at room temperature (20° C) and 5 °C for respectively two weeks and 3 days. The mean ratio of the clozapine concentration in DBS samples to that in plasma was 0.81 (95% CI 0.76 to 0.85).

Discussion: The Dried Blood Spot (DBS) analysis is a reliable method for therapeutic drug monitoring (TDM) of clozapine in daily practice. DBS may extend the opportunities of clozapine TDM in the ambulatory setting. The stability of DBS samples offers the opportunity of extending TDM to countries that lack the facility for clozapine TDM. The Dried Blood Spot (DBS) analysis is a reliable method for therapeutic drug monitoring (TDM) of clozapine in daily practice. DBS may extend the opportunities of clozapine TDM in the ambulatory setting. The stability of DBS samples offers the opportunity of extending TDM to countries that lack the facility for clozapine TDM.

M235. First intervention pharmacological treatment of involuntarily committed patients with schizophrenia, schizotypal or delusional disorder over a 16 year observation period

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Background: Patients suffering from schizophrenia or other delusional disorders often require treatment on locked wards. The current retrospective, longitudinal trial was conducted to investigate first intervention pharmacological treatment modalities in these patients after involuntary commitment to the Department of Psychiatry,

Psychotherapy and Psychosomatics of the Medical University Innsbruck.

Methods: Data collection comprised all involuntary admissions to the Department of Psychiatry and Psychotherapy of the Medical University Innsbruck in 1997, 2002, 2007 and 2012. Next to demographics, admission diagnosis and first intervention pharmacological treatment (antipsychotic and/or benzodiazepine medication, dosage, and mode of administration) were assessed.

Results: 66.5% of patients received medical treatment as first intervention (significant decrease from 72.8% in 1997 to 59.9% in 2012, $P=0.038$). Mean equivalent doses of antipsychotics decreased significantly from 459.9 to 179.6 mg chlorpromazine equivalents ($P<0.001$) whereas benzodiazepine doses showed a small, but significant increase from 20.9 to 28.7 mg diazepam equivalents, $P=0.017$. Orally administered medication was prescribed with a proportion of 66.7% for antipsychotics and 73.0% benzodiazepines, respectively. For APs, orally administered medication increased significantly from 55.6% in 1997 to 86.8% in 2012 ($P<0.001$). Within the group of antipsychotics second generation compounds (SGA) were used in 24.4% of cases in 1997 and in 92.5% in 2012 ($P<0.001$). **Discussion:** Our data confirm that the increasing use of SGAs which is well known for schizophrenia patients in general took also place in involuntarily committed patients.

M236. Antipsychotic-related fatal poisoning (England and Wales, 1993–2013)

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Background: The mortality rate from suicide for people with schizophrenia is 10–20 times that of the general population, accounting for some 28% of the excess mortality in schizophrenia. Antipsychotics are the mainstay of treatment of schizophrenia and yet self-poisoning with antipsychotics remains a potential means of suicide in patients prescribed them. Moreover, these drugs are not without side-effects, some of which are life-threatening. National mortality data are an important source for monitoring the effect of public health measures such as those aimed at reducing deaths from poisoning. From 1993–2000 antipsychotic-related poisoning deaths in England and Wales averaged some 55 annually and phenothiazines, principally thioridazine, predominated. Subsequently, prescription of second generation antipsychotics (SGAs) has continued to increase. We therefore evaluated the effect of the changes in antipsychotic prescribing that have occurred on antipsychotic-related fatal poisoning.

Methods: To evaluate the impact of this change on antipsychotic-related fatal poisoning, we studied such deaths (England and Wales, 1993–2013) recorded using International Classification of Diseases codes on the Office for National Statistics drug poisoning deaths database. We also studied antipsychotic prescribing in the community in relation to poisoning deaths using data from the Prescription Cost Analysis system (England and Wales, 2001–2013). Deaths attributed to adverse reactions in the course of normal treatment were not studied because these deaths are not classified as 'poisonings'.

Results: There were 1544 antipsychotic-related poisoning deaths (2.7% of all drug poisoning deaths). In all, 559 deaths (36% of all antipsychotic-related deaths) were attributed to unintentional poisoning. For most antipsychotics, the proportion of deaths in which the specific antipsychotic featured either alone, or only with alcohol, was 30–40%. For clozapine, the proportion of deaths attributed to either intentional self-harm, or undetermined intent was 44%, but for all other drugs except haloperidol the proportion was 56% or more. The annual number of antipsychotic-related deaths increased from around 55 per year 1993–8 to 74 in 2000, and then after falling to 53 in 2002 increased steadily to reach 109 in 2013. Deaths involving antipsychotics (10 or more deaths) were in the range 11.3–17.1 deaths per million prescriptions in England and Wales, 2001–2013. Almost all (96%) such deaths now involve SGAs which is keeping with the increase in annual numbers of community prescriptions of SGAs overall, driven by increases in prescriptions for olanzapine and quetiapine. In contrast, deaths involving thioridazine declined markedly in line with the marked decrease in prescriptions for thioridazine from 2001.

Discussion: The removal of thioridazine since December 2000 has had no discernable effect on the incidence of antipsychotic-related fatal poisoning in England and Wales. That such deaths have increased steadily since 2001 is in part attributable to an increase in unintentional deaths related to co-ingestion of opiates, principally diamorphine and methadone.

M237. Correlates of clozapine use after a first episode of schizophrenia compared to patients not prescribed clozapine: results from a long-term, prospective study of 105 first-episode patients

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Background: Objectives: To identify variables predicting clozapine use after a first episode of schizophrenia (FES).

Methods: Patients with FES and ≤ 15 days of antipsychotic treatment were followed during naturalistic treatment and those initiated on clozapine were compared with those receiving non-clozapine antipsychotics for ≥ 24 months regarding demographic and clinical baseline characteristics and adherence and relapse patterns during the follow-up. Treatment-resistant schizophrenia (TRS) was defined as ≥ 2 antipsychotic trials of adequate dose for ≥ 6 weeks.

Results: Altogether, 105 patients with FES (mean age = 22.6, males = 55.7%, follow-up = 72.1 ± 50.2 months) were included. Clozapine was initiated after 2.5 ± 1.1 adequate antipsychotic trials and 10.9 ± 9.3 months after meeting TRS criteria. In 8 of the 28 clozapine treated patients (28.6%) initiating clozapine during the first 12 months of follow-up (mean = 7.1 ± 3.3 (range = 3–12) months) premorbid childhood adjustment was significantly worse than in those starting clozapine later (mean = 78.5 ± 43.0 (range = 17–168) months). Compared to non-clozapine users ($n=77$), patients started subsequently on clozapine ($n=28$) had significantly more relapses in the first 6 months of follow-up prior to clozapine use (40.0% vs 13.2%, $P=0.005$) but were significantly less likely to have a first relapse despite treatment adherence (38.1% vs 73.3%, $P=0.01$). In multi-variable analyses, antipsychotic polypharmacy ($P=0.013$) and having a first relapse despite being adherent to antipsychotic treatment ($P=0.048$) independently predicted later clozapine use in logistic regression analysis.

Discussion: Clozapine use after FES was predicted by a first relapse while being adherent to non-clozapine antipsychotics, especially if the first relapse occurs within the first six months. Developmental childhood difficulties predicted significantly earlier clozapine use.

M238. Association between weight gain and remission status in first-episode psychosis

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Background: Weight gain is a side effect of antipsychotic medications in people with psychosis. Interestingly, several studies as early as the 1950s reported weight gain to be associated with symptom improvement. This led to the formulation of the "metabolic threshold", which states that metabolic abnormalities have some role in the clinical efficacy of antipsychotics. Here, we examined the relationship between clinically significant weight gain and symptomatic remission in a cohort of individuals with first-episode psychosis.

Methods: Patients diagnosed with their first psychotic episode were recruited and assessed at baseline and after 3 months of treatment. Weight and Positive and Negative Syndrome Scale (PANSS) were measured, and symptomatic remission status was recorded at 3 months. Clinically significant weight gain was defined as $\geq 7\%$ increase in weight from baseline. Remission status was defined at 3 months using the symptom criteria proposed by Andreasen *et al.* **Results:** Clinically significant weight gain was detected in 42% of the sample and 67% attained symptomatic remission at follow up. However, there were no significant differences between weight gain and remission status ($P=0.291$).

Discussion: Where specifically reported, most studies on weight gain and symptomatic improvement found an association in general psychopathology and not in core schizophrenia symptoms. When clinical outcome was defined as remission, which is widely accepted as the clinical outcome of interest, we found no relationship with weight gain. Our findings do not support the concept of a "metabolic threshold".

M239. Adjunctive lurasidone suppresses food intake and weight gain associated with olanzapine administration in rats

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Background: Lurasidone is an antipsychotic drug that demonstrates some valuable clinical properties including a favorable metabolic profile; it shows a relative lack of the weight gain that is common to many antipsychotic drugs, the consequences of which include increased risk of diabetes and cardiovascular disease. Of the antipsychotic drugs with a similar metabolic profile, aripiprazole and ziprasidone also demonstrate protective effects against olanzapine-induced food intake and weight gain in animals, paralleling some clinical findings. We hypothesized that lurasidone would have similar actions and have investigated the effects of this drug, in comparison with and combined with olanzapine, on acute food intake and short-term weight gain in rats.

Methods: Following habituation to experimental conditions, female Lister-hooded rats were given 30 mins access to a palatable mash food preparation. They were then given the appropriate i.p. injections; four groups of six animals received either 2x vehicle (saline), lurasidone (3 mg/kg) and vehicle, olanzapine (1 mg/kg) and vehicle, or olanzapine and lurasidone. Following drug administration all animals were given access to the food for a further 60 mins. Weight of initial and final food intake was measured. A further series of rats underwent a seven-day regime of once-daily administration of the above doses and free access to food and water. Prior to each dose the animals were weighed, and weight gain over the course of the study was monitored.

Results: The acute studies showed a significant increase in food intake following olanzapine in the absence of any significant effect of lurasidone administration, which remained significantly reduced below that for olanzapine. Co-administration of lurasidone with olanzapine suppresses the increase in food intake seen with the latter drug. Repeated dosing showed essentially the same effect. An increase in body weight over control animals was seen after seven days' administration of olanzapine, with no significant effect observed with lurasidone, while repeated administration of lurasidone with olanzapine reduced the effect of olanzapine alone on the increase in body weight.

Discussion: These findings support our initial hypotheses in showing that lurasidone, in addition to demonstrating a lack of effect on acute food intake and chronic weight gain in clear contrast to olanzapine, also demonstrates a protective effect on olanzapine-induced food intake and weight gain in rats. This indicates the drug to have an active anti-hyperphagic mechanism, rather than solely the absence of the pharmacological propensity for weight gain that is such a severe limitation of drugs such as olanzapine. The study thus suggests the clinical potential for such a protective effect of adjunctive lurasidone in antipsychotic-induced weight gain.

M240. Multidrug resistance 1 C3435T and CYP3A4*1B polymorphisms may determine antipsychotic response based on the five symptomatic domains of schizophrenia and related disorders

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Background: Recent evidence has demonstrated a large degree of overlap between substrate affinities of MDR1 and CYP3A4. These

overlapping of specificities may be useful to explain drug-drug interactions and genetic variability in antipsychotic response. The vast majority of antipsychotics are metabolized by CYP3A, and some of them seem to be important substrates for the P-glycoprotein, also known as multidrug resistance protein 1. However, the impact of genetic variants of MDR1 and CYP3A4 on antipsychotic response in schizophrenia remains still unclear. Therefore, our main goal was to investigate the potential influence of rs1045642 MDR1 and CYP3A4*1B polymorphisms on the five symptomatic domains of schizophrenia.

Methods: One hundred thirty-five schizophrenia patients (DSM-IV-TR) were enrolled in a 12-week prospective naturalistic study. Psychopathological assessment included the Positive and Negative Syndrome Scale (PANSS; 5-Factor Model), the Personal and Social Performance Scale (PSP) and the Clinical Global Impression-Severity Scale (CGI-S). Antipsychotic response rate was defined as a $\geq 30\%$ decrease in the PANSS total score and rs1045642 MDR1 and CYP3A4*1B were genotyped. Analyses of covariance models (ANCOVA) were applied to investigate the main effect of genetic variants of MDR1 and CYP3A4, as well as their interactions on mean changes in five symptomatic domains and functionality. Gender, DUP and olanzapine equivalent doses served as covariates.

Results: CYP3A4 1/1 genotype was associated with statistically significant antipsychotic response in terms of PANSS total scores ($P=0.018$), and higher improvement in the PANSS excitement subscale ($P=0.022$), PANSS anxiety and depression subscale ($P=0.007$) and the PANSS cognitive subscale ($P=0.019$). Statistically significant interactions between rs1045642 MDR1 and CYP3A4*1B polymorphisms were found in changes in functionality ($P=0.021$), being MDR1 T/T genotype associated with a better improvement in functionality ($P=0.015$). No other interaction effects were found with regard to the five-model factors of PANSS.

Discussion: Genetic polymorphisms in rs1045642 MDR1 and CYP3A4*1B may underlie differences in antipsychotic response in schizophrenia. Particularly, our findings suggest an influence of CYP3A4*1B polymorphisms on anxiety/depressive, excitement and cognitive symptoms, and a plausible association of MDR1 T/T genotype with higher functionality in schizophrenia.

M241. The impact of menopause in treatment outcomes in women with schizophrenia

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Background: Women with schizophrenia have a later age of onset than men. Women have also been found to experience a milder course of the disorder at least before menopause (Hafner, 2003). One of the hypothesis explaining this difference is that estrogens protect women against psychosis. If this is the case, the course and treatment response of women with schizophrenia should be different before and after menopause. We present a post-hoc analysis of the World-Schizophrenia Health Outcomes Study (W-SOHO) which explores the differences in treatment response for women before and after menopause.

Methods: The W-SOHO study is a three year follow-up study on the outpatient care of schizophrenia that included 17,876 patients from 37 countries. Patients were recruited by their treating psychiatrists when starting or changing antipsychotic medication. Evaluation was conducted during the normal course of care and was scheduled every six months after the baseline visit. Clinical Severity was assessed with the Clinical Global Impression-Schizophrenia (CGI-SCH) Scale. Quality of life was measured with the EuroQoL 5D. Remission was defined adapting the Andreasen criteria to the CGI-SCH scale (Haro *et al.*, 2008). Recovery was defined as two years of clinical remission with good social functioning. Treatment cohorts were defined based on the medication started at baseline. Menopausal status was not recorded in the study. Pre-menopausal women were considered those below 45 years of age and post-menopausal women those over 55 years. To account for the correlation between the visits of the same patient, mixed models with repeated measures (MMRM) were applied for the analysis of continuous variables and generalized estimating

equation (GEE) models for dicotomous variables. The analyses include 4,486 women below 45 years of age and 1,113 above 55 years.

Results: Age of first treatment was 25.8 (sd 6.9) years in women below 45 years of age (WB45) and 40.8 (sd 15.3) years in women over 55 years (WO55) ($P < 0.0001$). WO55 more frequently lived independently (61.7% versus 43.6%, $P < 0.0001$). The frequency of having paid employment was higher in WB45 than WO55 (20.4% versus 4.3%, $P < 0.0001$). Remission rates at last visit were 61.2% in WB45 and 49.9% in WO55 ($P < 0.0001$). Recovery rates were 19.4% and 7.5%, respectively ($P < 0.0001$). Quality of life at the last visit measured with the EuroQoL 5D Visual analog scale was 74.4 (sd 18.0) for WB45 and 68.8 (sd 18.9) for WO55 ($P < 0.0001$). CGI-overall severity ratings were 2.6 (sd 1.2) and 2.9 (sd 1.1), respectively ($P < 0.0001$). The regression models showed that WB45 starting treatment with olanzapine had a lower CGI overall severity rating at endpoint than women starting treatment with risperidone, quetiapine, amisulpride, and oral and depot typicals. In WO55, women starting treatment with olanzapine had a lower CGI overall severity endpoint than women starting treatment with risperidone, quetiapine, and oral typicals. There were no statistical significant differences with amisulpride, depot typicals and clozapine in this age group. Women who were working for pay and were socially active had a higher CGI overall severity score at endpoint in the two age groups. Additionally, in WB45 those with a spouse or partner and those who were receiving treatment for first time also had a lower CGI rating. The same pattern regarding medication was found for the analyses of remission.

Discussion: Women above 55 years of age (after menopause) had lower remission, recovery rates and worse quality of life than women below 45 (before menopause). In both groups of patients, before and after menopause, those starting treatment with olanzapine and clozapine had better outcomes than patients in other medication groups.

M242. Mortality and cumulative exposure to antipsychotics, antidepressants and benzodiazepines

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Background: Mortality related to psychotropic medications has gained much attention. However, there are very little data on the risk of death and cumulative antipsychotic load, and nothing is known about mortality versus cumulative exposure to antidepressants or benzodiazepines.

Methods: We identified all individuals with schizophrenia diagnosis ($N = 21,492$) aged 16 to 65 years, in Sweden by using prospectively collected nation-wide databases, and calculated all-cause and cause-specific mortality as function of cumulative low (< 0.5 DDD/day), moderate (0.5–1.5 DDD/day), and high (> 1.5 DDD/day) antipsychotic, antidepressant and benzodiazepine exposures from January 2006 to December 2010.

Results: When compared with no exposure, both moderate (adjusted HR 0.59, 95%CI 0.49–0.70) and high (0.75; 0.63–0.89) antipsychotic doses were associated with substantially lower overall mortality. Moderate antidepressant use was associated with a lower mortality (0.85, 0.73–0.98), and the risk of death was even lower for high dose (0.71, 0.59–0.86). Exposure to benzodiazepines showed a dose response for increased mortality (HR up to 1.74, 1.50–2.03 for high exposure). In a sensitivity analysis among first episode patients, the highest risk was observed for high-dose benzodiazepine use, with almost 4-fold mortality compared to the majority of patients with no benzodiazepine use.

Discussion: Moderate and high dose antipsychotic and antidepressant use were associated with about 15–40% lower overall mortality, whereas high-dose, chronic use of benzodiazepines was associated with up to a 70% higher risk of death when compared to no exposure. Since patients with anxiety and depressive symptoms may have a higher intrinsic risk of death, the finding for benzodiazepines may be attributable in some extent to residual confounding. It is important to realize that although monitoring of patients with moderate or high dose antipsychotic treatment is relevant, it is essential to focus the preventive interventions on those patients who have even higher risk of death, i.e. patients not using antipsychotics and patients using high doses of benzodiazepines.

M243. The influence of antipsychotic treatment on peripheral cytokines

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Background: Recent findings strongly implicate a role for the immune system in the etiology and pathophysiology of schizophrenia: large genome-wide association studies demonstrate an association of schizophrenia with genes related to the immune system (Schizophrenia Working Group of the Psychiatric Genomics 2014), activation of peripheral inflammation is present in schizophrenia (Uptegrove, Manzanares-Teson *et al.* 2014), and transcription of immune genes in the brain is upregulated (Hwang, Kim *et al.* 2013) in patients with schizophrenia. Indications of an influence of antipsychotics on peripheral markers of inflammation has been found (Tourjman, Kouassi *et al.* 2013), and the aim of the study was to evaluate the short-term influence of antipsychotic treatment on peripheral cytokines and high-sensitive C-reactive protein (CRP) in patients with schizophrenia-spectrum disorders.

Methods: 78 patients aged 18–65 years (mean 30, SD 11.7) with schizophrenia-spectrum disorders participating in a randomized, controlled trial of antipsychotic treatment (amisulpride/ aripiprazole/ olanzapine) were tested at baseline and after three weeks of treatment. The blood samples were drawn in the fasting state at the same time of the day. The 34 drug-naïve patients were analyzed separately. The statistical analysis was a paired samples t-test.

Results: All patients: PANSS total at baseline: 78.2, SD 13.7.

Cytokine analyses:

1. All patients:

TNF α ($n = 73$), $\Delta(V1-V3) = -4.15$, $P < 0.000$.

Interleukin (IL)6 ($n = 73$), $\Delta(V1-V3) = 223.71$, $P < 0.000$.

IL10 ($n = 73$), $\Delta(V1-V3) = -18.91$, $P < 0.000$.

E-selectin ($n = 73$), $\Delta(V1-V3) = -3300$, $P = 0.001$.

ICAM ($n = 73$), $\Delta(V1-V3) = -158066$, $P < 0.000$.

VCAM ($n = 73$), $\Delta(V1-V3) = 46674$, $P = 0.024$.

RANTES ($n = 74$), $\Delta(V1-V3) = -7290.27$, $P < 0.000$.

No significant differences for IL1 β , Interferon (IFN) γ , IL2, IL4, TNFR1, IL1sR1, high-sensitive (hs)CRP were found.

2. Drug-naïve patients:

TNF α ($n = 25$), $\Delta(V1-V3) = -5.64$, $P < 0.000$.

IL10 ($n = 25$), $\Delta(V1-V3) = -37.19$, $P < 0.000$.

IL1 β ($n = 27$), $\Delta(V1-V3) = 2.76$, $P = 3.5994E-7$.

ICAM ($n = 25$), $\Delta(V1-V3) = -236038$, $P = 0.002$.

RANTES ($n = 26$), $\Delta(V1-V3) = -9401.90$, $P < 0.000$.

No significant differences for IL-6, IFN γ , E-selectin, VCAM, IL2, IL4, TNFR1, IL1sR1, hsCRP were found.

Discussion: The measures of cytokines both in the whole sample and in the drug-naïve subsample at baseline and after three weeks of antipsychotic treatment indicate significant influence of antipsychotic treatment. The influence is predominantly anti-inflammatory as the pro-inflammatory cytokines IL1 β and IL6 are reduced, and the anti-inflammatory cytokine IL 10 is increased. The significance of the findings is underlined by the fact that in the analyses of the drug-naïve patients generally larger differences are found. Further studies must determine correlation with clinical symptoms and neurocognitive measures, and investigate the mechanism for the anti-inflammatory influence of these second-generation antipsychotic drugs.

M244. Rate and predictors of non-response to first-line treatment in first-episode schizophrenia

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Background: Objective: To a) estimate the rate of non-response to first-line treatment in first-episode schizophrenia, b) evaluate other outcomes associated with symptom non-response and c) identify

demographic, baseline clinical, and early treatment response predictors of non-response.

Methods: This was a single-site, longitudinal cohort study assessing the effects of treatment with flupenthixol decanoate according to a standardized protocol over 12 months in patients with schizophrenia, schizophreniform, and schizo-affective disorders.

Results: Of 126 patients who received at least one dose of study medication, 84 (67%) completed the study. Fifteen (12%) met our pre-defined criteria for non-response. Non-responders were younger, and at baseline had more prominent disorganized symptoms, poorer social and occupational functioning, poorer quality of life for psychological, social and environmental domains, more prominent neurological soft signs (NSS), and lower BMI. At endpoint the non-responders were characterized by higher levels of symptomatology in all domains, poorer functional outcome, poorer quality of life and greater cognitive impairments. They also had more prominent NSS and lower BMI. The strongest predictors of non-response were more prominent baseline NSS and poor early (7 weeks) treatment response.

Discussion: Results are consistent with a lower rate of refractoriness to treatment in first-episode schizophrenia compared with multi-episode samples.

M245. Modafinil combined with cognitive training improves neural efficiency during working memory relative to placebo combined with cognitive training in healthy volunteers: a randomized-controlled trial with fMRI

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Background: Working memory (WM) deficits are common in a range of mental disorders, for example, schizophrenia. As WM has such strong links to functional outcomes it represents a potentially critical target for therapeutic intervention, yet there is currently a lack of effective methods to improve cognitive functioning. Both pharmacological and cognitive training (CT) interventions have demonstrated only low to modest effect sizes for improving cognition. However, we recently have reported that modafinil, a wake-promoting agent, combined with CT over 10 sessions produced enhanced learning in healthy volunteers compared to CT with placebo (Gillean *et al.*, 2014).

Methods: This study aimed to investigate the neural changes in neural activity during WM following this 10-day period of combined modafinil and CT compared to placebo and CT. A subset of thirteen healthy subjects from our previous study underwent fMRI during a WM task before and after the 10-day trial - both sessions were off-drug and the training WM task from the CT was different to the fMRI task. We hypothesized that combining CT with modafinil would improve WM performance and produce changes in WM-related neural activity compared to the placebo and CT group.

Results: Results showed that behaviorally there was a significant group x time interaction. At follow-up compared to baseline there were gains with modafinil but a decline in the placebo group at high WM loads. Moreover, only the modafinil group showed significant reduction in WM Network activity required to perform the task and a significant diminution in Default Mode Network activity.

Discussion: This study suggests that adding modafinil to CT improves neural efficiency and performance compared to placebo, and that these effects are apparent after cessation of the period of modafinil administration and thus may be durable.

M246. GWAS analysis of treatment schizophrenia: interaction effect of childhood trauma

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¹CAMH

Background: It is relatively common to patients with schizophrenia to present treatment-resistance to antipsychotics and this represents a

challenge for improving the outcome in schizophrenia. Childhood trauma can increase the risk for psychiatric disorders and it can be also a risk factor for persistent positive symptoms in schizophrenia. The genetic factors of treatment-resistance are not ultimately clear and neither its association with non genetic factors.

Methods: Our sample consisted of 83 participants with schizophrenia spectrum disorders from white European ancestry, we conducted cross-sectional assessments to collect information regarding drug effectiveness, childhood trauma, general demographics. Using a genome-wide association analysis, we tested genome-wide single-nucleotide polymorphisms (SNPs) for their association with antipsychotic resistance. Two models were tested: A main model and an interaction model with the childhood trauma.

Results: Our analysis failed to demonstrate a significant relationship among 1,178,234 SNPs and treatment-resistance in both the main model and in the interaction model.

Discussion: Even though we could not find any significant results, treatment resistance has clinical relevance and it may have several underlying biological and non biological factors.

M247. Clozapine is prescribed once daily in a majority of patients in North America: findings from two psychiatric institutes in United States and Canada

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Background: Plasma half-life has routinely been used to establish the dosing schedule of antipsychotics; for example, it is recommended that agents with a short plasma half-life be administered multiple times per day. To date, however, several randomized controlled trials have shown that once-daily dosing of such antipsychotics is comparable to twice-daily dosing in terms of efficacy and tolerability, suggesting that once-daily dosing of antipsychotics is a viable option regardless of plasma half-life. This issue applies to clozapine as well, in that it has a relatively short plasma half-life. Despite this, in clinical practice clozapine is frequently administered once daily because of convenience and side effects such as a daytime sedation; however, there has been no literature reporting how frequently clozapine is administered once daily or the consequences in terms of efficacy and tolerability. As a starting point in addressing this gap in the literature, we conducted cross-sectional surveys at two research institutes/hospitals in United States and Canada to investigate the frequency of clozapine once-daily administration and differences in patients' demographic and clinical characteristics between different clozapine dosing regimens.

Methods: This two-site, cross-sectional survey was conducted at the Centre for Addiction and Mental Health (CAMH) in Toronto, Canada in August, 2015 and Zucker Hillside Hospital (ZHH) in New York, United States in September, 2015. The following data were collected: participants' demographic and clinical characteristics; dose and dosing regimen of clozapine; clinicians prescribing clozapine; use of other concomitant antipsychotic and psychotropic medications; and, scores on seven specific items from the Brief Psychiatric Rating Scale (BPRS) (only available for ZHH dataset).

Results: A total of 676 and 308 patients were included in CAMH and ZHH datasets, respectively. Mean \pm SD clozapine dose was 398 ± 151 mg/day and 371 ± 151 mg/day; > 200 mg/day or ≥ 300 mg/day was prescribed in 88.6% or 80.3%, and 84.4% or 72.1% of the patients in CAMH and ZHH, respectively. Clozapine was prescribed once daily in 75.1% and 74.4%; among those, 98.8% and 96.9% at bedtime; of the patients receiving > 200 mg/day or ≥ 300 mg/day, 72.5% or 71.3%, and 71.2% or 69.4% in CAMH and ZHH, respectively. A higher clozapine dose and use of anticholinergics were significantly associated with multiple dosing in both datasets. Older age and male gender were related to multiple dosing in CAMH and ZHH dataset, respectively. No significant difference was found in the rates of positive symptom remission between single vs. multiple clozapine dosing (79.7% vs. 80.5%, $P = 1.000$).

Discussion: To our knowledge, this is the first report specifically focusing on clozapine dosing and differences in patients' demographic and clinical characteristics between different dosing regimens.

Despite product monograph recommendation, clozapine was prescribed once daily in approximately 75% of patients and at bedtime in the vast majority. These findings support our hypothesis that clozapine, which has a relatively short half-life, is administered once daily in a majority of patients in actual clinical practice. Single clozapine dosing may reduce patient and clinician burden related to complex dosing regimens, and in doing so enhance clozapine utilization. Since this cross-sectional survey cannot determine whether single clozapine dosing is superior to multiple clozapine dosing in terms of efficacy and tolerability, further studies are needed to compare clinical outcomes between the two dosing regimens.

M248. Antipsychotic dose reduction in schizophrenia: a systematic review

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Background: While maintenance treatment with antipsychotics is critical to prevent negative consequences in schizophrenia, they are associated with various undesirable side effects at least in part in a dose-dependent manner. This underscores clinical relevance of minimizing antipsychotic exposure in the long run. On the other hand, once patients are stabilized, physicians as well as patients themselves are often reluctant to reduce the dose of antipsychotics during the maintenance treatment for fear of potential decompensation. As a result, a possibility remains that patients with schizophrenia continue to be maintained on higher doses of antipsychotics than actually necessary. The objective of this systematic review was to identify the factors for successful antipsychotic dose reduction by summarizing the studies addressing this topic.

Methods: We conducted a systematic literature search for studies examining antipsychotic dose reduction in schizophrenia in August 2015, using PubMed with the following search terms: (schizophreni* OR psychosis OR psychotic disorder*) AND (antipsychotic* OR neuroleptic OR tranquilizer) AND ("drug administration schedule"[MH] OR "dose-response relationship, drug"[MH]) AND adult[MH]. Cross-reference and hand searches were also performed.

Results: The literature search identified 29 relevant studies. Nineteen (66%) and 11 studies (38%) targeted first generation antipsychotics and long-acting injectable antipsychotics, respectively. Fifteen studies were randomized controlled trials (RCTs) comparing the effectiveness between reducing versus maintaining the dosage, while 14 were non-RCTs such as single-arm prospective trials. Relapse rates or changes in symptoms were compared between dose reduction and dose maintenance groups in 15 studies, and before and after the dose reduction in 5 studies. Among those 20 studies, 15 studies (75%) showed a significant improvement or no significant difference in symptoms, which was considered a successful dose reduction. Side effects, including extrapyramidal symptoms and cognitive impairment, improved following dose reduction in nine studies. Age of >40 years, duration of illness of >10 years, and post-reduction chlorpromazine equivalent dose of >200 mg/day or defined daily dose (DDD) of >0.5 appeared to be factors for dose reduction to be successful. In eight studies, patients who had experienced a clinical deterioration were restabilized by increasing the doses back to the baseline before reduction.

Discussion: The current systematic literature review found that antipsychotic dose reduction did not result in increased relapse rates in a majority of the studies. Moreover, it could be associated with an improvement in side effects. Older age, longer duration of illness, and modest dose reduction appeared to be associated with successful dose reduction. Thus, while moderate dose reduction of antipsychotics seems to be a reasonable treatment option in the maintenance phase, special caution should be exercised especially for younger patients with a relatively short illness duration. Limitations of the studies include variable study design and quality, relatively short duration of follow up after dose reduction, lack of universal consensus on relapse, and relative paucity of data with respect to newer generation antipsychotics. Further well-designed studies especially for second generation antipsychotics are warranted to shed further light on those findings and establish optimal dose reduction strategies.

M249. Long-acting injectable antipsychotics in first episode psychosis-perspectives of families

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Background: First episode psychosis (FEP) is highly responsive to treatment with antipsychotics. Poor adherence (50%) leads to high relapse rates. Efficacy of long acting injectables(LAI) is equal to oral preparation with improved adherence. Currently, psychiatrists offer LAI to only 35% of eligible patients and treat <20% of eligible patients with LAI.

Public opinion and the media often support the view that LAI involves an element of coercion and causes more adverse effects. The relatives of schizophrenic patients supported potential advantages of depot formulations more strongly than patients did. These findings are in accord with the consideration that relatives do not trust patients' medication adherence and thus might appreciate the advantage of depot formulations. Family members of patients with mixed psychiatric disorders endorse support for implantable medication. Main reasons were deleterious effects of the mental illness on their family member; improved adherence and less burden on the family. Reasons for not accepting an implantable antipsychotic were not wanting patient to try something new; perceived coercion and side effects of procedure. Illness severity influenced acceptance of implants by family members. However, severity of a patient's illness did not predict their own acceptance of implants. Family members tended to judge affected family member's illness as more severe than patients judged their own illnesses.

Methods: We used Qualitative study using grounded theory. The study was approved by the Queen's University Health Sciences REB and Chatham-Kent Health Alliance REB. Participants were recruited from a community hospital in Chatham-Kent. Family members of clients attending the FEP clinic were approached during accompanied clinic visits. Family members who maintain close contact with patient and involved in their psychiatric care were selected. Three adult males and seven adult females participated. Nine were parents and one was a grandparent. Each family member was interviewed by phone. Interviews were transcribed and coded actively by hand. Analysis was performed in parallel with interviewing.

Focused codes synthesized large sections of the data and were raised to the level of categories. Relationships between categories were further clarified by clustering, which enabled the later development of conceptual categories.

Results: Perceived benefits of LAI according to family members included themes such as convenience factors; improved adherence and maintaining clinical stability. Perceived reservations about LAI according to families included dislike of needles in general; possibility of adverse effects; association with injected drugs of abuse and perception of coercion. Factors affecting uptake of LAI according to family members included the influence of the clinical team; patient's own choice; insight into consequences of poorly controlled illness; parental influence as well as peer influence.

Discussion: Strengths of our study include the use of qualitative methodology which allows exploration of subject experience as well as inclusion of caregiver family members which provides unique perspective on LAI use. Limitations include the use of a specific population which may not allow generalization of data. We have not assessed the level of involvement of family member in caring for the individual with schizophrenia.

This study provides insights on the crucial role that family members play in the client's perception and acceptance of LAI in FEP.

M250. Early schizophrenia patients treated with once-monthly paliperidone palmitate over a 12-month period - a retrospective observational study

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Background: Little is known about patient characteristics and rehospitalization in newly diagnosed patients with schizophrenia

treated with long-acting antipsychotics. To retrospectively explore hospitalizations, drug utilization and clinical outcomes from medical records of young, 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 are patient characteristics, reason for PP initiation and hospitalization data.

Results: 84 patients were analyzed: Mean age (years) at first psychotic episode was 23.8(SD2.6), 23.9(SD2.6) at first antipsychotic treatment and 24.1(SD2.7, range 19-29) at initiation of PP. Time between first antipsychotic treatment and initiation of PP was 4.8(SD3.4, range 0-12) months. At PP initiation 42.9% of patients were in hospital, primarily for the management of the first episode/relapse (97.2%). Reason for PP initiation was: LAT favored over oral treatment for relapse prevention (56%), partial/non adherence with previous oral medication (20.0%), convenience (15.5%) or limited access to health care systems (2.4%). Mean time (days) between admission and initiation of PP, and between initiation of PP and discharge from hospital was 28.8 (SD23.0) and 23.2(SD24.5), respectively. 96.4% of patients were not hospitalized during the 12-month PP treatment period. 3/84 patients (3.6%) had a single hospitalization of 15.7(SD 8.1) days for management of episode/relapse.

Discussion: In this young, newly diagnosed schizophrenia population the number of hospitalizations following PP initiation was low. Main reason to initiate PP was clinicians favoring LAT over oral antipsychotic treatment for relapse prevention or due to partial/non adherence with previous oral treatment.

M251. Association of birth weight and the development of antipsychotic induced adiposity in individuals with schizophrenia

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Background: Though weight gain is a common side effect of antipsychotic treatment, there are no useful predictors of which patients are likely to be affected and to what degree. It has been shown that exposure to adverse conditions during intra-uterine life confers a vulnerability to the development of later life metabolic complications and low birth weight for gestational age has been shown to be a robust marker of such prenatal adversity. We hypothesized that patients with schizophrenia with a lower birth weight will have increased vulnerability to the weight inducing effects of antipsychotic treatment.

Methods: The relationship between birth weight and total and central adiposity, measured as body mass index (BMI) and waist-to-hip ratio (WHR) respectively, was examined in three groups: drug naïve first episode of psychosis (FEP) patients ($n=41$), treatment resistant schizophrenia (TRS) patients on clozapine ($n=42$) and matched healthy volunteers ($n=72$). All analyses were controlled for age, gender, and duration of treatment exposure.

Results: The final sample included only subjects on whom reliable data on birth weight was available. This included 41 drug naïve FEP patients, 42 individuals with TRS and 72 healthy controls. Groups do not differ in terms of birth weight and differences on the other variables are driven by the TRS group. There was a strong correlation between BMI and WHR across the whole sample ($r=0.59$, $P < 0.0001$). There was no correlation between age and birth weight ($r=0.11$, $P=0.17$). After controlling for age, sex and treatment duration, there was a significant effect of TRS group status on BMI ($T=6.06$, $P < 0.0001$), with TRS status being associated with higher BMI. Critically there was a significant negative TRS group x birth weight interaction ($T=-3.78$, $P=0.0002$) i.e. a unit increase in birth weight produces a corresponding decrease in adult BMI. For the WHR analysis, there was a significant effect of TRS group ($T=2.88$, $P=0.0046$) but the birth weight x treatment interaction term did not reach significance ($T=-1.72$, $P=0.087$). The significant effect of TRS group status was investigated further in the secondary analyses.

Lower birth weight in TRS patients was significantly associated with greater BMI ($T=-2.38$, $P=0.023$) and WHR ($T=-2.51$, $P=0.017$). There was no effect of smoking status on these associations

Discussion: Prenatal adversity, as indicated by the surrogate marker of a lower birth weight, confers an increased vulnerability to clozapine induced weight gain.

M252. Antipsychotic response rates and correlations with the five symptomatic domains in schizophrenia and delusional disorder: a case-control study

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Background: For many decades, delusional disorder (DD) has been considered a difficult to treat psychotic disorder, and lack of compliance to antipsychotics a core feature. Scientific evidence focused on treatment response in DD patients is scarce, and findings are still controversial. However, a systematic review highlighted that antipsychotics are first line treatments, and other co-morbid psychiatric conditions should be identified, as these may influence antipsychotic response in these populations (Skilton *et al.*, 2015). In this line, our research team (González-Rodríguez *et al.*, 2015) proposed a treatment decision model based on psychopathological complexity (i.e. symptomatic domains). Thus, the main aim of this study was to investigate whether schizophrenia and DD patients differ in antipsychotic response rates, and improvement in the five symptomatic domains. In a second step, our purpose was to correlate percentage of response with improvement in these five dimensions, as this issue has been poorly studied.

Methods: We carried out a 12-week case-control follow-up study at the Barcelona Clinic Schizophrenia Unit (BCSU). Thirty-seven delusional disorder (DD) patients were recruited (Cases), and thirty-six schizophrenia patients (Controls), all of them fulfilling DSM-IV-TR criteria. Controls were matched on age, sex, and duration of illness. Psychopathological assessment included the 5-factor model of PANSS, PSP for functionality, and the CGI-SCH scale. Antipsychotic response was defined as a reduction of $\geq 30\%$ on the PANSS total score, and antipsychotic compliance was measured by plasma level monitoring. In a first step, for comparisons between diagnostic groups, t and chi-square tests were performed and non-parametric tests when necessary. Analyses of covariance models (ANCOVA) were applied to evaluate the main effect of diagnostic group on primary outcomes. In a further step, associations between percentage of response and mean changes of the five factors of PANSS were investigated by using partial correlation analyses.

Results: Forty-five (65.2%) patients of the total sample were antipsychotic responders. There were no statistically significant differences in antipsychotic response between diagnostic groups, being 61.8% responders in the DD group and 68.6% in schizophrenia. When uncorrected, DD patients needed lower doses of antipsychotics ($P=0.025$) and had lower cigarette smoking rates ($P=0.022$) compared to schizophrenia patients. No statistically significant differences in mean changes of the five factors of the PANSS scale were found between both groups. After adjustment for olanzapine equivalent doses, smoking status and baseline body mass index (BMI), mean changes in negative symptoms were positively correlated with percentage of response, and cognitive improvement was negatively correlated with antipsychotic response in schizophrenia patients. Within DD patients, mean changes in CGI- positive subscale was associated with response to antipsychotics.

Discussion: Our findings support the notion that schizophrenia and DD patients do not differ in response rates, which is in line with recent systematic reviews. Surprisingly, in contrast with previous studies, lower doses of AP were needed in DD patients. The positive domain was specifically correlated with antipsychotic response in DD patients, while negative and cognitive symptoms were associated with response in schizophrenia, suggesting different patterns of antipsychotic response between both groups.

M253. Clinical predictors of treatment resistance in first episode schizophrenia; a 5 year follow up study

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Background: Clozapine remains the only evidence based antipsychotic for treatment resistant schizophrenia (TRS). The ability to identify a patient with treatment resistance (TR) is crucial in order to diminish the severe functional disability which may ensue if it is not recognized and correctly treated.

Methods: This is a longitudinal assessment of clinical outcomes in a cohort of 245 first-episode schizophrenia spectrum patients recruited as part of the Biomedical Research Centre (BRC) Genetics and Psychosis (GAP) study conducted in South London from 2005-2010. We examined the relationship between baseline demographic and clinical measures and the emergence of TR. We assessed for associations with early, and late onset TR, and non-TR, and differences between those TR patients treated with clozapine and those who were not.

Results: Seventy percent ($n=55$) of TR patients, and 23% of the total study population were treatment resistant from illness onset. Those who developed TR during the first five years of illness were more likely to have an early illness onset (< 20 years) (OR 2.66 95% CI 1.31-5.40) compared to those with non-TR. The relationship between an early age of onset (< 20 years) and TR was specific to patients of Black ethnicity (OR 3.71 95% CI 1.44-9.56); and patients of male gender (OR 3.13 95% CI 1.35-7.23).

Discussion: TR was strongly associated with an illness onset before 20. For the majority of the TR group, antipsychotic treatment resistance is present from illness onset, necessitating increased consideration for the earlier use of clozapine.

M254. Pharmacological characterization of the novel glycine transporter-1 inhibitor BI 425809 on target engagement *in-vivo* and in animal models related to cognitive symptoms of schizophrenia

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Background: Evidence from numerous clinical and preclinical studies has led to the hypothesis that hypofunction of N-methyl-D-aspartate (NMDA) receptors plays an important role in the pathophysiology of schizophrenia involving positive, negative and cognitive symptoms. One approach to counteract NMDA receptor hypofunction is the extracellular increase of the NMDA receptor co-agonist glycine by glycine transporter-1 (GlyT1) inhibition. Thus, inhibiting GlyT1 has the potential for treatment of cognitive symptoms of schizophrenia via strengthening glutamatergic neurotransmission. Indeed, previous studies with GlyT1-inhibitors could show memory enhancing effects in animal models related to schizophrenia (Wolkenberg and Sur, 2010). This study characterizes the potency and selectivity of the novel GlyT1 inhibitor BI 425809 and its effects on glycine increase in rat cerebrospinal fluid (CSF). In addition, BI 425809 was evaluated in two rodent cognition tasks addressing working memory or social recognition memory performance.

Methods: The molecular potency of BI 425809 for GlyT1 was determined by inhibition of [3H]-glycine uptake in human SK-N-MC cells and rat primary cortical neurons. Selectivity against GlyT2 and other off-targets was evaluated by inhibition of [3H]-glycine uptake in HEK cells overexpressing human GlyT2 and by receptor binding assays, respectively. Concentrations of glycine in rat CSF samples collected from cisterna magna following oral administration of BI 425809 were determined by HPLC-MS/MS technique. Regarding cognition, BI 425809 was tested after oral application in the mouse T-maze spontaneous alternation test and in the social recognition test in naive rats.

Results: The IC50 value of BI 425809 on GlyT1 was determined to be 4.0 nM in the SK-N-MC cells and 4.4 nM in rat primary neurons. BI 425809 demonstrated no relevant activity against GlyT2 (IC50 > 10 μ M) and 103 off-targets at 10 μ M. The compound led to a dose-dependent increase of glycine in rat CSF. Furthermore, BI 425809 could reverse MK-801 induced memory deficits in the mouse T-maze and improved memory performance in the rat social recognition task addressing working memory and social recognition memory, respectively.

Discussion: The results of this study demonstrate that BI 425809 is a potent and selective GlyT1 inhibitor. Systemic administration of BI 425809 led to an increase in glycine levels in the rat CSF demonstrating functional target engagement, i.e. GlyT1 inhibition in the brain. This shows that glycine levels in CSF can be used to assess GlyT1 inhibition centrally which might also be used to evaluate central target engagement in clinical trials. Confirming previous findings, BI 425809 showed memory enhancing effects in animal cognition tests further demonstrating that GlyT1 inhibition may be a potential approach to pharmacologically improve cognition in schizophrenia.

References:

Wolkenberg and Sur (2010), *Curr. Top. Med. Chem.*10:170-186.

M255. Examining the association between social cognition and functioning in individuals at ultra-high risk for psychosis

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Background: Social and role functioning is compromised for the majority of individuals at ultra high risk (UHR) for psychosis and it is important to identify factors that contribute to this functional decline. This study aimed to investigate social cognitive abilities, which have previously been linked to functioning in schizophrenia, as potential factors that impact on social, role and global functioning in UHR patients.

Methods: Thirty UHR patients were recruited from an established at risk clinical service in Melbourne, Australia and completed a battery of social cognitive, neurocognitive, clinical and functioning measures. We examined the relationships between all four core domains of social cognition (emotion recognition, theory of mind, social perception and attributional style), neurocognitive, clinical and demographic variables with three measures of functioning (the Global Functioning Social and Role scales and the Social and Occupational Functioning Assessment Scale) using correlational and multiple regression analyses.

Results: Performance on a visual theory of mind task (visual jokes task) was significantly correlated with both concurrent role ($r=0.425$, $P=0.019$) and global functioning ($r=0.540$, $P=0.002$). In multivariate analyses it also accounted for unique variance in global, but not role functioning after adjusting for negative symptoms and stress. Social functioning was not associated with performance on any of the social cognition tasks.

Discussion: Among specific social cognitive abilities only a test of theory of mind was associated with functioning in our UHR sample. Further longitudinal research is needed to examine the impact of social cognitive deficits on long-term functional outcome in the UHR group. Identifying social cognitive abilities that impact significantly on functioning is important to inform the development of targeted intervention programs for UHR individuals.

M256. Onset age as a predictor for clinical outcome in schizophrenia – a systematic review and meta-analysis

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Background: The aim of the research was to study the effect age at onset has on the long-term (min. two years) clinical outcome of schizophrenia through a systematic review and meta-analysis. The relationship between age at onset and the outcome of schizophrenia has remained a research topic with varying results from original

studies making it difficult to draw conclusions without a systematic approach. Yet in clinical practice it is not uncommon to assume a lower age at onset to result in worse prognosis as described in clinical textbooks.

Methods: The search for the original studies included four databases: Web of Science, PsycINFO, Pubmed and Scopus. In addition, a manual literature search was performed. For the meta-analysis the estimation of the relationship between age at onset and the outcome variables (categorized to remission, relapse, hospitalization, positive symptoms, negative symptoms and total symptoms) was done using correlation coefficients. The meta-analysis was performed as a random-effect analysis using Stata.

Results: Out of the 3448 search results, 81 fulfilled the inclusion criteria for this study (e.g. a minimum follow-up period of 2 years). Collected data included: the used diagnostic system, setting of the study (inpatient/outpatient), duration of schizophrenia at baseline, size of the sample, age at onset's definition and source, onset age, follow-up time, used outcome measures, and in comments the main result of the study and any other especially noteworthy information. For the systematic review over the clinical outcomes of remission, relapse, hospitalization, positive symptoms, negative symptoms and total symptoms the results were varying. For remission and relapse a small minority of the included studies reported any relationship between age at onset and the studied outcome. Thus, no clear relationship is evident. For relapsing, the included studies showed age at onset having a varying effect and thus, no clear relationship can be identified. For hospitalization there were 9 out of total 18 studies showing a statistically significant relationship between age at onset and the reported outcomes. The presented results, some relatively strong correlations, suggest that earlier age at onset results in more frequent or longer hospitalizations. Out of 11 studies with results for positive symptoms only one presented a significant relationship between age at onset and the outcome revealing that age at onset is not a predictor for that outcome. For negative symptoms the results were different: 6 studies out of 17 reported a significant relationship showing a weak to modest correlations. For total symptoms 2 out of 5 studies reported moderate correlations indicating that age at onset can have an effect on total symptoms. For global clinical outcome over a half of the included studies reported a statistically significant relationship. In these studies age at onset was nearly equally reported for having a positive or a negative relationship with the outcome and thus, the relationship is not showing a clear direction.

For the meta-analysis of the clinical outcomes there was a small but statistically significant relationship between age at onset and hospitalization ($n=9$; $r=0.197$, 95% CI 0.034-0.360; $P=0.018$) as well as negative symptoms ($n=8$; $r=0.161$, 95% CI 0.060-0.263; $P=0.002$) while other relationships were not significant.

Discussion: This was the first systematic review on the effects of age at onset of the disease on a wide variety of clinical long-term outcomes in schizophrenia. Based on the review, age at onset does not have a statistically significant relationship with most of the clinical outcomes. It does have a small but statistically significant association with hospitalization and negative symptoms.

M257. Levels of stress, tolerance to stress, and the relationship between stress and distress associated with attenuated positive symptoms in people at ultra-high risk for psychosis

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Background: The experience of stress is thought to play a role in the risk of developing psychotic disorders. It is important to investigate the nature of stress in those at Ultra High Risk (UHR) of developing psychosis so preventative treatment can be accurately targeted. Existing research has found those at UHR exhibit higher levels of stress and an increased sensitivity to stress when compared to healthy controls. Additionally, negative appraisals of attenuated positive symptoms have been found to be associated with higher levels of distress and poorer outcome in UHR patients. Despite this, little is known about the relationship between stress, tolerance to stress, and distress associated with attenuated positive symptoms in a UHR sample. The present study compares levels of stress and stress tolerance in UHR patients and controls, and investigates whether

stress and intolerance to stress predict level of distress related to positive symptoms in those at UHR.

Methods: Participants were help-seeking UHR patients ($n=17$) and healthy controls ($n=12$). Self-reported measures of stress, and scores collated from a semi-structured interview on tolerance to stress, were collected for both groups. Those in the UHR group were also asked to rate the level of distress they experienced in relation to their positive symptoms.

Results: Self-reported scores of stress and interviewer-rated scores of intolerance to stress were significantly higher for the UHR group than controls. Multiple linear regression found that both stress ($B=-0.20$, $t(16)=-0.42$, $P=0.68$) and intolerance to stress ($B=-3.85$, $t(16)=-1.49$, $P=0.16$) did not significantly predict level of distress associated with positive symptoms in the UHR group.

Discussion: These findings are consistent with existing literature that has found higher levels of stress and increased sensitivity to stress in UHR patients when compared to healthy controls. The results from the UHR group suggest stress and distress associated with attenuated symptoms of psychosis are distinct phenomena, implying such symptoms should be targeted separately when treating those at-risk of developing psychosis.

M258. Beyond a singular approach: exploring the multiple facets of motivation in schizophrenia

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Background: Motivational deficits are a prevalent feature of schizophrenia that are linked to poor functional outcomes for affected individuals. Objective investigations of motivation in schizophrenia, however, have been limited to studies focusing on few and isolated components of motivation. While providing valuable incremental knowledge, the complex interplay among discrete facets of motivation remains poorly understood. Given the significant clinical relevance and intricacy of the motivational system, a more extensive and comprehensive analysis of this system is needed. The present study aims to concurrently evaluate the multiple facets of the motivational system using objective paradigms, and discern their interrelationships and contributions to motivational impairments seen clinically in schizophrenia.

Methods: Nineteen patients with schizophrenia and 26 healthy controls, aged 18-55 years, participated in this study. Participants completed a series of clinical and cognitive assessments to evaluate severity of psychopathology and functioning. Discrete facets of motivation, operationalized as effort valuation, goal-directed decision making, reward prediction, reward learning, and hedonic capacity, were measured using the Effort Expenditure for Rewards Task (EEFRT), the Iowa Gambling Task (IGT), the Cued-Reinforcement Reaction Time Task (CRRT), Probabilistic Reward Learning (PRL) task, and the Evoked and Representational Responding Task (ERRT), respectively. Beyond objective evaluations, clinical amotivation was measured using the Scale for the Assessment of Negative Symptoms (SANS).

Results: Patients with schizophrenia performed significantly worse on some, but not all tasks. On the EEFRT, patients demonstrated impairments in the allocation of effortful choices across different probabilities and reward levels ($t=-3.681$, $P=0.001$). Goal-directed decision making on the IGT was also impaired, with patients making significantly less advantageous choices than controls ($t=-2.972$, $P=0.005$). In terms of CRRT performance, patients displayed reinforcement-related speeding significantly less frequently than healthy controls ($\chi^2=4.400$, $P=0.036$). Additionally, patients were significantly slower at reward learning compared to healthy controls ($t=2.18$, $P=0.008$). However, there was no difference in hedonic capacity evaluated with the ERRT between groups ($t=0.050$, ns). Follow up correlational analyses indicated significant relationships between EEFRT and IGT performance ($r=0.395$, $P=0.007$) and EEFRT and CRRT ($r=0.311$, $P=0.040$). Additionally, SANS scores were significantly negatively correlated with effort valuation ($r=-0.371$, $P=0.012$), goal-directed decision making ($r=-0.305$, $P=0.042$), reward

prediction ($r = -0.407$, $P = 0.006$) and reward learning ($r = -0.342$, $P = 0.041$).

Discussion: Patients with schizophrenia display significant impairments across multiple facets of motivation. Preliminary results suggest that patients are specifically impaired in their effort valuation, goal-directed decision making, reward prediction, and reward learning. Comparable hedonic capacity scores between groups, however, suggest that these impairments are not a function of reward insensitivity. Further, significant correlations between multiple tasks, and with clinical amotivation highlight the need to move away from investigating isolated facets of motivation, and towards a more comprehensive and multi-faceted approach. That is, our results suggest that motivation in schizophrenia is best understood as an intricate combination of mechanisms and underlying factors.

M259. Clinical and social trajectories of first episode psychosis patients over five years: the role of gender differences

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Background: The influence of gender in modulating several aspects of psychotic disorders, both at onset and during the illness course, has been reported by a number of studies. In terms of psychopathology, an increased presence of positive symptoms in women and of negative and disorganized symptoms in men has been documented. With regard to social functioning, females have found to express higher rates of work productivity, independent living and social relationships than males. The tendency of women towards having a better outcome seem to be related to later illness onset, better response to treatment and higher rate of compliance, but other factors of interest need to be explored. The aims of the present study were: 1) to determine how gender differences impact on changes in symptoms, social disability, and self-perceived needs; and 2) to identify longitudinal gender trajectories in in a large, epidemiologically-based cohort of FEP patients over a five-years follow-up period.

Methods: This study was conducted with a prospective longitudinal design within the framework of the Psychosis Incident Cohort Outcome Study (PICOS), a multisite naturalistic research aiming to examine the relative role of clinical, social, genetic, and morpho-functional factors in predicting clinical, and social outcomes in a large cohort of FEP patients treated by public mental health services located in the Veneto region. Patients were assessed at baseline (T0), after one (T1), two (T2) and five years (T5); follow-up assessment also included those no longer receiving treatment by mental health services. For the present study we used information gathered by a subset of measures included in PICOS: the Positive And Negative Syndrome Scale (PANSS), the Camberwell Assessment of Need (CAN) and the Disability Assessment Schedule (DAS-11).

Results: A total of 397 patients were assessed at baseline, 215 (54%) males and 182 (46%) females. At 1 year 286 patients were re-assessed, 108 (38%) males and 102 (36%) females. At two years a total of 233 patients were assessed again, of which 103 (44%) males and 83 (37%) females. At 5 years were re-assessed 185 patients, 103 (56%) males and 82 (44%) females. As revealed by PANSS scores, males patients at baseline showed higher rates of cognitive symptoms and impulse dyscontrol, while female patients were more depressed; at 5 years, male patients presented more negative symptoms, whereas females scored higher in the anxiety-depression domains. At baseline a higher percentage of male patients had very serious disability (DAS item score ≥ 4), especially in parental role and finding a new job. At 5 years male patients still expressed a serious disability (DAS item score ≥ 3) in finding a new job. As regarding the CAN scale, at baseline significant gender differences were detected in the functioning domain, with female patients reporting a higher number of total met and unmet needs. At five-year follow-up the only significant difference was found in the service domain, with male patients reporting higher numbers of unmet needs.

Discussion: Our study provides a contribution to a better understanding of the impact of gender on early years following psychosis onset and its differential impact on the various social and service-related factors that most probably contribute to the aetiopathogenesis of the disorder. Moreover, it highlights the lack of a gender perspective in the Italian public mental health services and the importance of gender based studies for improving the outcome of people suffering from severe mental disorders, especially when they're focused on individualized service planning, intervention models and gender-specific treatment guidelines adoption.

M260. Insight and adherence in primary and secondary persistent negative symptoms: a longitudinal investigation of first-episode schizophrenia

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Background: Negative symptoms are consistently related to worse functional outcome and represent an unmet therapeutic need in people with schizophrenia. To examine changes in clinical insight and medication adherence in relation to primary and secondary persistent negative symptoms (PNS), compared to those that achieve remission. Design: A 12-month longitudinal analysis, as part of an ongoing, naturalistic outcome study based in an early intervention integrated clinical-research service. Participants: Clinical sample of 275 first-episode of schizophrenia (FES) patients treated from January 2003 through July 2015.

Methods: Clinical insight: awareness of illness, belief in response to medication, and belief in need for medication. Primary PNS was defined as the presence of at least one negative symptom rated at a moderate level for at least six consecutive months and not secondary to positive, depressive, and extra-pyramidal symptoms. Remission was defined following the consensus definition from 2005. Final groups included: pPNS (primary PNS, $n = 75$), sPNS (secondary PNS, $n = 79$), non-PNS ($n = 76$), and remitted ($N = 45$). Significant P -value set at 0.01 (0.05/5).

Results: There were significant main effects of group for insight of 'illness' (Wald $\chi^2 = 26.7$, $P < 0.001$) and 'response to medication' (Wald $\chi^2 = 25.2$, $P < 0.001$), but not regarding 'belief in need for medication' (Wald $\chi^2 = 10.4$, $P = 0.02$). In general, patients with pPNS and sPNS displayed poorer insight of 'illness' and 'response to medication' across the 12-month period; however, values did not significantly differ from the non-PNS group but did from the remitted group. All four groups did not differ on adherence levels across the 12-month period (Wald $\chi^2 = 10.4$, $P = 0.02$).

Discussion: pPNS, sPNS, non-PNS patients displayed equally poor insight over the first 12-months of treatment that did not significantly differ. Moreover, adherence did not significantly differ among all four groups. In sum, pPNS patients show poor insight but this may be due to a lack of proper treatments available to this group of people.

M261. Are self-report measures of social functioning associated with real-life social functioning? An ESM study in patients with schizophrenia and healthy control individuals

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Background: Maladaptive social functioning is one of the core manifestations of schizophrenia and functional recovery often remains an unmet therapeutic challenge. Social functioning is usually assessed by means of questionnaires, such as the Social Functioning Scale (SFS; Birchwood *et al.*, 1990). Despite the frequent use of the SFS, validation of this scale using real-life measures of social functioning is lacking (Oorschot *et al.*, 2012). One way of obtaining real-life measures of social functioning is through the use of the Experience Sampling Method (ESM). This study aims at examining the association between SFS dimensions and real-life measures of social functioning in a sample of patients with schizophrenia and healthy control individuals.

Methods: 117 participants (54 patients with schizophrenia and 63 healthy controls) completed the self-report version of the SFS and a 6-day ESM survey (max. 10 beeps/day). Two SFS subscales were used in this study: withdrawal (time spent alone, initiation of conversations, social avoidance, and time spent at home) and interaction (number of friends, romantic relationship, quality of communication). Higher SFS scores reflect better social functioning. The ESM protocol contained questions about the actual amount of time spent alone vs. with others, the actual location (at home vs. outside of home), and the appraisal of the social context (e.g. I feel threatened by this company). Direct comparisons between the SFS subscales and corresponding ESM items were performed using Spearman correlations or multilevel linear regression models.

Results: The SFS withdrawal subscale was significantly associated with the percentage of time spent alone, both in patients with schizophrenia ($r = -0.435, P = 0.001$) and controls ($r = -0.275, P = 0.001$). However, it was not associated with the percentage of time spent at home (both $P > 0.05$). In patients with schizophrenia, the SFS withdrawal subscale was associated positively with ESM ratings of feeling at ease while in the company of others ($\alpha = 4.29, \beta = 0.12, P = 0.007$) and negatively with wanting to be alone while in the company of others ($\alpha = 3.42, \beta = -0.12, P = 0.02$). It was not associated with ratings of feeling threatened while in the company of others ($\alpha = 2.36, \beta = -0.07, P = 0.09$) or enjoying being alone ($\alpha = 5.49, \beta = -0.08, P = 0.144$). None of these associations was significant in controls. The SFS interaction subscale was not significantly associated with the corresponding ESM items (percentage of time spent with friends or partner, ratings of feeling at ease while in the company of others) in both groups (all $P > 0.05$).

Discussion: Our results indicate that the SFS withdrawal subscale adequately reflects the severity of social isolation (percentage of time spent alone) and some aspects of social avoidance in patients with schizophrenia. On the contrary, the SFS interaction subscale is not related to daily-life measures of amount and quality of interaction with familiar persons. Weak or no relations between the SFS and ESM ratings were found in the control group. Altogether, the present study suggests that the SFS captures some aspects of daily-life social dysfunctions but may not be sensitive enough to uncover subtle variations, especially at higher ends of the continuum. These findings carry important methodological implications for future studies aimed at identifying predictors of daily-life social functioning in patients with schizophrenia.

M262. A 6-year follow-up of patients with severe schizophrenia undergoing intensive and comprehensive treatment: clinical and functional outcomes

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Background: To increase treatment compliance and consequently to reach clinical and rehabilitation goals in people with schizophrenia is a main challenge in their treatment. The purpose of this study was to know the retention in treatment (and reasons for discharge) of people with severe schizophrenia enrolled in a specific, intensive, comprehensive and community program for them; and also to know treatment (clinical and functional) outcomes.

Methods: A 6-year prospective, observational study of patients with severe schizophrenia (ICD 10: F 20; CGI-S = > 5) undergoing specific severe mental illness program ($N = 200$; average age = 43.1 ± 10.6 years old; 58% men and 42% women). Assessment included the Clinical Global Impression-Severity scale (CGI-S), the Camberwell Assessment of Needs (CAN) and the WHO Disability Assessment Schedule (WHO-DAS). Time in treatment and reasons of discharge were measured. Laboratory tests (hematology, biochemistry and prolactin levels), weight, medications prescribed and adverse effects were reported. Hospital admissions in the previous six years and during the follow-up were measured. Main statistical analyses were to compare scale scores and laboratory test results before and after 6 years of treatment (CI = 95%).

Results: CGI at baseline was 5.86 ± 0.7 . After six years 48% of patients continued under treatment (CGI = $4.31 \pm 0.8; P < 0.01$); 31% were medical discharged (CGI = $3.62 \pm 1.6; P < 0.001$) and continued non intensive treatment in mental health units; DAS decreased in the four

areas (self-care and employment $P < 0.01$; family and social $P < 0.005$) and also CAN (17.2 ± 2.8 vs. $9.1 \pm 3.2; P < 0.01$); 7% had moved to other places, continuing treatment there; 8% were voluntary discharges. Eight patients died during the follow up; three of them committed suicide (1.5%). 45% of all of them were treated with atypical long-acting antipsychotics, with good tolerability and few side effects or relevant biological parameters alterations (among them, only 4% were voluntary discharges). There were significantly less hospital admissions than during the previous 6 years: $1.9(1.8)$ vs. $0.3(0.2)$ ($P < 0.001$).

Discussion: Retention of severe mentally ill patients with schizophrenia in a specific and intensive care program was really high; and seemed to help getting in remarkable clinical and functional improvement. Long-acting medication also seemed to be useful on improving treatment adherence, mainly due to their good tolerability.

M263. Active recovery triad. A new initiative to provide hope and perspective for patients with severe mental illness in need of long-term clinical care

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Background: In the Netherlands major transitions are taking place in the care of people with (serious) mental illness (SMI). The current initiative termed "Active Recovery Triad" aims at improving the mental health care for those patients who have been considered the "permanent" residents of psychiatric hospitals. To date, this group has benefited little from all the innovations in mental health care that have been introduced in the past decades. But not only patients, also mental health workers in this long-term protective care are in need of renewal and momentum to improve the quality of care. Clients and professionals can be considered as trapped in a world which, despite their good intentions, makes them powerless to provide ultimate personalized care.

Methods: ART aims to present a nationwide, inspiring and guiding framework for developing long-term care so that 1) mental health care in long-term facilities is both truly recovery oriented and evidence based, and 2) more patients can set the next step towards more independent living and community participation.

Results: Notable challenges of ART are increasing the involvement of patients in an active daily life, reducing coercion and compulsion, and offering a hopeful perspective. All these challenges will be met by using the dynamics of the triad of client, resource group and mental health workers.

Discussion: To assess the effects of ART, a monitoring instrument was developed by which institutions and/or departments can monitor to which extent the ART model is implemented. Additionally, the relationship between implementation success and psychosocial variables will be assessed.

M264. Interpersonal consequences of subclinically reduced expressiveness - an EMG study of facial expressions

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Background: Synchronized movements are essential to establish interactional flow between interaction partners. Recently, schizophrenia has been associated with a deficit in movement synchronization, possibly accounting for interpersonal difficulties. In this study, we tested whether the negative symptom domain of reduced expressiveness is associated with a reduction in facial expression synchronization and interactional success in mentally healthy participants.

Methods: Sixty participants discussed life events in 30 same-sex dyadic interactions and afterwards evaluated the interaction. We assessed reduced expressiveness with the respective subscale of the Clinical Assessment Interview for Negative Symptoms (CAINS) and synchrony of smiling and frowning behavior during the interactions using electromyography. Separating low and high scorers on CAINS reduced

expressiveness via median-split resulted in three groups of dyads: low/low, low/high, and high/high.

Results: In general, synchronization of smiles but not frowns could be observed in the dyads. Smiling synchrony was highest in low/low dyads and lowest in high/high dyads, forming a significant linear trend across the three dyad groups. A similar effect was observed for the evaluation of the interactions, so that low/low dyads rated the interaction most favorably and high/high dyad least favorably.

Discussion: Thus, reduced expressiveness was associated with less smiling synchrony and less interactional success. However, smiling synchrony was not associated with interactional success, possibly because, in this sample of healthy participants, smiling synchrony was on a generally normal level in all groups so that participants based their judgements more on other interpersonal factors such as verbal content. In conclusion, our results indicate that reduced expressiveness may underlie the synchronization deficit reported in schizophrenia and at the same time has detrimental effects on interpersonal success.

M265. Language disturbance and functional outcome following first episode psychosis

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Background: The role of language in determining functional outcome in psychotic disorders is uncertain. Formal thought disorder (FTD) is a type of language disturbance that may be evaluated as a unitary or dimensional construct. Dimensions of FTD provide insights into social functioning in individuals with established psychosis and it has been suggested that communication disorders may represent a potential target of intervention in psychotic disorders. We aimed to address several gaps in the literature: 1) to evaluate the predictive value of FTD in relation to both social and occupational functioning following first episode psychosis (FEP); and 2) to compare the predictive value of FTD dimensions to that of FTD as a unitary construct. In doing so we aimed to clarify the clinical course and prognostic value of FTD in early psychosis.

Methods: Participants were recruited through the DETECT Early Intervention in Psychosis Service in Dublin, Ireland between February 2009 and July 2014; they were evaluated at FEP presentation and 1 year later. Cases of affective and non-affective psychotic disorders were included. The MIRECC GAF was used to evaluate social and occupational functioning; change in functioning score was entered as the dependent variable in regression analysis. FTD dimensions were assessed with the SAPS and SANS; factor analysis identified disorganized, verbose and impoverished FTD dimensions (disFTD, verFTD, and povFTD, respectively). FTD as a unitary construct was identified with the SCID-IV. Diagnosis, symptoms, duration of untreated psychosis (DUP) and premorbid adjustment (PA) were all evaluated with structured instruments. Funding was provided by the Health Research Board of Ireland.

Results: Two hundred and forty participants were assessed at baseline and 1 year. The level of occupational and social functioning improved significantly over the course of the year ($r=0.42$ and $r=0.52$ respectively, both $P<0.001$). The severity of disFTD and verFTD reduced significantly over the course of the year ($r=-0.28$ and $r=-0.26$ respectively, both $P<0.001$), however povFTD did not ($r=-0.01$, $P=0.75$). For those who demonstrated any type of FTD at 1 year it followed a persistent course in 50% of those affected and an emergent course in the other 50%. Resolution of each FTD dimension score was significantly predictive of both occupational and social functioning on univariate analysis (beta values range 0.12-0.20). On multivariable analysis however, only the disFTD dimension had a significant association with improved social functioning (beta=0.13, $P<0.05$) but not occupational functioning (beta=0.13, $P=0.06$). FTD as a unitary construct was not predictive of either social or occupational outcome on univariate analysis and therefore was not evaluated with a multivariate analysis.

Other predictors of functional outcome included: baseline level of functioning, schizophrenia diagnosis, DUP, PA, and resolution of positive and negative symptoms. The multivariate models in this study explained 52% of the variance in occupational functioning outcome and 63% of the variance in social functioning outcome.

Discussion: An improvement in disFTD has a unique contribution to improvement in social but not occupational functioning in FEP when controlling for a wide range of clinical variables. A dimensional and longitudinal evaluation of FTD provides more clinically useful information than that provided by a unitary or cross-sectional evaluation of FTD. Dimensions of FTD follow different trajectories over the course of the first year of illness and may become more circumscribed with longer follow-up. Communication disorders may be considered a potential target for intervention in psychotic disorders.

M266. Long term trajectories of positive and negative symptoms in first episode psychosis: a 10 year follow-up study in the OPUS Cohort

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Background: Knowledge about course of illness can help clinicians to develop effective interventions and improve treatment outcomes. The goal of this study was to construct positive and negative symptom trajectories based on structured clinical assessments collected over 10 years within a cohort of people with first episode psychosis.

Methods: A cohort of 496 people with first episode psychosis (ICD-10, F20-28) originally recruited for the OPUS study (1998-2000) and treated in community psychiatric services were rated on clinical symptoms at 5 different occasions across ten years. Psychopathology was assessed using the Scales for Assessment of Positive and Negative Symptoms. Symptom trajectories were constructed using Latent Class Analysis.

Results: Five distinct trajectories were identified for positive symptoms (response- 47%, delayed response-12%, relapse-15%, non-response 13% and episodic response 13%). Four distinct trajectories were identified for negative symptoms (response-28%, delayed response-19%, relapse 26% and non-response 27%). Multivariable regression analysis of baseline characteristics identified that longer duration of untreated psychosis (OR 1.27-1.47, $P<0.05$) and substance abuse (OR 3.47-5.90, $P<0.01$) were associated with poorer positive symptom trajectories (higher levels of psychotic symptoms) whilst poor social functioning (OR 1.34-5.55, $P<0.05$), disorganized symptoms (OR 2.01-2.38, $P<0.05$) and schizophrenia diagnosis (OR 5.70-8.86, $P<0.05$) were associated with poorer negative symptom trajectories (higher levels of negative symptoms). A proportion of people displayed significant changes in symptoms several years after diagnosis.

Discussion: Trajectories of illness for positive and negative symptoms were heterogeneous amongst people with first episode psychosis. Positive symptoms showed a general pattern of reduction and stabilization over time whilst negative symptoms typically showed less variation over the ten years. Results have implications for the focus, timing, and length of interventions in first episode psychosis.

M267. Validation of a German version of the resilience scale for adults (RSA)

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Background: The aim of this study was to examine the psychometric properties of a German version of the Resilience Scale for Adults (RSA) from Odin Hjemdal and Oddgeir Friberg. The RSA is a multi-dimensional resilience questionnaire, which measures dispositional resources, family support and external supporting systems. Until now,

it's not possible to assess resilience as a dynamic construct including personal, familiar, and social resources in German speaking countries. **Methods:** The RSA was translated from English to German and then retranslated based on the World Health Organization (WHO) guidelines for the process of translation of instruments. A non-clinical sample ($N=702$) were assessed cross-sectional and online-based with questionnaires on resilience, perceived social support, quality of life, and general psychopathology. The assessed data were checked on age (exclusion: <18 , >70 or no age recorded), completeness (exclusion: demographic data/RSA missing, more than 10% missing items per scale) and uni- as well as bivariate outliers resulting in $n=524$. The psychometric properties of the RSA were examined regarding factor structure, internal consistency, and construct validity. **Results:** The confirmatory factor analysis adequately supported the suggested six-factor solution of the original RSA: perception of self, planned future, social competence, family cohesion, social resources, and structured style. Further, the results indicated a high internal consistency with a Cronbach's alpha of 0.9 for the RSA overall. Construct validity was supported by significant correlations between RSA and a validated German resilience scale (RS-25) as well as perceived social support and general psychopathology. In line with previous findings, females scored significantly higher on all RSA subscales except for perception of self and planned future. **Discussion:** The German version of the Resilience Scale for Adults is a valid and suitable questionnaire for assessing protective factors. A six-factor structure as demonstrated for the original RSA, could be acceptably confirmed for the German version, too. These protective factors are important determinants of the psychological health and important predictors for therapeutic success.

M268. Psychopathology and functioning in patients with a recent onset psychosis (ROP) - first results from the PRONIA study

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Background: Psychotic disorders are associated with serious deterioration of functioning even before the first psychotic episode. Numerous findings demonstrated an association between negative symptoms and psychosocial deficits. In contrast, results concerning an association of positive symptoms and level of functioning are less consistent. The current analysis aims at investigating the relation of functioning and different types of (attenuated) positive symptoms as well as basic symptoms in patients with a recent onset of psychosis (ROP) patients. **Methods:** PRONIA ('Personalized Prognostic Tools for Early Psychosis Management') 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 of ROP individuals defined by a first onset of an affective or non-affective psychotic episode according to DSM-IV-TR within the past 24 month before baseline assessments. Furthermore, diagnostic criteria had to be met within the past three month and intake of neuroleptics in an antipsychotic dose range was limited to a cumulative number of 90 days since first onset. Positive symptoms were assessed by the Structured Interview of

Prodromal Symptoms (SIPS 5.0). The current analysis considered the score of the perceptive item P4 and the sum score of the non-perceptive items P1, P2, P3, and P5. Basic symptoms were assessed by the Schizophrenia Proneness Instrument, adult version (SPI-A). Scores were calculated for the cluster 'Cognitive disturbances' (COGDIS, nine items) as well as for the combination of COGDIS and the cluster 'Cognitive-Perceptive Disturbances' (COPER, summing up to 14 items). Level of functioning was assessed by 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: The GF:Social scores correlated significantly with the scores of the perceptive SIPS item, whereas none of the functioning scores showed a significant correlation with the non-perceptive scores. Regarding basic symptoms, significant negative correlations were observed between GF:Social as well as the GAF score and the combined COPER/COGDIS score and between each functioning score and the COGDIS score.

Discussion: With regard to positive symptoms, our analysis indicated that perceptive and non-perceptive positive symptoms may have a differential impact on functioning. Furthermore, we showed for the first time that particularly cognitive basic symptoms contribute significantly to the well-known functional deterioration in psychosis patients. This may open a new avenue to the understanding of the psychological as well as neurobiological mechanisms underlying the early and often persistent development of functional deficits in this group.

M269. Attitude toward medication, subjective well-being, and psychopathology in the early treatment of schizophrenia patients

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Background: Schizophrenia patients' attitude toward psychopharmacotherapy is a cornerstone in the context of medication adherence and therefore symptom improvement. This study examines potential correlations between attitude toward medication, subjective well-being, and psychopathology in the early treatment of schizophrenia patients.

Methods: Patients meeting diagnostic criteria of schizophrenia spectrum disorder according to ICD-10 starting monotherapy with an atypical antipsychotic were included into the study. The "Drug Attitude Inventory" (DAI), and the scale "Subjective Well-being under Neuroleptic Treatment" (SWN-K) were administered after 2, 4, and 12 weeks of treatment. At the same points in time, psychopathology was rated by means of the "Positive and Negative Syndrome Scale" (PANSS) to analyze potential correlations.

Results: Data of 30 patients were available for analysis. The SWN-K total score negatively correlated with the PANSS total score at week 2 ($P=0.041$), and 4 ($P=0.007$), but did not after 3 months time. The DAI total score did not correlate with the PANSS total score at any time point. Furthermore, we did not find a significant correlation between the SWN-K total score, and the DAI total score at any time point.

Discussion: The results show that attitude toward medication and subjective well-being under antipsychotic treatment represent two potentially independent factors, that are not correlated with psychopathology symptoms in the course of antipsychotic treatment. Taken together, these findings underline the importance of adherence monitoring in the early treatment of schizophrenia patients.

M270. Characterizing outcome preferences in patients with psychotic disorders: a discrete choice conjoint experiment

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Background: While the majority of patients treated for schizophrenia will achieve a remission of their symptoms, few will meet criteria for

recovery or be employed full-time. To explain the variation in outcomes observed, greater understanding is needed about what outcomes are most important to patients. Conjoint analysis methods that were developed in the fields of mathematical psychology and marketing are now used extensively in health economics for quantifying individual preferences. Discrete choice conjoint experiments (DCEs) involve developing a survey in which respondents are required to make choices between combinations of attributes, each presented with a range of levels. DCEs have the advantage over traditional surveys of simulating real-world decision making. We designed a DCE to characterize outcome preferences for patients with psychotic disorders and to determine whether there are distinct classes of respondents with different outcome preferences.

Methods: Subjects were recruited from two hospital outpatient clinics, one primarily for individuals with a first episode of psychosis and the other for individuals with schizophrenia and related psychotic disorders. Twelve outcomes were included: psychotic symptoms, medication side effects, physical health, work, income, housing, independence, family, friends, intimate relationships, religious faith, and recreational activity. Using Sawtooth Software's SSI Web version 7.4, these attributes were incorporated into a computerized survey with 15 choice tasks. Sawtooth Latent Class software was used to calculate utility values and importance scores for each level of the attributes. Latent class analysis was carried out to determine whether participants were distributed into distinct classes with different outcome preferences.

Results: Surveys were completed by a total of 300 subjects; 100 from the first episode service and 200 from the schizophrenia clinic. The respondents ranged in age from 15 to over 75 years of age; 62% were male and 72% were Caucasian. Latent class analysis revealed that the sample was divided equally between two groups of respondents with an average maximum membership probability of 0.96. Group 1 ($N = 152$) showed a strong preference for being employed full-time, in a long-term relationship, and for having more money than required for their basic needs. Group 2 ($N = 148$) showed a strong preference for not working and not being involved in intimate relationships. Both groups preferred living independently and spending time with friends and family. Respondents from the first episode service were more likely to be in Group 1 than Group 2 (68% vs. 32%) compared to respondents from the schizophrenia clinic (42% vs. 58%) (chi-squared = 18.03; $P < 0.001$). Group 1 was significantly younger, less symptomatic, more educated and had higher parental education than Group 2. The two groups did not differ on measures of happiness and life satisfaction.

Discussion: We have demonstrated using a DCE that individuals with psychotic disorders are distributed between two subgroups that differ on a number of key outcome priorities. Membership in these subgroups cannot be fully explained by age and stage of illness as approximately one third of respondents receiving services for a first episode of psychosis were in the subgroup that prioritized not working. Individuals who are more symptomatic, have greater cognitive and social deficits, and are from lower socioeconomic backgrounds may be more inclined to maintain their current outcomes. Understanding patient priorities is important for interpreting the outcomes described for psychotic disorders and for planning services to support patients in achieving their goals.

M271. "I'm out of synch and on my own. I am a schizophrenic." a mini ethnography of patients diagnosed with schizophrenia in Poland

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Background: This paper analyzes a single session of Dance Movement Therapy (DMT) with patients diagnosed with mental disorders, especially those on the schizophrenia spectrum, attending Daily Psychiatric Rehabilitation Unit in one of the hospitals in Poland, recovering from active psychosis into more residual stages of disability. Socio-cultural and political conditions that patients with schizophrenia are living with in Poland that are deeply implicated in creating the constant crisis, lack of stability and social support that occurs in their daily lives, have been explored. A short vignette about patients experience during year-long DMT treatment focusing on

what is the significance of being a schizophrenic revealed social suffering of patients, such as social stigma, rejection, abandonment, discrimination, rejection, isolation, dependency, and violation to their individual rights to a healthy life. Implications of findings for DMT field, showing how DMT might be not only an appropriate mode of treatment, but also provide an outlet for patients, that allows them for creative and not-directive way of expression of their personal and social suffering, will be discussed.

Methods: Performance analysis of a single session that represents the socio-cultural and political conditions of patients diagnosed on the schizophrenia spectrum, such as constant crisis, lack of stability and social support. Participants: 40 patients (ages 18 to 56) diagnosed with mental disorders attending Daily Psychiatric Rehabilitation Unit in one of the hospitals in Poland.

Results: Among the story reflected in the DMT session socio-cultural problems such as feelings of rejection, being misunderstood and stigmatized, dependency and rights, unjust social exclusion of people with mental disorders, social withdrawal, poverty of language, and the dependency on the medical system, are the main issues that have been identified by patients.

Assigning the patient a role of uselessness, worthless and incapable limit patient's activity, diffuse or detract from intellectual competencies, and deepen social alienation. Allowing a person with a diagnosis of mental illness, to return to "healthy" and "normal" society seems to be a major challenge that involves the construction of new ways of looking at each patient's capabilities.

Discussion: A common belief that schizophrenia is an incurable disease. Culturally, too many people approach the mentally ill person with fear and misconceptions. Assessment, rejection, and stigmatization of the patient are out of place and likely deepen the feelings of loneliness, misunderstanding and further isolation from the environment or culture at large.

Although, it is not easy to change ingrained prejudices and fear characterized by social attitudes towards mental illness and those who have it, it seems to be crucial to shift the perspective. Since much can be learned about the disease and its symptoms, course, and prognosis from the biomedical model, a culturally acceptable mode of assessment and treatment, practitioners committed to this culturally viable approach can become catalysts of change. The desire to know should replace fear, regardless of whether the disease affects ourselves, our loved ones, or simply ones we do not know. Each of us has some impact on how reality is constructed with a diagnosis of schizophrenia. Looking at patients not as "subjects" of illness but as recipients of a culturally constructed reality that often results in a loss of personal, social, and professional confidence and self-esteem, may then lead to a downslide and chronicity. Changing the mindset, openness, seeing opportunities rather than restrictions looks like a good start. We are all architects of the social reality.

M272. Instruments to measure public stigma and self stigma – a review

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Background: In the past years more and more research focused on stigma of mental health problems. Two important terms within stigma research are public stigma and self stigma. Public stigma refers to stigmatization of people with mental health problems by the general public, while self stigma is the internalization of public stigma. Along with the increase in research came an increase in instruments to assess stigma, with the last review of instruments for public stigma dating from 2004 and the last review for self stigma from 2010, an update seems in place. In this renewed review we focus on instruments for both public stigma and self stigma.

Methods: A search has been performed using Embase, PsycInfo and Medline with various search terms in the following categories: stigma, psychometrics, measurement, psychiatry. In all categories there had to be at least one hit. The search produced 92 hits in total, 10 hits were doubles. The remaining 82 articles were evaluated, focusing on whether it actually concerned articles about measuring stigma in mental health problems. After this, 29 hits remained, which were

sorted into public stigma and/or self stigma, and finally their psychometric quality was evaluated.

Results: In general the first thing that draws attention is the fact that the psychometric properties of the majority of available instruments can be considered 'satisfactory' at most. Fortunately, there are some exceptions, for measuring public stigma the most promising instruments are Attitudes to Severe Mental Illness Scale (ASMI), Barriers to Access to Care Evaluation Scale (BASE) and Mental Illness: Clinician's Attitudes Scale (MICA). For self stigma the most promising instruments are Internalized Stigma of Mental Illness (ISMI) and Stigma Scale (SS). **Discussion:** The scarcity of instruments with good psychometric properties for measuring stigma is remarkable. Considering the impact stigma can have on people suffering from mental health problems, more research should focus on validation of instruments measuring public stigma as well as self stigma.

M273. Impaired cardiorespiratory fitness (CRF) in schizophrenia

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Background: The increased risk of premature mortality in people with schizophrenia is recognized and has been demonstrated in multiple countries and healthcare systems. Potential causes of this excess mortality include suicide, lifestyle, medication side effects, underuse of health services and underlying disease processes. The WHO Global Health Risks report (2009) highlighted physical inactivity as the 4th most important global mortality risk factor. The importance of this and other mortality risk factors have been poorly evaluated in schizophrenia (Wildgust & Beary, 2010). Much recent research has focused on features of the metabolic syndrome in relation to the observed reduced life expectancy in those with schizophrenia.

Cardiorespiratory fitness (CRF) is an important health-related component of physical fitness and is highly correlated with cardiovascular and all-cause mortality in the general population but has been largely overlooked in schizophrenia. The few early studies which have explored aerobic function in schizophrenia (Carlsson *et al* 1968; Deimel & Lohmann 1983) found it to be impaired. Koivukangas *et al* 2010 showed that teenagers who went on to develop schizophrenia had lowered CRF. Bredin *et al* 2013 found 46% of her patients had aerobic capacity below what is considered to be required for independent living. Reduced peak oxygen (V_{O_2}) uptake has implications for cardiovascular health and quality of life in patients with schizophrenia (Heggelund *et al*, 2011).

Methods: We undertook a systematic review of the relationship between CRF and schizophrenia as a basis for a subsequent meta analysis. We followed PRISMA guidance.

Results: Our systematic review demonstrates both clinically and experimentally this is an under researched area. Small numbers coupled with heterogeneous schizophrenia/control samples and multiple non comparable outcomes precluded a robust meta analysis. However, all studies reviewed which examined aerobic function in people with schizophrenia showed it was impaired compared with controls. There are observable differences in peak oxygen uptake in all ten identified studies reporting quantitative results. Six studies reported peak oxygen uptake with comparable subject characteristics and demonstrated a mean V_{O_2} (ml/min/kg) in those with schizophrenia of 23.1 (SD 6.4) and in controls 34.0 (SD 5.8) ($P=0.013$).

Discussion: A 30% difference between controls and patients is likely to be clinically significant. The mean V_{O_2} peak levels which we found in schizophrenia are of the same order of magnitude as reported in mild COPD (Ganju *et al* (2010)). CRF is not measured in clinical practice. Our findings suggest that it may be important as a risk factor for premature mortality and impaired independent living. Potentially, lowered CRF may underpin low physical activity in schizophrenia. The current review adds further to the view that schizophrenia is not solely a disorder of the brain but is associated with extra-cerebral manifestations such as metabolic abnormalities which may pre-date frank psychosis. However, our systematic review poses more questions than it answers. It is unclear as to whether lower CRF is associated with symptom clusters such as negative symptoms and cognitive impairment. Low CRF is a risk factor for premature death in the general population and may explain some of the variance in people with schizophrenia. Practically it would be important to determine whether

improvement in CRF is accompanied by an improvement in mental state, social function, and improved longevity. If a balanced understanding of schizophrenia and associated health risks are to be addressed then the current focus on metabolic parameters should be widened to include CRF.

M274. Development of the subjective recovery scale for the patients with schizophrenia (SRS)

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Background: Recovery is defined as a complex process of developing a new meaning and purpose in life as an individual with severe mental illness grows beyond the catastrophic effects of the disease. Although, aspects of recovery can be measured to some extent objectively on the expert consensus, there is still no subjective measurement for the assessment of recovery accepted by every culture. As it is difficult to find a proper scale for the assessment of subjective recovery, recommended that every culture should develop own measurement scale. As we know, no scale to assess the individual recovery process is available in Turkey. The aim of this study is to develop a Subjective Recovery Scale (SRS) that culture-sensitive, and to examine its validity and reliability.

Methods: To form the questionnaire, the authors had an interview with a focus group constituted by the patients ($n=15$) and family members ($n=18$) on the meaning of recovery for them. It was discussed some 40 items related to recovery process from the literature, and afterward decreased the number of items to 24. This 24-item subjective recovery scale administered to the patients, along with other scales - the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impression-Severity (CGI-S), the Global Assessment of Functioning (GAF), and the Schizophrenia Quality of Life Scale (SQLS). Internal consistency reliability was assessed by Cronbach's alpha coefficients, and test-retest reliability was assessed by the intraclass correlation coefficient (ICC) in a randomly selected subsample ($n=30$). Exploratory and confirmatory factor analyses and correlations with other scales were used to examine the factor-based validity, concurrent, and construct validity of the SRS. The sample was composed of 80 patients with schizophrenia ($n=67$) and schizoaffective disorder ($n=13$) according to DSM-IV, diagnosed by the experienced psychiatrist in a community mental health center. Patients' mean age was 42.4 ± 11.0 years, mean level of education was 7.8 ± 3.9 years, and most of them was male (75.0%).

Results: Cronbach's alpha coefficient was 0.88 for the overall SRS. ICC generally indicated good test-retest reliability. Factor analysis revealed three-factor structure: (a) goal/success orientation, and reliance, (b) self-confidence, (c) hope, and willingness to ask for help. Four items extracted from the scale, because of low level of confidence (< 0.50). The overall SRS score significantly correlated with the QLSS ($R=0.910$; $P<0.0005$), GAF ($R=0.933$; $P<0.0005$), PANSS ($R=-0.915$; $P<0.0005$), and CGI ($R=-0.893$; $P<0.0005$).

Discussion: This study confirmed the reliability and validity of the 20-item SRS for the people with schizophrenia living in community.

M275. Assessing the relevance of the quality of life scale 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 as measured by the study's primary endpoint, the total score on the Heinrichs-Carpenter Quality of Life Scale (QLS) (Naber *et al.*, 2015).

The 21-item QLS is a clinician-administered, semi-structured interview designed to assess deficit symptoms and functioning during the preceding 4 weeks in patients with schizophrenia (Heinrichs *et al.*, 1984). Higher scores indicate better clinical condition, less impairment or more normal functioning, and potentially overall higher levels of HRQOL. The QLS provides a total score and individual scores for four domains: Interpersonal Relations, Instrumental Role, Intrapsychic Foundations, and Common Objects and Activities.

The objective of the current study was to gain a better understanding of the importance and relevance of the QLS 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 United States (Raleigh, NC, and St. Louis, MO). Semi-structured interview guides incorporating content from the QLS were used to guide the discussions, including questions on the meaning and importance of the QLS items and domains as well as those that were most likely or prone to change based on the level of functioning. Patients and caregivers were also asked to rank-order the QLS domains according to their perceptions of importance and their contribution to patients' QOL and functioning. For the purpose of the participant's understanding in elaborating on each of the QLS domains, the original dimensions were re-named.

Results: A total of 12 interviews were conducted with patients, and 17 caregivers participated across 4 focus groups. Patients were 58% male with a mean age of 42 years (range, 25-62) and diagnosed with schizophrenia for a mean 16 years (range, 2-47). Caregivers were primarily female (71%) with a mean age of 46 (range, 24-70).

The QLS domain Intrapsychic Foundations (e.g., sense of purpose, motivation, emotional interaction, happiness) was deemed most important by both patients and caregivers, and was also considered the domain most likely/prone to change. Interpersonal Relations (e.g., relationships with family and friends, and social activities) and Instrumental Role (e.g., being able to work, being successful, feeling satisfied) were both second in importance to patients but third and fourth, respectively, to caregivers, as they placed more importance on Common Objects and Activities (e.g., things to have, things to do).

Discussion: Content measured on the QLS was considered relevant, important, and with the propensity to change and improve. Concepts related to the patient's sense of purpose, motivation, and were strong drivers toward overall QOL. These findings help to establish the content relevance in supporting the QUALIFY study's findings.

M276. On the relationship between delusions and quality of life in schizophrenia

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Background: This study examined the relationship between delusions and objective and subjective quality of life (QoL) in schizophrenia (Sz). Previous findings have been limited and inconsistent. A number of intermediate factors in this relationship have been proposed, including poor insight, self-monitoring, and preoccupation. However, to date no study has investigated if QoL effects differ by delusion type. Additionally, the relationship between delusions and both types of QoL has not yet been concurrently investigated in a single sample. Such a distinction is plausible; notably given evidence that persecutory and grandiose delusions have been found to differ in both cognitive and emotional processing profiles (Garety *et al.*, 2013). We aimed to investigate (1) the effect of delusions on both objective and subjective QOL in a single sample, and if (2) the relationship between delusions and both types of QOL differed between persecutory and grandiose delusions. We hypothesized that increasing severity of delusions would be associated with reduced objective and subjective QOL. We tentatively expected that persecutory delusions would have a negative effect on subjective QoL with the reverse true for grandiosity. No specific hypotheses were made for objective QoL.

Methods: 54 patients with schizophrenia/schizoaffective disorder ($M=43.35$, $SD=10.74$), were administered Lehman's (1988) QoL Interview (QoLI) to assess both objective and subjective QoL. Participants were also administered the MATRICS Consensus Cognitive

Battery (MCCB), the PANSS and the MADRS. Mean QoL z-scores were calculated based on the scores of 48 healthy control participants.

Results: Two hierarchical regressions were run for each of the PANSS ratings for suspiciousness/persecution (P6) and grandiosity (P5) with objective and subjective QoL as individual DVs. MADRS depression scores and MCCB Overall Cognitive Scores were entered as Block 1 and 2 respectively. No relationships with objective QoL were observed for both delusion types; however only P6 significantly predicted subjective QoL scores, $\beta=-0.26$, $t(48)=-2.11$, $P<0.05$, accounting for 6.5% of the variance in subjective QoL scores, $F(1,48)=4.46$, $P<0.05$.

Discussion: The results support the influence of positive symptoms on QoL in schizophrenia. However, this seems to be limited to subjective QoL; delusions as a whole do not seem to influence the objective QoL domains examined here. No definitive difference in QoL effects by delusion type was demonstrated. Consequently, it may be that the aberrant thinking processes that underlie delusions more generally may be responsible for poorer perceptions of subjective QOL. This is the first study to examine this, and only the second to link delusions to subjective QoL, so replication is necessary. More broadly, the findings suggest that symptom type is a key area of consideration for patient outcome.

M277. First episode psychosis fidelity scale

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Background: The purpose of this study was to develop and test the feasibility, reliability and validity of the First Episode Psychosis Services Fidelity Scale (FEPS-FS). Fidelity refers to the degree of implementation of standards of evidence-based practice (EBP). Fidelity scales provide a list of objective criteria by which a program or intervention is judged to adhere to reference standards interventions. Bond *et al.* 2000 distinguish four research uses of fidelity measures, each addressing different aspects of validity; a) ensuring model adherence in program evaluations, b) facilitating communication in the literature, c) synthesizing a body of research, and d) identifying critical ingredients of program models. Fidelity scales have also been used in mental health services research for evaluating the implementation of evidence based practices. Outside of health services research, fidelity scales have been used for program accreditation and to determine eligibility for funding. Although fidelity measurement has been increasingly used in mental health services research its application in FEPS has been limited.

Methods: There were three steps in the study; first, transforming previously identified essential evidence-based components into a fidelity scale comprised of operationally defined components each anchored with a five-point scale. This work was done by a team comprised of a fidelity expert, first episode psychosis experts and an epidemiologist. Second, examining the reliability and utility of the fidelity scale in a 7-center study in a range of programs from academic health centers to rural counties in the United States and Canada. Third, comparing item content for the new scale with three other published fidelity scales.

Results: The expert team developed concrete descriptors for each component and explicit ratings so that each item could be rated on a scale from 1 to 5. When tested in real world programs, data collection proved feasible and reliable (intra-class correlation coefficient 0.842, (95% CI: 0.795- 0.882). Discriminative validity was supported by finding a mean score of 86% on programs judged to be exemplary FEPS programs compared to 70% for a site judged not to meet standards. Content validity was supported by comparison with three other fidelity scales which identified 17 items common to all scales with the FEPS-FS having the highest proportion of common items (55%) and the highest proportion of all its items shared with each of the other scales (74 - 80%).

Discussion: The First Episode Psychosis Fidelity scale is a feasible, compact, reliable and valid measure of adherence to evidence based practices for first episode psychosis services. It is based on knowledge synthesis rather than on a specific program model and thus can be applied in any first episode psychosis services thereby allowing for

comparisons across program models. It is in form that is appropriate for application in a variety of research projects.

M278. Discontented residents of sheltered homes: better functioning and worse quality of life

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Background: As the amount of psychiatric hospital beds have decreased over the last decades for schizophrenia patients with decreased functioning, they are placed in different types of supported housing instead of supporting them to live independently in the community. The expense of this supported housing can be high for municipalities. We wanted to find out if there were some residents, in two sheltered homes in Southern Finland, who could manage with sufficient support and would feel more comfortable living on their own.

Methods: We asked 85 residents of two sheltered homes about their contentment of their present housing, from where and on whose initiative they were moved, how they managed their self-care tasks, physical health, functioning (SOFAS), subjective quality of life, depressive symptoms (Beck's Depression Inventory) and psychiatric symptoms (Brief Psychiatric Rating Scale).

Results: The mean age of the participants was 47.6 years. Of the residents, 70% had schizophrenia diagnosis, 14% schizoaffective disorder, 5% brain injury or mild developmental disability and 11% had other diagnoses. For their current housing, 37% of the residents had come from other sheltered housing, 21% were previously living alone and 22% had come from hospital. 53% considered their current housing the best place for them to live, 28% said it was not the best for them and 19% had no opinion. When asked about preferred type of living, 32% said current housing, 45% said independent living and 23% preferred living either in hospital, in another sheltered home or with relatives. BPRS score ranged from 7 to 76 points, the mean being 37.7 points.

The one-third of residents who considered their current housing not the best for them had significantly better hand grip strength (t -test = 2.24, $df = 1$, $P = 0.0410$), had less often difficulties in managing their self-care tasks ($\chi^2 = 5.6239$, $df = 1$, $P = 0.0177$) and more often wanted to live independently ($\chi^2 = 10.2626$, $df = 1$, $P = 0.0059$) than those who preferred their current housing. They also reported worse quality of life, suffered less often from pain, had less often problems in mobility and had higher scores in SOFAS, but the differences were not statistically significant. There was no difference between the groups in the following: where they used to live before, who suggested present housing, status of physical health, depressive symptoms, BMI, activities of daily living and BPRS score.

Discussion: Residents of the two sheltered homes had severe psychiatric disorders, such as schizophrenia, but most of them did not have severe psychiatric symptoms according to BPRS-UCLA. Those who did not consider their current living place at the sheltered home ideal for them reported better functioning and state of health than those who preferred their current living arrangement. Patients with better functioning also reported worse subjective quality of life. This may indicate that they are frustrated with their current living situation in the sheltered home. With sufficient support these residents could try living on their own and their self-esteem could rise as well as their quality of life. One promising intervention strategy for outpatients with schizophrenia is CAT (cognitive adaptation training), which compensates for cognitive impairments and improves adaptive functioning.

M279. Devolvement of the danish OPUS-fidelity-scale for specialized early intervention teams

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Background: The efficacy of the OPUS treatment has, in a randomized clinical trial, been proved to be very strong comparing to treatment as usual. Proliferation of Specialized Early Interventions (SEI) (OPUS-

teams), are increasing in Denmark. However, a prerequisite for upholding the positive effects along with the establishment of new OPUS teams is of course maintaining of critical components similar to the concept that was tested in the randomized trial. However, there is a lack of fidelity-scales for SEI services', and it is currently not possible to measure presents or absents of critical components in current and future OPUS teams. We therefore want to establish an OPUS fidelity-scale.

Methods: First step: Based on essential evidence-based components of SEI services we interviewed experts from five Danish OPUS team regarding critical elements of OPUS treatment, an adapted version of the Delphi Consensus method in order to develop the fidelity scale. Second step: test of the scale in 19 SEI teams in Denmark. In March and April 2016 the scale will be tested in 19 SEI teams in Denmark by face to face interview.

Results: A preliminary 18-point scale was conducted. The scale was divided into two dimensions; one concerning the structure of the OPUS team and a second comprising the character and content of the treatment. Each component can be rated either 1 or 0 (0 point = fulfilling the requirements for the components; and 0 point = the requirements was not met. Highest score was a total of 18 points, and in order to "pass" the OPUS-fidelity scale at elite level, the total score must be between 15-18 of which 5 of the components are mandatory.

Discussion: Development of a fidelity scale can be an important tool for securing the quality of OPUS treatment and it can serve as inspiration for an international accepted common fidelity scale.

M280. Analyzing the impact of early detection on duration of untreated psychosis: quantile regression

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Background: The duration of untreated psychosis (DUP) has been robustly associated with poorer outcomes across multiple healthcare systems. Several studies have tested the effectiveness of different early detection strategies to reduce DUP, while several others are underway. The highly skewed distribution of DUP poses a challenge for traditional statistical methods and limits the strength of inferences about the relative effectiveness of different early detection strategies. Researchers have employed a variety of approaches to overcome this difficulty. One option is to use categorical divisions of "long" and "short" DUP based on various cut-offs (e.g. < 3 months, < 12 months etc.) or a median split, while another is to apply nonparametric statistical tests that compare the entire distribution of DUP variable across groups. Transformation of data (e.g. log-transformation) to approximate normality is likely advisable such that conventional statistical methods to compare means of normal data can be employed. However, all these approaches have limitations. First, the absence of good evidence for a threshold above which DUP is more consequential limits the usefulness of the categorical approach. Second, the results of nonparametric analytical methods or the log-transformation approach are difficult to interpret and translate for clinical practice. More importantly, the skewness of DUP may reflect the heterogeneous causes of untreated psychosis. Conventional statistical methods that focus on deriving inferences of mean response may fail to capture the differential effect of covariates across different sections of the DUP distribution.

Methods: We propose an alternative analytical strategy to deal with skewed DUP distributions. Quantile regression is a method to model the conditional quantiles (cutpoints splitting a frequency distribution into a given number of equal sized partitions, e.g. 10-quantiles [deciles] 100-quantiles [percentiles]) of response variables using independent variable(s). Unlike ordinary least square regression, it is able to estimate the heterogeneous effects of a predictor on different quantiles of outcome rather than a uniform effect on a mean outcome measure. Other advantages include no normality assumption for the error term, robustness to outliers, and the use of all data to fit statistical models.

Results: To illustrate the advantage of this strategy, we made up a dataset by simple quadruplicating DUP data from a completed clinical study and compared the results of different analytic approaches,

including ordinary least square regression both arithmetic and log scale, Wilcoxon rank test (nonparametric method), regression on median, and quantile regression. The first four methods failed to identify a significant difference between the groups with respect to DUP in months. However, quantile regression was able to find that DUP at the 0.6 quantile was significantly greater in one group compared to the other (difference 4.0 month, 95% CI 1.1 month to 6.9 month, $P=0.008$).

Discussion: Our findings suggest that quantile regression may offer a number of advantages over the conventional methods in analyzing the impact of early detection on duration of psychosis.

M281. Outcome evaluation of a Canadian first episode psychosis program

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Background: Rapid detection and intensive early psychosis intervention (EPI) were first identified as standard of care in Australia, the UK, and Scandinavia. In 2004 dedicated funding resulted in the development of over 30 EPI programs in Ontario Canada. Evidence shows that EPI programs are linked to reduced symptoms of psychosis, relationship disruption, academic, vocational and social impairment, emergency visits, hospitalizations, and contact with the legal system. We present outcome data on patients treated at On Track, the EPI program in Ottawa Ontario Canada. On Track provides interdisciplinary care, nurse or social worker case management, and psychiatrist follow up combined with group and individual phase-of-recovery based interventions. Using a clinical pathway (assessment, acute psychosis, stabilization, and reintegration stages) we offer patient and family education and support, healthy lifestyle, recreational, vocational, cognitive behavioral, and cognitive remediation groups.

Methods: Patients were 17-48 years with a first episode of psychosis treated for six months or less, without severe substance use, bipolar disorder, developmental delay, or prominent forensic history. Data included demographics, vocational, and educational status, hospital and emergency admissions, length of stay in hospital, symptom rating scales (Positive and Negative Symptom Scale, Global Assessment of Function, Clinical Global Impression), movement disorders (Abnormal Involuntary Movement Scale), and quality of life (Wisconsin Quality of Life Client Questionnaire). We report one year follow-up data.

Results: The mean age of the sample ($N=95$) was 26.4 years ($SD=7.5$); 61% male; 81% English speaking and 9.5% Francophone. Referral sources varied: The Ottawa Hospital (54.7%), family physician (10.5%), psychiatrist or psychiatric hospital (11.6%), and self/family/friend (6.3%).

In the two years pre-admission to On Track, 65.3% were admitted at least once. Comparing baseline rates with endpoint (6-12 months post-admission), mean hospital admission rates declined from 1.09 ($SD=1.11$) to 0.06 ($SD=0.23$), emergency visits declined from 1.68 ($SD=1.41$) to 0.07 ($SD=0.30$) and days hospitalized decreased from 17.86 ($SD=20.95$) to 1.32 ($SD=8.14$). Mean AIMs scores at baseline and end point were low (0.39 & 0.51 respectively). There were significant ($P < 0.000$) changes on rating scales from baseline to one year follow up. PANSS total scores reduced from 70.67 ($SD=19.67$) to 53.13 ($SD=18.01$). GAF scores increased from 49.24 ($SD=13.57$) to 61.78 ($SD=17.54$). CGI scores decreased from 4.36 ($SD=1.13$) to 2.87 ($SD=1.14$). Academic enrollment increased by 45% and unemployment decreased by 33%.

Discussion: Patients enrolled at On Track experienced significant improvements in PANSS, GAF & CGI scores, reductions in hospitalizations, ER visits, and days in hospital, and increases in school attendance and independent work at one year follow-up. Our sample has the same age and sex distribution as reported in the one year outcome data of the OPUS EPI trial (Petersen *et al.*, *BMJ*, 2005). On Track and OPUS baseline GAF scores were 49.58 and 41.6 respectively. This likely reflects On Track allowing up to 6 months of preadmission treatment versus the three months allowed for OPUS. On Track one year GAF scores were higher than OPUS scores, 61.8 vs 51.7 respectively. Mean hospital stays were lower for the Canadian sample (1.32, $SD=8.14$) vs the Danish sample (14, $SD=62.2$). The percentage

of On Track clients not working or in school at one year was comparable to the OPUS sample. The case managers to patients ratio at On Track (1:25) was higher than that of OPUS (1:10) suggesting that similar outcome results may be achievable with higher caseloads.

M282. Impact of the "unlocking and treatment" intervention on family burden: a follow-up study for the families where locking of patients with SMI were practiced

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Background: In 2005, a demonstration program known as "686" was implemented in China to improve access to evidence-based care and to promote human rights for people with severe mental disorders. As part of the 686 Program, teams "unlocked" and provided continuous mental health care to people with severe mental illness (SMI) who were found in restraints and largely untreated in their family homes. We conducted a nation-wide two-stage follow-up study to measure the impact of the "unlocking and treatment" intervention on the well-being of patients' families. We hypothesized that the families would benefit from the intervention and the improvements achieved could be largely sustained through 2012.

Methods: 266 patients unlocked from 2005 in "686" demonstration sites across China were recruited in Stage One of the study in 2009. In 2012, 230 of the 266 cases and their families were re-interviewed. We explored the impact of patient mental illness on the well being of families, taking changes in caregivers' ratings of their family burden experiences as a subjective measure. Family members were asked to rate their subjective experiences on analog scales for the five categories of family burden—stigma, psychological pressures, economic burden, loss of personal energy, and interpersonal relationships. We utilized pre-post tests to analyze the changes over time following the unlocking efforts.

Results: 96% of patients were diagnosed with schizophrenia. Prior to unlocking, their total time locked ranged from two weeks to 28 years, with 32% having been locked multiple times. When comparing family members' evaluations on how much they were affected by the patients' mental illness, 2009 post-unlocking scores illustrated significant improvement in caregivers' experience with a reduction in rating scores on each of the measures of family burden ($P < 0.0001$). Although measures of family burden except stigma ($P=0.1089$) increased slightly from 2009 to 2012 ($P < 0.0001$), the improvement in five categories of family burden ratings were largely sustained ($P < 0.0001$).

Discussion: Family caregivers described significant reductions in feelings of stigma, psychological pressures, economic burden, loss of personal energy, and negative personal relationships following the "unlocking and treatment" intervention, and the benefit sustained through 2012.

M283. Extent of monitoring and intervention for physical health issues in the Singapore early psychosis intervention programme (EPIP)

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Background: Life expectancy in people with schizophrenia is 20% lower than in others. Although levels of suicide and other violent deaths are higher in people with schizophrenia, most of the increased mortality in this group is the result of higher levels of cardiovascular disease and other physical health problems. In the latest National Audit of Schizophrenia in UK, a major finding was the significant deficiencies in monitoring and management of physical health problems in people with schizophrenia. This finding prompted the College to work with several professional bodies to develop a quality improvement tool, the Lester Cardiometabolic Resource, to promote better physical health care for people with psychosis. The resource recommends these monitoring following initiation/change of antipsychotics and/or mood stabilizers: Weight – at baseline, weekly in the

first 6 weeks, at 12 weeks and annually; Lifestyle review (i.e. smoking, diet, and physical activity); BP; FPG/HbA1c; Lipid profile – at baseline, at 12 weeks and annually; Personal/Family history of CHD; WC – at baseline and annually. In practice, there have been anecdotal reports of monitoring frequency far exceeding the recommended duration for various reasons. We examined the extent of monitoring and interventions for physical health problems in EPIP with the following specific objectives: To examine the frequency of cardiometabolic monitoring (weight/BMI; WC; BP; FPG; Lipid profile; Lifestyle review); establish the prevalence of physical health problems (i.e. obesity; diabetes; dyslipidemia; hypertension); examine the interventions performed for these physical health problems.

Methods: All consecutive patients who were accepted into EPIP from July to December 2013, and were still on follow up at the end of 1 year (i.e. December 2014), were included into the study. Their case notes and electronic medical records were examined to ascertain the necessary clinical information.

Results: At baseline, 77.5% of patients had their weight/BMI recorded; 0% had their WC recorded; 80% had their BP recorded; 72.5% had their FPG/Lipid profile measured; 57.5% had their smoking status documented and 62.5% had their alcohol status documented. At the 1-year follow-up, the corresponding figures dropped to 70%, 0%, 50%, 20%, 2.5%, and 5%, respectively. At baseline, 15% of patients had pre-existing obesity; 2.5% had hypertension; 2.5% had diabetes mellitus; and 12.5% had dyslipidemia. At the end of 1 year, in addition to the patients who had these pre-existing medical issues, 15% of patients were documented to have developed obesity; 7.5% hypertension; 10% dyslipidemia; and none were documented to have developed diabetes mellitus. Of those who had developed obesity, only three-quarters were given diet and lifestyle modification advice. Of those who had developed dyslipidemia, only half were either given the necessary advice or were referred to primary care physicians for further management. None of the patients who had developed hypertension were documented to have received the necessary interventions.

Discussion: This study highlights the gross deficiencies in the monitoring and management of cardiometabolic problems even in a specialized early psychosis program. Despite the inadequacy of monitoring, a significant proportion of patients were found to have developed cardiometabolic issues within a year of their illness. It is very likely that were many other patients with undetected and untreated medical conditions. To be able to achieve the ultimate aim of reducing morbidity and mortality in patients with severe mental illness, it is vital for the treating team to identify emerging physical health issues as early as possible so that adequate and timely interventions can be administered.

M284. Deviation from the 12-hour standard sampling time during therapeutic drug monitoring of clozapine – does it matter?

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Background: Clozapine is an atypical antipsychotic drug, recommended as first-line treatment for treatment-resistant schizophrenia. Several factors can influence serum (s)-clozapine and hence cause dose-related adverse reactions or change treatment response. Therapeutic Drug Monitoring (TDM) in clozapine treated patients is often used even though its relevance for optimal pharmacological treatment has been debated. TDM samples are standardized as 12 hours post-dose values. In everyday clinic, sampling time often deviates from the standardized 12 hours. However, the clinical importance of this deviation remains unknown.

The aim of this study is to describe variation in s-clozapine and s-N-desmethyl-clozapine as the sampling time deviated up to 2 hours from the standardized 12 hours.

Methods: This was an open-label, pharmacokinetic study, in which patients with schizophrenia, aged 18-64 years and on stable treatment with clozapine for at least a month, were enrolled for venous blood sampling at 10, 11, 12, 13, and 14 hours post-dosing.

Co-medication, BMI, white blood cell count (WBC), smoking- and caffeine habits were recorded and compliance, and exact time of drug administration were documented by calling the patient at an agreed time of drug consumption. Serum concentrations of clozapine and the metabolite N-desmethyl-clozapine were measured from each blood sample, using ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS-MS). A susceptible to deviation of sampling time, subgroup analysis with the following covariates was conducted: sex, age, body mass index (BMI), co-medications, caffeine intake, smoking, and signs of infection.

Results: 46 subjects were included in the study. One patient suffered a serious adverse reaction (SAR), agranulocytosis. No other adverse events occurred. Results will be presented at the meeting.

Discussion: The results and their implication for therapeutic drug monitoring (TDM) will be discussed.

M285. Cardiac and cardiometabolic adverse effects in children and adolescents during treatment with aripiprazole or quetiapine ER – 12-week results from the tea study

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Background: The evidence for choices between antipsychotics for children and adolescents with schizophrenia and other psychotic disorders is limited. The purpose of the present study is to compare the cardiac and cardiometabolic effects of aripiprazole vs. quetiapine ER in youths with first-episode psychosis (FEP).

Methods: Youths aged 12-17 years were randomized to aripiprazole or quetiapine ER in the 12-week, double-blinded, randomized Tolerability and Efficacy of Antipsychotics (TEA) trial. Patients were assessed at baseline, week 2, week 4, and week 12. Primary outcome was baseline-to-endpoint change in weight, secondary outcomes were changes in body mass index (BMI) z-score and waist circumference (WC) z-score, blood pressure, lipid and glucose metabolism parameters, and change in the Hodges-corrected QT interval (QTcH).

Results: Patients ($n = 113$), 82% with schizophrenia, 30% males, mean age 15.8 years (SD 1.36) were randomized to quetiapine ER ($n = 55$) or aripiprazole ($n = 58$). During the 12-week treatment, patients receiving quetiapine ER experienced a significant increase in weight, BMI z-score and WC z-score. Patients in the aripiprazole group had significantly smaller increases in anthropometric outcomes. Patients in the quetiapine ER group experienced significant increases in total cholesterol, low density lipoprotein, triglycerides, triglyceride/high density lipoprotein ratio, insulin, and homeostatic model assessment of insulin resistance. A small, but statistically significant increase in QTcH was seen in the quetiapine ER group while a significant decrease in blood pressure was seen in the aripiprazole group.

Discussion: In youths with FEP, quetiapine ER was associated with significantly greater weight gain, metabolic disturbances, and cardiac impulse delay than aripiprazole. Cardiometabolic risk factors should be considered when choosing antipsychotic medications.

M286. Differences in emotion recognition and attributional style between patients with schizophrenia and healthy controls

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Background: Attributional style and face emotional recognition have been reported to be impaired in psychosis and schizophrenia.

Attributional bias is a cognitive bias that refers to systematic errors made when people evaluate or try to find a reason for their own behavior and that of others. People with schizophrenia usually have the tendency to externalize blame for negative events (externalizing bias), externalize blame to other people (personalizing bias) or attribute positive events to themselves and negative events to others (self-serving bias). The objective is to assess the differences in emotion recognition and attributional style between people with schizophrenia and healthy controls.

Methods: 19 chronic patients with schizophrenia and 17 healthy controls completed the Personal and Situational Attributions Questionnaire (IPSAQ) and an emotion face recognition computer program. **Results:** Significant differences were not observed in the overall emotion recognition between people with schizophrenia and healthy control groups, but we found significant differences in the recognition of fear between both groups ($P=0.007$). With regard to attributional style, differences were statistically significant compared with controls. Patients made a greater number of positive attributions to others ($P=0.010$), negative internal attributions ($P<0.001$) and personalizing bias ($P=0.001$). The healthy control group made a greater number of positive attributions to situations ($P=0.002$), negative attribution to situations ($P<0.001$) and self serving bias ($P=0.002$).

Discussion: Taking into account the results found in the recognition of fear, people with schizophrenia recognized fear worse than healthy controls, and also presented higher personalizing bias and a tendency to blame other people or themselves, instead of situations in their attributional style.

M287. Neurological soft signs as predictors of clinical outcome for a multi-element psychosocial intervention on FEP patients and their families in the cluster-randomized controlled get up piano trial

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Background: Neurological Soft Signs (NSS) are prevalent in patients with first-episode and chronic schizophrenia suggesting that their presence are not confounded by antipsychotic treatment and are stable across the different stages of the illness (Chan *et al.*, 2010). Recently, it has been suggested that NSS are associated with specific brain structural and functional connectivity changes, mainly involving the cerebello-thalamo-prefrontal network (Zhao *et al.*, 2014), which has been associated with the presence of negative symptoms (Chan *et al.*, 2015). Interestingly, the persistence of negative symptoms account for much of the long-term morbidity and poor functional outcome (Rabinowitz *et al.*, 2012). Moreover, a meta-analysis confirms that NSS scores decrease in the clinical course of schizophrenia with remission of psychopathological symptoms; and that the reduction is more pronounced in patients with a remitting course of schizophrenia than in those with non-remitting (Bachmann *et al.*, 2014). In a first-episode schizophrenia sample, it has been found that non-responders patients had more prominent NSS at baseline (Chiliza *et al.*, 2015). The latter findings could lead to the hypothesis that NSS scores could be identified as a course predictor. However, when contrasted with healthy controls, NSS scores obtained in schizophrenia patients, even after remission, remained significantly higher during follow-up indicating that NSS comprise both state- and trait-features (Bachmann *et al.*, 2014). The aim of the study is to examine if NSS are predictors of clinical outcome for the experimental treatment in a large sample of first episode psychosis patients participating in the GET UP PIANO Trial (Ruggeri *et al.*, 2015). This cluster-randomized trial compared the effectiveness of a multi-element psychosocial intervention for patients

(CBT) and their families vs treatment as usual (TAU) in community mental health centers (CMHCs).

Methods: Patients were assessed at both BL and FU with PANSS (Kay *et al.*, 1987) and NES (Buchanan and Heinrichs, 1989). Analyses were executed by estimating random effects linear regression models with CMHC as a random effect. Each model included treatment allocation, a NES sub-scale as predictor and their interaction. We used an alpha level of 0.05 for all main effects and interactions.

Results: At BL 294 patients were assessed by NES, 194 in the experimental group (58.7% male, mean age 29) and 100 in the TAU group (53.0% male, mean age 32). The two groups differed in age ($P=0.027$), but not in gender, level of education, IQ, handedness, and NSS sub-scales. Sensory integration sub-scale predicted the negative item poor rapport ($P=0.027$), while motor coordination sub-scale predicted the negative items blunted affect ($P=0.010$) and emotional withdrawal ($P=0.013$) and the GAF ($P=0.048$).

Discussion: The novelty of the present study is the use of NSS sub-scales as predictors of clinical outcome for a multi-element psychosocial intervention in FEP patients. The evidence that some NSS subscales exhibited significant predictive effects on specific aspects of psychopathology, regardless receiving the experimental treatment, may lead to use them as early markers of clinical outcome.

M288. Intra-abdominal fat gain in patients initiating treatment with clozapine

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Background: Patients under pharmacological treatment with clozapine exhibit a certain amount of clinical characteristics, while being at risk of diverse metabolic side effects, for instance weight gain. Weight increase is related with cardiovascular and endocrine pathologies probably due to an specific increment of visceral fat. However our actual measurements are indirect, as abdominal perimeter or body mass index do not reflect the specific changes in fat storage and computer tomography or magnetic resonance imaging are extremely costly.

We have assessed the evolution of visceral fat using a simple non-invasive technique of bioelectrical impedance in patients initiating clozapine and have correlated its measures with anthropometric and clinical parameters.

Methods: Five patients who initiate clozapine treatment were evaluated with a Tanita Viscan AB 140[®] and correlate the intraabdominal fat evolution with the abdominal perimeter, age and gender. A linear mixed model analysis was conducted being intra-abdominal fat the independent variable, gender fixed factor and age, and abdominal perimeter covariates.

Results: A significant association was found between visceral fat and waist circumference over time ($t=2.457$; $P=0.049$)

Discussion: Our results suggest that visceral fat gain in clozapine treatment is associated with abdominal perimeter. Our low number of subjects might have reduced our capacity to detect differences.

M289. Glucose disturbances at the onset of serious mental illnesses

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Background: Patients with serious mental illnesses exhibit a reduced lifespan compared with the general population, a finding that can not

solely rely on high suicide risk, low access to medical care and unhealthy lifestyle. The main causes of death are medical related pathologies such as type 2 diabetes mellitus; however pharmacological treatment might play a role.

Methods: We compared a two hour glucose load in naïve patients at the onset of a serious mental illness ($N=102$) (84 patients with a first episode of schizophrenia and related disorders, 6 with a first episode of bipolar disorder and 12 with a first episode of major depression disorder) with another psychiatric diagnose, adjustment disorder ($N=17$) and matched controls ($N=98$).

Results: Young patients at the onset of serious mental illnesses showed an increased two hour glucose load compared with adjustment disorder and the control group. Mean two hour glucose values [Standard Deviation] were: for schizophrenia and related disorders 106,51 mg/dL [32.0], for bipolar disorder 118.33 mg/dL [34.3], for major depressive disorder 107.42 mg/dL [34.5], for adjustment

disorder 79,06 mg/dL [24.4] and for the control group 82,11 mg/dL [23.3] ($P < 0.001$).

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