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ABSTRACTS OPEN

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SIRS 2016 PLENARY (PL) AND SYMPOSIA (S)
* Presenting authors

Saturday, 2 April 2016

13:00 Registration
18:00 Keynote lecture: Susannah Cahalan
19:15 Opening night reception

Sunday, 3 April 2016

8:00 Registration
8:30 **Plenary Presentation (PL)**
PL1. Positive allosteric modulators of muscarinic acetylcholine receptors as a novel approach for treatment of schizophrenia, P. Jeffrey Conn
9:30 Break
10:00 **Plenary presentation (PL)**
PL2. The recovery project: the who, what, where and when of psychological treatments, Til Wykes
11:00 Poster session/lunch
13:00 **Symposia presentations (S)**
S3. I did it! The experience of self-agency in schizophrenia, Chair: Neeltje van Haren; Discussant: Tilo Kircher
S4. Improving identification and treatment of early phase psychosis, Chair: John Kane, Discussant: Robert Zipursky
S5. Childhood trauma and psychosis: mechanisms, symptom profiles, outcome, and treatment, Chair: Ruud Van Winkel, Discussant: Robin Murray
S6. Cannabis and psychosis: what now for dopamine?, Chair: Michael Bloomfield, Discussant: Marta Di Forti
S7. How can sex hormones influence psychosis and cognitive abilities in men and women with schizophrenia?, Chair: Thomas Weickert, Discussant: Raquel Gur
S8. Alterations in hippocampal activity, glutamate and GABA before the onset of psychosis, Chair: Philip McGuire, Discussant: Anthony Grace
15:00 Break
15:30 **Symposia presentations (S)**
S9. The pivotal role of glia in schizophrenia: providing molecular insights for developing new therapies, Chair: Johann Steiner, Discussant: Kolja Schiltz
S10. Psychotic experiences in the e-generation: measuring symptoms, functioning and long term course in young people, Chair: Annegien Bartels-Velthuis, Discussant: Pia Jeppesen
S11. Schizophrenia and mortality - different aspects, different solutions, Chair: Carsten Hjorthøj, Discussant: John McGrath
S12. The WHO international classification of functioning core sets: a consensus process for key components of functioning for schizophrenia, Chair: Oscar Pino, Discussant: William Carpenter
S13. Exciting new findings about dopamine, Chair: Bita Moghaddam, Discussant: Marco Bortolato
S14. Cognitive remediation: effects on social cognition and new insights on mediators and moderators of treatment outcomes, Chair: Marieke Pijnenborg, Discussant: Torill Ueland

Monday, 4 April 2016

8:00 Registration
8:30 **Plenary presentation (PL)**
PL15. Toward predictive psychiatry – prognostic and diagnostic applications of pattern recognition methods, Nikolaos Koutsouleris
9:30 Break
10:00 **Plenary presentation (PL)**
PL16. Precision medicine for psychosis: challenges and promise, Raquel Gur
11:00 Poster session/lunch
13:00 **Symposia presentations (S)**
S17. Neuroimaging biomarkers for psychiatric disorders in adolescence and young adulthood: prediction of risk, transition and illness course, Chair: Hugo Schnack, Discussant: Stephen Lawrie
S18. Neuroimaging approaches to treatment outcome in schizophrenia, Chair: Robert Buchanan, Discussant: Shitij Kapur

S19. Psychosis in children and adolescents: from the prodrome to schizophrenia, Chair: Anne Katrine Pagsberg, Discussant: Celso Arango
S20. Characterizing a putative "traumagenic" subtype of psychosis, Chair: Mary Cannon, Discussant: Ian Kelleher
S21. NMDAR antibodies and their relevance for schizophrenia, Chair: Belinda Lennox, Discussant: Joseph Masdeu
13:00 **Pharmaceutical pipeline presentations**
15:00 Break
15:30 **Symposia presentations (S)**
S22. Negative symptoms - integrating clinical and neuroimaging perspectives, Chair: Silvana Galderisi, Discussant: Celso Arango
S23. The role of development and stage of psychotic illness on characteristics of longitudinal neurocognitive functioning, Chair: Larry Seidman, Discussant: Abraham Reichenberg
S24. Duration of early intervention and the critical period, Chair: Merete Nordentoft, Discussant: Max Birchwood
S25. Movement disorders: a non-mental core symptom of psychotic disorders and the importance of instrumental screening, Chair: Peter Van Harten, Discussant: Jim Van Os
S26. Non-traditional methods of classification in psychosis: applying a precision medicine model, Chair: Katherine Burdick, Discussant: John McGrath
S27. Elephant in the room: glia contribution to mental disorders, Chair: Mikhail Pletnikov, Discussant: Akira Sawa

Tuesday, 5 April 2016
8:00 Registration
8:30 **Plenary presentation (PL)**
PL28. Convergent evidence linking neonatal vitamin D status and risk of schizophrenia, John McGrath
9:30 Break
10:00 **Plenary presentation (PL)**
PL29. Balancing plasticity/stability across brain development, Takao Hensch
11:00 Poster session/lunch
13:00 **Symposia presentations (S)**
S30. Trajectories of children-adolescents at risk of major affective and non-affective disorders: exploring the period preceding the "chr risk phase" for preclinical staging of risk and implications in clinical practice, Chair: Michel Maziade, Discussant: Patrick McGorry
S31. Symptom dimensions in schizophrenia – brain correlates and personalised treatment options, Chair: Werner Strik, Discussant: Stephan Heckers
S32. Excitation/inhibition balance disturbances in schizophrenia: from circuits to large-scale networks, Chair: Peter Uhlhaas, Discussant: Patricio O'Donnell
S33. Negative symptoms: why they are so important and yet so difficult to treat?, Chair: Matteo Cella, Discussant: Til Wykes
S34. Lifespan development of schizophrenia and how the treatments improve the outcomes, Chair: Matti Isohanni, Discussant: Silvana Galderisi
S35. Social (cognitive) functioning in schizophrenia: mechanisms, course and treatment, Chair: Avi Reichenberg, Discussant: Junghee Lee
15:00 Break
15:15 Oral presentations
17:15 Break
17:30 Oral presentations

Wednesday, 6 April 2016
8:00 Registration
8:30 **Plenary presentation (PL)**
PL36. Feeding from bedside into bench, and back to bedside: towards better understanding of schizophrenia, Koko Ishizuka
9:30 Awards ceremony
10:00 Break
10:30 **Symposia presentations (S)**
S37. Second chance: what would senior schizophrenia researchers do if they could start over again?, Chair: E. Fuller Torrey, Discussant: Mark Weiser
S38. Global perspectives on stigma in the clinical high risk state for psychosis: new empirical advances, Chair: Lawrence Yang, Discussant: Antonio Lasalvia
S39. Clinical and neurobiological impact of physical exercise interventions in schizophrenia, Chair: Hilleke Hulshoff Pol, Discussant: Peter Falkai
S40. Zooming in on the synapse in schizophrenia, Chair: David Cotter, Discussant: Chang-Gyu Hahn
S41. Microglia in schizophrenia, Chair: René Kahn, Discussant: Darryl Eyles
S42. Back to the hippocampus: investigating hippocampal abnormalities in early psychosis, Chair: Mary Cannon, Discussant: Anthony David

PL. Positive allosteric modulators of muscarinic acetylcholine receptors as a novel approach for treatment of schizophernia

P. Jeffrey Conn[1]
[1]*Vanderbilt University Medical Center*

Abstract: Previous clinical studies as well as a large number of cellular and animal behavioral studies suggest that selective activators of M1 and/or M4 subtypes of muscarinic acetylcholine receptors (mAChRs) could provide a novel approach to treatment of schizophrenia. Especially exciting is the possibility that such agents could have efficacy in treatment of positive, negative, and cognitive symptoms in schizophrenia patients. Unfortunately, previous efforts to develop selective agonists of individual mAChR subtypes have not been successful and previous compounds have failed in development because of adverse effects due to activation of multiple mAChR subtypes. Furthermore, the relative roles of M1 and M4 in mediating the overall therapeutic effects of less selective mACh agonists are not understood. We have been highly successful in developing highly selective positive allosteric modulators (PAMs) of both M1 and M4 that have excellent properties for in vivo studies and potential development as drug candidates. Interestingly, selective M1 PAMs have robust efficacy in improving specific domains of cognitive function in animal models but do not have antipsychotic-like effects. In contrast, selective M4 PAMs have robust antipsychotic-like effects in animal models. Electrophysiology and genetic studies are providing important new insights into the mechanisms by which M1 and M4 PAMs act in specific cortical and midbrain circuits. These studies provide an exciting new approach to that has potential for treatment of multiple symptom clusters in schizophrenia patients.

PL2. The recovery project: the who, what, where and when of psychological treatments

Til Wykes[1]
[1]*Institute of Psychiatry, Psychology & Neuroscience*

Abstract: Psychological treatments aimed at symptoms or behaviours that impede recovery now have a relatively strong database but it is not clear which treatments are more effective and when. Tailoring treatment, considering adherence and personal goals will tax the current evidence base but clinicians still need to make decisions. Data to help them will be discussed in this plenary lecture.

S3. I did it! The experience of self-agency in schizophrenia

S3.1 Self disturbance: a construct to integrate phenomenology and neurocognition in early psychosis?

Barnaby Nelson[1], Emily Li[1], Thomas Whitford[2], Lukasz Gaweda[3], Nuwan Leitan[4], Louis Sass[5], Lavoie Suzie[1]*

[1]Orygen Youth Health Research Centre; [2]University of New South Wales; [3]Medical University of Warsaw; [4]University of Melbourne; [5]Rutgers University

Background: Over recent years there has been a striking similarity in the findings of phenomenological and neurocognitive studies of psychosis. Both areas of research indicate that schizophrenia is characterised by disturbance of the basic sense of self. This refers to the implicit, background sense of ownership and agency in moment-to-moment experience. Phenomenological research has identified an array of unusual subjective experiences in schizophrenia (e.g., anomalous cognitive, affective, and physical experiences) consistent with disturbance of the basic self. Neurocognitive research indicates that psychotic disorders are characterised by "source monitoring deficits" (confusion between internal and external sources of information) and "aberrant salience" (unusual prominence of certain objects, stimuli, and associations). These neurocognitive disturbances are consistent with and may give rise to the subjective experience of basic self-disturbance in psychosis. However, this has not yet been directly empirically tested. Objectives: 1.To test whether there is an association between phenomenological measures of basic self-disturbance and

neurocognitive measures of source monitoring deficits and aberrant salience in early psychosis patients. 2.To test whether phenomenological measures of basic self-disturbance and neurocognitive measures of source monitoring deficits and aberrant salience predict transition to psychotic disorder in ultra high risk for psychosis (UHR) patients.
Methods: We are currently recruiting to a pilot study designed to test this integrative model of psychosis onset. Participants are being recruited from Orygen Youth Health, a youth mental health service in Melbourne, Australia. The target sample size is 30 UHR patients and 30 first episode psychosis (FEP) patients. All participants are assessed at baseline and the UHR participants are assessed again one year later in order to determine transition to psychosis status. Assessments consist of a range of clinical measures of basic self disturbance and other clinical features (EASE, CAARMS, SCID, SOFAS) and neurocognitive (cognitive and psychophysiological) measures of source monitoring deficits and aberrant salience. Analyses will determine the relationship between these measures and their predictive utility.
Results: To date, 20 UHR (mean age = 19 years, male = 40%) participants and 5 FEP participants have been recruited. The study rationale, study design and preliminary data will be presented at the conference. EASE self-disturbance scores in the sample recruited to date are comparable to EASE scores in a previous UHR cohort recruited at our clinic, in which basic self disturbance predicted transition to psychosis. Baseline data comparing basic self disturbance and a neurocognitive measure of aberrant salience from a separate cohort of UHR participants (approximate $N = 150$ from the EU-GEI study) will also be presented.
Conclusions: This study may have theoretical implications, as it may contribute to developing a cross-domain model of mechanisms driving the onset of psychosis, and clinical implications, as it may lead to the introduction of supplementary tools to improve our ability to identify young people at highest risk of psychotic disorders and contribute to preventive treatments in this group.

S3.2 Schizotypy and the awareness of intention: variability in the timing of intention awareness predicts schizotypy scores

James Moore*[1], J. Bravin[1]
[1]*University of London*

Background: Unusual experiences of control over one's actions are common in patients with schizophrenia. For example, patients suffering from delusions of control feel that their voluntary actions are under the control of an external force. Early cognitive theories explained these unusual experiences of control as resulting from faulty monitoring of intentions prior to movement (Frith & Done, 1988). Here we return to this idea, examining awareness of intention using Libet's clock task (Libet *et al.*, 1983).
Methods: We investigated the relationship between schizotypy in a non-clinical sample and individual differences in performance on this task.
Results: We found that variability of intention judgements was uniquely predictive of schizotypy. That is, the more variable these judgements, the higher the schizotypy score.
Conclusions: The relevance of these findings for schizophrenia will be discussed.

S3.3 Premotor signals affecting the subjective experience of agency - an fMRI study in schizophrenia patients and healthy volunteers

Martin Voss*[1], Valerian Chambon[2], Dorit Wenke[1], Simone Kühn[3], Patrick Haggard[4]
[1]*Humboldt University;* [2]*University of Geneva;* [3]*Max Planck Institute for Human Development;* [4]*University College London*

Background: Most theoretical frameworks on the Sense of Agency (SoA) focus on the retrospective inference from action outcomes. However, brain processes before movement onset, such as movement selection, may also contribute to the experience of the SoA. When healthy volunteers are subliminally primed regarding which of two actions to make, their reaction times are decreased. Moreover, such priming has a second, independent effect: participants also report a stronger feeling of control over an external event triggered by their (subliminally primed) action (Wenke *et al.*, 2010).
Methods: In a functional magnetic resonance imaging (fMRI) experiment, we combined subliminal priming of actions with explicit judgements of agency. In cued and free choice trials, subjects had to make speeded key presses in response to left- and right-pointing arrow masks and had to rate their subjective experience of agency over the subsequent action effects. Action selection was primed by subliminal stimuli: In half of the trials, prime and the mask/target were compatible, while on the remaining trials they were incompatible.
Sixteen right-handed healthy adults (3 females and 13 males aged 23–43 years), and sixteen right-handed, chronically ill people with schizophrenia (5 females and 11 males aged 24–49 years) participated in the study.
Results: As expected, priming influenced both reaction times, and free choices. Importantly, schizophrenic patients showed the same effects of subliminal priming on reaction times, but showed reduced or even reversed effects of priming on subjective ratings for the sense of agency. Neuroimaging results showed that the prospective sense of agency was negatively associated with activation of the angular gyrus (AG). Moreover, there was a distinctive pattern of connectivity between the angular gyrus, and lateral or medial prefrontal action selection areas underlying cued and free choices, respectively. Schizophrenic patient showed normal activation of these action selection areas, but, crucially, did not show the connectivity with the angular gyrus, nor the correlation between angular gyrus BOLD response and prospective agency.
Conclusions: In healthy participants, we suggest that angular gyrus generates experiences of agency or non-agency, by processing frontal action selection signals. Importantly, this network operated in a similar way for cued choices, and for free choices, suggesting a general architecture for monitoring action selection signals. This communication was impaired in patients suffering from schizophrenia. Altered connectivity in this circuit may underlie the abnormal action awareness that characterises schizophrenia.

S3.4 Neural and clinical consequences of self-agency processing in schizophrenia

Neeltje Van Haren*[1], Merel Prikken[1], Robert Renes[1], Anouk Van Der Weiden[1], René Kahn[1], Henk Aarts[1]
[1]*University Medical Centre Utrecht*

Background: People usually feel they cause their own actions and the consequences of those actions, also referred to as the experience of self-agency. Schizophrenia patients typically fail to experience agency over their own actions and exhibit difficulties in distinguishing their own actions from those of others (e.g., as in delusions of control, hallucinations).
Normally, the experience of agency arises when the outcome of an action matches the outcome one had in mind before performing the action (goal-based agency inference). In case of ambiguity (e.g., more than one actor, several possible outcomes), which is often the case in social situations, one may unconsciously use contextual information to guide feelings of agency. Indeed, there is consistent evidence that in an ambiguous context briefly presenting (i.e., priming) an outcome before it occurs enhances experienced self-agency over the outcome in healthy subjects (prime-based agency inference). Previously, we showed that patients were not able to use such implicitly available information to inform feelings of self-agency. Here we present data on 1) the association between abnormal prime-based agency processing and symptoms (specifically those related to either over or under-attribution) and 2) the brain areas that are related to inferring self-agency over action outcomes in the context of goal-directed behavior.
Methods: Fifty-four patients and 54 controls performed a prime-based agency inference task, in which experienced agency was measured after briefly priming a matching or mismatching outcome before participants performed an action and observed the outcome. The Positive and Negative Symptoms Scale (PANSS) and Comprehensive Assessment of Symptoms and History (CASH) were administered to assess psychopathology. Of these, 31 patients and 31 controls performed another goal and prime-based agency inference task while functional magnetic resonance images were obtained.

Results: Matching relative to mismatching outcome primes enhanced agency over the outcome of an action in healthy controls (Cohen's drm = 0.89), but not in patients (Cohen's drm = 0.19). No significant association was found between the ability to make prime-based inferences and PANSS subscale scores, but patients with symptoms of underattribution of agency showed significantly lower agency ratings. In the fMRI experiment, both groups experienced stronger agency when their goal matched (vs. mismatched) the outcome as was expected. However, region of interest analyses revealed that only controls showed the expected involvement of the medial prefrontal cortex and superior frontal gyrus, whereas in patients the agency experience was not related to brain activation.
Conclusions: We showed that specifically symptoms of underattributing agency are related to a less strong agency experience in general. In addition, the fMRI findings are in line with the previously reported hypofrontality in patients with schizophrenia. How agency processing is related to other measures of social cognition will be discussed in this symposium.

S4. Improving identification and treatment of early phase psychosis

S4.1 Pathways to care in early psychosis: the role of the internet and social media

Michael Birnbaum[1], Christoph Correll[2], Asra Rizvi[3], John Kane[2]*

[1]North Shore-LIJ; [2]The Zucker Hillside Hospital, Hofstra North Shore LIJ School of Medicine; [3]The Zucker Hillside Hospital

Background: Numerous studies have shown that the duration of untreated psychosis (DUP) in first episode patients is substantially longer than then expected or desired. In addition, a considerable body of research suggests that longer duration of untreated psychosis is associated with poorer outcomes in a variety of domains, once treatment is initiated. The recent NIMH-funded RAISE-ETP study which enrolled 404 first episode psychosis patients at 34 clinics in 21 states across the U.S. reported a median DUP of 74 weeks and found DUP to be a significant moderator of treatment effect in response to a comprehensive care model of integrated psychopharmacology and psychosocial treatment. Therefore, the reduction of DUP is a critical target in an attempt to produce better symptomatic and functional outcomes in early phase psychosis.
Methods: In order to understand potential obstacles to early identification and treatment as well as understanding the potential role of the internet and social media, we developed a questionnaire to retrospectively explore trajectory to care and the psychological factors involved in the decision to seek care, determine resources used to obtain information and inform decision to seek care with a focus on social media habits and changes in patterns of social media use/activity while also exploring how clinicians might improve utilization of social media. Patients between the ages of 15-35 with onset of psychosis in the last 2 years responded to 75 questions in an interview with a trained clinician.
Results: Data has been collected on 99 patients with first episode psychosis or attenuated psychotic syndrome. The mean age is 20 and the sample includes slightly more men than women. The majority of patients have utilized social media, on average over two hours/day and checking at least nine times. The majority attributed their changes in mood, thought processes and/or behavior to stress and the majority thought that the symptoms would pass. Participants reported waiting 15 weeks before reaching out to anyone and 45% used the Internet as their primary source of information, twice the rate of consulting family or friends. Though the majority reported changes in social media use the patterns varied with some increasing and others decreasing utilization. Further details will be reported.
Conclusions: Given the ubiquitous role that the Internet and social media play in the lives of young people, it is important for us to better understand the potential of these platforms to advance our efforts in educating youth regarding mental illness and especially in identifying and engaging those who might be experiencing the onset of significant symptoms and signs. This work suggests considerable potential in that regard.

S4.2 The STEP-ED project: a population based approach to early intervention for psychosis

Vinod Srihari*[1], Cenk Tek[1], Mcglashan Thomas[1], Scott Woods[1], Sinan Guloksuz[1], Jessica Pollard[1], Matcheri Keshavan[2], Larry Seidman[2]

[1]Yale University; [2]Harvard Medical School

Background: The STEP program completed the first US based RCT of a comprehensive first-episode service in 2013. Building upon this, the program has now launched an Early Detection campaign that targets a defined population residing in 10 surrounding towns. The goal of the campaign is to shorten delays into care at STEP, further improve outcomes for an epidemiologically representative sample of new onset cases and demonstrate a model of population based early intervention that targets all incident cases rather than focusing on just those that are currently presenting for care. The campaign will engage with a broad group of community stakeholders to transform local pathways to care.
Methods: The guiding questions for this study are whether a U.S. adaptation of a successful early detection approach undertaken in Norway (TIPS) can substantially reduce the duration of untreated psychosis (DUP) and improve outcomes beyond existing speciality first-episode services (FES) in a policy-relevant U.S. setting. The quasi-experimental design includes one site that delivers FES (STEP, New Haven) plus an Early Detection (ED) campaign to reduce DUP in its catchment area, while a control site (PREP, Boston) will continue to deliver equivalent FES without ED. We hypothesize that DUP will be reduced significantly in the early detection site compared to the usual detection site. Also, we hypothesize that this reduction in DUP will translate into improvements 1 year outcomes at the ED site compared to the non-ED site, demonstrating the 'added value' of ED to already established and effective FES. The primary outcome of DUP will be measured in a consistent manner at both sites using the Structured Interview for Prodromal Syndromes Scale (SIPS). 1 year outcomes will be measured at both sites across three broad domains: 1) clinical status: including hospitalization rate and relapse, suicidality, aggression and symptom scales; 2) functional status: including ability to work or attend age appropriate schooling, social functioning and quality of life and 3) costs: broadly measured to include costs of treatment and social and forensic services used. The Early Detection campaign will include a social marketing component targeting patients and families to increase help-seeking behavior, professional outreach to improve the rapidity of referral to STEP from local agencies and operationalizing rapid responsiveness of the STEP clinic to referrals, all with the aim of minimizing DUP. Analysis for DUP will be centered on the primary outcome of the proportion arriving to each FES with a DUP ≤ 3 months. Analysis for 1 year outcomes will be centered on proportions who are vocationally engaged at each site.
Results: Preliminary results from the ongoing campaign will be presented including social marketing data and the profile of recruited subjects. The particular strengths of social media (vs. mass media) in delivering more actionable information to refine a public education campaign in real time will be presented in addition to traditional clinical assessments of included participants.
Conclusions: Early detection campaigns that can shorten DUP will need to become an increasingly routine part of the work of first-episode services that seek to impact the health of a population beyond the traditional subgroups who currently are able to present for care. The STEP-ED study offers one way to mount such a campaign and to measure impact with the robust metric of DUP.

S4.3 Effectiveness of early intervention services for patients with early psychosis: systematic review and meta-analysis of specialized care versus usual or modular care

Christoph Correll*[1], Britta Galling[1]

[1]The Zucker Hillside Hospital

Background: Early intervention and integrated care are hoped to significantly improve outcomes and, possibly, change the trajectory of the illness in patients with a first episode of schizophrenia. Several individual trials have been conducted and one older systematic review

exists, bit no comprehensive meta-analysis exists that incorporates all recently completed studies and examining all available outcomes.
Methods: Systematic literature search of PubMed/PsycInfo/Embase/clinicaltrials.gov without language restrictions from database inception until 09/10/2015 for randomized trials comparing of Specialized Care versus Usual or Modular Care in ≥ 20 patients with a study-defined diagnosis of a first psychotic episode or early-phase schizophrenia-spectrum disorder (e.g., psychotic disorder not otherwise specified (NOS), schizoaffective disorder, schizophreniform disorder or delusional disorder). Random effects meta-analysis, using as effect size measures standardized mean difference (SMD) or risk ration (RR) ± 95% confidence intervals (CI).
Results: Meta-analyzing 8 studies ($n = 1{,}956$; age = 26.28 ± 2.56 (range = 16-65) years; male = 64%; trial duration = 16.5 ± 6.8 (range = 9-24) months) specialized case was superior to treatment as usual (TAU) regarding all-cause discontinuation (studies = 8, RR = 0.661, 95%CI = 0.569-0.769, $P < 0.0001$) and number of hospitalizations (studies = 6, RR = 0.633, 95%CI = 0.462-0.866, $P = 0.004$). Interestingly, specialized interventions were only superior to usual care for the outcome of ≥ 2 psychiatric hospitalizations ($P = 0.002$), but not for ≥ 1 admission ($P = 0.368$). Integrated, specialized services were also superior to usual modular care for total psychopathology (SMD = -0.389, 95%CI = -0.602—0.177, $P < 0.0001$), positive symptoms ($P = 0.010$) and negative symptoms ($P = 0.002$). Global Assessment of Functioning scale scores mere marginally higher in the integrated service groups ($P = 0.053$). Additional analyses, including rates of employment/education, will be presented after obtaining more complete data from individual studies.
Conclusions: Integrated early intervention services appear to have significantly advantages over usual care.in patients with first episode schizophrenia. Prevention of hospitalization seems to be most effective for subjects at high-risk for multiple relapses. Cost-effectiveness and implementation issues need to be examined and addressed to be able to provide integrated services more widely.

S4.4 Mobile behavioral sensing in outpatients and inpatients with schizophrenia

Dror Ben-Zeev*[1], Rui Wang[2], Saeed Abdullah[3], Rachel Brian[1], Emily Scherer[1], Marta Hauser[4], Lisa Mistler[5], Andrew Campbell[2], Tanzeem Choudhury[3], John Kane[4]

[1]*Dartmouth Medical School;* [2]*Dartmouth College;* [3]*Cornell University;* [4]*The Zucker Hillside Hospital;* [5]*New Hampshire Hospital*

Background: Mobile phones are playing a growing role in the modernization of healthcare. Smartphones come with multiple embedded sensors that measure movement, location, acoustics, and ambient light. These can be harnessed to capture an abundance of information pertaining to their users' behaviors and environments passively. We conducted two proof-of-concept studies with individuals with schizophrenia and schizoaffective disorder to examine the feasibility and acceptability of behavioral sensing in this population.
Methods: Outpatients ($N = 9$) and inpatients ($N = 11$) were provided with smartphones with research software that activated the device sensors (i.e., microphone, multi-axial accelerometers, light sensors, GPS, Bluetooth receiver) to collect behavioral and contextual data over two and one week periods, respectively. Speech was captured by the microphone, which was activated every 2 minutes to capture ambient sound. The system processed data in real-time to extract and store features to infer the presence of human speech (i.e., energy, relative spectral entropy, autocorrelation peak values) without collecting conversation content. Activity was captured by the smartphone accelerometers that detected movement. The system generated and stored an activity rating every 2 seconds. Location was captured differently for the two study samples: For outpatients, we used Android location services which fuse Global Positioning System, WiFi, and cellular network data to provide an optimized estimate. For inpatients, Bluetooth beacons were installed throughout an inpatient unit. Participants' smartphones received and recorded signals sent by these beacons and study software recorded their specific locations. At the end of the data collection periods participants rated this novel monitoring approach.
Results: Participants adhered to the study protocol and sensing successfully captured a range of behavior; on average, outpatients were active 2.5 hours and were proximal to human speech 4.4 hours a day. They covered a daily distance of 9 miles and spent 16.7 hours in one location. Inpatients were active an average of 2.1 hours a day, and proximal to human speech 4.4 daily. They spent 5.5. hours in the men's and women's halls, where they were around human speech 0.8 hours and were active 24.7% of the time; 2.1 hours near the nurse station, where they were around human speech 0.7 hours and were active 32.1% of the time; 0.9 hours in the kitchen, where they were around human speech 0.4 hours and were active 29.7% of the time; 0.5 hours in the day room/ lounge, where they were around human speech 0.1 hours and were active 28.9% of the time. Usability and acceptability ratings indicated participants felt comfortable with sensing (96%), and that most would be interested in receiving system-generated feedback (67%) and suggestions (66%). Approximately 20% reported that sensing made them upset. A third of inpatients were concerned about their privacy but no outpatients expressed this concern.
Conclusions: To our knowledge, this is the first report describing the feasibility and acceptability of smartphone sensing for behavioral tracking in schizophrenia. Our findings suggest patients are willing and able to engage in behavioral sensing. Many individuals with early phase psychosis have grown up using mobile technologies, and new generations of "digital natives" are emerging. With the aid of software that can repurpose smartphone sensors, and with appropriate protection of patient privacy, these widely-used devices can be leveraged as objective and scalable behavioral monitoring strategies that could inform early detection and prevention efforts.

S5. Childhood trauma and psychosis: mechanisms, symptom profiles, outcome, and treatment

S5.1 Trauma, attachment and dissociation: moving towards process-focused psychological interventions for psychosis

Filippo Varese[*1], *Katherine Berry*[1]

[1]*University of Manchester*

Background: Recent meta-analytic syntheses have established robust associations between psychosis and exposure to traumatic events. The identification of mediating psychological mechanisms for this robust relationship is fundamental to the theoretical understanding of psychosis, and the development of effective psychosocial treatments for distressing symptoms. Insecure attachment and dissociation have been postulated as promising candidate mechanisms that may contribute to the vulnerability to key symptoms such as hearing voices, and the distress often associated with psychotic experiences.
Methods: Based on recent meta-analytic work and systematic reviews by researchers at the University of Manchester, this presentation will provide an overview of current evidence base for the relationship between these psychological processes and specific symptoms of psychosis.
Results: Overall, the literature suggest strong associations between exposure to traumatic life events and subsequent difficulties in the domains of attachment and dissociative experiences. Evidence from cross-sectional studies suggest that the apparent association between trauma and psychotic symptoms is mediated by attachment difficulties and dissociative process, but the exact interplay between these two processes, their possible interaction with other risk factors and the extent to which they are predictive of specific psychosis require further corroboration.
Conclusions: Based on the available evidence, we provide a theoretical formulation of how trauma, attachment difficulties and dissociation might increase vulnerability to psychosis, and highlight areas requiring additional research inquiry. Promising psychological interventions targeting dissociation and/or attachment difficulties that could be integrated to standard cognitive-behavioural therapies and improve clinical outcomes in individuals with distressing psychotic experiences will be considered in the light of this evidence.

S5.2 The role of childhood abuse in the course and outcome of psychotic disorders over 10 years

Helen Fisher*[1], Paola Dazzan[1], Julia Lappin[1], Margaret Heslin[1], Gillian Doody[2], Peter Jones[3], Robin Murray[1], Craig Morgan[1]
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Background: Increasing evidence suggests that exposure to traumatic events in childhood is linked to the emergence of psychotic disorders in adulthood. However, the impact of childhood trauma on the longer-term outcomes of psychosis is largely unknown. Initial research suggests that early trauma is associated with worse clinical and functional outcomes amongst those with psychotic disorders. However, these studies suffer from a range of methodological limitations. Therefore, this presentation will explore the impact of childhood abuse on the course and outcomes of psychotic disorders over a 10-year period utilising comprehensive assessment tools in an epidemiological sample of 214 first-presentation psychosis patients.
Methods: Data are drawn from the Aetiology and Ethnicity of Schizophrenia and Other Psychoses (AESOP) study of individuals from South London and Nottingham, UK, who presented to mental health services for the first time with psychosis between 1997-2000. Information on childhood abuse was obtained retrospectively using the Childhood Experience of Care and Abuse Questionnaire at baseline and extensive information on psychosis course and functional outcomes over the subsequent 10 years was obtained via face-to-face interview or clinical records.
Results: Psychosis cases who reported exposure to physical, sexual or emotional abuse prior to age 17 were more likely to achieve remission within 6 months of first presentation than non-exposed cases (OR = 2.91). However, they were at increased risk of self-harm (OR = 3.3) and suicide attempts (OR = 2.3), had more severe positive psychotic symptoms (OR = 3.2) and were less likely to be employed (OR = 0.4) during the 10 year follow-up period.
Conclusions: Childhood abuse was not associated with a worse clinical course of psychotic disorder over a 10 year period in this sample, though when symptoms were present they tended to be more severe. However, those reporting a history of abuse posed a greater risk to themselves and had poorer vocational outcomes. These findings suggest that Early Intervention Services should screen new patients for childhood abuse and be mindful that those exposed may require additional support to improve their functional outcomes.

S5.3 Using a stratified approach in psychiatry – implications for treatment and the search for underlying mechanisms of mental illness

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

S5.4 Treating PTSD in psychosis with prolonged exposure of eye movement desensitization and reprocessing: a randomised controlled trial

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Background: Post-traumatic stress disorder is prevalent in about 1 in 6 in patients with psychotic disorders. Prolonged Exposure (PE) and Eye Movement Desensitization and Reprocessing (EMDR) are recommended and effective treatments, but patients with psychosis are excluded from both routine treatment and scientific trials due to fear of exacerbation of psychotic symptoms.
Methods: In the 'Treating Trauma in Psychosis trial (T-TIP) 155 patients with a psychotic disorder and comorbid PTSD were randomly assigned to PE, EMDR or Waiting List (WL). Participants received 8 sessions of 90- minutes therapy in PE or EMDR. No stabilizing interventions or skills training preceded therapy with standard protocols. The first session comprised psycho-education about PTSD and target selection. In sessions 2 to 8 traumas were treated, starting with the most distressing experience. Baseline, post-treatment, 6-month follow-up and 12 month follow-up assessments were made.
Results: Participants in both PE and EMDR showed greater reduction of PTSD symptoms than those in WL. Between group effect sizes were large. Almost two-third of the participants in the treatment groups achieved loss of diagnosis. Treatment effects were maintained at six-month follow up for both PE and EMDR. Twelve month follow-up data will be presented.
Conclusions: Standard PE and EMDR protocols appear to be effective, safe and feasible in patients with psychosis.

S6. Cannabis and psychosis: what now for dopamine?

S6.1 Psychosis and the psychopharmacolgy of cannabinoids

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Background: Reports dating as far back as 2700 BC, in the Chinese pharmacopeia, indicated that excess consumption of "ma-fen" (the fruit of the cannabis plant) will produce visions of devils and over a long term "makes one communicate with spirits and lightens one's body". Today it is well known that excessive use of cannabis can induce short-lived paranoia and psychotic like experiences in otherwise healthy individuals. However, these effects vary greatly from individual to individual with as of yet no clear signs as to who might be more vulnerable.

It wasn't until early 1960 s when the main active compounds of cannabis was isolated, Δ9-tetrahydrocannabinol (THC), by the grandfather of cannabinoid research Prof Rafael Mechoulam. This discovery allowed researchers to explore the specific dose-dependent psychotomimetic effects of THC, as well as potential underlying mechanisms.
Methods: In this talk I will present results from a series of experimental studies in which healthy volunteers were administered intravenous doses of THC.
Results: In a first study, intravenous THC (2.5 mg) induced a significant increase in PANSS positive symptoms ($P < 0.001$) compared to placebo in roughly 50% of the volunteers. These effects correlated strongly with the participant rated scale CAPE ($P < 0.001$). In a second study, THC (1.25 mg) induced psychotic symptoms ($P < 0.001$) in 40% of participants, which correlated with a significant reduction in bifrontal theta coherence ($P < 0.01$) as measured by EEG. Within the same sample THC also induced symptoms of salience ($P < 0.05$) and ipseity disturbance ($P < 0.05$) which were related to reduction of inter trial coherence – another measure of neural synchrony. In a third study, THC (1.5 mg) induced positive psychotic symptoms on the PANSS ($P < 0.001$) and paranoid symptoms on the SSPS ($P < 0.005$) scale in 42% of the healthy volunteers. These effects were blocked by co-administration of the antipsychotic cannabinoid cannabidiol (CBD). However, THC-induced psychotic symptoms were not related to changes in measures of neural synchrony. Lastly, in a small pilot study exploring the effect of THC when co-administered with Δ9-tetrahydrocannabivarin (THCV), a lower dose of THC (1 mg) failed to significantly induce positive psychotic symptoms (CAPE) or paranoia (SSPS) (both $P > 0.05$).
Conclusions: Taken together, these results indicate a significant inter-individual variability of THC-induced psychotomimetic effects in otherwise healthy people; as well as a potential threshold dose below which THC does not induce such symptoms. There exists some preliminary evidence which indicate THC related psychotic experiences may be related to disruptions to neural synchrony.

S6.2 The effects of delta-9-tetrahydrocannabinol (THC) on dopamine synthesis and release: evidence from pre-clinical and clinical studies

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Background: Cannabis is the most widely used illicit recreational drug in the world and over 50% of young people in the USA report use of the drug. Cannabis use is linked to a number of mental disorders including psychosis, addiction and depression, as well as cognitive impairment. Δ9-tetrahydrocannabinol (THC) is the main psychoactive component in cannabis, and has been linked to the rewarding and addictive aspects of cannabis use, as well as the induction of psychiatric symptoms and cognitive impairments. The THC content of cannabis has been increasing in recent years and synthetic analogues ('spice'; 'legal highs') are also now widely available. Given the clear public health implications, there is therefore pressing interest in understanding the neurobiological effects of THC and its analogues. Recent evidence has shown that THC produces complex effects on the brain's dopamine system, which are likely to contribute to the drug's recreational and harmful effects. Yet, there are inconsistencies between the preclinical and clinical findings which challenge the field. It is thus timely to review the evidence and provide a framework for understanding the inconsistencies between the preclinical and clinical findings.
Methods: We will review studies assessing dopamine synthesis, release, and neuron activity and morphology using radiolabelled ligands, microdialysis and in vivo electrophysiological studies.
Results: Dose-dependent THC-induced increases in dopamine synthesis, release and neuron fir have been reported in the majority of animal studies (Diana *et al.* 1998; Wu *et al.* 2000) Cadoni *et al.* 2015). The effects of THC administration on brain total dopamine content in will also be examined, reporting on high performance liquid chromatography. Acute THC administration increases total dopamine content, whilst chronic THC administration decreases total dopamine content (Polissidis *et al.* 2010). Positron emission tomography (PET) studies in humans have reported decreased dopamine synthesis capacity in chronic cannabis users.
Conclusions: THC and cannabis produce complex dose-dependent and duration-dependent effects on the dopamine system which may not be consistent with widely proposed iterations of the dopamine hypothesis of schizophrenia.

S6.3 Clinical neuroimaging studies of the effects of cannabis in psychosis

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Background: Research on environmental risk factors in schizophrenia had previously focused on either psychosocial stress or drug exposure, with limited investigation of their interaction. A heightened dopaminergic stress response in patients with schizophrenia and individuals at clinical high risk (CHR) supports the dopaminergic sensitization hypothesis. Cannabis has been suggested to contribute to the development of schizophrenia, possibly through a cross-sensitization with stress.
Methods: Twelve CHR and 12 cannabis-using CHR (CHR-CU, 11 dependent) subjects underwent [(11)C]-(+)-PHNO positron emission tomography scans, while performing a Sensorimotor Control Task (SMCT) and a stress condition (Montreal Imaging Stress task). The simplified reference tissue model was used to obtain binding potential relative to non-displaceable binding (BPND) in the whole striatum, its functional subdivisions (limbic striatum (LST), associative striatum (AST), and sensorimotor striatum (SMST)), globus pallidus (GP), and substantia nigra (SN). Changes in BPND, reflecting alterations in synaptic dopamine (DA) levels, were tested with analysis of variance.
Results: SMCT BPND was not significantly different between groups in any brain region ($P > 0.21$). Although stress elicited a significant reduction in BPND in the CHR group, CHR-CU group exhibited an increase in BPND. Stress-induced changes in regional BPND between CHR-CU and CHR were significantly different in AST ($P < 0.001$), LST ($P = 0.007$), SMST ($P = 0.002$), SN ($P = 0.021$), and whole striatum ($P = 0.001$), with trend level in the GP ($P = 0.099$). All subjects experienced an increase in positive (attenuated) psychotic symptoms ($P = 0.001$) following the stress task.
Conclusions: Our results suggest altered DA stress reactivity in CHR subjects who concurrently use cannabis, as compared with CHR subjects. Our finding does not support the cross-sensitization hypothesis, which posits greater dopaminergic reactivity to stress in CHR cannabis users, but adds to the growing body of literature showing reduced DA (stress) response in addiction. Taken together with other PET findings that long-term cannabis use is associated with hypodopaminergia, these findings are not consistent with the hypothesis that cannabis increases psychosis risk via presynaptic hyperdopaminergia.

S6.4 Non-dopaminergic pathways from THC to psychosis: GABA deficits enhance the psychotomimetic effects of Δ9-THC

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Background: The enhanced vulnerability of schizophrenia patients to the effects of cannabinoids like delta-9-tetrahydrocannabinol (THC) may be related to gamma-aminobutyric acid (GABA) deficits which have been well characterized in the disorder. The brain cannabinoid (CB1R) and GABA systems are closely linked. The current study tested the hypothesis that a GABAergic deficit enhances the psychotomimetic effects of THC in healthy volunteers.
Methods: Healthy subjects ($n = 27$) were enrolled to receive iomazenil (IOM; a Benzodiazepine inverse agonist) followed by placebo THC, placebo IOM followed by THC, IOM followed by THC, placebo IOM followed by placebo THC in a randomized, double-blind crossover

design over 4 test days. Psychotomimetic effects, perceptual alterations, and subjective were captured before and after drug administration. Electroencephalography (EEG) was recorded while subjects engaged in a three-stimulus auditory "oddball" P300 task.
Results: While THC produced significant increases in psychosis-relevant symptoms (Positive and Negative Syndrome Scale; PANSS) IOM did not. Importantly, the combination of IOM and THC produced greater psychosis (PANSS) compared to THC alone and also produced the greatest deficits in the P300b amplitude. Furthermore, only the combination of IOM and THC produced significant increases in perceptual alterations. Iomazenil did not significantly alter the pharmacokinetic of THC. The combination of IOM and THC did not increase measures of "stoned/high" (Visual Analog Scale; VAS) compared to THC alone, indicating that the combination of IOM and THC effects were specific to psychosis.
Conclusions: Pharmacological induction of a GABA deficit in healthy humans can enhance the psychosis-relevant behavioral and psychophysiological effects of THC. These data suggest that the enhanced vulnerability to cannabis and THC in schizophrenia patients may be explained by underlying GABA deficits. The close interplay between the CB and GABAergic systems in several brain regions provides a mechanistic framework to understand the study findings.

S7. How can sex hormones influence psychosis and cognitive abilities in men and women with schizophrenia?

S7.1 Sex differences and effects of sex steroid hormones in animal models of schizophrenia

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Background: There are prominent gender differences in the occurrence and symptoms of psychiatric illnesses such as schizophrenia. These illnesses are likely caused by a combination of genetic, hormonal and environmental factors but the interactive mechanisms remain unclear.
Methods: Our studies have modelled 'two hit' gene-environment interactions and the role of sex steroid hormones in animals. Genetic models include mice or rats deficient in brain-derived neurotrophic factor (BDNF), reelin, or neuregulin, and we investigated sex differences in the long-term effects of drugs of abuse or corticosterone treatment (CORT) to simulate chronic stress.
Results: In male maternally-separated rats, CORT induced memory deficits which were not observed in controls. There were no CORT effects in females; however these animals displayed anhedonia-like behaviour which was not observed in males. Male/female-specific behavioral changes in maternally-separated rats were correlated with differential effects on exon-specific BDNF expression in the dorsal hippocampus, prelimbic cortex and nucleus accumbens between the sexes. Further studies showed that in male BDNF heterozygous mice, CORT treatment resulted in deficits in spatial memory which were not observed in wildtype controls or female mice. These 'two hit' effects were accompanied by sex-specific alterations in regional NMDA receptor subunit expression. Qualitatively different 'two hit' effects were observed with BDNF deficiency and drugs of abuse, such as cannabis and methamphetamine. These studies suggest that the effect of developmental factors may be modulated by estrogen as it interacts with the expression of neurotrophic pathways such as BDNF/TrkB gene expression and signaling. Indeed, in animal and human studies we observed differential effects of estrogen and testosterone in behavioral paradigms with relevance to schizophrenia, such as prepulse inhibition (PPI) and spatial memory. For example, in ovariectomized rats, estrogen treatment was able to block the disruption of PPI caused by acute dopaminergic stimulation with apomorphine. Similar results were obtained in a neurophysiological, paired-pulse paradigm. In wildtype mice, ovariectomy induced deficits in spatial memory which could be prevented by estradiol implants. In contrast, ovariectomy or estradiol treatment did not alter spatial memory in BDNF heterozygous mice.
Conclusions: In conclusion, animal models of schizophrenia development reveal sex-specific vulnerability to environmental factors to induce behavioral and molecular deficits. Overall, these studies could be relevant for our understanding of sex differences in psychiatric illnesses and potential treatments based on sex steroid hormones.

S7.2 Sex hormones to improve symptoms and cognition in schizophrenia

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Background: Sex differences in disease incidence, onset and course suggest that sex hormones and oxytocin may play a protective role in the pathophysiology of schizophrenia. This quantitative review summarizes available evidence on the efficacy of sex hormones and oxytocin in the treatment of schizophrenia.
Methods: Only double-blind, placebo-controlled, randomized studies were included. Primary outcome measures were total symptom severity, subscores for positive and negative symptoms and cognitive performance. Effect sizes were calculated for individual studies and pooled in meta-analyses to obtain combined, weighted effect sizes (Hedges' g) for augmentation with estrogens, selective estrogen receptor modulators (SERMs), testosterone, dehydroepiandrosterone (DHEA), pregnenolone, and oxytocin.
Results: Twenty-four studies were included, examining a total of 1149 patients. Significant effects were found for estrogen action (ten studies), regarding total symptom severity (Hedges' $g = 0.63$, $P = 0.001$), positive symptoms (Hedges' $g = 0.42$, $P < 0.001$), and negative symptoms (Hedges' $g = 0.35$, $P = 0.001$). Subgroup analyses yielded significant results for estrogens in premenopausal women (six studies) for total, positive and negative symptoms, and for the selective estrogen receptor modulator (SERM) raloxifene in postmenopausal women (three studies) for total and negative, but not for positive symptoms. Testosterone augmentation in males (one study) was beneficial only for negative symptom severity (Hedges' $g = 0.82$, $P = 0.027$). No overall effects were found for DHEA (four studies), pregnenolone (four studies), and oxytocin (six studies). Results for cognition (twelve studies) were too diverse to be included in a meta-analysis, inspection of these data showed no consistent benefit.
Conclusions: Estrogens and SERMs could be effective augmentation strategies in the treatment of women with schizophrenia, although estrogens cannot be given for longer duration without combining them with progestrogen. Future larger trials are needed to study long term effects and effects on cognition.

S7.3 Molecular explanation for estrogens role in schizophrenia lays the foundation of novel treatment for men and women

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Background: Estrogen by binding to the estrogen receptor has potent trophic effects on neurons and glia. We have found that the levels of estrogen receptor does not differ greatly according to sex or to psychiatric status (schizophrenia, bipolar or depression). However, we have found that the type of brain estrogen receptor alpha varies, with more individuals with schizophrenia being more likely to express splice variants encoding truncated versions of the estrogen receptor alpha.
Methods: We transfected CHOK-1 cells with constructs encoding the normal and schizophrenia-related truncated forms of the ER (individually or in combination) along with a luciferase reporter plasmid (3x ERE-luc reporter). Next, we added estrogen and ralxoifene to determine the extent to which these agents may be able to overcome the abnormal estrogen receptor function and to increase gene expression from estrogen response elements (EREs). We also confirmed these effect in the neuronal-like SHSY5Y cells.
Results: Using a luciferase assay, we found that mRNA encoding a truncated ESR1 significantly attenuates gene expression at estrogen-response elements demonstrating a dominant negative function. Further, we showed that raloxifene was capable of doubling the ERE-driven luciferase activity when the schizophrenia-related forms of ER were transfected into cells.
Conclusions: We have demonstrated that people with schizophrenia were more likely to express a truncated estrogen receptor in cerebral

cortex and that most individuals express a combination of various types of estrogen receptor in brain. We also found that truncated estrogen receptor blocks the normal estrogen receptor function. Importantly, this block of function can be overcome with raloxifene treatment supporting the use of raloxifene as an adjunctive treatment in schizophrenia.

S7.4 Hormonal influences on cognition and brain activity in schizophrenia

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Background: Sex steroids influence cognition and brain activity; however, the role of sex steroids in the cognitive and neural dysfunction associated with schizophrenia is unknown. This presentation will report on five studies designed to determine the extent to which hormones are related to cognitive abilities and neural activity in the brains of people with schizophrenia.
Methods: In four studies men with schizophrenia or schizoaffective disorder were compared to healthy men in relation to cognitive abilities and neural activity during fMRI emotional response inhibition, emotional face recognition and unexpected reward/reward omission (prediction error) tests. A series of regression analyses were performed to determine the extent to which circulating sex steroid hormone levels predict cognition and brain activity in men with schizophrenia and healthy men. Sex steroid receptors were also localized in the human midbrain to determine the potential for direct effects of testosterone on dopamine neurons. A separate study administered the selective oestrogen receptor modulator raloxifene to men and women with schizophrenia to determine the extent to which raloxifene would improve cognition and increase brain activity.
Results: There were no significant differences in circulating testosterone levels between men with schizophrenia and healthy men. Circulating testosterone levels significantly predicted performance on verbal memory, processing speed, and working memory in men with schizophrenia but testosterone levels were not related to symptom severity and did not predict cognitive function in healthy men. Higher testosterone levels were associated with greater accuracy and reduced prefrontal activation during response inhibition and emotional face recognition in men with schizophrenia. Strong positive correlations were obtained between testosterone and ventral striatal activity during prediction-error in healthy men, whereas significant inverse correlations were shown in men with schizophrenia. Dopamine neurons were sex-receptor immunoreactive in human midbrain. Raloxifene significantly improved memory, attention, and significantly increased hippocampal activity in men and women with schizophrenia relative to placebo.
Conclusions: The results suggest that circulating testosterone influences both cognition and brain activity in men with schizophrenia. Testosterone can have differential effects on brain activity in men with schizophrenia relative to healthy men depending on cognitive task demands and brain region recruited. The selective oestrogen receptor modulator raloxifene can improve memory, attention and increase hippocampal brain activity in both men and women with schizophrenia. Thus, overall the results from these studies demonstrate strong evidence for the role of hormonal influences on cognitive abilities in men and women with schizophrenia and provides a potential novel treatment for cognitive deficits in schizophrenia.

S8. Alterations in hippocampal activity, glutamate and GABA before the onset of psychosis

S8.1 Resting hyperperfusion of the hippocampus, midbrain and basal ganglia in people at high risk for psychosis

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Background: Animal models suggest that psychosis develops as a result of hyperactivity in the hippocampus driving the subcortical dopamine system. We tested this hypothesis by measuring striatal dopamine function, and resting perfusion in the hippocampus, basal ganglia and midbrain in people at high risk of psychosis.
Methods: Pseudo-Continuous Arterial Spin Labelling (pCASL) imaging was used to measure resting cerebral blood flow (rCBF) in 52 individuals at Ultra High Risk (UHR) for psychosis and 27 healthy volunteers. The severity of psychotic symptoms was assessed using the Comprehensive Assessment of At Risk Mental State (CAARMS). The UHR subjects were re-assessed after a mean of 17 months, using the same measures as at baseline. 18 F-DOPA PET was used to measure striatal dopamine synthesis at baseline.
Results: At baseline, relative to healthy volunteers, UHR subjects showed elevated rCBF in the hippocampus, basal ganglia and midbrain. In the UHR sample, symptomatic improvement was associated with longitudinal reductions in rCBF in the hippocampus and ventral striatum. Subjects whose symptoms had resolved such that they no longer met UHR criteria showed a longitudinal reduction in left hippocampal rCBF that was not evident in subjects who remained in a high-risk state or had become psychotic. At baseline, healthy volunteers showed a negative correlation between hippocampal rCBF and striatal DA levels but this association was absent in UHR subjects.
Conclusions: A high risk for psychosis was associated with increased resting activity in the hippocampus, midbrain and basal ganglia. Subsequent resolution of the high- risk state was linked to a normalisation of activity in these regions. These findings are consistent with animal models that propose that psychotic symptoms are generated when hippocampal hyperactivity drives subcortical dopamine dysfunction.

S8.2 Elevated hippocampal glutamate levels predict the later onset of psychosis

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Background: Animal models suggest that hippocampal glutamate function plays a key role in the pathophysiology of psychosis, and recent neuroimaging studies have reported increased hippocampal glutamate levels in unmedicated patients with schizophrenia. However, it is unclear if hippocampal glutamate function is altered before the onset of the disorder. We addressed this issue by examining hippocampal glutamate levels in subjects at Ultra High Risk (UHR) for psychosis.
Methods: 68 individuals who met UHR criteria and 30 healthy volunteers participated in the study. Levels of glutamate in the left hippocampus were assessed using proton magnetic resonance spectroscopy at 3 Tesla (PRESS: Point-RESolved Spectroscopy; TE = 30 ms; TR = 3000ms; 96 averages; voxel size 20x20x15). Spectra were analysed using LCModel version 6.3-0 A, and water-scaled glutamate levels were corrected for voxel CSF content. The UHR subjects were scanned at first clinical presentation, and then followed up for a mean duration of 19 months. Subsequent to scanning, 9 UHR subjects made a transition to psychosis, as defined using the criteria in the Comprehensive Assessment of At-Risk Mental State (CAARMS). Group differences were determined using two-sample t-tests (two groups) or one-way ANOVA (three groups).
Results: There were no significant group differences in hippocampal glutamate levels between controls and UHR subjects (6.94 ± 0.92 and 7.14 ± 1.16). The UHR sample was subdivided according to clinical outcome into transition and non-transition subgroups. There was a trend towards differences in hippocampal glutamate levels across these two subgroups and the control group ($P = 0.069$). Post-hoc tests revealed that UHR subjects who subsequently developed psychosis had higher glutamate levels than both UHR subjects who did not become psychotic (7.87 ± 0.87 vs 7.03 ± 1.17, $P = 0.042$) and controls (7.87 ± 0.87 vs 6.94 ± 0.92, $P = 0.011$). There were no differences between controls and UHR subjects who did not develop psychosis.

Conclusions: These data indicate that hippocampal glutamate levels were selectively elevated in the subgroup of UHR subjects who subsequently made a transition to psychosis. This is consistent with animal models that propose that elevated glutamatergic function in the hippocampus is fundamental to the onset of psychosis. Our findings also suggest that neuroimaging measures of hippocampal glutamate function could be used to help predict outcomes in people at high risk of psychosis in a clinical setting.

S8.3 GABAergic dysregulation in individuals at ultra-high risk for psychosis investigated with proton magnetic resonance spectroscopy

Gemma Modinos*[1], Fatma Simsek[2], Jamie Horder[1], Matthijs Bossong[3], Carly Samson[1], Matilda Azis[1], Beverly Quinn[4], Ilaria Bonoldi[1], Oliver Howes[5], James Stone[1], Paul Allen[6], Philip McGuire[1]

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Background: Abnormalities in γ-aminobutyric acid (GABA) are proposed to play a central role in the pathophysiology of schizophrenia by animal and postmortem studies. Preclinical findings show that reduced cortical GABA interneuron function leads to increased activity in the hippocampus, resulting in dopaminergic system overdrive. Neuroimaging studies have described abnormal cortical GABA neurotransmission in the prefrontal cortex, and increased hippocampal resting-state activity in patients with schizophrenia. However, it remains unclear how GABAergic dysfunction influences hippocampal resting-state activation, and whether these abnormalities are present in individuals at ultra-high risk (UHR) for psychosis.
Methods: We used proton magnetic resonance spectroscopy (MRS) at 3.0 Tesla to quantify GABA levels in the dorsomedial prefrontal cortex (dmPFC) in 17 subjects who met criteria for an Ultra High Risk of psychosis (UHR), and 17 age- and gender-matched healthy controls. All spectra were analysed using LCModel. Brain perfusion was measured with arterial spin labeling (ASL) MRI. ASL images were preprocessed with SPM8. Between-group differences in dmPFC GABA concentrations were examined with a two-sample t-test in SPSS. Within the UHR group, associations between cortical resting-state perfusion (regions of interest in hippocampus and dmPFC) and GABA levels were examined using multiple regression in SPM8. Effects were considered significant at $P < 0.05$ after family-wise error correction (FWE).
Results: Lower prefrontal GABA levels were found in individuals at UHR for psychosis compared to healthy controls ($P = 0.04$). Within the UHR group, dmPFC GABA concentrations in the dmPFC were positively correlated with hippocampal perfusion ($P = 0.042$ FWE), and inversely correlated with dmPFC perfusion ($P = 0.004$ FWE).
Conclusions: Our results show that prefrontal GABA dysregulation in subjects at Ultra-High Risk for psychosis directly influences abnormal hippocampal and prefrontal resting-state activation. These changes reflect an increased vulnerability to psychosis and may predate the first episode of frank psychosis. These UHR subjects are currently being followed-up to assess whether altered GABA levels are related to clinical and functional outcomes.

S8.4 Altered relationship between hippocampal activation and subcortical dopamine function in people at ultra high risk of psychosis

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Background: Psychosis is thought to develop as a result of hippocampal dysfunction driving increased subcortical dopamine activity and the aberrant processing of salience. We examined this model in people at ultra high risk (UHR) of developing psychosis.
Methods: Functional MRI and18-FDOPA PET were used to measure hippocampal responses to salient stimuli and dopamine synthesis capacity in 14 UHR subjects and 16 healthy volunteers.
Results: There was a significant group difference in the relationship between hippocampal responses to both rewarding and aversive stimuli and dopamine function in the striatum and the midbrain. Within the hippocampal region, these differences were particularly evident in the left subiculum and parahippocampal gyrus.
Conclusions: These findings suggest that vulnerability to psychosis is associated with an alteration in the relationship between the hippocampal region and the subcortical dopamine system, consistent with data from animal models.

S9. The pivotal role of glia in schizophrenia: providing molecular insights for developing new therapies

S9.1 Histology and biochemistry of white matter in psychiatric disease

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Background: Diffusion tensor imaging of live individuals and biochemical studies of autopsy brains show abnormalities in the white matter of people with schizophrenia. White matter damage commonly contributes to developmental disorders, which may include schizophrenia, and to late-life dementia, which is common in schizophrenia and in depression. However, histological evidence for white matter pathology is less convincing, never demonstrating demyelination and showing at most equivocally elevated levels of reactive astrocytes or microglia. We summarize here the results of histological and biochemical analyses of white matter in autopsy brains of over 200 individuals with schizophrenia, with major depressive disorder, or without evidence of psychiatric disease.
Methods: DSM-IV psychiatric diagnoses, or their absence, were made by interviews with informants who knew the deceased well, review of medical records, or both, with standardized instruments. To evaluate myelin integrity, a neuropathologist rated each field in a systematic, uniform, random sample of Verhoeff-stained paraffin sections of prefrontal white matter. Damaged myelin was identified by immunohistochemistry of sections from the same blocks for degenerating myelin basic protein (MBP); photographs comprising the entire section were segmented with Visiomorph software, and quantified as the fractional area of staining. Numerical densities of resting (surveying) and activated microglia were estimated stereologically with a physical disector on paraffin sections double-labeled for ionized calcium-binding adapter molecule 1 (Iba1) and cluster of differentiation 68 (CD68). mRNA for MBP, myelin-associated glycoprotein (MAG), 2′-,3′- cyclic nucleotide 3′-phosphodiesterase (CNP), and proteolipid protein 1 (PLP1) was measured in dorsal and ventral prefrontal white matter and cingulum bundle by branched DNA assay (Affimetrix Panomics QuantiGene 2.0).
Results: We found no effect of diagnosis on myelin integrity or degradation, but there were statistically significant effects of age on both. Microglial densities showed no effect of diagnosis, but there were statistically significant effects of age and suicide. In ventral prefrontal white matter and cingulum bundle, there was significantly less mRNA for MAG, CNP, and PLP1 in schizophrenia than in nonpsychiatric cases or major depression. There were significant correlations between microglial activation and mRNA for myelin-related proteins.
Conclusions: Despite the use of methods sufficiently sensitive to detect subtle changes with aging, we find no association of schizophrenia or major depression with the histological appearance of prefrontal white matter. However, mRNA for several myelin-related proteins is lower in schizophrenia than in nonpsychiatric brains or major depression. These results suggest the possibility of diminished turnover of myelin in schizophrenia.

S9.2 Connecting the energy dysfunction observed in schizophrenia brains to glia cells in vitro

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Background: While comparing the proteomes of 6 post-mortem brain regions and cerebrospinal fluid from schizophrenia patients to controls, we consistently observed alterations in energy metabolism. Besides, differences on cell growth and maintenance, myelination processes and astrocytes markers have also been observed repeatedly. Our question was: is the energy dysfunction observed in schizophrenia brains being originated in neurons, glia cells or in both?
Methods: Neuronal, oligodendroglial, astrocytic and microglial cell lines were treated acutely (8 hours) and chronically (72 hours) with MK-801 and further submitted to state-of-the art proteomic analyses. Additionally, glycolysis enzymes were analyzed by western blot considering the differential status of this metabolic pathway in schizophrenia.
Results: MK-801-treated astrocytes, and especially MK-801-treated oligodendrocytes displayed several proteins differentially expressed which overlapped exactly with previous findings of schizophrenia human brains. On the other hand, MK801-treated neurons displayed very few differences in their proteome, an overlap with previous findings in human brain tissue below 10%. More interestingly, the dysregulation of glycolytic enzymes in MK801-treated oligodendrocytes are very similar to our observations in schizophrenia brain tissue, corroborating with recent findings about of the importance of oligodendrocytes in the energy status of the brain.
Conclusions: Proteomic data have provided integrated pictures of the biochemical systems involved in schizophrenia. The treatment of cell cultures with neural transmission agonists and antagonists and antipsychotic medication may provide insights about the molecular interaction of schizophrenia as well as useful leads about the molecular role and involved pathways of each cell type in the disorder.

S9.3 Clozapine promotes glycolysis and myelin lipid synthesis in cultured oligodendrocytes

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Background: Clozapine displays stronger systemic metabolic side effects than haloperidol and it has been hypothesized that therapeutic antipsychotic and adverse metabolic effects of these drugs are related. Considering that cerebral disconnectivity through oligodendrocyte dysfunction has been implicated in schizophrenia, it is important to determine the effect of these drugs on oligodendrocyte energy metabolism and myelin lipid production.
Methods: Effects of clozapine and haloperidol on glucose and myelin lipid metabolism were evaluated and compared in cultured OLN-93 oligodendrocytes. First, glycolytic activity was assessed by measurement of extra- and intracellular glucose and lactate levels. Next, the expression of glucose (GLUT) and monocarboxylate (MCT) transporters was determined after 6 and 24 h. And finally mitochondrial respiration, acetyl-CoA carboxylase, free fatty acids, and expression of the myelin lipid galactocerebroside were analyzed.
Results: Both drugs altered oligodendrocyte glucose metabolism, but in opposite directions. Clozapine improved the glucose uptake, production and release of lactate, without altering GLUT and MCT. In contrast, haloperidol led to higher extracellular levels of glucose and lower levels of lactate, suggesting reduced glycolysis. Antipsychotics did not alter significantly the number of functionally intact mitochondria, but clozapine enhanced the efficacy of oxidative phosphorylation and expression of galactocerebroside.
Conclusions: Our findings support the superior impact of clozapine on white matter integrity in schizophrenia as previously observed, suggesting that this drug improves the energy supply and myelin lipid synthesis in oligodendrocytes. Characterizing the underlying signal transduction pathways may pave the way for novel oligodendrocyte-directed schizophrenia therapies.

S9.4 DISC1 induced expansion of the hindbrain oligodendrocytes progenitors in forebrain during development – relevance to schizophrenia

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Background: Genetic, neuroimaging and gene expression studies suggest a role for oligodendrocyte (OLG) dysfunction in the pathophysiology of schizophrenia. DISC1 is a risk gene for schizophrenia with a well-documented role in neuro- and oligodendrogenesis. The truncated human DISC1 (hDISC1) mutation influences OLG differentiation and proliferation of glial progenitors in the developing cerebral cortex concurrent with reduction of OLG progenitor markers in the hindbrain. Concurrent reduction of OLG progenitor markers in hindbrain regions during fetal stage suggested expansion of hindbrain glial progenitors into the forebrain of hDISC1 mice.
Methods: We examined gene and protein expression of the molecular determinants of hindbrain OLG development (Egr2/Krox20 and Nkx2-2) at different developmental time points in hDISC1 mice and in the superior temporal cortex of persons with schizophrenia ($N = 61$) and compare them to those of cognitively normal controls ($N = 59$). DISC1 -Nkx2-2 interactions were assessed by proximity ligation assay.
Results: We found ectopic upregulation of gene and protein levels of hindbrain markers of glial progenitors (Egr2 and Nkx2-2) in the forebrain of hDISC1 (E15) embryos, while forebrain glial progenitor's markers (Gsh2 and Emx1) were reduced. DISC1 and Nkx2-2 were co-expressed and interacted in glial progenitor cells. Overexpression of hDISC1 impaired interactions between DISC1 and Nkx2-2, which was associated with increased differentiation of OLG and upregulation of hindbrain OLG markers (LAMA1 and MPZ) suggesting a suppressive function of endogenous DISC1 in OLG specialization of Nkx2-2 glial progenitors during embryogenesis.
Consistent with findings in hDISC1 mice, several markers of myelinating Schwann cells (PRX, LAMA1 and MPZ) were significantly upregulated in the superior temporal cortex of persons with schizophrenia.
Conclusions: These findings show a significant effect of truncated hDISC1 on developmental positioning of OLG identity cells along the rostrocaudal axis and their glial specification. Dislocation of OLG lineage cells due to their abnormal migration and premature differentiation may affect cerebrocortical organization and contribute to the pathophysiology of schizophrenia.

S10. Psychotic experiences in the e-generation: measuring symptoms, functioning and long term course in young people

S10.1 Course of auditory vocal hallucinations in childhood: 11-year follow-up study

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Background: Childhood auditory vocal hallucinations (AVH) are mostly transient but may predict clinical outcomes. Little is known about their course over time and associations with risk factors, and how this may inform early intervention. Therefore, we followed a case-control sample from a general population survey on AVH in 3870 children, and examined associated psychopathology and risk factors at two time-points, after five years (T1) respectively 11 years (T2) from baseline (T0).
Methods: From the case-control sample, 293 adolescents (age 18-19) participated in T2, presented as online assessment of AVH, other

psychotic experiences (with the Community Assessment of Psychic Experience; CAPE), psychopathology (with the Depression, Anxiety and Stress Scale; DASS-21), traumatic experiences (with the Trauma Screening Questionnaire; TSQ), and cannabis use.
Results: The AVH 6-year (T1-T2) persistence rate was 18.2% and the AVH 11-year (T0-T2) persistence rate was 6.2%.T2 participants with AVH had higher CAPE scores in all three dimensions (positive, negative and depressive), on both frequency and distress, than participants without AVH. AVH were associated with higher levels of depression and anxiety, and with more traumatic events and concomitant distress. The proportion of participants at risk for PTSD was significantly higher in those with AVH compared to those without AVH. Cannabis use in the past year was not associated with AVH. The group who reported AVH twice/thrice over the three assessments (but not the group who reported AVH once) reported more psychotic experiences and related distress more traumatic events and were more at risk for PTSS compared to the group without AVH ever.
Conclusions: Early childhood AVH are mostly transitory. AVH in adolescence are associated with affective dysregulation and with traumatic events. We did not question the participants on health care consumption, which may have resulted in the relatively favourable outcome as some of the participants may have been treated for unpleasant experiences. More prospective studies are therefore needed to replicate our findings. Follow-up of participants with a two- and threefold positive AVH screening at the age of about 24/25 years is worthwhile and intended.
Based on our results, large-scale programmes for early AVH detection are not feasible. However, examining the presence and development of co-morbid psychopathology is recommended. Given the evident association between traumatic events and AVH, it is advisable to sensitively inquire about childhood adversity in help-seeking youngsters presenting with AVH and, if necessary, address these traumas.

S10.2 Psychotic experiences in a community sample of youths: relationship with mental distress and global functioning

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Background: Psychotic experiences are far more common in young people in the population than psychotic disorder. They are associated with a number of adverse outcomes but there has been little research on associations with functioning and distress. We wished to investigate functioning and distress in a community sample of adolescents with psychotic experiences.
Methods: Two hundred and twelve school-going adolescents were assessed for psychotic experiences, mental distress associated with these experiences, global (social/occupational) functioning on the Children's Global Assessment Scale, and a number of candidate mediator variables, including psychopathology, suicidality, trauma (physical and sexual abuse and exposure to domestic violence) and neurocognitive functioning (MATRICS consensus neurocognitive battery).
Results: Seventy five percent of participants who reported psychotic experiences reported that they found these experiences distressing (mean score for severity of distress was 6.9 out of maximum 10). Participants who reported psychotic experiences had poorer functioning than participants who did not report psychotic experiences (respective means: 68.6, 81.9; OR = 0.25, 95% CI = 0.14-0.44). Similarly, participants with an Axis-1 psychiatric disorder who reported psychotic experiences had poorer functioning than participants with a disorder who did not report psychotic experiences (respective means: 61.8, 74.5; OR = 0.28, 95% CI = 0.12-0.63). Candidate mediator variables explained some but not all of the relationship between psychotic experiences and functioning (OR = 0.48, 95%CI = 0.22-1.05, $P < 0.07$).
Conclusions: Young people with psychotic experiences have poorer global functioning than those who do not, even when compared with other young people with psychopathology (but who do not report psychotic experiences). A disclosure of psychotic experiences should alert treating clinicians that the individual may have significantly more functional disability than suggested by the psychopathological diagnosis alone.

S10.3 The MHASC application assessing early-onset hallucinations in the touch-screen generation

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Background: Digital device issues leave few areas untouched and children effectively appear at the forefront of this technological revolution. Interestingly, being diagnosed with a mental disorder does not affect the use of digital devices. In this general context, how does media technology change the way we assess hallucinations in children and adolescents?
Methods: Here is presented the MHASC app., dedicated to assessing complex early-onset hallucinations. By fully exploiting the advantages of 7-to-10-inch tablets, this app is intended to elicit the direct participation of children and adolescents in a user-friendly environment capable of increasing the reliability of descriptions of early-onset hallucinations while avoiding an overload with distracting stimulation. Two different interfaces have been implemented: a) a "professional dashboard" for the adult that initiates the assessment and allows access to the analysis tools; b) a "child/adolescent interface" [7 to 18 years-olds.]. This second interface begins by the customization of the child's avatar, which will accompany her or him during the entire session, providing help when necessary.
Results: In complement to the quantification of common features of hallucinatory experiences that are combined to generate severity scores and hallucinatory profiles in various sensory modalities (e.g., frequency, intensity, conviction, insight, degree of control, discomfort in daily life, distress, emotional valence, coping strategy), the MHASC app. assesses the development and acquisition of cognitive functions that may help the clinician to diagnose or hypothesize, such as theory of mind or mental imagery. The cognitive modules of the MHASC app. have been independently validated. A first version of the MHASC is currently being validated in France and will progressively integrate new modules in 2016 (e.g., EMA).
Conclusions: Because we are convinced that the combination of such technological advancements may lead to significant benefits in the rigorous assessment of early-onset hallucinations, MHASC appears to be an ideal mHealth tool for multi-center research projects. This app. will also be translated into multi-language versions (i.e., English and Dutch are scheduled in early 2016) with the support of the International Consortium of Hallucination Research, a platform that was originally established to motivate research in hallucinations, to promote scientific rigor and to enhance international collaborative work on the topic.

S10.4 Introducing the white noise task in childhood: associations between speech illusions and psychosis vulnerability

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Background: Auditory verbal hallucinations are common during child development and may arise due to dysregulation in top-down processing of sensory input. This study was designed to examine the frequency and correlates of speech illusions measured using the White Noise (WN) task in children from the general population. Associations between putative risk factors for psychotic disorder and speech illusions with/without attribution of affective salience were examined.

Methods: A total of 1486 11-12-year old children of the Copenhagen Child Cohort 2000 were examined with the WN-task. Psychotic experiences and negative affect were determined by semi-structured interviews and observer-based ratings using items from the Kiddie-SADS-PL.
Results: A total of 145 (9.8%) children experienced speech illusions, 102 (70.3%) of these experienced illusions with affective content. Children who had experienced hallucinations during the last month significantly more often experienced affectively salient speech illusions in the WN-task (IQ adjusted OR = 2.01; 95% CI1.06-4.04). Negative affect in the last month and lifetime also significantly predicted affectively salient speech illusions (IQ-adjusted OR 2.01; 95% CI1.05-3.83 and OR1.79; 95% CI 1.11-2.89, respectively).
Conclusions: Speech illusions could be provoked in typically developing children during a test paradigm using white noise exposure. The findings suggest an affectively driven pathway to auditory hallucinations involving dysregulation in top-down processing of sensory input.

S11. Schizophrenia and mortality - different aspects, different solutions

S11.1 Substance use and mortality in schizophrenia, bipolar disorder, and unipolar depression

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Background: People with severe mental illness have both increased mortality and are more likely to have a substance use disorder. We assessed the association between mortality and lifetime substance use disorder in patients with schizophrenia, bipolar disorder, or unipolar depression.
Methods: In this prospective, register-based cohort study, we obtained data for all people with schizophrenia, bipolar disorder, or unipolar depression born in Denmark in 1955 or later from linked nationwide registers. We obtained information about treatment for substance use disorders (categorised into treatment for alcohol, cannabis, or hard drug misuse), date of death, primary cause of death, and education level. We calculated hazard ratios (HRs) for all-cause mortality and subhazard ratios (SHRs) for cause-specific mortality associated with substance use disorder of alcohol, cannabis, or hard drugs. We calculated standardised mortality ratios (SMRs) to compare the mortality in the study populations to that of the background population.
Results: Our population included 41 470 people with schizophrenia, 11 739 people with bipolar disorder, and 88 270 people with depression. In schizophrenia, the SMR in those with lifetime substance use disorder was 8·46 (95% CI 8·14–8·79), compared with 3·63 (3·42–3·83) in those without. The respective SMRs in bipolar disorder were 6·47 (5·87–7·06) and 2·93 (2·56–3·29), and in depression were 6·08 (5·82–6·34) and 1·93 (1·82–2·05). In schizophrenia, all substance use disorders were significantly associated with increased risk of all-cause mortality, both individually (alcohol, HR 1·52 [95% CI 1·40–1·65], $P < 0·0001$; cannabis, 1·24 [1·04–1·48], $P = 0·0174$; hard drugs, 1·78 [1·56–2·04], $P < 0·0001$) and when combined. In bipolar disorder or depression, only substance use disorders of alcohol (bipolar disorder, HR 1·52 [95% CI 1·27–1·81], $P < 0·0001$; depression, 2·01 [1·86–2·18], $P < 0·0001$) or hard drugs (bipolar disorder, 1·89 [1·34–2·66], $P = 0·0003$; depression, 2·27 [1·98–2·60], $P < 0·0001$) increased risk of all-cause mortality individually.
Conclusions: Mortality in people with mental illness is far higher in individuals with substance use disorders than in those without, particularly in people who misuse alcohol and hard drugs. Mortality-reducing interventions should focus on patients with a dual diagnosis and seek to prevent or treat substance use disorders.

S11.2 Mortality in schizophrenia and bipolar disorder: clinical and serological predictors

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Background: The reduced life expectancy of persons with schizophrenia has been established in multiple studies from around the world and is due largely to death from natural causes. Like schizophrenia, bipolar disorder is also associated with premature mortality due to death from natural causes although fewer studies have been performed in this group. Cigarette smoking, antipsychotic medications, and co-occurring diabetes have been associated with this premature mortality. Recent studies indicate that individuals with schizophrenia and bipolar disorder have increased rates of exposure to microbial agents and also have abnormal levels of some immune markers. However, there has been only limited investigation of the role of these factors in studies of mortality. The purpose of this study was to identify the determinants of death from natural causes in persons with schizophrenia and with bipolar disorder examining demographic, serological, and clinical factors.
Methods: We prospectively assessed a cohort of persons with schizophrenia and one with bipolar disorder with a clinical evaluation and a blood sample from which immune and infectious disease markers were measured. Mortality was determined with data from the National Death Index following a period of up to 14 years. We examined the role of demographic, clinical, and serological factors on natural-cause mortality in multivariate models. Years of potential life lost was also calculated.
Results: The study sample consisted of 1116 individuals: 710 with schizophrenia and 406 with bipolar disorder. The mean age at baseline was 39.9 years (□ 12.0) for the schizophrenia group and 35.7 years (□ 13.0) for the bipolar disorder group. The schizophrenia patients were followed for a median observation period of 7.45 years (range 6 days – 13.9 years) and the bipolar disorder patients of 4.59 years (range 11 days – 11.6 years). The total number of person-years of observation was 5,292 for the schizophrenia group and 2,239 for the bipolar disorder group. A total of 43/710 (6.1%) persons with schizophrenia and 12/406 (3.0%) with bipolar disorder died of natural causes. In the schizophrenia group, mortality was predicted by cigarette smoking (RR = 4.42, $P = .0018$); higher level of antibodies to Herpes Simplex Virus-Type 1 (RR = 2.09, $P = .017$); the presence of an autoimmune (RR = 2.54, $P = .025$), cardiac (RR = 2.23, $P = .016$), gastrointestinal (RR = 1.89, $P = .039$), and respiratory disorder (RR = 2.19, $P = .018$), after adjustment for demographic variables. Additive effects were found for smoking plus each of these comorbid conditions: compared with persons with neither risk factor, the RR of mortality for smokers with autoimmune disease was 10.3 ($P = 0.00036$); with cardiac disease, RR = 16.4 ($P = 0.0062$); with gastrointestinal disease, RR = 7.60 ($P = 0.0012$); with respiratory disease, RR = 10.6 ($P = 0.00029$) and with high antibodies to HSV-1, RR = 5.54 ($P = 0.00068$). In the bipolar disorder group, mortality was predicted by lower cognitive score (RR = 0.95, $P = .0085$) and the presence of type 1 or 2 diabetes (RR = 3.90, $P = .026$).
Conclusions: Mortality was elevated compared with the general population in both schizophrenia and bipolar disorder with approximately 20 years lower life expectancy. The predictors of this elevated mortality include cigarette smoking, co-occurring medical conditions, infectious exposures, and clinical factors such as lower cognitive functioning. The combination of smoking and baseline medical conditions yielded extremely high risks of natural death in schizophrenia. Given this dire outcome, there is even greater call for clinicians who provide psychiatric and somatic medical care for these patients to work aggressively to promote smoking abstinence.

S11.3 Epidemiological and biological correlates of premature mortality in people with psychosis

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Background: Understanding the causes of premature mortality in people with schizophrenia and related disorders requires research from both epidemiological and biological perspectives. Many deaths are from cardiovascular (CV) disease, so the first part of this presentation looks at the incidence of WHO-defined risk factors for CV morbidity and mortality in a large cohort of people with psychotic disorders. The second study investigates telomere length in young men with schizophrenia, compared with matched controls. Telomere length is an indication of cell aging; the telomeres become

progressively shortened over the life span, until the cell is no longer able to divide and enters senescence.
Methods: The first study included 1156 people aged 18-64 years, diagnosed with psychosis, who had participated in the SHIP study. The 2009 World Health Organisation (WHO) Global Health Risks Report was used as a framework to determine which risk factors (RF) for CV disease were present in men and women with psychosis.
The second study involved 47 men aged 25-36 years with schizophrenia and 50 controls matched for age, gender, and postcode. There were no differences between groups in years of education, parental age, BMI, or alcohol consumption.
Results: Men with psychosis had an average of 3.5 (SD 1.3) RF and women had an average of 3.2 (SD 1.3) RF. The most common RF were obesity, poor diet, physical inactivity and smoking.
Mean telomere length (base pairs) was 5171.7 (SD 1007.29) in the schizophrenia group and 6140.4 (SD 1254.5) in controls, t(97) = -4.220, $P = 0.000$. This difference was not accounted for by differences in education, employment, income, relationships, or living arrangements. The schizophrenia group used more tobacco and illicit drugs, had poorer physical health, more perceived stress and were less active, but none of these factors correlated with telomere length. There was no difference between groups in BMI, and no correlation between BMI and TL in either group.
Conclusions: People with psychosis have a high prevalence of CV risk factors. The most common RF should be able to be directly impacted by lifestyle interventions. The WHO risk factors provide a good picture of the overall risk profile of individuals.
Telomeres are significantly shorter in young men with schizophrenia, and this is not accounted for by social, economic or lifestyle factors. This may be intrinsic to the disease itself, or reflect factors not measured in this study.

S11.4 Homelessness as a risk factor for mortality: a Danish nationwide register-based cohort study

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Background: The excess mortality among homeless people remains high. However, whether homelessness is a risk factor of death independent of mental disorders and substance abuse is uncertain. Better knowledge of this relationship can have implications for future efforts aiming at improving homeless people's health. The aim of this study was to analyse the effect of homelessness on all-cause and cause-specific mortality, with attention to the independent effect and in combination with a schizophrenia spectrum diagnosis and other specific psychiatric diagnoses including substance use disorders.
Methods: We conducted a nationwide register-based cohort study of the Danish population 2000 through 2011. Homelessness was defined as having at least one contact to a homeless shelter in Denmark during the study period. The association between homelessness and mortality was analysed taking into account important confounders. Mortality rates among homeless people with specific psychiatric diagnoses were compared with the general population.
Results: For death from medical conditions, after adjustment for psychiatric diagnoses including substance abuse, homeless men and women had a mortality rate ratio [MRR] of 2.85 (95% confidence interval [CI] = 2.73, 2.98) and 3.66 (95% CI = 3.37, 3.97), respectively, compared with the general population. For death from external causes (suicide, unintentional injuries, and homicide), the figures were for men and women 5.23 (95% CI = 4.85, 5.64) and 11.74 (95% CI = 10.18, 13.55). After full adjustment including socioeconomic factors in a sub-cohort born 1982-1993, homeless mortality was four times that of the general population (MRR 3.94; 95% CI = 3.10, 5.02). Very high mortality rates were found for homeless people with a psychiatric diagnosis.
According to death from diseases and medical conditions, homeless men and women with a schizophrenia spectrum diagnosis had a MRR of 7.41 (95% CI = 6.53, 8.40) and 7.86 (95% CI = 6.37, 9.70), respectively. For both sexes, no difference in the homelessness effect on death from diseases and medical conditions was found between those with a schizophrenia spectrum diagnosis and those without psychiatric contact. However for external causes, a lower effect of homelessness was found among men with a schizophrenia spectrum diagnosis than among men without a psychiatric diagnosis. Among the women, no difference was found, and the homelessness effect was lower among women with a schizophrenia spectrum diagnosis than among women who also had a substance use diagnosis (dual diagnosis). In contrast to this result, among the men the effect of homelessness was higher for those with a schizophrenia spectrum diagnosis than for those with a dual diagnosis. The MRRs for homeless men and women with a schizophrenia spectrum disorder were according to death from external causes 41.75 (95% CI = 35.74, 48.77) and 82.61 (95% CI = 62.44, 109.28), respectively.
Conclusions: The excess mortality among homeless people can to a high degree but not fully be explained by psychiatric morbidity. People experiencing homelessness and have a schizophrenia spectrum diagnosis have very high mortality rates, especially for external causes. However, homelessness increases mortality independent of and in combination with a schizophrenia spectrum diagnosis and, thus, homelessness is an important predictor of mortality. Results also suggest problems with undiagnosed disorders, especially among men. Furthermore, problems with non-adherence to treatment are likely to explain some of the differences in homelessness effect on death from external causes.

S12. The who international classification of functioning core sets: a consensus process for key components of functioning for schizophrenia

S12.1 Social disconnectedness in schizophrenia and in the general community: do they look the same?

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Background: Social disconnectedness (SD) is one of the key features of schizophrenia. SD refers to an objective, long-standing, lack of social / family relationships and minimal participation in social / family activities, and it is distinct from subjective loneliness. It is also a major public health problem that is associated with a wide range of negative health effects, including early mortality. Importantly, SD exists on a continuum. It is common among individuals with schizophrenia but it is also surprisingly common in the general community. Little is known about SD in the community. There has been almost no effort to recruit such individuals and to compare them with schizophrenia, and that was the goal of this initial study.
Methods: To recruit people with SD from the community, we ran an ad that solicited "healthy individuals … who have few friends, or have little need of friends, or typically prefer to do activities alone." We received 66 calls, conducted a brief phone screening, and conducted 30 interviews. The sample was 39% female, mean age of 46.0 (9.0), and mean education of 15.5 (2.5). Two of the interviewed participants (6.7%) had psychotic symptoms. These subjects were not included in the summarized data, which was based on 28 remaining participants. Among these 28 subjects, 2 had a history of recurrent depression and 3 had a history of anxiety disorder. Most had some personality disorder traits, and 8 (29%) met criteria for a personality disorder (3 paranoid, 1 schizotypal, 2 avoidant, 2 schizoid).
Results: Data were collected on self-report variables for degree of social interactions, social anhedonia, approach versus avoidance motivation, loneliness, autistic traits, and a performance measure of facial affect perception. The SD sample showed the following characteristics: - Social networks: Very low on measures of social networks. In addition, the individuals had a very high score (> 2 std. from control values) on the Social Anhedonia Scale. - Approach versus avoidance: Greatly reduced social approach compared to published scores. However, they were in the normal range for social avoidance. Notably, social approach scores correlated with social networks (r's = .40 -.54), but the correlation for social avoidance scores were lower and non-significant. - Loneliness: Less than half were lonely. Based on scores from a large community sample 11/28 (39%) of the participants would be considered lonely. - Autism: No autistic tendencies. No subject scored in the autistic range.

- Facial affect performance: Performance on a social cognition test of facial affect perception was intact compared with healthy controls from our previous studies. Finally we compared the levels of SD in this group from the general community to previously collected data on individuals with schizophrenia, bipolar disorder, and healthy controls not recruited for SD. Notably, the level of SD is essentially the same in the SD community sample and those with schizophrenia. Bipolar disorder was intermediate between healthy controls and the other samples.
Conclusions: In summary, using a targeted recruitment, we assessed a sample from the general community that had SD at roughly the same levels seen in schizophrenia. Thus, it is possible to recruit a community sample exhibiting substantial levels of SD. After excluding two individuals who had psychotic symptoms, these individuals have levels of SD that are comparable to people with schizophrenia, but they do not have notable deficits in social cognition. Instead their disconnection may be driven more by low social approach motivation.

S12.2 A closer look at functioning – what are international classification of functioning, disability and health core sets and how they can be used

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Background: A selection of categories from the entire International Classification of Functioning, Disability and Health (ICF) for specific health conditions, condition groups and settings, ICF Core Sets (ICF-CS) have been developed to facilitate a systematic and comprehensive description of functioning for use for various purposes and in diverse settings. Functioning is described as the human experience related to the physiological and psychological functions of the body, body organs and structures, the execution of tasks, and involvement in everyday situations and in society, and viewed in dynamic interaction with a health condition, personal and environmental factors.
Methods: An ICF-CS can serve as a minimal standard for the assessment and documentation of functioning and health in comprehensive single or multi-professional clinical encounters. ICF-CS can foster interprofessional communication and encourage health care professionals of a multidisciplinary team to consider potentially relevant aspects of functioning, even in areas of functioning outside of their respective disciplines. They can also help guide the planning of patient/client and functioning-oriented health care services and serve as a framework for evaluating changes in the functioning status over a certain time period.
Results: The utility of ICF-CS is versatile and is not limited to clinical practice. They can be applied in research, population surveys, and in vocational rehabilitation – to name a few.
Conclusions: It is important to note that ICF-CS tell you what to measure, and not how to measure the respective categories. The utility of ICF Core Sets is optimized when employed together with a metric.

S12.3 Preliminary studies for the development of the international classification of functioning, disability and health core sets (ICF-CS) for schizophrenia

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Background: The process of developing an ICF-CS implies three different phases (Cieza, Ewert, Üstün, Chatterji, Kostanjsek, Stucki, 2004; Grill, Stucki, 2011; Kirchberger, Coenen, Hierl, Dieterle, Seissler, Stucki *et al.*, 2009, Selb *et al.*, 2015). The first phase consists of four preparatory studies that capture different perspectives: an empirical multicenter study (clinical perspective), a systematic literature review (researcher's perspective), a qualitative study (perspective of patients), and an expert survey (health professionals' perspective). In phase two, the resulting set of "candidate" ICF categories is provided to the experts and health professionals who participate in an international consensus conference during which they decide on the ICF categories to be included in the respective ICF-CS. The final phase in the process involves implementing the first version of the ICF-CS.
Methods: ICF-CS have been developed for several health conditions including two mental disorders, i.e., depression and bipolar disorders. In 2013, the University of Barcelona and the ICF Research Branch together with a consortium of researchers in Spain, the Netherlands and the United States had taken on the task of developing an ICF-CS for schizophrenia. The aim of the project was to identify indicators of functioning as represented by ICF categories that would enable us to better and more comprehensively understand schizophrenia. Having these "indicators" will provide the foundation for developing a valid and evidence-based questionnaire on functioning of persons with schizophrenia.
Results: Firstly, a multicenter cross-sectional study with five centers in Spain was carried out. A total of 127 patients diagnosed with schizophrenia, 92 male and 35 female, were included. Health professionals completed a protocol consisting on patients' socio-demographic information, condition-specific data and a WHO ICF checklist prepared for this particular study. A total of 95 ICF categories were extracted from this preparatory study.
Secondly, a systematic literature review on published studies involving patients with schizophrenia was conducted. Electronic databases (i.e., CINAHL, Pubmed, and PsycINFO) were searched to include journal articles published in English between 2008 and 2012. There were identified 3584 original articles, and 348 were randomly selected to be studied more in depth. After examining abstracts for inclusion or exclusion, 206 studies were analyzed. A total of 70 ICF categories were extracted from this preparatory study. Thirdly, a qualitative study using focus groups was carried out. Sessions were developed according to a topic guide including six open-ended questions. A total of 11 focus groups were digitally recorded, i.e., seven groups of patients diagnosed with schizophrenia ($n = 45$), and four groups of people living with patients ($n = 25$; three groups with relatives, and one group with institutional caregivers). A total of 149 ICF categories were extracted from this preparatory study. Lastly, a cross-sectional, internet-based survey with expert health professionals from six WHO regions was conducted. A pool of experts, which included psychiatrists, psychologists, nurses, occupational therapists and social workers, was surveyed to identify problems in functioning and environmental factors of individuals with schizophrenia. One hundred and eighty-nine experts responded to the questionnaire. A total of 95 ICF categories were extracted from this preparatory study.
Conclusions: In this presentation results from the four preparatory studies are presented and discussed.

S12.4 The comprehensive and brief international classification of functioning, disability and health core sets (ICF-CS) for schizophrenia

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Background: The results of the preparatory studies were presented at an international consensus conference, a multi-stage, iterative, decision-making and consensus process that took place 12-14 May 2015 in Barcelona, Spain. At this consensus conference, schizophrenia experts from different countries worldwide and working in a broad range of professions decided which ICF categories should be included in the first version of the ICF Core Sets for schizophrenia. They based their decision on the 184 second level candidate categories that resulted from the four preparatory studies.
Methods: The sequential process of developing the Core Set, and the resulting instruments (Comprehensive and Brief Core Sets) of the consensus conference is presented. The decision-making process consists of alternating working group (WG) and plenary sessions. The experts participants are divided into three homogeneous WGs that reflect an equal representation of professions/disciplines, WHO regions and gender. The WG sessions enable the participants to discuss pros and cons of include each candidate ICF category in the Comprehensive ICF-CS thereby considering factors like commonality between the categories, frequency in the schizophrenic population, clinical utility and the results of preparatory studies. Following WGs sessions the participants convene in plenary to share the WG results in order to discuss the "ambiguous" categories (Selb, *et al.*, 2015).

The second part of the decision-making process involves deciding on the Brief ICF-CS. Participants are requested to rank the most essential ICF categories from the Comprehensive ICF-CSs in three consecutive ranking sessions. The results of the individual rankings are statistically calculated and common ranking arises. Following the final ranking session, the process of deciding the "cut-off" for each ICF component begins. Each expert is asked to decide how many ICF categories per ICF component would be important to include in the Brief ICF-CS. (Selb, *et al.*, 2015).
Results: The experts included 97 categories in the Comprehensive ICF Core Set and 25 categories in the Brief ICF-CS. The specific categories of each ICF-CS are shown in this presentation. The Comprehensive ICF-CS can guide multidisciplinary assessments of functioning in persons with schizophrenia, and the brief version is ideal for use in both clinical and epidemiological research, since it includes a small and practical number of categories, but sufficiently wide for finding utility in clinical assessments.
Conclusions: ICF-CS are evidence-based, are applicable for use in multidisciplinary settings, and are also considered international, since in the consensus conference participants are recruited from all six WHO world regions. ICF-CS are being designed with the goal of providing useful standards for research, clinical practice and teaching, and it will stimulate research and will improve understanding of functioning, health and environmental factors in schizophrenia.

S13. Exciting new findings about dopamine

S13.1 Dopamine neurotransmission in schizophrenia: new findings from combined PET and fMRI studies

Anissa Abi-Dargham[*1], *Mark Slifstein*[1], *Jared Van Snellenberg*[1]

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Background: Prefrontal cortical hypodopaminergia has been proposed to underlie prefrontal cortical dependent cognitive deficits in schizophrenia. We undertook combined PET and fMRI studies in drug free or drug naïve patients with schizophrenia and healthy controls matched for age, gender, ethnicity and familial socioeconomic status to test: 1) amphetamine induced dopamine release in dorsolateral prefrontal cortex (DLPFC) 2) BOLD fMRI activation during a working memory task in the same subjects and 3) to examine the relationship between PET and fMRI outcome measures.
Methods: PET imaging with the D2/3 radiotracer [11C]FLB457 before and following 0.5 mg/kg P.O. amphetamine. BOLD fMRI during the self-ordered working memory task (SOWT). 20 patients with schizophrenia (SCZ) and 21 healthy controls (HC) participated. We measured the percent change in binding potential (ΔBPND) in DLPFC following amphetamine, BOLD activation during the SOWT compared to the control task, and the correlation between these two outcome measures.
Results: We observed: 1) significant differences in the effect of amphetamine on DLPFC BPND (ΔBPND in HC: - 7.5 ± 11%, SCZ: +1.8 ± 11%, $P = 0.013$), 2) a significant relationship between ΔBPND and BOLD activation in DLPFC in the overall sample including patients with SCZ and HC.
Conclusions: These results provide the first in vivo evidence for a deficit in the capacity for dopamine release in DLPFC in schizophrenia. Furthermore, dopamine release in the DLPFC relates to working memory-related activation of this region, suggesting that blunted release may affect frontal cortical function.

S13.2 A molecular signature of dopamine dysregulation exists in the substantia nigra in schizophrenia

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Background: Schizophrenia involves a presynaptic dopamine dysfunction, identified by positron emission tomography (PET) in both the substantia nigra and the associative striatum. However, it is unknown how gene expression of dopamine-pathway related molecules are changed in the substantia nigra in schizophrenia. We investigated how gene expression levels of dopamine-related molecules are changed in the human substantia nigra from schizophrenia and control brains.
Methods: We examined mRNA expression by quantitative PCR of the dopamine synthesis molecules, tyrosine hydroxylase (TH) and aromatic acid decarboxylase (AADC), dopamine reuptake molecules, dopamine transporter (DAT) and vesicular monoamine transporter 2 (VMAT2), dopamine receptor D2 (DRD2) isoforms as well as dopamine breakdown enzymes, catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO) A and B in the substantia nigra of control ($n = 29$) and schizophrenia post mortem brains ($n = 29$) provided by the New South Wales Brain Bank, Sydney, Australia.
Results: We found no change in TH mRNA ($P = 0.67$) levels but a 35% increase in AADC mRNA ($P = 0.041$) levels in the substantia nigra from schizophrenia brains compared to control brains. We also detected a 36% ($P = 0.014$) and a 43% ($P = 0.0002$) decrease in VMAT2 and DAT mRNA, respectively, as well as a 30% ($P = 0.04$), 37% ($P = 0.02$) 36% ($P = 0.007$) and 25% ($P = 0.04$) decrease in DRD2pan, DRD2short, DRD2long and DRD2longer mRNA, respectively, in substantia nigra from schizophrenia brains compared to control brains. Expression of MAOA mRNA was increased by 38% ($P = 0.02$) in substantia nigra from schizophrenia brains compared to control, whereas MAOB ($P = 0.4$) and COMT ($P = 0.6$) expression was unchanged. None of these measures correlated with daily, last dose or lifetime chlorpromazine equivalents or with duration of illness.
Conclusions: These data provide evidence of changes in dopamine pathway-related molecules in the region of dopamine cell bodies and highlights changes proximal to the presynaptic dopamine dysfunction reported in the striatum of schizophrenia patients. These changes include potential increases in dopamine synthesis (consistent with PET imaging studies) as well as potential decreases in dopamine transport and autoreception and a potential increase in one dopamine breakdown enzyme. This study identifies a molecular signature of dopamine dysregulation in the substantia nigra in schizophrenia. Studies are underway to determine whether these gene expression changes are translated to protein changes in cortical and/or subcortical targets and/or at the level of the somatodentritic field of the dopamine neurons.

S13.2 Adolescent dopamine development, netrin-1, and vulnerability to schizophrenia

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[1]*McGill University*

Background: Adolescence is an age of heightened vulnerability to develop psychiatric disorders that involve alterations in medial prefrontal cortex (mPFC) circuitry and cognitive dysfunction. The maturation of mPFC function is linked to the establishment of dopamine connectivity within this region. The organization of mesocortical dopamine circuitry however is a protracted process, which peaks in adolescence and ends only in early adulthood. Because of its extended developmental course, the shaping of this dopamine projection is particularly susceptible to life experience. Yet, there is a significant gap in our knowledge about mechanisms of adolescent mPFC dopamine development and about how they are influenced by experience.
Methods: Molecular, neuroanatomical, neurochemical, electrophysiological, and behavioral experiments in different lines of transgenic mice generated in my laboratory.
Results: We identified the guidance cue genes, netrin-1 and its receptors DCC and UNC5C, to control target recognition decisions by dopamine axons specifically in adolescence. In doing so, this set of molecular cues determines the extent and organization of the dopamine innervation to the mPFC, influencing significantly (a) the structure and function of mPFC pyramidal neurons and (b) cognitive processing, including behavioral inhibition. Genetic variations in netrin-1/DCC /UNC5C molecules confer susceptibility or resilience to develop schizophrenia-like phenotypes in mice and are associated with this illness in humans.
Conclusions: By orchestrating mesocortical dopamine connectivity in adolescence, the netrin-1/DCC/UNC5C signaling cascade appears to determine differential vulnerability to schizophrenia-like psycho-

pathology. Pharmacological and prophylactic interventions earlier in life may alter the function of this signaling pathway in the dopamine system and in turn may have an impact on disease outcome. The idea of netrin-1/DCC/UNC5C as therapeutic targets during adolescence is compelling given the increasing consensus that interventions at the earliest signs of disease may be more effective.

S13.4 A novel role for dopamine regulation of striatal and cortical information processing

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Background: Dopamine neurotransmission in the prefrontal cortex and striatum is critical to cognitive processes such as attention, working memory as well as motivation. These cognitive processes and deficits have been linked to modulation of network activity in PFC and striatum. However, experimental evidence describing a causal relationship between the activity of dopamine neurons and global cortical and striatal activity is lacking.
Methods: In freely moving TH::Cre rats, we optogenetically stimulated dopamine neurons in the ventral tegmental area (VTA) and simultaneously recorded local field potentials (LFPs) in the medial prefrontal cortex. In a separate cohort, we utilized optogenetic to simultaneously measured global hemodynamic changes using blood oxygenation-level dependent (BOLD) and cerebral blood volume-weighted (CBVw) fMRI. Dopamine neurons were stimulated using bursting paradigms that resemble the activity patterns of these neurons during motivated behaviors.
Results: We found that burst activity of VTA dopamine neurons is sufficient for increasing the power of high gamma ($>$ 55 Hz) but not low gamma (35–55 Hz) oscillations in the. More importantly, we found that activation of VTA dopamine neurons increased BOLD and CBVw fMRI signals robustly and predominantly in the dorsal striatum (DS), even when compared to VS that receives the densest VTA dopamine innervation in the brain.
Conclusions: These results suggest that mesolimbic and nigrostriatal dopaminergic circuits might be functionally connected and that fMRI signal abnormalities observed in dorsal striatum in schizophrenia could be directly related to aberrant activity in VTA dopamine neurons. These findings, thus, provide a novel framework for understanding dopamine-dependent functions/disorders and interpreting data obtained from human fMRI studies.

S14. Cognitive remediation: effects on social cognition and new insights on mediators and moderators of treatment outcomes

S14.1 Improvement of social cognition deficits in chronic schizophrenia after CRT

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Background: Cognitive remediation therapy (CRT) improves basic cognition in patients with schizophrenia, but its effect on other relevant factors such as social cognition and functional outcome has not been extensively studied yet.
Methods: In this hospital-based study, 101 outpatients with schizophrenia were recruited from the Mental Health Network in Bizkaia (Spain). All of the subjects underwent a baseline and a 5-month assessment that examined basic neurocognition, social cognition, clinical symptoms and functional outcome according to the Global Assessment of Functioning (GAF) scale, Disability Assessment Schedule from World Health Organization (DAS-WHO) and UPSA-brief. In addition to receiving standard treatment, patients were randomly assigned either to receive neuropsychological rehabilitation (REHACOP) or to a control group. REHACOP is an integrative program that taps all basic cognitive functions and social cognition: emotional perception and recognition, attributional bias, Theory of mind, and Ethics.
Results: The REHACOP group showed significantly greater improvements at 3 months in the areas of basic neurocognition and negative symptoms compared with the control group (Cohen's effect size for these changes ranged from d = 0.47 to d = 0.58). Also, significant improvement was observed in social cognition measurements in the REHACOP group except for atributional bias (emotional perception $P < 0{,}011$, emotional perception $P < 0{,}004$, theory of mind $P < 0{,}000$), attributional bias $P < 0{,}374$). These improvements were associated to significantly recovery in GAF (d = 0.61), DAS-WHO total scores (d = 0.57), and UPSA (d = 0.60).
Conclusions: CRT may be useful for social cognition as well as negative symptoms and functional disability in schizophrenia. These findings support the integration of neuropsychological rehabilitation into standard treatment programs for patients with schizophrenia. The Rehacop have previously demonstrated efficiency for general cognition in schizophrenia but at this clinical trial for the first time, also demonstrate efficiency for social cognition.

S14.2 Exploring the role of metacognition in cognitive and functional change following a new generation metacognitive cognitive remediation programme for people with schizophrenia

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Background: Cognitive remediation (CR) is a psychological therapy which improves cognitive and social functioning in people with schizophrenia. It is now being implemented within routine clinical services and mechanisms of change are being explored. We designed a new computerised CR programme, CIRCuiTS, fit for these purposes, that is underpinned by a metacognitive model of the relationship between cognitive and functional change and has an integrated focus on the transfer of cognitive skills to daily living. We report results from a large trial which tested its efficacy, and investigate the role of metacognition in facilitating cognitive and functional changes.
Methods: A two arm single blind randomised superiority trial comparing CIRCuiTS plus treatment-as-usual (TAU) with TAU alone in 93 people with a diagnosis of schizophrenia. Cognitive, metacognitive, social functioning and symptom outcomes were assessed at pre- and post-therapy and three months later.
Results: There were significant improvements in visual memory at post-treatment and follow-up, and a trend for improvements in executive function at post-treatment ($P = 0.056$) in favour of the CIRCuiTS group. Improvement in visual memory was predicted by the use of a higher number of strategies rated as 'useful' within each session. Social function was also differentially and signficantly improved for the CIRCuiTS group at post-treatment but not follow-up and this improvement was specifically predicted by improved executive functions. Both strategy use and executive functions are aspects of metacognitive regulation. A novel narrative measure of metacognition administered to a subset of 63 participants, which showed strong baseline associations with a variety of cognitive functions, suggested that for those with no metacognitive improvements, cognitive improvements were a good predictor of functioning changes. However, for those who showed improved metacognition, changes in functioning were no longer predicted by cognitive changes. These preliminary findings support the notion that improving metacognition may enable people to minimise the impact of cognitive difficulties on functioning.
Conclusions: CIRCuiTS was beneficial for improving memory and social functioning. Aspects of improved metacognition were significant predictors of both these improvements, although for those who showed improved metacognition on a narrative measure, functioning improvements appeared to be less reliant on cognitive changes. This evidence supports a role for metacognition in the moderation of cognitive and functioning changes in schizophrenia.

S14.3 Reading the mind of the avatar: demonstration of a new virtual reality social cognition training for people with psychotic disorders

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Background: Individuals with psychotic disorders commonly experience deficits in social cognition and limited social functioning. Social Cognition Training (SCT) has been shown to have beneficial effects on proximal social cognition tasks, but generalization to social functioning is limited and interventions may not have long-term effects. We speculate that this may be due to limited ecological validity of SCT stimuli, and the absence of opportunities for guided practice in realistic, dynamic social interactions.
Methods: We propose that this problem could be solved by providing SCT in virtual reality (VR). VR allows for practice of skills in situations mimicking real life, yet is safe and controllable, and facilitates structured training guided by a therapist. The proposed intervention aims to improve social cognition through CRT principles such as errorless learning, scaffolding, and coaching. It builds complex social cognitive skills, such as higher-order Theory of Mind, upon elementary social processes, such as facial affect perception.
Results: The virtual reality SCT consists of four modules: 1) facial affect recognition training: encountering avatars showing emotion and identifying their affective expressions; 2) facial affect recognition in social contexts: identifying and understanding expressed emotions using social contextual information; 3) Theory of Mind (ToM) training (progressing from simple, first-order scenarios to complex, higher-order ToM): encountering increasingly complex social situations and inferring virtual characters' mental states; and 4) integration and practice of FAR and ToM in dynamic interactions with virtual characters, that change according to clients' choices and psychophysiological responses in the interactions. Training is delivered using four interactive virtual environments that are common in daily life situations: a shopping street, a super market, a bus and a café.
Conclusions: The intervention described above, as well as plans to empirically test its efficacy, are demonstrated and presented in further detail.

S14.4 Training of social cognition in psychotic disorders: a meta-analysis

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Background: Impaired social cognition is highly common in people with psychotic disorders. To ameliorate these impairments, various kinds of Social Cognition Training (SCT) have been developed. These interventions vary in characteristics and efficacy, raising the question which kinds of SCTs work, for which domains and functional outcomes, and for whom.
Methods: For this meta-analysis, randomized controlled studies documenting SCTs were identified and characteristics of patients and interventions, and outcome details were extracted. Cohen's d was used as a measure of general effect size and subsequently analyzed in a general meta-analysis, categorical meta-analyses and meta-regressions.
Results: SCT had moderate to large significant effects on emotion perception (d = .75), social perception (d = .61), general social cognition (d = .52), theory of mind (d = .60), and on functioning (d = .69), but not on attribution (d = -.07). These effects were not maintained for follow-up measures. Interventions targeting multiple social cognitive domains were shown to have larger effects on proximal social cognition measures and functional outcomes than interventions focusing on a specific social cognitive domain. Specific interventions for facial affect recognition produced larger effect sizes in social and emotional perception domains than interventions that targeted several social cognitive domains, but these effects failed to generalize or persist. Of the patient characteristics that were investigated (age, education level, medication dose, illness duration) as moderators of treatment outcome, only age was identified as a significant moderator (b = -.11), indicating that older individuals may benefit less from SCT. None of the intervention characteristics (duration, intensity, group size) were found to be significant moderators of outcome.
Conclusions: While SCT showed promising effects on both proximal and functional measures of social cognition directly post-treatment, its failure to produce long-term effects warrants an investigation into its workings and mechanisms, and particularly the aspects that still need improvement.

PL15. Toward predictive psychiatry – prognostic and diagnostic applications of pattern recognition methods

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Abstract: Recently, both high-dimensional 'omics' data and powerful multivariate pattern analysis tools have become available for psychiatric research. These developments have stirred the hope that predictive signatures could be extracted from these multi-modal databases with far-reaching potential for individualized prognosis and (differential) diagnosis of schizophrenic, affective and neurodegenerative disorders. Yet, given the crisis of the current neuropsychiatric taxonomy and the inefficiencies of univariate statistics, it remains unclear (1) if robust mappings between neurobiological patterns and the traditional clinical diagnostic entities actually exist, and (2) whether these patterns generalize enough to be encapsulated into clinically useful 'biomarkers'. The lecture will first review concepts and the state-of-the-art of multivariate pattern analysis (MVPA) in psychiatric research, putting the focus on candidate markers for individualized risk stratification and differential diagnosis of schizophrenia-spectrum and mood disorders. Strengths and pitfalls of MVPA will be discussed in terms of sensitivity to overfitting, to center and data acquisition effects as well as to population biases. Preliminary data from the PRONIA study (www.pronia.eu) will be presented in order to exemplify the current status and the challenges to be addressed by predictive psychiatry. Candidate neuroimaging, neurocognitive and clinical prediction models developed by means MVPA technology will be described by (1) reporting sensitivity, specificity and accuracy of prognostic and (differential) diagnostic predictions in patients with schizophrenia-spectrum and affective psychoses, (2) visualizing underlying patterns, and (3) discussing the moderating influence of diagnostic boundaries psychopathological features, disease courses, brain maturation and environmental variables on prediction performance. MVPA may provide a powerful and adaptive set of statistical tools to decompose the complexity of psychiatric phenotypes into their most predictive components. The designs of the next-generation translational studies have to take into account the strengths and pitfalls of these methods in order to assess which of these components have the highest bench-to-bedside. Tential.

PL16. Precision medicine for psychosis: challenges and promise

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Abstract: Consistent with the goals of precision medicine to re-define illness mechanistically through elucidating the pathophysiology from gene action to symptoms, large scale genomic studies have been linking genomic variation to continuous quantitative phenotypes. Such an approach can lead to early detection and pathological processes enabling early intervention. This paradigm shift is now applied in psychiatry with an increased focus in schizophrenia research on early identification of psychosis as the process emerges. Convergent approaches integrate phenotypic features with neurocognitive and neuroimaging measures in large -scale studies. Most studies have examined help seeking youths. This presentation highlights complementary strategies to probe the underlying neurobiology of psychosis risk. The first, most widely applied is the study of help-seeking individuals who present with subthreshold psychotic symptoms and are at high risk for psychotic illness. The second, community-based samples of youths with no known

neurogenetic syndrome. The Philadelphia Neurodevelopment Cohort illustrates such an approach. The third, the study of youths with a known genetic syndrome, the 22q11.2 Deletion Syndrome (22q11DS) that confers significant increased risk for psychosis (~25%), emerging in adolescence and early adulthood.
Methodological considerations and emerging finding across strategies will be discussed and the implication for early identification and intervention emphasized.

S17. Neuroimaging biomarkers for psychiatric disorders in adolescence and young adulthood: prediction of risk, transition and illness course

S17.1 Machine learning in psychiatric neuroimaging: introduction and applications in adolescent offspring of patients with schizophrenia or bipolar disorder

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Background: The past decade has seen much progress in the field of making individual predictions based on neuroimaging data. Early evidence for the use of machine learning in psychiatric neuroimaging was characterized by proof-of-principle studies using relatively small samples and/or trying (successfully) to make the distinction between healthy subjects and (chronic) patients with a single, stable, diagnosis of, e.g., schizophrenia. Meanwhile, the field has moved forward to more challenging and clinically useful tasks such as the detection of risk of a disorder, prediction of transition to psychosis, fine-splitting between different (subtypes of) disorders, and illness course. To date, these studies often use larger samples, independent validation samples, and multi-center setups.
Methods: The first part of this talk will contain a short introduction to the machine learning technique and its application to psychiatric neuroimaging, especially magnetic resonance imaging (MRI). Examples of published studies in schizophrenia are presented, discussing: (1) Performance measurement (e.g., prediction accuracy); (2) The importance of sample size; (3) What we can learn about the underlying brain pathology; and (4) the assessment of generalizability, i.e., the capability of a prediction model to make accurate predictions in new subjects.
Results: In the second part, we will present new results of applying machine learning to discriminate between adolescent offspring ($N = 157$; age 10-19 year) of patients with schizophrenia, patients with bipolar disorder, and healthy parents. It is shown that this familial risk of a disorder can be detected with above chance level in the structural MRI brain images and that there is significant overlap between the two disorders in the brain regions that play a role in this detection at this age.
Conclusions: Risk of bipolar disorder and schizophrenia can be detected from structural MRI brain images of adolescent offspring using machine learning. The emerging signs of the disease in the brains of these high-risk subjects are discussed in relation to the brain abnormalities found in adult patients. Further investigations of these subtle brain abnormalities could lead to clinically useful markers for the early prediction of schizophrenia and bipolar disorder.

S17.2 Neuroanatomical features as transdiagnostic biomarkers of psychosis and autism spectrum disorders

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Background: A transdiagnostic approach to psychiatric nosology is central in the National Institute of Mental Health's Research Domain Criteria Project (Insel *et al.* 2010). In this context, psychosis and high functioning autism spectrum disorders (ASD) are complex neurodevelopmental disorders that share symptomatology but it is not clear if they also share neurobiological abnormalities. Structural insular cortex deficits may be a transdiagnostic endophenotype for different psychotic and non-psychotic diagnoses (Goodkind *et al.* 2015). This meta-analysis did, however, not include ASD though evidence for structural insular deficits in ASD exists. To assess transdiagnostic deficits Goodkind *et al.* (2015) evaluated cortical volume, which is a composite of cortical thickness and surface area. Thickness and surface area are influenced by different sets of genes, may have a low correlation, show different neurodevelopmental trajectories early and later in life, and may be the result of different neurodevelopmental pathways during corticogenesis (Rakic, 1999). We examined insular thickness, surface area and volume in a direct comparison of children and adolescents with early-onset first-episode psychosis (FEP, onset before 18 years), high-functioning ASD, and healthy subjects. We evaluated, firstly, whether both disorders shared insular thickness, surface area and volume alterations with respect to healthy controls. Secondly, in both disorders we evaluated whether abnormalities in thickness and surface area spatially overlapped.
Methods: T1-weighted high-resolution magnetic resonance imaging (MRI) scans of 85 participants (30 ASD, 29 FEP, 26 healthy controls, age range 10-18 years) were obtained from the same MRI scanner using the same acquisition protocol. All subjects were recruited at the Child and Adolescent Psychiatry Department at the Hospital Gregorio Marañón, Madrid, and Spain. The FreeSurfer analysis suite was used to quantify local estimates of the metrics thickness, surface area, and volume.
Results: After correction for multiple comparisons and with respect to the healthy control group, ASD and FEP subjects had spatially overlapping insular deficits for each metric. The transdiagnostic overlap of deficits was greatest for volume (55% of all insular points where a deficit was detected), then surface area (42%) and smallest for thickness (18%). Insular thickness and surface area deficits did not overlap significantly in ASD and overlapped only in 8% of all insular points that had either a thickness or surface area deficit in FEP.
Conclusions: Morphological insular deficits are common to FEP and high functioning ASD when compared to healthy participants. The pattern of morphological deficits was similar in both disorders, i.e. a largely non-overlap of insular thickness and surface area. The non-overlap of insular thickness and surface area provides further evidence that these properties of the cortex are the result of two independent processes driving corticogenesis, both of which are affected in FEP and ASD. The shared deficits between FEP and ASD emphasize the potential strength of insular cortex morphology measurements as transdiagnostic biomarkers of mental health disorders.

S17.3 MRI-based risk stratification in clinical high-risk individuals: state-of-the-art and challenges ahead

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Background: The analysis of structural MRI using advanced statistical learning methods has yielded candidate brain markers with the capacity to facilitate individualised risk stratification in persons at clinical high-risk (CHR) for psychosis. Still, these potential biomarkers have been derived from relatively small and well-controlled samples thus leaving the question unanswered whether generalizability to larger, more heterogeneous, multi-site CHR populations can be achieved. Furthermore, it remains unclear whether predictive brain signatures represent stable patterns of the psychosis prodrome or alternatively, whether they evolve along different dysmaturational trajectories that lead to the diverse clinical phenotypes of psychosis and its neighboring conditions.
Methods: The talk will first summarize the current knowledge on the prediction of psychosis in CHR populations using machine learning and MRI technology. Then, preliminary data from the PRONIA study ("Personalised Prognostic Tools for Early Psychosis Management) will be presented in order to discuss the influence of brain dysmaturation, multi-site data acquisition and diagnostic specificity on the performance of prognostic biomarkers.
Results: (1) Predictive performance of neuroanatomical and neurofunctional models in estimating individual clinical and functional outcomes measured in terms of sensitivity, specificity, balanced accuracy, diagnostic odds ratios. (2) Kaplan-Meier analyses of these prediction models for individualised risk stratification. (3) Generalizability

estimates across different CHR cohorts, (4) Neuroanatomical mapping of prediction models and specificity analysis with respect to overlapping clinical phenotypes such as established psychosis and depression.
Conclusions: The available data indicate that individualized prognostic evaluation and risk stratification has considerable potential in improving the early identification of adverse mental health outcomes in at-risk populations. Major challenges for the application of these predictors are population-related MRI-related technological heterogeneity.

S17.4 Stratifying psychosis outcome at illness onset using MRI-based univariate approaches and pattern classification methods

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Background: Early and long-term outcomes following the first-episode of psychosis are very heterogeneous, with approximately 50%-60% of patients responding to the first antipsychotics, and 30% developing an incapacitating illness course. Identifying early which individuals will develop a worse illness course is paramount and can reduce disability and healthcare costs, eventually improving long-term outcome.
Methods: We examined brain structure in multiple datasets of patients at their first psychotic episode ($n = 260$), using structural Magnetic Resonance Imaging and Diffusion Tensor Imaging. All patients were followed up for periods ranging from 3 months to 6 years. Neuroanatomical and morphological measures were evaluated, including grey matter volumes, cortical morphology, white matter integrity and the connectome. We used univariate volumetric, Freesurfer and TBSS approaches, graph analysis and multivariate approaches like Support Vector Machine (SVM).
Results: At onset, smaller volumes, particularly of frontal and temporal cortices and striatum, were predictive of subsequent illness episodes with significant accuracy (70% correctly classified; $P = 0.005$). Furthermore, brain alterations of likely neurodevelopmental origin (reduced frontal and temporal gyrification and altered white matter microstructure of interconnecting tracts) were evident in those individuals who did not respond to treatment in the first 12 weeks (all $P < 0.05$ corrected). The analysis of structural networks from DTI data showed that these patients also had lower global ($P = 0.02$) and local ($P = 0.05$) compared to responders, together with lower centrality of the left precuneus, with lower degree and strength (both $P < 0.01$). The analysis of structural covariance of cortical folding also showed a pattern of perturbed maturational relationship among brain regions, with a reduction in measures such as small-worldness (a biological network formed by nodal – brain – units), with increased segregation and reduced integration and efficiency in most brain regions. We also observed further brain changes after illness onset, with a third of patients showing hippocampal volume increase over the 6 years after illness onset, in association with better clinical, functional and cognitive outcomes (all $P < 0.03$).
Conclusions: Neuroanatomical and morphological alterations are already present at illness onset, and may help identifying those individuals more likely to develop a poorer outcome and to benefit from targeted interventions. However, further brain changes take place after onset, possibly in relation to environmental factors like exposure to stress, exercise, medications or psychoactive substances. While information on brain structure can help advance patient stratification in psychiatry, understanding factors that affect brain plasticity can contribute to modifying illness trajectories.

S18. Neuroimaging approaches to treatment outcome in schizophrenia

S18.1 Advantages and challenges of multi-site neuroimaging data in schizophrenia

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Background: From the initial arguments over whether 12 to 20 subjects were sufficient for an fMRI study, sample sizes in psychiatric neuroimaging studies have expanded into the tens of thousands. These large-scale imaging studies fall into several categories, each of which has specific advantages and challenges. In particular, planned multi-site mega studies pour intense efforts into strictly having the same protocols for their data collection. This brings with it incredible advantages over less controlled data aggregation techniques, but also has a number of important challenges. It has even led some to question whether data from different MRI scanners can be combined at all.
Methods: Drawing from the experiences of several multi-site neuroimaging studies, we can assess the effects of differences in scanners on structural, functional, and DTI data. The issues include differences in image warping, signal to noise ratios, and the effects these image differences have on different measures of resulting data. We can also identify different analysis techniques to reduce these effects in different imaging modalities. We also examine the issues of data sharing, standardizing data structures to improve cross-site and cross-study communication.
Results: Common issues with multi-site neuroimaging studies remain, even the studies which carefully control subject recruitment, screening, assessment and training, and scanning preparation, calibration, quality assurance and data management. However, this is neither specific to neuroimaging (any large clinical trial faces the problems of incomplete or noisy data) nor a particularly insurmountable problem through the application of a variety of quality assurance steps and image processing and analysis approaches.
Conclusions: The careful control and designed experimental manipulations of a multi-site prospectively planned neuroimaging study creates the richest datasets for answering both the originally hypothesized questions, and novel exploratory analyses going forward. Both the original analysis and later data sharing hold incredible potential for impact at the level of the individual patient. However, to realize this potential requires both standardized data collection and sharing efforts, so that there is more staying power in the datasets for re-use and new applications. It also requires training the next generation of neuropsychiatric researchers in "Big Data" techniques—how to deal with increased volume, variety, and veracity of the data--in addition to traditional experimental methods. The increased access to data along with the needed informatics demands a new emphasis on integrative scientific methods.

S18.2 Neuroimaging and machine learning algorithms to identify biological subtypes of schizophrenia

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Background: Research has shown that conventional treatments are less effective at treating schizophrenia patients who suffer from prominent negative symptoms. We have previously shown in patients with the deficit schizophrenia subtype, who suffer from prominent negative symptoms, that diffusion-based measures of certain white matter tracts and regional connectivity patterns are altered in relation to other schizophrenia patients and healthy controls. In this study, multivariate classification methods were used on neuroimaging scans to identify features that predict differences between the deficit and non-deficit schizophrenia groups. As previous findings show significant differences in diffusion measures of white matter tracts between the two groups, we hypothesized that the tracts identified as being different in the previous work will identify predictive features in the multivariate models. The ultimate goal is to identify these features at first presentation, prior to the onset of persistent negative symptoms.
Methods: T1 and diffusion tensor imaging (DTI) scans were collected for 18 deficit and 18 non-deficit schizophrenia patients. Both gray matter and white matter measures were compared between the two groups where gray matter was measured as cortical thickness and white matter as mean diffusivity (MD), axial diffusivity (AD), radial diffusivity, and fractional anisotropy for white matter tracts. A random forest multivariate classifier was used to run three separate models: regional cortical thickness only, diffusion measures of white matter tracts only, both combined. The predictive power of each model was assessed using leave-one-out-cross-validation. Area under the curve

(AUC) of the Receiver Operating Characteristic plot was used to compare the three models. Features in each model were ranked for their predictive value using the Gini coefficient. Finally, a ridge penalized logistic regression model was run using only the most predictive features.
Results: Comparison of the three models showed that the white matter tracts only model (AUC = 77%, Accuracy = 77%, Positive Predictive Power (PPV) = 75%) was superior to both the cortical thickness only (AUC = 44%) and the combined (AUC = 70%) models. The top features selected for ridge regression were AD and MD of the inferior longitudinal fasciculus (ILF) and the uncinate fasciculus (UF). The ridge penalized logistic regression model provided an additional level of optimization than random forest alone, such that diffusion measures of the ILF and UF led to improvement of all classification metrics. This approach provided an AUC = 84%, Accuracy = 77%, Sensitivity = 72%, Specificity = 83%, and PPV = 81%.
Conclusions: Diffusion-based measures of white matter provide good accuracy in classifying patients suffering from the deficit subtype of schizophrenia compared to other patients with schizophrenia. Classification may provide a way for clinicians to differentiate patients early in their prognosis and subsequently test and provide group-specific interventions prior to full expression of prominent negative symptoms. As predictive models may help in guiding clinical trials for negative symptoms, and improving patient care, two important goals for future studies would be replication of the current findings and efforts to improve the predictive power of the current model. We are currently working on a replication cohort with a larger sample size that could be used to provide further evidence for these findings. Adding more features to the current model may also help identify other highly predictive features. Our work also helps confirm the neural circuitry of the deficit subtype, which can accelerate therapeutic innovation.

S18.3 The role of pet in optimizing treatment outcome

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Background: Molecular Positron Emission Tomography uses radiotracers to image and quantify neuroreceptors, transmitters and enzymatic processes. PET can play a major role in optimizing treatment outcome by allowing: 1- discovery or validation of new targets that can guide preclinical drug discovery, 2- testing new approaches to engage these targets for therapeutic intervention, 3- testing the relationships between these targets and the course of illness, independent of the drug intervention, and 4- testing the degree of target engagement and treatment response at different doses, which is the most common application.
Methods: PET relies on two principles to allow basic quantification of receptor availability: reaching equilibrium within the time frame of the scanning session between the radiotracer and its target protein, and obtaining measures at negligible occupancy of the target. We will define the main outcome measures and their built in assumptions.
Results: We will provide illustrations for some of these areas of application from recent work. 1- The recent documentation of topographical changes within the dopaminergic system affecting extrastriatal regions in schizophrenia will be reviewed (1). This finding provides direct support for development of D1 agonists or other interventions aiming at increasing dopaminergic transmission in extrastriatal brain regions, 2- PET can allow fast early decision in the drug development process by screening among few molecules to proceed with the one that has best brain penetrance to peripheral toxicity ratio, thus speeding the drug development process, 3- In schizophrenia PET has clearly shown that striatal dopamine predicts conversion during the prodromal phase of the illness (2) and predicts treatment response (3). These studies have been well replicated across labs and will be reviewed. 4- We will show recent data to illustrate the use of PET in assessing occupancy in the late stage of drug development and how this can be used to optimize dose selection.
Conclusions: We will conclude by highlighting the areas of need: imaging of intracellular targets, non dopaminergic targets and the need for collaborations across sites to enlarge samples and maximize the scientific benefit from the limited funding for such an expensive tool.

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S18.4 From the genome to the connectome: detecting biomarkers of antipsychotic drug response

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Background: The first episode of psychosis may be the most critical period in the life of an individual with schizophrenia, and remains the most opportune time for the study of key mechanisms that influence treatment response and outcome of this often chronically disabling disorder. Several factors render the first episode a critical research window: first episode patients are generally young, and therefore within a relatively restricted age range; they have a shorter duration of psychotic symptoms; and less illness-related functional and social impairment related to chronicity of illness. Perhaps most critical is that first episode patients have minimal prior psychopharmacological treatment, reducing medication confounds for research aimed at identifying the neurobiological substrates associated with illness and the prediction of illness course.
Methods: We have assessed a cohort of 198 schizophrenia-spectrum patients (ages 15–40) participating in a 12-week clinical trial of the second generation antipsychotics (SGAs), aripiprazole and risperidone. The primary assessments were conducted prior to the initiation of treatment and during 12 weeks of double-blind treatment. This presentation will focus on results using genetic, neurocognitive and neuroimaging indices to identify predictors of SGA response in this cohort.
Results: Pharmacogenetic substudy: Previously, we have found that a polymorphism in the promoter region of the DRD2 gene significantly influenced antipsychotic drug efficacy in first episode patients, as well as in more chronically ill patients. As the PGC consortium reported that a locus near the DRD2 gene attained genome-wide significance for association to schizophrenia, we assessed the relationship of this new DRD2 locus to treatment response and found evidence that variation at this risk locus was associated with positive symptom treatment response. Neurocognitive substudy: Twelve weeks of treatment with aripiprazole and risperidone had minimal effects on cognitive function. Although performance on indices of general cognitive function, working memory, and verbal learning improved over time, change was mediated by improvements in both positive and negative symptoms, reflecting "pseudospecificity" or practice effect. At baseline, however, a measure of planning and reasoning significantly predicted whether positive symptom remission was achieved during the 12-week trial. Neuroimaging substudy: We utilized seed-based rs-fMRI analysis to examine the relationship between pretreatment functional connectivity and subsequent response to SGA treatment. A striatal connectivity index was established as a predictor of treatment response and replicated in a second sample. Sensitivity and specificity in the replication sample suggests potential clinical application. Post-treatment rs-fMRI scans identified a different set of striatal connections that changed as a function of successful treatment.
Conclusions: These data suggest that identification of biomarkers of antipsychotic drug response is feasible in first episode patient populations. The next steps will include combining modalities to

more robustly predict response and identify treatment targets, as well as to further develop more effective intervention strategies that help ameliorate the suffering of patients with these devastating and disabling disorders.

S19. Psychosis in children and adolescents: from the prodrome to schizophrenia

S19.1 Age-related characteristics of attenuated positive symptoms syndrome

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Background: The attenuated positive symptoms syndrome (APSS) is considered an at-risk indicator for psychosis. However, the characteristics and developmental aspects of APSS as well as the combined risk criteria of APSS and basic symptom criteria (BS), including self-experienced cognitive disturbances (COGDIS) remain under-researched.
Methods: Based on the Structured Interview of Prodromal Syndromes (SIPS), the prevalence of APSS was examined in two samples: (1) adolescent inpatients, and (2) adolescents and adults seeking help in an early recognition program for schizophrenia and bipolar-spectrum disorders. Both samples were divided into APSS vs. non-APSS and compared across multiple characteristics. In sample (2), BS and COGDIS were additionally rated using the Schizophrenia Proneness Instrument for Adults/Children and Youth and co-occurrence with APSS was compared across 13-17, 18-22 and 23-35 year-olds.
Results: Of 89 adolescent inpatients (age = 15.1 ± 1.6, female = 58.4%), 21 (23.6%) fulfilled APSS. Of 213 help-seeking individuals (age = 21.0 ± 6.0, female = 38.5%), 94 (44.1%) met APSS. In adolescent inpatients, APSS was associated with more co-morbid disorders (2.7 ± 1.0-/2.2 ± 1.3), major depressive disorder (61.9%/27.9%), oppositional defiant disorder/conduct disorder (52.4%/25.0%), and personality disorder traits (57.1%/7.4%). APSS youth were more severely ill having higher SIPS total positive, negative and general symptoms, depression and global illness ratings, and lower global assessment of functioning (GAF). In multivariable analysis, lowest GAF score in the past year (odds ratio (OR) = 51.15 (95% confidence interval(CI) = 2.46-2439.0) and social isolation (OR = 27.52 (95%CI = 3.36-313.87) were independently associated with APSS (r2 = 0.302, $P < 0.0001$). Although psychotic disorders were excluded, 65.2% (APSS = 57.1%, non-APSS = 67.7%, $P = 0.38$) received antipsychotics.
In the age-mixed sample of help-seeking individuals, in addition to higher ratings of several symptom domains in APSS+ individuals, APSS-status was associated with suicidality, and younger age (18.3 ± 5.0 vs. 23.2 ± 5.9 years, $P < 0.0001$). The prevalence of APSS was highest in adolescents (68.8% in 13-17 year-olds) compared to 24.7% in 23-35 year-olds (OR = 0.22) (95%CI = 0.13-0.38). Within APSS+ individuals, significantly fewer adolescents fulfilled combined risk criteria of APSS+/BS+ or APSS+/COGDIS+ compared to the older age groups.
Conclusions: In adolescent inpatients, APSS youth were more impaired, showing a complex entanglement with a broad range of psychiatric symptoms and disorders, including depression, impulse-control and, especially, emerging personality disorders.
In the sample of help-seeking individuals, the high prevalence of APSS and the infrequent co-occurrence of APSS+/COGDIS+ in adolescents compared to older age groups may point to a higher proportion of non-specific or transient, rather than risk-specific attenuated positive symptoms in adolescents. Longitudinal studies, underway with the two presented cohorts, are expected to shed further light on the predictive value of the APSS in adolescence for the future development of psychosis.

S19.2 Differentiation between the prodrome to schizophrenia-spectrum and bipolar-spectrum disorders: can we separate clinical high-risk states?

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Background: Schizophrenia and bipolar disorder are among the most debilitating psychiatric disorders. Currently available management options are still too often insufficient. Long treatment delays and the inability to effectively and safely delay/prevent the full disorder preclude effective targeted and early secondary prevention. Moreover, heterogeneity of psychosis and affective spectrum disorders with genetic and phenomenological overlap complicate the conceptualization, measurement and effective early intervention during the clinical high-risk or "prodromal" stage and first episode phase of schizophrenia-spectrum and bipolar-spectrum disorders. Early identification and, ideally, early secondary prevention are preeminent goals.
Methods: We administered the Bipolar Prodrome Symptom Scale-Prospective (BPSS-P), a semistructured interview and rating scale, to 80 individuals who were initially identified as clinical high-risk (CHR) for psychosis based on the presence of at least one moderate severity attenuated negative or attenuated positive symptom on the Scale of Prodromal Syndromes and to 33 healthy controls (HC). Presence of moderate severity attenuated mania symptoms, including mood elevation or irritability plus at least one other item on the mania scale of the BPSS were used to differentiate those who may be at clinical high-risk for mania (CHR-M) from those who may be at risk for schizophrenia (CHR-SZ).
Results: The CHR-M group scored significantly higher on all individual BPSS mania items, the total mania symptom score and the total general symptom score compared to the CHR-SZ and HC groups, respectively, whereas the two CHR groups had comparable scores on the total depression symptom score. The two CHR groups did not differ on total attenuated positive or negative symptom severity, or on global functioning scores. However, the CHR-M group scored significantly higher on mania specific measure than the CHR-SZ and HC groups, respectively.
Conclusions: There are clear methodological and practical complications in characterizing and operationalizing high-risk status for bipolar disorder and differentiating it from the much more defined high-risk status for schizophrenia-spectrum disorders. Compared to the schizophrenia clinical high-risk state, the bipolar high-risk state is complicated by the following features: episodicity; high degree of antecedent and comorbid psychiatric conditions; depression both as an independent disorder; precursor or illness component; frequency of mood disturbances in adolescence; combination of A and B criteria with partial overlap with other psychiatric conditions; the requirement of 4 or 5 concurrent symptoms for a diagnosis of mania; and psychosis as a potential outcome with bipolar disorder. The BPSS-P may help to differentiate individuals at CHR for bipolar disorder from those at CHR for schizophrenia. While the results suggest the presence of attenuated mania symptoms that may be specific to the bipolar prodrome, the thresholds for the severity and number of attenuated mania-like symptoms need to be determined by prospective studies.

S19.3 Illness course and outcome in early onset schizophrenia: a nationwide Danish register case-control study

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Background: To assess psychiatric outcomes of schizophrenia in a Danish cohort of patients with early onset schizophrenia (EOS, < 18 years of age) and adult onset schizophrenia (AOS).
Methods: Cases included all patients i) aged 0-40 years, and with ii) a first-episode of ICD-10 defined schizophrenia (F20.x) in the Danish Psychiatric Central Research Registry, iii) ≥ 1 psychiatric hospitalization with schizophrenia; and iv) diagnosed during the years 1996-2012. Patients were split into EOS and AOS groups. The control sample was randomly selected from the registry of all Danish citizens and sampled at the time when cases received a first-episode schizophrenia

diagnosis. In addition, controls were age-matched and without a schizophrenia diagnosis, but could have other psychiatric diagnoses. The cases were both compared to each other (AOS vs EOS) and each compared to age-matched controls in order to analyze the effect of age of onset on the outcome. Primary outcomes were number of days in psychiatric inpatient treatment (bed days). Secondary outcomes included psychiatric hospitalizations and death. In addition, diagnostic data were linked to other Danish registers containing social and health-related data. Data were analyzed descriptively and with linear regression models, adjusting for duration of follow-up.
Results: Altogether, a total of 11,925 patients with schizophrenia and 44,912 controls were included. 941 patients had EOS (7.9%). Patients were followed in the registers for a mean of 8.3 years after first-episode schizophrenia (EOS = 7.1 ± 4.6 years vs. AOS = 8.4 ± 4.9 years), controls for 8.6 ± 5.0 years. The EOS group contained significantly less males than the AOS group (45.9% vs. 63.8%, $P < 0.001$). Mean age at first-episode schizophrenia was 26.6 ± 6.6 (EOS = 16.5 ± 2.9 vs. AOS = 27.4 ± 6.1).
Using crude analysis, the total number of bed days were 411.8 ± 534.3 for cases and 3.6 ± 42.9 for controls ($P < 0.001$). EOS and AOS did not differ significantly (EOS = 406.4 ± 527.1 vs. AOS = 412.3 ± 535.0, $P = 0.75$). Cases had on average 10.6 ± 15.3 admissions, whereas age-matched controls had 0.14 ± 1.7 ($P < 0.001$). Again AOS and EOS did not differ significantly (EOS = 10.3 ± 16.4 vs. AOS = 10.6 ± 15.3, $P = 0.48$). During follow-up, EOS and AOS had similar number of admissions for schizophrenia (EOS 6.7 ± 9.8 vs. AOS 6.9 ± 10.6, $P = 0.65$) as well as bed days (EOS 318.8 ± 468.2 vs. AOS 316.9 ± 460.8, $P = 0.90$). When adjusting for follow-up duration from diagnosis, EOS had 0.4 more admissions than AOS (95% CI -0.37-1.1, $P = 0.24$) and 38.3 more bed days (95% CI -9.1-67.6, $P < 0.05$).
Both EOS and AOS had a 6.5-fold increased risk of death during follow-up compared to the age-matched controls ($P < 0.001$). Results for additional outcomes will be available at the time of the meeting.
Conclusions: Patients with schizophrenia have on average over 100 times more bed days and psychiatric admission compared to age-matched controls. Controlling for follow-up duration, EOS patients had significantly more psychiatric bed days than AOS patients. Both groups had significantly poorer outcome and higher risk of death than age-matched controls.

S19.4 Antipsychotic treatment for children and adolescents with schizophrenia spectrum disorders: a systematic review and network meta-analysis

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Background: Few randomized controlled trials (RCTs) have investigated the treatment with antipsychotic drugs in early-onset schizophrenia (EOS, onset < 18 years). Especially, head-to-head studies comparing different antipsychotics are sparse. Network meta-analysis (NMA) offers a tool for expanding the evidence base by combining direct and indirect trial data.
The objective was to determine the comparative effectiveness in terms of relative efficacy and safety of antipsychotic drugs used in EOS.
Methods: Data Sources: We performed a systematic search of MEDLINE, the Cochrane Library, and Clinicaltrials.gov.
Study selection: RCTs allocating children or adolescents with schizophrenia spectrum disorders to an antipsychotic drug or to a comparator group (placebo or another antipsychotic drug). Data Extraction and Synthesis: Independent reviewers extracted study data and assessed risk of bias. Network (random effects) meta-analysis was applied using the change from baseline in the trials, and results for the arm-based network analyses were analyzed and interpreted as standardized mean differences (SMDs).
Main outcomes and measures: For benefit, improvement in schizophrenia symptoms, and for harm occurrence of weight gain, plasma-triglyceride increase, extra-pyramidal symptoms (EPS), akathisia, and frequency of discontinuation.
Results: Twelve 6-12 weeks trials (2,157 participants with schizophrenia-spectrum disorders, age range = 8-19 years, 61% males), covering treatment with 8 antipsychotics (aripiprazole, asenapine, paliperidone, risperidone, quetiapine, olanzapine, molindone, ziprasidone) were included in the analysis. Among drugs, benefits assessed on the Positive and Negative Syndrome Scale scores were comparable, except for inferiority of ziprasidone. Reduction on the Clinical Global Impression (CGI) – Severity score was greater for olanzapine compared to aripiprazole and asenapine. There were no differences among drugs on beneficial outcomes, such as CGI-improvement score, response rates, depressive symptom reduction or global/social function improvement. Weight gain was primarily associated with olanzapine. EPS and akathisia were primarily associated with molindone.
Conclusions: The NMA proved useful in adding data on drugs that have not been compared to an active comparator or placebo in RCTs. Comparative effectiveness evaluation focusing on the "least harm" principle combined with at least moderate effect found that ziprasidone had limited or no effect, molindone was inferior with respect to EPS and akathisia, and olanzapine had an unfavorable profile regarding weight gain. This leaves aripiprazole, asenapine, paliperidone, quetiapine and risperidone as potential first line agents. However, each of these antipsychotics was still associated with significant levels of different side effects.

S20. Characterizing a putative "traumagenic" subtype of psychosis

S20.1 Childhood events and psychosis in bipolar affective disorder

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Background: There has been increasing interest in the association between childhood trauma and psychosis. Proposals for potential mechanisms include affective dysregulation and cognitive appraisals of threat, yet few large-scale clinical studies exist in affective psychosis.
We hypothesise that within bipolar disorder (BD), childhood events will show a significant association with psychosis, and in particular with symptoms driven by dysregulation of mood or with a persecutory content.
Methods: 2019 participants were recruited as part of our programme of research into the genetic and non-genetic determinants of BD (www.bdrn.org). Data on lifetime ever presence of psychosis and specific psychotic symptoms were determined by detailed structured interview with case note review. Childhood events were recorded after self-report questionnaire and case note information.
Results: There was no relationship between childhood events, or childhood abuse, and psychosis per se. Childhood events were not associated with an increased risk of persecutory or other delusions. Significant associations were found between childhood abuse and auditory hallucinations, strongest between sexual abuse and mood congruent or abusive voices. These relationships remain significant even after controlling for lifetime ever cannabis misuse.
Conclusions: Within affective disorder, the relationship between childhood events and psychosis appears to be relatively symptom-specific. It is possible that the pathways leading to psychotic symptoms differ, with delusions and non-hallucinatory symptoms being influenced less by childhood or early environmental experience.

S20.2 Trauma and transition to psychosis in the ultra high risk population: results from a long term follow up study

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Background: Studies indicate a high prevalence of childhood trauma in patient cohorts with established psychotic disorder and in those at

risk of developing psychosis. A causal link between childhood trauma and development of psychosis has been proposed. We aimed to examine the association between experience of childhood trauma and the development of a psychotic disorder in a large "Ultra High Risk"(UHR) for psychosis cohort.
Methods: The data was collected as part of a longitudinal cohort study of all UHR patients recruited to research studies at the PACE clinic between 1993 and 2006. Baseline data was collected at recruitment to these studies. The participants completed a comprehensive follow-up assessment battery (mean time to follow-up, 7.5 years, range 2.4 to 14.9 years), which included the Childhood Trauma Questionnaire (CTQ), a self-report questionnaire that assesses experience of childhood trauma. The outcome of interest was transition to a psychotic disorder during the follow-up period.
Results: Data was available on 233 individuals. Total CTQ trauma score was not associated with transition to psychosis. Of the individual trauma types, only sexual abuse was associated with transition to psychosis ($P = 0.02$). The association remained when adjusting for potential confounding factors. Those with high sexual abuse scores were estimated to have a transition risk 2-4 times that of those with low scores. Sexual abuse scores tended to be higher in those who developed a non-schizophrenia like psychotic disorder.
Conclusions: The findings suggest that sexual trauma may be an important contributing factor in development of psychosis for some individuals. We further investigated whether this association was mediated by depression, anxiety, dissociation, manic symptoms or mood swings. None of the potential mediators (assessed by the HAM-D, HAM-A and the CAARMS symptom scales) significantly mediated the total association between sexual abuse scores and transition. At the point of transition, the mechanistic pathway from sexual trauma to psychosis does not appear to operate through affective symptoms.

S20.3 Trauma, stress reactivity and prediction of outcome in the ultra high risk population: data from the neurapro-e study

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Background: Recent years have witnessed renewed interest in the relationship between psychosis and trauma, such as childhood sexual, physical and emotional abuse. While studies indicate an association between history of childhood trauma and psychotic disorders, the nature of this relationship remains controversial due to methodological limitations of the studies, including inconsistencies around definition and measurement of trauma, the cross sectional design of most studies, difficulties with choosing adequate control groups and the lack of incorporating putative mediating or moderating variables. The ultra high risk for psychosis (UHR) population is particularly valuable in the investigation of the relationship between childhood trauma, HPA axis dysfunction, post-traumatic intrusions, stressful life events and psychotic symptoms. First, this population allows for the prospective investigation of the development of frank psychotic symptoms (hallucinations, delusions, thought disorder) in relation to childhood trauma and post-traumatic intrusions. Second, it allows researchers to use a control group (UHR patients who do not develop psychotic disorder) that matches the experimental group (UHR patients who do develop psychotic disorder) in almost all variables apart from presence or severity of traumatic events.
Objectives, This study aimed to: 1. Assess the prevalence of traumatic events in the UHR population. 2Assess whether a history of traumatic events predicts outcome (transition to psychotic disorder, lack of remission of symptoms and poor functioning) in the UHR population. 3. Investigate the relationship between a history of childhood trauma, HPA axis dysfunction, stressful life events and vulnerability to develop psychotic symptoms in the UHR population.
Methods: This study collected data from the international Neurapro-E trial of omega-3 polyunsaturated fatty acids (PUFAs) in the UHR population. 304 UHR participants were randomised to PUFA+cognitive behavioral case management (CBCM) versus placebo+CBCM for 6 months with the primary outcome being transition to psychotic disorder at the end of the 6 month treatment period. The trauma and stress measures consisted of: history of childhood trauma (CTQ), post traumatic stress disorder symptoms (IES-R), attributional style (IPSAQ), daily stress (the "Hassles" scale), and morning saliva samples for cortisol analysis.
Results: Of the 304 participants, 96 (32%) provided data relating to this trauma and stress study. Participants are currently being followed up for various medium-term outcomes (2 years +). Data is currently being analysed and will be presented at the conference.
Conclusions: This is a valuable data set in which to investigate the relationship between childhood trauma, neuroendocrine function, post-traumatic intrusions, stressful life events and emergence of psychotic symptoms, overcoming some of the methodological limitations of previous reports.

S20.4 Interplay between childhood victimisation and familial liability in the persistence of psychotic symptoms during adolescence

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Background: Psychotic symptoms are reported by approximately 1 in 20 children and increase the risk of developing clinically-relevant psychosis in adulthood, especially when these symptoms persist. Developing a better understanding of what predicts persistence is crucial to identify children with the highest risk in order to effectively target preventive interventions. Initial studies suggest that early exposure to victimisation may increase the likelihood of psychotic symptoms persisting. However, such associations may be explained by genetic factors influencing exposure to such risky environments or increasing sensitivity to the detrimental impact of victimisation. Therefore, using a large prospectively assessed birth cohort, we investigated the interplay between various forms of childhood victimisation and family psychiatric history (a proxy for genetic risk) in predicting the persistence of psychotic symptoms during adolescence.
Methods: Data on 4724 children were drawn from the UK Avon Longitudinal Study of Parents and Children (ALSPAC). Mothers reported on children's exposure to physical abuse, sexual abuse and domestic violence in early childhood, and children self-reported on bullying victimization prior to 8.5 years. Parents reported on occurrence of depression and schizophrenia amongst family members during pregnancy and in the initial 4 years after birth of the study child. Children were interviewed regarding psychotic symptoms at 12 and 18 years of age.
Results: All forms of childhood victimisation were associated with persistence of psychotic symptoms from 12 to 18 years of age. However, family psychiatric history was associated with both reported exposure to victimisation and symptom persistence, indicative of a proxy gene-environment correlation. Nevertheless, adjusting for familial liability did not measurably impact on the victimisation-persistence associations and no proxy gene-environment interactions were found.
Conclusions: Reported exposure to victimisation in childhood increased the likelihood of psychotic symptoms persisting through adolescence, independent of proxy genetic risk for relevant psychiatric disorders. These findings tentatively suggest that interventions should be focused on young adolescents experiencing psychotic symptoms who have a history of direct or indirect exposure to victimisation in order to prevent the problematic persistence of these symptoms and potentially avert later development of clinically-relevant psychosis.

S21. NMDAR antibodies and their relevance for schizophrenia

S21.1 Antibodies to neuronal cell surface antigens in psychiatric disease

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Background: Antibodies to voltage-gated potassium channel complexes were first found in acquired neuromyotonia, a condition caused by peripheral nerve hyperexcitability that leads to muscle fasciculations, muscle cramps and pain. Subsequently, the same antibodies were identified in patients with Morvan's syndrome and then in subacute-onset of limbic encephalitis. The potassium channel antibodies are now known to be directed at other proteins that are complexed with the channels in situ, such as LGI1 and CASPR2. These proteins help localise (CASPR2) and modify (LGI1) potassium channel function, and the antibodies bind to extracellular epitopes and are pathogenic in vitro. CASPR2 antibodies are most frequent in rare Morvan's syndrome which has been misdiagnosed as schizophrenia, and some patients with limbic encephalitis present with psychosis. LGI1 antibodies are common in limbic encephalitis.
Methods: Since 2007, 100 s of patients have been identified with a more complex form of encephalopathy and antibodies to NMDA receptors (NR1 principally). These are mainly younger women and children and present with predominant psychiatric features and movement disorders. Ovarian teratomas are common in the adult females but rare in the children.
Results: Each of these diseases shows a very good respond to immunotherapies such as steroids, plasma exchange and intravenous immunoglobulins. If the response is poor, second line therapies such as rituximab and/or cylclophosphamide are helpful. Some require longer term immunosuppression with azathioprine or mycophenolate.
Conclusions: Because of the psychiatric presentations in many of these patients, there have been a number of cohort studies published looking for antibodies to these proteins in patients with psychiatric disease particularly schizophrenia or first episode psychosis. The assays used have been variable, and the results are not yet consistent between different cohorts. Nevertheless, it is quite clear that some individual patients present with predominantly psychiatric features, have antibodies to neuronal surface proteins and may respond well to immunotherapies.

S21.2 Clinical phenotype of patients with NMDAR antibodies

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Background: Autoantibodies to neuronal cell surface receptors and related proteins have been described in association with encephalopathy syndromes that frequently feature psychiatric symptoms, usually psychosis, as a prominent part of the phenotype. Following the initial recognition that these syndromes can cause psychosis as part of a wider encephalopathic picture there has been considerable interest within psychiatry in the question of whether these autoantibodies may be associated with psychotic symptoms within psychiatric patient groups such as those diagnosed with a first episode of psychosis or, more chronically, with schizophrenia-spectrum disorders. We aimed to provide a definitive estimate of the prevalence of cell surface autoantibodies in patients presenting to first episode psychosis services in the UK compared to an age-, gender- and ethnicity-matched group of healthy controls.
Methods: 37 sites across England recruited a total of 230 patients experiencing their first episode of psychosis. Inclusion criteria consisted of anyone between 14 and 35 years of age, less than 6 weeks on antipsychotic medication. 105 Control participants were age, gender and ethnicity matched. All patients and controls gave a blood sample. We undertook clinical and cognitive assessments using PANSS, GAF, ACE-III, Catatonia rating scale. Sera were tested, blind to group. In Oxford on the NMDAR-ab live cell-based assay
Results: 2.6% first episode patients were positive for NMDAR antibodies, none of the controls were positive. Of the other antibodies tested, 7.4% patients were positive for VGKC (voltage gated potassium channel) antibodies, 3.5% at a high level (above 400 pmol/l) and 3% of patients were positive for ANA antibodies above the threshold of 1/160, none of which were positive for additional antibodies. 3.8% of controls had low levels of VGKC antibodies; 8.6% of controls were positive for ANA antibodies. Analyses were carried out to compare antibody positive and negative patients on measures of clinical presentation (PANSS), functioning (GAF) and cognition (ACE-III). Independent samples Mann Whitney-U test found no significant difference between positive and negative patient groups on any clinical or cognitive measure.
Conclusions: We have replicated our previous study and demonstrated that 6.1% of patients with a first episode of psychosis have a level of antibodies to either the NMDAR or VGKC receptor that may be clinically relevant. However there are no distinguishing clinical characteristics in the patients positive for antibodies, indicating that all patients with first episode of psychosis should be tested for these antibodies.

S21.3 Impact of anti-NMDA receptor autoantibody from schizophrenic patients on membrane receptors using single molecule imaging

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Background: The flourishing identification of circulating autoantibodies against neuronal receptors in neuropsychiatric patients has fostered new conceptual and clinical frameworks. At the same time, their detection in multiple neurological and psychiatric disorders, as well as in case of healthy subjects, raised questions on their physiopathological mode of action and possible use as biomarkers.
Methods: Using single molecule and classical imaging approaches, we will here discuss recent findings obtained in live hippocampal neurons in which we explore the synaptic impact of purified autoantibodies against glutamate NMDA receptor (NMDAR-Ab) from schizophrenic patients and matched healthy controls.
Results: Although NMDAR-Ab IgG from schizophrenic patients and healthy subjects equally target membrane GluN1-NMDAR in live hippocampal neurons, only NMDAR-Ab from schizophrenic patients strongly, specifically (no impact on other related membrane receptors), and acutely (minute range) alters the dynamic organization of synaptic NMDAR and its direct membrane interactor, EphrinB2 receptor.
Conclusions: We will thus argue that NMDAR-Ab are heterogeneous in their molecular pathogenicity, supporting a role of the pathogenic autoantibodies in "autoimmune psychosis" and calling for caution in using NMDAR-Ab as generic diagnostic biomarkers for neuropsychiatric disorders.

S21.4 Neurocognitive phenotype and imaging abnormalities of patients with NMDAR antibodies

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Background: NMDAR encephalitis belongs to a group of recently discovered autoimmune encephalitides associated with autoantibodies targeting neuronal surface antigens. Patients develop a severe neuropsychiatric clinical picture with anxiety, agitation, hallucinations, delusion as well as dyskinesias, epileptic seizures, hypoventilation and decreased levels of consciousness. Cognitive deficits are a further hallmark of the disease and mainly include profound amnesia, executive dysfunction and attentional deficits. Severity of these deficits correlates with the delay of immunotherapy initiation and the deficits persist in the majority of patients despite an otherwise remarkably good recovery. The disease is furthermore characterized by a clinico-radiological paradox, i.e., normal cerebral routine MRI results despite the severe clinical presentation. However, advanced imaging techniques have recently identified characteristic abnormalities in patients with NMDAR encephalitis.
Methods: We have undertaken multimodal imaging in the largest cohort of patients with NMDAR encephalitis studied to date, including structural and functional MRI.

Results: Resting state functional MRI analyses identified reduced functional connectivity of the hippocampus with the anterior default mode network that correlated with the patients' memory performance. Diffusion tensor imaging revealed extensive white matter changes, which were most prominent in the cingulum and correlated with disease severity. Further analyses showed pronounced structural hippocampal damage with bilateral atrophy of the input and output regions of the hippocampal circuit and impaired hippocampal microstructural integrity; both measures likewise correlated with memory performance and disease severity and duration.
Conclusions: After introducing the cognitive deficits and neuroimaging characteristics of NMDAR encephalitis, this talk will contrast these findings with observations in other autoimmune encephalitides and will furthermore explore similarities of clinical presentation, cognitive deficits and imaging characteristics with observations in schizophrenia.

S22. Negative symptoms - integrating clinical and neuroimaging perspectives

S22.1 Progressive brain changes associated with persistent negative symptoms following a first episode of psychosis

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Background: Negative symptoms have been strongly linked to a poorer functional outcome in both enduring schizophrenia and early psychosis. Several studies examining the association with neuropsychological measures have repeatedly observed a significant link between verbal memory impairment and negative symptoms severity. As part of a one-year longitudinal neuroimaging study in first episode psychosis, we examined the volume of medial temporal lobe regions known to play a key role in memory functions. We hypothesized that patients presenting with persistent negative symptoms (PNS) will show smaller volume of those regions relative to non-PNS patients.
Methods: Overall, 101 patients with a first episode of psychosis (FEP) had a scan at baseline and 75 had a 1-year follow-up scan. Following the PNS definition (moderate to severe presence of negative symptoms for six month combined with low levels of positive, depressive and extrapyramidal symptoms), patients were separated between PNS and non-PNS groups. A first group ($n = 79$) included patients with PNS ($n = 28$) and the other group ($n = 73$) included patients without PNS. All participants were assessed on an exhaustive neuropsychological battery that included a measure of episodic verbal memory at baseline. They were also canned twice (baseline, 1-year) on a 1.5 T MRI and differences in parahippocampus and hippocampal volumes were estimated by FreeSurfer. Finally, a group of 146 healthy controls provided normative neuropsychological data.
Results: Data from the healthy controls were used to transform the patient data into z-scores. At the behavioral level, patients with PNS significantly performed worst (z = -1.54) than non-PNS patients ($P < .001$) on verbal memory measure. At the brain level, Compared to the non-PNS patients, those with PNS had a significantly smaller parahippocampal volume ($P = 0.021$) but did not differ in hippocampal tail volume ($P = 0.424$). Finally, there was a significant decrease in right PHC volume in the PNS patients over the one year follow-up period ($P = 0.002$) with a trend-level decrease on the left ($P = 0.085$).
Conclusions: This study provides evidence that patients with a first episode of psychosis who experience PNS early on, exhibit significant verbal memory impairments and those seem to selectively relate to volume of the parahippocampal gyrus at baseline. Moreover, our longitudinal study revealed a progressive volume decrease in that same region in the PNS group. These results provide evidence that patients with PNS represent a distinct clinical group at the behavioral and brain levels and as such. Considering the progressive nature of brain changes observed, these negative symptoms should be the target of psychosocial, pharmacological or somatic interventions early on to prevent such brain loss.

S22.2 The impact of negative symptom domains on real-life functioning of people with schizophrenia and first-degree relatives

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Background: Recent literature suggests that the two negative symptom factors "Avolition" and "Expressive Deficit" (ED) have a different impact on patients' functional outcome and reflect different pathophysiological mechanisms.
Methods: In a large multicenter study of the Italian Network for Research on Psychoses, the impact of illness-related variables (including Avolition and ED assessed by the Brief Negative Symptom Scale), personal resources and context-related factors on real-life functioning was modeled by using a structural equation model in 921 patients with schizophrenia living in the community. A similar model was tested in 383 non-affected first degree relatives. Neural bases of avolition were investigated in an fMRI study involving 28 schizophrenia subjects living in the community and treated with second generation antipsychotics only. Apart from the factors Avolition and ED, the Heinrichs Quality of Life index of Motivation was used. Brain activation was studied during a Monetary Incentive Delay task.
Results: In the study of the Italian Network for Research on Psychoses Avolition, but not ED, showed a strong association with functional outcome in both patients and their first-degree relatives. The association was both direct and indirect; the latter one was mediated by Resilience and Internalized stigma. In the fMRI study the activity of the dorsal caudate during reward anticipation was significantly associated with real-life motivation and avolition. No relationship of ED with striatal activity was found.
Conclusions: In a large sample of people with schizophrenia living in the community avolition showed a significant impact on functional outcome. A dysfunction of the dorsal striatum might be involved in the pathophysiology of avolition.

S22.3 The neural basis of distinct negative symptom dimensions in schizophrenia

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Background: The negative symptoms of schizophrenia can be separated into two factors - apathy and diminished expression. This division is of particular interest, because different pathophysiological mechanisms might underlie these factors. We conducted two functional magnetic resonance imaging experiments to specifically address the relationship of apathy and diminished expression with reward processing and reward-cognition interaction.
Methods: 27 patients with schizophrenia treated with atypical antipsychotics and 25 control subjects participated in the study. The primary symptom ratings were conducted with the Brief Negative Symptom Scale. For assessment of reward anticipation subjects performed a variant of the monetary incentive delay task. Reward-cognition interaction was investigated with a n-back working memory task including financial incentives.
Results: In patients with schizophrenia activation of the ventral striatum was negatively correlated with apathy (r = -.47, $P = .01$), but not with diminished expression (r = -.001, $P = .97$). These correlations were significantly different from each other according to Steiger's Z-Test. In contrast, in the reward-cognition interaction ACC activation in patients was significantly correlated with diminished expression (r = -.39, $P = .03$), but not with apathy (r = -.01, $P = .94$). Again these correlations were significantly different from each other. All of these results remained significant when controlling for antipsychotic dose, cognitive impairment and depressive symptoms.
Conclusions: We believe that these findings represent the first evidence for a double dissociation of apathy and diminished expression on a neural level. Apathy is specifically associated with reduced activation of the ventral striatum during reward anticipation, while diminished expression is specifically associated with ACC activation during reward x cognition interaction. Thus, our data support the notion that different pathophysiological mechanisms underlie the two negative symptom dimensions and might have to be

addressed separately when developing treatment approaches to negative symptoms.

S22.4 New clinical and neuroimaging investigations of real-world motivation deficits in schizophrenia in the context of virtual reality assessments

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Background: Motivation deficits are a central feature of the negative symptoms of schizophrenia, and are linked to the significant functional impairment experienced by individuals with the illness. Effective treatments, however, for these motivation deficits remain elusive. In efforts to advance our understanding of specific motivation deficits that may inform treatment development, we utilized novel virtual reality-based strategies to examine real-world effortful behavior and goal-directed action planning, combined with structural and functional neuroimaging to investigate the neurobiological correlates of these deficits.
Methods: Stable outpatients between 18 and 55 years old with schizophrenia (SZ) and matched healthy controls (HC) were recruited for these studies. All participants underwent clinical and neurocognitive assessments, and evaluations of real-world effortful behavior and goal-directed action planning. Participants subsequently underwent functional MR imaging while performing a virtual reality progressive ratio (ViPR) task to evaluate effortful behavior, as well as structural MRI and diffusion tensor imaging.
Results: 107 participants (50 SZ and 57 HC) underwent clinical and computerized assessments of effortful behavior and goal-directed action planning, with 38 participants (19 SZ and 19 HC) subsequently undergoing MR imaging. Clinical findings revealed significant impairments in effortful behavior in SZ patients, as well as impaired activation in the dorsolateral prefrontal cortex (DLPFC), supplementary motor area (SMA), inferior frontal gyrus, anterior cingulate (ACC), and dorsomedial prefrontal cortex (dmPFC) compared to HCs. Moreover, effortful behavior was significantly correlated with right DLPFC and left putamen activity. Impaired effortful behaviour was also correlated with deficits in white matter microstructural integrity in the cingulum bundle and superior longitudinal fasciculus. SZ participants also evinced clinical impairments in real-world goal-directed action planning and execution that was significantly correlated with white matter microstructural integrity in the uncinate, inferior fronto-occipital, and superior longitudinal fasciculi.
Conclusions: Across a series of clinical and neuroimaging investigations using novel virtual reality-based assessments of specific aspects of motivation we identified significant impairments in both effortful behavior and goal-directed action planning and execution. Our neuroimaging findings suggest that functional impairments in key reward brain regions underlie the clinical deficits in effortful behaviour seen in SZ. In addition, there appeared unique structural brain correlates of effortful behavior and goal-directed action planning. These findings provide insights into the neurobiology of impaired real-world motivation in schizophrenia, and may offer potential targets for novel therapeutic brain intervention strategies to treat motivation deficits in schizophrenia.

S23. The role of development and stage of psychotic illness on characteristics of longitudinal neurocognitive functioning

S23.1 Cognitive and functional outcome in early-onset schizophrenia: 13- and 20-year follow-up

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Background: Early Onset Schizophrenia (EOS) is rare and of substantial interest, since studies of these patients provide insight into the development of the disorder. Prospective, longitudinal, multi-assessment studies of the same individuals with EOS are rare in the field and provide a unique opportunity to examine long-term changes. By identifying early predictors of later disabilities, early treatments may alter morbidity and mortality.
Methods: The main aim of the study was to investigate cognitive function in children aged 12-18 years with EOS)($n = 15$) compared to children with ADHD ($n = 19$) and healthy controls ($n = 30$) in a longitudinal design over 13 years and 20 years. Another aim was to investigate if cognition at baseline was related to measures of functional outcome 13 years and 20 years later. The individuals were retested with the same comprehensive cognitive test battery as used at baseline, and also reassessed with various symptom and behavior ratings and functional outcome measures.
Results: Individuals with EOS showed a significant decline or arrest in cognition after 13 years compared with the other 2 groups, particularly in verbal memory, attention, and processing speed. Executive function, memory and attention were related to social and community functioning in individuals with EOS. For the individuals with ADHD no significant predictions were found although functional outcome was poor.
Conclusions: These results stand in contrast to the stability of cognitive functioning reported in the majority of longitudinal neurocognitive studies in adults with schizophrenia. The impairments found in the current study may be specific to individuals with EOS due to interaction between ongoing brain maturation during adolescence and disease-related mechanisms and/or secondary to neuroleptic treatment in young age and/or social isolation. For both clinical groups treatment should focus on training of social skills and activities of daily living to enhance the long-term functional outcome. For the individuals with EOS cognitive remediation should also be considered. Preliminary results from an ongoing 20-year follow-up study of the same study groups will also be presented and discussed. In the late twenties the cognitive functions are supposed to be fully matured. If there is a decline in cognition in EOS from baseline to 13-year follow-up but no decline between 13-year to 20 year follow-up, the decline documented at 13-year follow-up may support the hypothesis of a progressive pathological process in maturation of the frontal lobe during adolescence. However, if the cognitive decline continues when the individuals with EOS are in their thirties, it may indicate a more general degenerative process in EOS. To address these questions, a prospective longitudinal design of long duration with several sampling time points is necessary.

S23.2 Cognitive profile and cognitive recovery after a first episode of adult-onset schizophrenia: one-year longitudinal study

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Background: Cognitive deficits are well established by the first psychotic episode in adult-onset schizophrenia and are maintained over the course of schizophrenia. The profile of cognitive deficit and the extent of cognitive recovery following a first episode remains unclear, as cognitive tests in batteries used in longitudinal studies have usually not been previously co-normed on community samples.
Methods: In a 12-month longitudinal study of 71 first episode adult-onset schizophrenia patients treated at the UCLA Aftercare Research Program, the MATRICS Consensus Cognitive Battery (MCCB) was administered at a stabilized outpatient baseline point and 6 and 12 months later. Relapse, hospitalization, and functional outcome were also evaluated.
Results: A MANOVA with repeated measures indicated significant cognitive domain and time main effects and a significant cognitive domain X time interaction. At each of the three assessment points, speed of processing, attention/vigilance, and visual learning were the cognitive domains with the most severe deficits relative to community norms. The overall cognitive composite score improved over time, particularly in the first 6 months. Significant improvements over the first outpatient year were observed in speed of processing, verbal learning, visual learning, and reasoning and problem solving, but not in attention/vigilance, working memory, or social cognition. At the one-year point, cognitive deficits remained 0.74 to 1.33 SDs below community norms across domains. One-year test-retest correlations

were high across domains (r = .66-.85) and very high (r = .91) for the overall composite score. Neither relapse nor hospitalization significantly predicted the amount of overall cognitive improvement over one year, but the magnitude of cognitive improvement was significantly related to the improvement in role functioning over the year.
Conclusions: These results indicate that certain cognitive deficits after onset of adult-onset schizophrenia show partial recovery over a 12-month outpatient treatment period, while remaining strongly correlated with the level of cognitive impairment observed at a stabilized baseline point. Only two of the four cognitive domains that show partial recovery during this period are ones for which deficits were most severe at baseline, nor is the pattern accounted for by known practice effects for the cognitive tests in the MCCB. The extent of cognitive recovery over the year was significantly associated with the amount of improvement in role functioning, supporting with longitudinal change data the view that cognitive deficits are likely contributors to everyday functional recovery in the initial course of schizophrenia.

S23.3 Neurocognition and duration of psychosis before and after start of treatment: what predicts the course of schizophrenia?

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Background: Neurocognitive impairment and the course of neurocognitive functioning may be important in understanding the pathogenesis of schizophrenia. A substantial proportion of schizophrenia-spectrum patients exhibit a cognitive impairment at illness onset. However, results concerning the long-term course of neurocognition diverge to a certain grade. Furthermore, it is of importance to find out what predicts the long-term course of neurocognition.
It has been proposed that being psychotic in itself has a toxic effect on the brain, and a substantial number of studies have addressed the neurotoxicity hypothesis. Duration of untreated psychosis (DUP), and accumulated time in psychosis after start of treatment, in particular the first period after start of treatment, is of interest to investigate to find out if it has an impact on the course of schizophrenia.
Methods: In the 10-year follow-up of participants in the TIPS study, 261 first-episode psychosis patients were assessed neuropsychologically on one or more occasions. Patients were tested after remission of psychotic symptoms and reassessed 1, 2, 5, and 10 years after inclusion (Barder *et al*, 2013; Rund *et al*, 2015). The neurocognitive battery consisted of California Verbal Learning Test, Wisconsin Card Sorting Test, Controlled Oral Word Association Task, Trail Making A and B, and Finger Tapping. We calculated a composite score by adding the z-scores of 4 tests that were only moderately intercorrelated, not including Finger Tapping.
DUP, duration of treatment after start of treatment, remission, and relapse were reliably defined and examined with regard to predictive value in relation to the course of neurocognition.
Results: Data were analyzed by a linear mixed model. The composite score was stable over 10 years. No significant relationship between psychosis before (DUP) or after start of treatment and the composite score was found. Stable remission during the first year predicted better neurocognitive functioning.
Conclusions: The results confirm what has been found in some previous studies, but of which only two had an equally long follow-up period as in the present study: There is great stability in neurocognitive functioning over time. This significantly weakens the assumption that schizophrenia is a neurodegenerative disorder. Further, the findings provide no support for the neurotoxicity hypothesis, and cast doubt on the assumption that the DUP is of crucial importance for the neurocognitive course and outcome in psychosis. However, stable remission during the first year predicted neurocognitive functioning, indicating that treatment response in the first year is a key variable, and that the early clinical course is a good predictor for the long-term course. Methodological imitations of this study are that there is no healthy control group, we had limited control over medication effects on neurocognition, and there was a large drop-out of patients. The strength of the TIPS study are that it is a large, clinical epidemiological sample, and that the participants have been followed over a very long time period with five assessments of the same neurocognitive domains.
References:
1. Barder *et al*. Front Hum Neurosci, 2013.
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S23.4 Neurocognitive functioning in the second phase of the North American prodrome longitudinal study

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Background: Neurocognitive dysfunction is a hallmark feature of schizophrenia and is evident across all phases of the illness. A growing body of research identifies neurocognitive impairment in individuals at clinical high risk (CHR) for psychosis especially in those who later develop psychosis. In this second phase of the North American Prodrome Longitudinal Study (NAPLS-2), we evaluated an extensive range of neurocognitive functions in the largest sample to date, to identify the core cognitive dysfunctions in the CHR state and those associated with transition to psychosis.
Methods: Participants were 689 CHR individuals (including 89 who transitioned to a psychotic disorder after baseline assessment) and 265 healthy controls from eight sites across North America administered a neurocognitive battery consisting of 19 tests at the baseline assessment, including the MATRICS Battery. CHR participants with testing were a mean age of 18.5 years at initial assessment (18.1 years for those who transitioned to psychosis). Factor analysis yielded four meaningful factors consisting of Executive Function/ Visual Planning, Verbal Abilities, Attention and Working Memory, and Declarative Memory. Individual tests were also evaluated. Multivariate analyses were carried out evaluating effects of group, medication, general cognitive ability and conversion status on cognitive functioning.
Results: Individuals at CHR were impaired in all dimensions compared to controls at a mild to moderate level, CHR participants who transitioned to psychosis were significantly more impaired compared to controls in Declarative Memory, and Attention and Working Memory, which had large effect sizes (hedges g > .80). Those who converted to psychosis were significantly more impaired in Declarative Memory than nonconverters. These impairments were not accounted for by general cognitive ability or medication status. Similar results were observed in never medicated participants. The profile of deficits in those who converted was inconsistent with a general deficit syndrome. Analyses are ongoing to evaluate change over time at one year in controls, converters and nonconverters
Conclusions: Neurocognitive impairment is a robust characteristic of the CHR group, especially in those who later develop psychosis. This could not be attributed to general cognitive ability or medication status. Both verbal and visual declarative memory and attention and working memory tests were most sensitive to the tendency to develop psychosis amongst those at CHR. These data suggest that the neurocognitive disorder of converters is independent of medication effects and while more severe than observed in premorbid periods, is less severe than observed in fully psychotic first episode individuals. Further analyses will identify potential change over time

S24. Duration of early intervention and the critical period

S24.1 Duration of early intervention and the critical period: insights from cohort and controlled studies from Hong Kong

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Background: The critical period hypothesis proposes that the outcome of psychotic disorders is largely determined within the first few (critical) years. This has provided a rationale for focusing intervention resources in the initial years to obtain the best possible outcome. Since 2001 Hong Kong has developed an early intervention program (EASY) which provided early psychosis case management to young patients with first episode psychosis between the ages of 15 and 25. Together with many intervention programs at the time, we adopted

an intervention for a period of 2 years following the initial episode. Whether 2 years is an optimal period was addressed subsequently by a randomised controlled study.
Methods: We randomised patients in the second year of the EASY service to either one more year of intervention (3 year all together), or to transition to standard care (2 years intervention followed by one year standard care). The primary outcome was functioning. We measured outcome using two different measurement scales at six months and one year following randomisation.
Results: Patients receiving an additional year of intervention continued to improve in functioning in the third year, while the functioning level of the control group remained unchanged from baseline.
Conclusions: We conclude that after two years, further improvements in outcome could still be enhanced with an additional year of intervention. We also found that in the third year, although not making further improvements, the outcome did not decline in those who had transited to generic care.

S24.2 A randomized controlled study of five vs. two years of specialized early intervention service

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Background: Specialized Early Intervention services (SEI) for first episode psychosis are more effective than regular care for the treatment of positive and negative symptoms, medication adherence, rates of relapse, substance abuse disorders, functional outcome and quality of life at two-year treatment follow up. However, follow up studies suggest that these benefits are not maintained when SEI is not sustained beyond 2 years. The objective of this trial was to test the efficacy of a 3-year extension of a SEI service (following 2 years of SEI prior to randomization for a total 5 year period) for the maintenance and consolidation of therapeutic gains as compared to regular care following 2 years of SEI.
Methods: Following an initial 2 years of SEI, patients were randomized to receive either 3-years of continued SEI or regular care. SEI was provided within the McGill University network of SEI services and comprised of: modified assertive case management; psycho education for families; multiple family intervention; cognitive behavioural therapy; and substance abuse treatment and monitoring. Blinded evaluations of patients in both conditions on all outcome variables were conducted every three months. The primary outcome measure was proportion of patients in full remission and the mean length of remission achieved in the final two years of follow-up post-randomization.
Results: A total of 220 patients were randomized to either extended SEI ($n = 109$) or to regular care ($n = 111$). Preliminary results based on all patients randomized suggest that a significantly higher proportion of patients dropped out in the regular care (control) compared to those in continued SEI (experimental) (51% vs 17.3%), respectively); a lower proportion of the control group completed at least 18 out of the 36 months of the study (49 vs 82%). Analyses on the primary outcome measures as well as some secondary measures (e.g., functional outcome) for the entire data set will be completed in Dec 2015 and will be presented as part of the symposium.
Conclusions: The "critical period" hypothesis posits that within a five year window the effects of the nascent psychotic illness can be countered and the impact of the disorder on symptomatic and functional outcomes can offset through active and sustained SEI. Our findings suggest that providing SEI throughout this critical may facilitate gains to be sustained over time as compared to intervention delivered for a shorter period (2 years) followed by regular care. Findings from this study have implications for service provision in first episode psychosis. Challenges of transferring patients to regular care will also be discussed.

S24.3 How long should early intervention last? Results from a randomized clinical trial of the effect of five-years versus two-years specialized assertive intervention for first episode psychosis – the OPUS-II trial

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Background: Since the discovery of anti-psychotic treatment, development of specialized, assertive programs involving families represents the most significant progress in treatment. The Danish OPUS I trial was the largest trial in first-episode psychosis in the world. The OPUS I trial found that it was possible to improve clinical outcome in first episode psychosis through a specialized early intervention service (SEI). However, the five-year follow-up showed that, except from OPUS-patients being less institutionalized, the positive clinical effects were not sustained, when the intensive treatment was terminated. The question arose whether two years of SEI were too short. This represents a clear rationale for the OPUS II-trial, investigating if five years of SEI is more appropriate to ensure long lasting clinical effect.
Methods: In the OPUS II trial, based on calculation of sample size, 400 patients were randomized to three years further OPUS treatment versus transfer to standard treatment. Patient were recruited from the existing OPUS teams which normally provides 2 years of treatment. The OPUS II trial complies with the extended CONSORT criteria. The primary outcome measure is negative symptoms, which are the most disabling symptoms, closely associated to labour market affiliation. Secondary out-comes are, remission of both negative and psychotic symptoms, client satisfaction, hospitalization, labour marked affiliation, substance abuse, working alliance, living independently, compliance to medication and self-efficacy.
Results: The follow-up interviews ended in July 2015 with 72% of participants attending the follow-up interview. We are now in the early phase of analysing the data, but these are not finished in time for symposium submission. The results will be finished by time for the SIRS conference and all main results will be presented.
Conclusions: Based on the results we will try to draw a conclusion regarding the effect of prolonged early intervention.

S24.4 Neurobiological changes during the early phase of psychosis and clinical response

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Background: Schizophrenia is characterised by presynaptic dopaminergic dysfunction and cortical glutamate alterations. However it is not known if alterations are progressive during the early phase of the illness or how this relates to outcome.
Methods: [18 F]-DOPA PET measures of striatal dopamine synthesis capacity and MR spectroscopy measures of glutamate levels in anterior cingulate cortex were acquired in cohorts of drug naive/ free people at ultra high risk of psychosis (total $n = 75$) as well as a cohort of drug naïve/ free patients experiencing their first episode of psychosis ($n = 22$) and a cohort of treatment responders and non-responders ($n = 56$) and matched controls (total $n = 86$). The high risk and first episode cohorts received repeat scans and follow-up to determine change in dopamine and glutamate function and their subsequent clinical outcome.
Results: Dopamine synthesis capacity increased from the prodrome to the first psychotic illness (effect size = 0.7, $P < 0.05$). Furthermore there was a main effect of time on glutamate levels during the at risk period ($P < 0.05$) as well. Dopamine synthesis capacity at baseline in the first episode patients was directly correlated with symptom improvement ($r = 0.7$, $P < 0.0.001$). Furthermore responders showed a change in dopamine synthesis capacity, which was not seen in non-responders. Chronic non-responders showed significantly elevated glutamate levels relative to treatment responders (effect size = 0.7, $P < 0.05$)

Conclusions: These data indicate that dopamine and glutamate function change during the prodrome and early phase of psychosis, and that these changes are linked to clinical outcome. These findings indicate that there are neurobiological changes during the early phase of psychosis that are linked to clinical state and that persistent non-response is linked to persistent glutamate alterations. This supports early intervention to reduce or prevent progressive neurobiological changes.

S25. Movement disorders: a non-mental core symptom of psychotic disorders and the importance of instrumental screening

S25.1 Instrumental measurement of bradykinesia and dyskinesia in psychosis and individuals at risk

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Background: Movement disorders (MD) are frequently found in any stage of psychotic disorders: in patients with schizophrenia, in antipsychotic naïve patients with first episode of psychosis, in individuals Ultra High Risk of psychosis (UHR), and even in genetically vulnerable siblings of patients with schizophrenia. Clinically most relevant, MD predict poor prognosis in antipsychotic naïve patients with first episode of psychosis and conversion to psychosis in UHR subjects (1-3). MD are very suitable for instrumental assessment which has several advantages, (i) lack of observer bias, (ii) high reliability and (iii) high sensitivity to detect even subclinical MD. Furthermore, portable monitoring devices provide the opportunity for assessment in real-world environments for a longer period. The enormous progress in technological (mobile) devices that can measure movements opens new possibilities in the research to MD in these patients groups.
Methods: One device measures bradykinesia with a wearable motion-capture system (XSENS technology). Validation was based on the correlation between the Unified Parkinson Disease Rating Scale (bradykinesia subscale) and the XSENS data, and the reliability was tested in a subgroup. This device measures the same aspects of the motor tasks as a clinical rating scale, overall speed and amplitude of movement and the respective variance thereof.
A second device measures dyskinesia by the use of force variability. Mean force variability will be taken as a proxy for upper extremity dyskinesia. Subjects are asked to press a button with constant pressure. The button is connected to a load cell attached to a monitor showing a graph indicating the pressure exerted, providing participants with immediate feedback. Force in the 0–3 Hz frequency range will be used as this measures dyskinesia best and is unaffected by resting tremor which manifests itself in the 4–6 Hz frequency band.
Results: Bradykinesia Included were 64 long-term treated patients (mean age (SD) 53.0yrs (10.9)). The validity of the device measuring bradykinesia was good ($r2 = 0.56$, $P < 0.01$) and the reliability was high (ICC.90, $P < 0.01$). Dyskinesia: Previous studies of Caligiuri *et al.* have shown that force variability measured with a load cell is a sensitive (sensitivity 82% and specificity 75%) and reliable measure for dyskinesia (ICC = 0.85, $P < 0.01$) (4). We transformed the instrument to a feasible 3D printed device of 3 by 4 cm with an USB connection and software that transforms the pressure on the load cell in a graph on a monitor and directly stores the data
Conclusions: These devices are valid and reliable to detect subtle MD. They are designed in a way that they can be used in clinical practice with minimal training. Instrumental measures of MD may thus enhance early detection in subjects at risk and aid outcome monitoring in psychosis.
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S25.2 Decreased right-handedness and somatosensory asymmetry in youth at ultrahigh risk for psychosis

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Background: A body of work focusing on language dominance, motor laterality, and neuroimaging research suggests that reduced cerebral hemispheric asymmetry is a core feature of schizophrenia. However, there is little consensus about whether reduced dextrality (right-handedness) is present in those at ultrahigh risk (UHR) for psychosis. One explanation for this lack of agreement is that previous work on handedness has focused on self or rater report. Technological advancements in computerized tablets as well as innovative neuroimaging methodologies may allow examination of subtle motor abnormalities and brain asymmetries that cannot be assessed with traditional methods. Examining cerebral dominance in the years immediately preceding the onset of psychosis can significantly inform etiological conceptions of psychosis—highlighting novel biomarkers and treatment targets.
Methods: A total of 95 demonstrated right-handed neuroleptic free UHR ($n = 39$) for psychosis and matched healthy control participants ($n = 56$) were assessed with structured clinical interviews at a baseline visit. Participants completed an innovative handwriting task using a digital tablet computer to assess dextrality. A laterality quotient for frequency of pen stroke (LQFREQ) were calculated using kinematic variables from the participant's right and left hands and used to assess relationships to positive and negative symptoms. In addition, 91 participants completed a 3 T MRI scan to assess asymmetry of language, motor, and sensory region of interest volumes. Left and right medial and superior temporal regions, as well as pre and postcentral gyrus were parcellated using Freesurfer software. Laterality quotients for each region were calculated to assess hemispheric asymmetry. A subset of the sample (26 UHR and 29 controls) returned after 12-months to complete clinical interviews in order to examine relationships between handwriting laterality and progression of psychosis risk symptoms.
Results: The LQFREQ for the UHR group ($M = -.28$, $SD = .46$) was significantly closer to zero compared to healthy controls ($M = -.4$, $SD = .32$), $t(92) = 2.57$, $p \leq .05$, suggesting that the UHR group was less lateralized to the right hand. Decreased dextrality accounted for 8% of the variance in worsening positive symptoms within the UHR group after 12 months. Neuroimaging results revealed that the UHR group ($M = .02$, $SD = .04$) had significantly less asymmetry in the postcentral gyrus $t(89) = 2.09$, $p \leq .05$ compared to healthy controls ($M = .04$, $SD = .05$). However, brain asymmetries were not linked to motor behavior in this sample.
Conclusions: Movement abnormalities tied to aberrant neurodevelopment have been proposed to be a key sign of risk for psychosis. However, to date, our understanding of laterality and cerebral asymmetry during this critical period has been limited. Importantly, this is the first study to examine handedness in UHR individuals using handwriting kinematic measurements. Findings that decreased right-handedness was associated with the progression of more severe positive symptoms over a 12-month period provide support for the theory that disrupted cerebral asymmetry and altered hemispherical dominance may serve as a novel biomarker for the progression of psychosis risk. Future work linking instrumentally-assessed motor behaviors to sensitive neuroimaging methodologies is sorely needed.

S25.3 Resting state functional connectivity in the motor loop correlates with hypokinesia in schizophrenia

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Background: Motor signs are an important intrinsic component of schizophrenia, detected in prodromal subjects, first episode and chronic patients1. Neuroimaging studies suggest that alterations in the cerebral motor circuit are critically involved in motor symptoms of schizophrenia2. Hypokinesia is frequently observed in schizophrenia and associated with negative symptom severity. Wrist actigraphy allows continuous and objective assessment of hypokinesia3. Motor

activity levels correlated with resting state cerebral blood flow in cortical motor areas as well as with white matter ultrastructure of motor tracts4. Ineffective structural connectivity between basal ganglia and cortical premotor areas resulted in hypokinesia in schizophrenia5. However, the functional associations of hypokinesia are still unknown. Here we tested the correlation of real life motor behavior and functional connectivity in the motor circuit in schizophrenia.
Methods: In 25 patients with schizophrenia spectrum disorders and 25 healthy controls wrist actigraphy was applied to assess motor activity levels. Most patients currently received antipsychotic medication, but patients were free of medication related motor side effects. The subjects underwent functional and structural brain imaging at 3 T. BOLD resting state functional connectivity between key regions of the motor system was determined using the CONN toolbox in Matlab. Linear regression analyses were applied to determine the association between activity levels and functional connectivity.
Results: In contrast to healthy control subjects, patients with schizophrenia had increased functional connectivity in thalamocortical connections of the motor circuit. Resting state functional connectivity was particularly increased between caudate and motor/premotor areas as well as between thalamus and primary motor cortex (M1). Increased functional connectivity between caudate and M1 as well as between thalamus and M1 predicted increased activity levels of real life motor behavior.
Conclusions: Hypokinesia in schizophrenia results from ineffective functional connectivity in the motor loop. This finding corroborates previous results of structural neuroimaging. Thus, aberrant functional coupling within the cerebral motor circuit drives some of the motor symptoms seen in schizophrenia. Again, objective assessment of motor behavior helped to disentangle brain-behavior associations. Noninvasive brain stimulation techniques may in the future aid restoration of functional connectivity and thus alleviate hypokinesia in schizophrenia patients.
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S25.4 Instrument-based assessment of dyskinesia across dimensions of genetic liability for psychosis and severity of psychopathology

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Background: Dyskinesia has been reported in first-episode psychosis and those at ultrahigh risk of developing psychosis (UHR). Basal ganglia dysfunction is believed to underlie dyskinesia, and dyskinesia in UHR is associated with striatal volume abnormalities (1) and is predictive of conversion to psychosis (2). Instrumental assessment of dyskinesia yields high-resolution quantification of motor function, and digitized handwriting assessment revealed abnormal handwriting kinematics in UHR (3). Aim 1 of this study examined whether dyskinetic movement is present in first-degree relatives, who carry unexpressed genetic liability for the development of schizophrenia. Given the presence of motor dysfunction across a range of psychological disorders (4) as well as the proposal that certain motor abnormalities (including dyskinesia) form a core non-mental symptom of psychosis specifically (5), Aim 2 examined dyskinesia across various symptom dimensions of severe psychopathology. Aim 3 examined dyskinesia and its relation to symptoms of psychosis in medication-free people with schizophrenia in the absence of medication confounds potentially affecting both motor function and symptom severity.
Methods: 57 people with schizophrenia ($n = 41$) or schizoaffective disorder ($n = 16$) (SZ), 48 first-degree biological relatives of people with a psychotic disorder (REL), 18 people with bipolar affective disorder (BD) and 51 nonpsychiatric controls (CN) completed a handwriting task on a computerized tablet. Participants wrote "lleellee" in cursive in 1, 2 & 4 cm vertical boundary conditions. Dyskinesia was quantified by calculating average normalized jerk (ANJ), a measure of the changes in acceleration over the course of a pen stroke. Data were log-transformed and subjected to a group x size repeated measures ANOVA. For Aim 3, 12 unmedicated SZ and 20 CN wrote "today is a nice day" in cursive. Mean pen pressure and SD were calculated for each participant across strokes.
Results: There was a main effect of group ($F(3,166) = 3.868$, $P = .01$); SZ ($M = 1.435$, $SE = .039$) had higher ANJ than CN ($M = 1.271$, $SE = .038$) and REL ($M = 1.28$, $SE = .039$) ($P < .001$). ANJ for BP ($M = 1.366$) fell between SZ and REL. ANJ was significantly associated with the ideas of reference SPQ subscale in REL (1cm: $r = .319$, $P = .033$). There were significant correlations between ANJ and BPRS disorganization in SZ (1cm: $r = .302$, $P = .024$), and ANJ and total SANS in BP (4cm: $r = .528$, $P = .029$). Correlations with chlorpromazine equivalent doses were not significant. In the unmedicated sample, pen pressure variability was significantly higher in SZ versus CN, and correlated with PANSS positive symptoms ($r = .6$, $P < .05$) in unmedicated SZ.
Conclusions: Increased handwriting dysfluency in SZ is consistent with models of the disorder implicating hyperdopaminergia in the basal ganglia. The absence of similar dysfluent movements in REL provides evidence that dyskinetic movements may be a specific risk marker for eventual conversion to psychosis. The intermediate performance of BP and the negative symptom correlate suggest that symptoms associated with psychosis rather than mood lability are related to dyskinesia in BP. The SPQ correlate in REL suggests a potential biological link between experiences along the psychosis spectrum and movement dysfluency. The relationship between pen pressure variability and symptom severity in unmedicated SZ implicates a possible shared dopamine dysregulation mechanism in instantiation of both motor output and core symptoms in SZ.
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S26. Non-traditional methods of classification in psychosis: applying a precision medicine model

S26.1 Empirical classification of psychotic patients using neurocognitive profiles

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Background: Data from family-based and genome-wide association studies converge to suggest a significant overlap in the molecular genetic risk factors for schizophrenia (SZ) and bipolar disorder (BD). This suggests that overlapping genetic variants that influence risk for these illnesses do so via effects on shared dimensional phenotypes. Among these shared traits, neurocognitive impairment, is of particular clinical relevance as it does not adequately respond to available treatments and it is among the strongest predictors of functional disability across both disorders. Moreover, there is strong evidence that neurocognitive impairment is influenced by genetic factors in both SZ and BD, making this an endophenotype that is critical toward understanding trans-disorder pathophysiology. The identification of the relevant molecular networks associated with neurocognitive functioning in psychosis is not only an important step in elucidating the causes of these disorders, but also in identifying novel treatment options for this disabling symptom domain. Our work is focused on neurocognition as a critical dimension that is directly associated with disease risk, with the goal of identifying the clinical and molecular factors that underlie cognitive impairment in psychosis.

Methods: To test for the existence of discrete neurocognitive subgroups, we utilize hierarchical cluster analyses including the 7 MATRICS Consensus Cognitive Battery (MCCB) domain scores to first determine the optimal number of clusters based on the observed data. Data analyses are agnostic to DSM categories such that classification of subgroups is based primarily upon cognitive profiles. Groups are then compared across a range of demographic, clinical, and biological measures (cytokines; DNA) to identify potential predictors of cognitive outcome. Ultimately, predictive modeling will be utilized to better understand the relationships among predictors and the assumed directionality of effects.
Results: The utility of this approach will first be demonstrated by describing recently published work (Burdick *et al.* 2014) showing differentiation of 3 cognitive subgroups in patients with bipolar disorder. Unpublished data from a subset of the bipolar sample ($n = 40$) will be presented that indicate unique peripheral inflammatory signatures in these cognitive subgroups in bipolar disorder derived from a large multiplex assay of cytokines and growth factors. Finally, new analyses will be presented using the same classification method but including the full range of psychotic illness ($n \sim 400$ patients with affective and non-affective psychoses) and three distinct subgroups will be characterized. Genetic results will not be described as the full sample will be required for adequate power and data collection is ongoing.
Conclusions: Data from these studies may provide new insights into the cognitive architecture across a range of psychotic disorders and help to identify the factors that contribute to the disabling neurocognitive impairment associated with these illnesses.

S26.2 Polygenenic risk scores among cognitive subtypes of psychosis

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Background: Shared polygenic risk for schizophrenia (SZ) and bipolar-I disorder (BD) has been established in several studies, and may be associated with shared intermediate phenotypes for these disorders. At the same time, delineation of subtypes of patients with SZ and BD who share common cognitive profiles – typically representing severe 'cognitive deficit' (CD) or relatively 'cognitively spared' (CD) performance on a range of tests – provides a means of examining biological similarities among cognitive subtypes that span these diagnostic categories.
Methods: Participants were 103 clinical cases with SZ ($n = 39$) or BD ($n = 28$), and 36 healthy controls recruited as part of the Imaging Genetics in Psychosis Study. Clinical participants were allocated to either a cognitive deficit (CD) or cognitively spared (CS) subtype via two-step cluster analysis of performance on eight cognitive domains (general verbal ability, verbal memory, visual memory, executive function, processing speed, visual processing, language ability, and working memory); there were no HCs with a CD profile. All participants were genotyped using the Infinium PsychArray BeadChip, in collaboration with the Psychiatric Genomics Consortium (PGC); Polygenic Risk Scores (PRS) were calculated using imputed data for approximately 93,000 SNPs, according to previous findings of the PGC. We examined differences in polygenic risk among CD and CS cases, relative to HC, in the context of estimates of polygenic risk among traditional diagnostic categories. We also examined associations between polygenic risk scores and performance on individual cognitive domains, within each of the cognitive subgroups.
Results: Polygenic risk scores were highest in CD the group, followed by CS cases, then HC; the mean PRS for CD cases was higher than the SZ group as a whole. Within the CD subgroup only, higher PRS scores were significantly associated with scores on cognitive domains of attention and language, and poor reversal learning on the executive function (Intra-Extra Dimensional Shift) test.
Conclusions: Patients with SZ or BD with severe cognitive deficits across a number of domains show higher PRS than their cognitively spared counterparts. In addition, polygenic risk estimates are associated with specific cognitive abilities only in SZ or BD cases with other severe cognitive deficits. These findings highlight the utility of investigating genetic and biological similarities among cognitive subtypes that span current diagnostic categories.

S26.3 Prospects for genetic subtyping in polygenic disease

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Background: Common, multifactorial diseases such as schizophrenia may represent heterogeneous collections of aetiologically and clinically more homogeneous underlying pathologies. In the context of a highly polygenic outcome, here we investigate the extent to which a purely genetic analysis of genome-wide common variant data may be able to unpack such heterogeneity by assigning individual patients to genetically derived subtypes.
Methods: Analysis of genome-wide polymorphism data is routinely used to identify substructure in samples when individuals belong to different ancestries. This substructure induces correlations between thousands of unlinked alleles genome-wide, which provide detectable signatures for methods such as principal components analysis and latent class analysis. Although, compared to population differences, the extent of genetic differentiation will be orders-of-magnitude smaller when considering individuals in the same population with and without a polygenic disease, this nonetheless begs the question as to whether similar approaches could in theory uncover hidden structure among individuals with the same disease, indicative of genetically-driven disease heterogeneity. In the context of a polygenic disease, when focusing only on a subset of nominally disease-associated variants, and controlling for actual ancestry-based substructure, one could potentially use genetic data to uncover hidden subtypes of disease that reflect different polygenic components of genetic risk. The success of such an approach will depend on the strength of the available association data and the true nature of the underlying heterogeneity
Results: I will first present theoretical results based on simulated data to explore the conditions under which a genetic dissection of polygenic subtypes is feasible. Based on principal components analysis and latent class analysis, I will then apply these approaches to a large Swedish study of schizophrenia. Finally, I will consider the extent to which accounting for potential hidden aetiological "substructure" in cases could be expected to increase power to detect subtype-specific disease variants, where the subtypes are not known a priori.
Conclusions: As genetic correlation analysis can suggest that related disorders can be "lumped" together on some level, patterns of genetic variation in cases with the same disorder can in theory be used to "split" existing diagnostic categories. More refined classifications of patients may improve future research efforts and, ultimately, patient care, to deliver on the promises of precision medicine.

S26.4 Parsing neurobiological variance in psychosis via brain based biomarkers

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Background: Biological reformulations of disease have revolutionized many medical disciplines, but classification and treatment of brain diseases subsumed by psychiatry rely on clinical phenomenology, despite the call for alternatives. Even bipolar disorder with psychosis (BDP) and schizophrenia (SZ), the two major and ostensibly distinct psychosis categories, do not 'breed true'. There is overlap in susceptibility genes and phenotypes across BDP, SZ, and considerable similarity between different psychotic disorders on symptoms, illness course, cognition, psychophysiology, and neurobiology. Drug treatments for these conditions overlap extensively. 'Psychosis' could be a final endpoint for multiple psychotogenic etiologies, as 'congestive heart failure' is a common endpoint of cardiac, renal and pulmonary disorders, all of which are best ameliorated with distinct treatments. Clinical phenomenology remains the primary means for diagnostic classification of psychoses despite considerable evidence this method incompletely captures biologically meaningful differentiation. Effectively capturing unique neurobiological classes in psychosis may facilitate achievement of multiple important goals, including supporting development of novel agents for clinical therapeutics.

Methods: Rather than relying on clinical diagnoses as gold standards, the Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP) consortium leveraged neurobiological heterogeneity among psychosis cases to delineate subgroups independent of their phenomenological manifestations. This presentation will describe the scientific and theoretical issues that lead to our approach, the approach itself, and a main scientific outcome of the first iteration of B-SNIP. Briefly, A large biomarker panel (neuropsychological, stop signal, saccadic control, and auditory stimulation paradigms) characterizing diverse aspects of brain function was collected on schizophrenia, schizoaffective, and bipolar disorder psychosis cases ($n = 711$), their first-degree relatives ($n = 883$) and demographically comparable healthy subjects ($n = 278$). Biomarker variance across all paradigms was leveraged to create 9 integrated variables that were used to capture neurobiological variance among the psychosis cases.
Results: Multivariate taxometric analyses identified three neurobiologically distinct psychosis Biotypes that did not respect clinical diagnosis boundaries. The same analysis procedure using clinical DSM diagnoses alone as the criterion variables was best described by a single severity continuum (schizophrenia worse than schizoaffective worse than bipolar psychosis); this was not the case for the Biotypes. External validating measures (social functioning, neuroanatomy, familial data, psychophysiology, and polygenic risk) supported the distinctiveness of these subgroups compared to clinical diagnosis, indicating the possibly enhanced utility of neurobiological versus clinical categorization schemes for usefully differentiating psychosis subtypes.
Conclusions: Identifying specific brain alterations via similar approaches may undergird translational research across clinical, molecular, and pharmacological domains that promote development of treatments with specific etio-pathological targets. There are multiple challenges on the road to such successful outcomes, but these challenges provide multiple opportunities for psychiatry to lead in the development of novel approaches to understanding multiple disorders of brain function.

S27. Elephant in the room: glia contribution to mental disorders

S27.1 Interactions between glia and extracellular matrix in schizophrenia

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Background: Growing evidence shows that interactions between glial cells and the brain extracellular matrix (ECM) are required for neurodevelopment and key adult neural functions. Chondroitin sulfate proteoglycans (CSPGs), main ECM components, are secreted by glia into the ECM, where they mediate emerging glial functions. CSPGs secreted by astrocytes are critical to the formation and maintenance of specialized ECM structures, e.g., perineuronal nets, which in turn interact with glia to control synaptic plasticity and glutamatergic transmission. Distinct glia/CSPG clusters we recently described in human subjects, are hypothesized to function as specialized macrodomains affecting neuronal activity. Oligodendrocyte precursor cells (OPCs) strongly express CSPGs, including brevican and OPC-selective NG2, which potently regulate oligodendrocyte maturation, nodes of Ranvier and myelination. Converging evidence points to CSPG/ECM abnormalities in schizophrenia (SZ). We tested the hypothesis that CSPG expression in glial cells may be altered in subjects with SZ.
Methods: Quantitative light and confocal microscopy were combined to measure astrocytes and OPCs expressing CSPGs in the amygdala of healthy control and SZ subjects. Corresponding mRNA was measured by qRT-PCR.
Results: Our results show markedly altered numbers of astrocytes and OPCs expressing CSPGs in SZ. Astrocytes labeled with the lectin wisteria floribunda agglutinin (putatively detecting the chondroitin sulfation (CS) pattern CS-4) show striking increases in SZ, ranging from 400 to 1100% with respect to control subjects. In contrast, glial cells expressing the CSPG aggrecan and glial/CSPG clusters expressing the CS-6 pattern were significantly reduced in SZ. Astrocytes expressing CD44, a hyaluronan receptor that potently affects OPC migration and maturation, were also robustly decreased. Consistent with this latter finding, numbers of NG2-positive OPCs were substantially lower in SZ.
Conclusions: Together, these results point to encompassing abnormalities affecting glia/ECM interactions in SZ. Speculatively, as suggested by GWAS findings, these abnormalities may result from genetic vulnerabilities related to ECM remodeling enzymes, which may represent a common denominator, impacting a broad range of ECM molecules and thus glia/ECM interactions. As a result, seemingly unrelated functions, such as synaptic plasticity, volume transmission and myelination, may be disrupted, contributing to key aspects of the pathophysiology of SZ.

S27.2 Cell-specific vulnerability to adolescent cannabis exposure: the expanding role of astrocytes

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Background: The role of psychiatric genetic risk factors in astrocytes remains poorly understood, including the mechanisms whereby astrocytes mediate adverse effects of environmental factors. Astrocytes express cannabinoid receptor 1 (CB1) chronic adolescent stimulation of which with tetrahydrocannabinol (THC) produces cognitive impairment. We evaluated how selective astrocytic expression of a genetic risk factor, mutant Disrupted-In-Schizophrenia-1 (DISC1), moderated cognitive dysfunction following adolescent cannabis exposure
Methods: Control and mutant DISC1 mice were treated daily with 8 mg/kg, sc of Δ9-THC for 21 days beginning at postnatal day (P) 30 or P90. A separate cohort of mice was identically treated with THC and was given doxycycline (DOX) food to shut down expression of mutant DISC1 during treatment. In addition, a separate cohort of mice was given chronic injections of amphetamine (AMPH, 1 mg/kg, ip) to verify specificity of cannabis effects. 3 weeks after treatment, the different cohorts of mice were evaluated in cognitive tests. Afterwards, mice were sacrificed, and parvalbumin+(PV) neurons number estimation and RNAseq of hippocampal tissue samples were performed.
Results: Compared to control groups, THC-treated DISC1 mice exhibited deficits in spatial recognition memory, object recognition and new placement recognition. These deficits were no longer present in THC-DISC1 mice given DOX, indicating the critical role of adolescent expression of mutant DISC1. Adult exposure to THC or adolescent treatment with AMPH did not affect cognitive tasks in mutant DISC1 mice. Adolescent THC exposure produced a synergistic decrease in the number of PV+ neurons and significant changes in cAMP and adenosine signaling in the hippopotamus.
Conclusions: Our findings indicate that adolescent interactions of astrocytic mutant DISC1 and cannabis exposure synergistically produce cognitive deficits and GABA neurons pathology in adult mice. Altered cAMP and adenosine signaling might contribute to cognitive dysfunction in mice. The data suggest a new role for astrocytes in mediating adverse effects of adolescent exposure to cannabis to contribute to cognitive dysfunction in psychotic disorders.

S27.3 Glial dopamine controls neuronal network activity and functions in the prefrontal cortex

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Background: The prefrontal cortex (PFC) supports higher-order cognitive functions for the coordination of complex behaviors including learning and memory, decision making and social interactions. Although the complex cognitive processes handled by the PFC and its extensive interactions with many brain regions are unequivocally subject to numerous neuromodulations, the dopaminergic (DAergic) innervations originating from the ventral tegmental area (VTA) exerts a particularly prominent control on the activity of this brain region. Extracellular levels of dopamine are, therefore, tightly regulated within a narrow range of concentrations. In the adult PFC, a proper background level of DA sets the responsivity of the glutamatergic synaptic network through homeostatic mechanisms and is essential for optimizing frontal cognitive functions. Beside, neurons the brain parenchyma homes also astrocytes which are the most abundant cell-type. Over the last 20 years, accumulating

evidence have shown that astrocytes exerts profound homeostatic functions in the brain and may participate to neuronal communication through the release of neuroactive molecules. However, whether and how astrocytes participate in regulating the homeostatic functions of dopamine has never been investigated in details.
Methods: Here we combine confocal and electron microscopy to reveal the presence in astrocytes of bona fide proteins involved in the metabolism and transport of DA. We find that a subset of cortical astrocytes express the vesicular monoamine transporter type 2 (VMAT2). Using conditional gene inactivation we analyse the impact of VMAT2 deletion in astrocytes on synaptic transmission, synaptic plasticity but also on cognitive and social behaviors. Then, viral-mediated gene replacement but also L-DOPA administration was used to rescue observed phenotypes.
Results: We found that a large fraction of cortical astrocytes express bona fide proteins involved in the metabolism and also VMAT2 indicating that these astrocytes may metabolize DA and store it in order to release it. In order to investigate the role of astrocytic VMAT2 in DA homeostasis, we generated an inducible knock-out mice line in which VMAT2 is specifically deleted in astrocytes. Upon deletion of VMAT2, we observed a profound hypodopaminergic state in the PFC. Then analysis of DA release from astrocytes using in vivo microdialysis reveals that VMAT2 is crucial for astrocytes to actively release DA. Functional analysis using electrophysiological recordings in acute PFC slices of glutamatergic synapses show that synaptic transmission, short- and long-term plasticity are severely altered indicating that DA released by astrocytes is crucial for the normal functions of excitatory synapses. Analysis of working memory, behavioral flexibility, anxiety and social interactions in different tests revealed that mice lacking astrocyte VMAT2 display cognitive impairments, increased anxiety and stereotypic behavior, all of which are reminiscent of schizophrenia. Interestingly, treating the animals with L-DOPA or reintroducing VMAT2 in astrocytes abolishes all deficits we observed.
Conclusions: Our results show that DA represents a novel secreted molecule used by astrocytes to actively control brain functions.

S27.4 Glioproteomics to define the role of glia in neuroinflammatory diseases

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Background: Glia are heterogeneous and multi-functional, which mediate many supportive functions for the brain homeostasis. Recently, paradigm shift from the neurocentric to the gliocentric view of the brain has been proposed, and the complexity of the brain has been revealed by the recent studies on the novel functions of glia in the brain homeostasis as well as neuronal functions.
Methods: Glia also participated in neuroinflammation, which is a major component of many brain disorders. Especially, proteins secreted from glial cells can be a fundamental source for diagnostic markers and therapeutic targets for the neuroinflammatory diseases.
Results: Over the last decade, we investigated the role of astrocyte-secreted proteins such as LCN2, L-PGDS, PTX3, and HMGB in CNS heath and disease. In particular, a pathological role of LCN2 has been investigated in a variety of animal models, including stroke, chronic pain, Parkinson's disease, vascular dementia, multiple sclerosis, etc.
Conclusions: Here, our recent data obtained from global brain ischemia and hypoperfusion model will be introduced. Application of optogenetic approach to understand the role of glia-derived LCN2 in hippocampus will be also discussed.

PL28. Convergent evidence linking neonatal vitamin D status and risk of schizophrenia

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Abstract: Unravelling the aetiology and pathogenesis of brain disorders is a task that requires multidisciplinary skills, integration of data from different domains and tenacity. This lecture will present convergent evidence from epidemiology, genetics, and neuroscience aimed at finding modifiable risk factors for schizophrenia. In this Lecture I will outline the results of a large replication study that confirms the association between low neonatal vitamin D concentration and an increased risk of schizophrenia. In addition, based on slice electrophysiology and wide-field calcium imaging, I will present new evidence that links vitamin D with neurobiological mechanisms identified in recent GWAS studies for schizophrenia. Most importantly, if future studies confirm the association between developmental vitamin D deficiency and risk of schizophrenia, then it raises the tantalizing prospect of the primary prevention of mental disorders, in a manner comparable to folate supplementation and the prevention of spina bifida.

PL29. Balancing plasticity / stability across brain development

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Abstract: Maturing neural circuits are dramatically shaped by their environment, creating sequential windows of opportunity and vulnerability to early experience across brain regions. This lecture examines the biological bases of such 'critical periods' in development. Targeting specific GABA circuits by genetic or pharmacological manipulation can robustly accelerate or delay onset. Conversely, lifting a variety of brake-like factors which normally emerge to stabilize adult networks can reactivate plasticity. Notably, the mechanisms which open (excitatory-inhibitory circuit balance) or close (molecular brakes) these windows of circuit rewiring are increasingly implicated in cognitive disorders, such as autism and schizophrenia. This suggests mis-timed maturational processes may contribute, which in turn could be strategically leveraged to rescue circuit function. In particular, the interplay of most of these cell-autonomous and extrinsic factors converge upon fast-spiking, parvalbumin-positive cells, whose high metabolic demands render them sensitive to oxidative stress. Focusing on the cellular/molecular biology of these pivotal cells underlying trajectories of cortical processing and plasticity offers new insights into disease etiology and potential therapeutic approaches.

S30. Trajectories of children-adolescents at risk of major affective and non-affective disorders: exploring the period preceding the "CHR risk phase" for preclinical staging of risk and implications in clinical practice

S30.1 Transdiagnostic antecedent-based strategy for early detection of individuals at risk of severe mental illness: a forbow study report

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Background: The poor functional outcomes of individuals who are offered interventions at the prodromal stages of mental illness highlight the needed for an earlier identification of risk. Molecular genetic and longitudinal studies of developmental psychopathology suggest that both the genetic risk and antecedent psychopathology overlap between major mood and psychotic disorders. Therefore, we propose a transdiagnostic strategy using a combination of family history and psychopathological antecedents to identify individual at high risk for severe mental illness early enough to provide opportunity for pre-emptive early intervention.
Methods: The Families Overcoming Risk and Building Opportunities for Well-being (FORBOW) study enrols youth (age 7-21), including offspring of parents with schizophrenia, bipolar disorder, and severe recurrent major depressive disorder as well as control offspring of healthy parents. To date, 220 offspring (mean age 11.6) and 343 parents have participated in FORBOW and the enrolment is ongoing. The offspring are followed up annually with a 96% retention and 409 completed assessments. On each occasion, raters blind to parent diagnosis assess the antecedents of affective lability, anxiety, basic symptoms and psychotic symptoms as well as full spectrum of mental and behavioural disorders with the Kiddie-Schedule for Affective

Disorders and Schizophrenia (K-SADS) and the Structured Interview for DSM Disorders (SCID).
Results: Each of the four antecedents was more common among offspring of parents with severe mental illness than among comparison offspring: affective lability (34% vs 19%), anxiety (29% vs. 8%), basic symptoms (15% vs 4%) and psychotic symptoms (27% vs. 11%). Of those with one or more antecedents at baseline, 75% also had an antecedent on a follow-up one year later. To date, 7 onsets of major mood or psychotic disorders were prospectively identified, of which 6 were preceded by one or more antecedents and all 7 occurred in offspring of affected parents. One onset of schizophrenia in a 12 year old male offspring of a parent with depression was preceded by all four antecedent. Two new onsets of bipolar disorder (age 15 and 17, one female and one male, both offspring of parents with bipolar disorder) were each preceded by 3 antecedents including affective lability, anxiety and psychotic symptoms. Of the four new onsets of major depressive disorders (age 13-15, three females and one male, all offspring of parents with mood disorders), three were preceded by one or more antecedents (2 anxiety, 2 affective lability, 1 psychotic symptoms). The number of antecedents at baseline predicted new onsets of mood and psychotic disorders on follow-up with an odds ratio of 2.4 (95%CI 1.3 to 4.4, $P = 0.006$).
Conclusions: The combination of family history and psychopathological antecedents constitutes a feasible strategy for early identification of risk. Initial experience suggests high acceptability and uptake of pre-emptive early interventions in non-treatment seeking individuals identified through this strategy.

S30.2 The determinants of the onset and course of early mood disorders: a controlled 10-year follow-up study of offspring of parents with bipolar and unipolar mood disorders

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Background: The determinants of the onset of bipolar and unipolar mood disorders are still only partially elucidated. Moreover, although several studies on the offspring of parents with mood disorders have documented elevated rates of these disorders in their offspring during adolescence, their course and clinical relevance in adulthood has hardly been studied. Accordingly, using a prospective high-risk study design, our aims were to establish the risk of psychopathology in offspring in function of two major sources of heterogeneity of mood disorders, i.e. the subtype of the parental mood disorder (bipolar (BPD) and major depressive disorder (MDD)) and its age of onset. Moreover, within the same cohort of offspring we prospectively assessed the occurrence of mood episodes and treatment seeking after the age of 18 years in those who already met criteria of BPD during childhood or adolescence. Conversely, we determined the type of preexisting psychopathology during childhood and adolescence in offspring who exhibited BPD or MDD in young adulthood.
Methods: Clinical information was collected on 81 treated probands with BPD, 64 with MDD and 63 medical controls as well as their 202 spouses and 372 children aged 6-17 years at study entry (mean age: 10.0 years). Offspring were interviewed every 3 years with a mean duration of follow-up of 10.6 years. Assessments of parents and offspring were based on direct diagnostic interviews using the Diagnostic Interview for Genetic Studies (parents and offspring of 18 years and older) and the Kiddie-Schedule for Affective Disorders and Schizophrenia (offspring aged 7 to 17.9 years). Parental age of onset was dichotomized at the age of 21 years.
Results: Offspring of parents with early onset BPD entailed a nearly eight times higher risk of BPD than those of controls, whereas the risk of BPD was not increased in offspring of bipolar parents with an onset after 21 years or in those of a parent with MDD. Although approximately a sixth of the offspring of bipolar parents met criteria for a BPD, only few sought treatment. However, among offspring who revealed mood disorders during childhood or adolescence more than a third experienced new mood episodes in adulthood. Conversely, more than half of the offspring who experienced BPD or MDD during adulthood already previously exhibited such episodes.
Conclusions: Our results provide support for a strong and independent familial aggregation of BPD from MDD and the heterogeneity of BPD based on patterns of onset. Although the offspring of parents with BPD reveal increased rates of BPD during adolescence with a significant risk of recurrence in adulthood, additional longitudinal research is needed to study which of these early mood disorders convert into clinically relevant disorders in adulthood and to identify the determinants of this conversion

S30.3 Early signs of bipolar disorder. a study on symptomatology among prospectively followed bipolar offspring

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Background: Early recognition of bipolar disorder (BD) remains challenging. In the Dutch bipolar offspring study (Mesman et. al. AJP 2013), we aim to explore the early signs of BD among children of a parent with bipolar disorder prospectively followed from adolescence into adulthood.
Methods: The Dutch bipolar offspring study ($n = 140$, age range 12-21 years, since 1997) psychiatrically evaluated children of a parent with bipolar disorder at baseline, 1-, 5-, and 12-year follow-up (retention rate 77%) using the K-SADS-PL and the SCID. Subthreshold and threshold symptomatology was assessed with the K-SADS-PL at baseline.
Results: Among offspring with a (mild) unipolar mood disorder at baseline, subthreshold manic symptoms (elated mood, decreased need of sleep and racing thoughts), suicidal ideation and middle insomnia were specifically associated with a transition to bipolar disorder during follow-up. Among offspring without any mood disorders at baseline, the development of a unipolar mood disorder was predicted by subthreshold depressive mood, recurrent thoughts of death, marked feeling of tension, marked self-consciousness and compulsions.
Conclusions: The study extends our knowledge on the prodromal stadia of bipolar and unipolar mood disorders among offspring at high familial risk for developing BD. Findings of this study indicate that subthreshold manic symptomatology may be an important key prognostic factor for BD onset. Findings of this study provide potential targets for early recognition and preventive intervention programs.

S30.4 Aggregation of risk indicators in offspring of patients affected by affective or non-affective psychoses: teachings from Québec longitudinal high-risk families for the staging of the childhood-adolescence risk trajectory

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Background: Adult patients with major psychoses (MP; schizophrenia, bipolar disorder and major depression) display indicators of brain dysfunctions that are detectable in children-adolescents born to an affected parent (Maziade, Schizophr Res 2013). Many established liability indicators for MP (eg cognitive impairments, childhood trauma, and attenuated symptoms of psychosis, childhood non-psychotic DSM diagnoses, and cannabis use) are derived from high-risk studies and can document the early developmental course of risk trajectories. Our objectives were i) to depict with liability indicators or endophenotypes the developmental portrait of young offspring born to an affected parent descending from multi-affected kindreds; ii) to describe the outcome of the offspring who have reached the age of incidence and progressed to an axis I DSM-IV disorder; iii) to look at the converters' developmental portrait 10 years earlier; and iv) to use these empirical data to define a model of preclinical staging of risk in childhood-adolescence.
Methods: We used a stepwise selection strategy from a 25-year follow-up of 48 kindreds densely affected by MP (Maziade, Mol Psychiatry 2005). We started upstream with 1500 adults (405 were affected by

MP). Downstream in the younger generations, we longitudinally collected extensive measures of cognitive domains (Maziade, Schizophr Bull 2011), attenuated symptoms of psychosis, non-psychotic DSM diagnosis and/or an episode of poor GAF functioning in childhood-adolescence, childhood trauma, and cannabis use in 84 children-adolescents. After an average follow-up of 10 years, around half of the offspring had reached the age of disease incidence. Thirty offspring who converted to an axis I disorder or MP were compared to those who remained healthy at age 30 in terms of developmental trajectories and liability indicators.
Results: 62% of the 84 offspring displayed 2 or less liability indicators and 38% had 3 or more (mode value = 2). The 15 offspring who converted to a major affective or non-affective disorder presented, in childhood-adolescence, significantly more aggregation of liability indicators than the 20 offspring who remained healthy in adulthood (2.9 indicators on average, versus 1.9 for healthy offspring as adults (Wilcoxon rank test; Z = 2.71, p = .007). The offspring who developed other axis I diagnoses as adults presented as much clustering as the converters. Based the observed clustering process of risk indicators, we staged the remaining 49 offspring who had not yet reached the age of disease incidence according to their individual degree of clustering (addition of 1 to 5 indicators). We observed a high clustering variability among offspring which allowed us to distribute the high risk youths into a model of staging.
Conclusions: A high degree of aggregation of risk indicators was found in high-risk offspring. Any risk indicator alone had moderate predictive power and, in the converters, a process of clustering of liability indicators happened years before disease incidence. Such an aggregation may be compatible with the multifactorial polygenic theory with a threshold. Remarkably, in metabolic cardiovascular disorders (Maziade, JAMA Ped 2014), a clustering of risk indicators is also observed in children at risk and is presently considered in practice guidelines. The clusterization of liability indicators may provide an empirical basis for the modeling of preclinical staging of children at risk to be used in preventive research.

S31. Symptom dimensions in schizophrenia – brain correlates and personalised treatment options

S31.1 The neurobiology of formal thought disorder: specific for schizophrenia?

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Background: Speech and language disorders, such as concretism and formal thought disorder (FTD) are core symptoms of Schizophrenia, but do occur to a similar extent in other diagnoses such as bipolar disorder and major depression.
Methods: We will review clinical rating scales of FTD and introduce a new, validated scale, the TALD. Further, structural and functional brain imaging data will be reviewed and own novel findings presented, relating speech and language dysfunctions to neural networks, within schizophrenia and across the "functional psychoses".
Results: The impact of genetic variance and glutamatergic pathways (NMDA receptor blockage) on brain function will be addressed with a particular focus on speech and language (dys-) function.
Conclusions: We demonstrate, from the genetic to the brain structural and functional level, that particular aspects of the neural language system is disrupted in patients with FTD across traditional diagnoses.

S31.2 Formal thought disorder in non-clinical individuals with auditory verbal hallucinations

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Background: Auditory verbal hallucinations (AVH) and formal thought disorder (FTD) may originate from the same aberration in the language system. The hypothesis of a shared neurobiological basis would be strengthened by the presence of FTD in individuals who frequently experience AVH, but do not meet DSM-IV criteria for a psychotic disorder.
Methods: In this study, FTD was quantified in 40 non-clinical subjects with AVH, in 50 healthy subjects without AVH and in 40 schizophrenia patients with AVH. Recorded speech samples were analysed by one rater who was blind to the presence/absence of AVH and to diagnosis, using the Thought and Language Index.
Results: Negative FTD was barely present in non-clinical subjects with AVH and in healthy controls without AVH. Positive FTD, however, was significantly higher in both groups experiencing AVH than in controls without AVH. Severity of positive FTD did not differ significantly between non-clinical subjects with AVH and schizophrenia patients with AVH.
Conclusions: Negative FTD (alogia) appears not to be associated with AVH. However, the fact that positive FTD (disorganised speech) in schizophrenia patients with AVH is equally high in non-clinical subjects with AVH indicates that these two symptoms tend to co-occur, which may be suggestive of a shared neurobiological substrate.

S31.3 Causes of the variable efficacy of RTMS in the treatment of auditory hallucinations in schizophrenia: from placebo effect to brain morphology modifications

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Background: Repetitive transcranial magnetic stimulation (rTMS) shows a high inter-subjects variability in the efficacy of the treatment of auditory verbal hallucinations (AVH) in schizophrenia. Besides the stimulation parameters and the location of the target which can induce variable efficacy of rTMS, 2 other factors could contribute to variable efficacy of rTMS, the placebo effect and the brain morphology modifications in patients with schizophrenia (SCZ).
Objectives: The aim of this presentation is to demonstrate the involvement of these both factors in the efficacy of rTMS. Meta-analyses were conducted in 21 articles concerning 303 patients treated by sham rTMS (study 1). The links between anatomical characteristics underlying the temporal cortex target and the efficacy of the rTMS were researched (study 2).
Methods: Study 1: Weighted effect sizes, Hedges's g were calculated taking into account the type of sham condition used, the design of the study (parallel vs crossover), and the efficiency of active rTMS compared to sham rTMS. Study 2: In 15 patients with schizophrenia (DSM IV) treated by rTMS, scalp to cortex distances (SCDs) and gray matter densities (GMDs) were measured in two regions of interest: the motor cortex where the resting motor threshold (rMT) was assessed and the superior temporal sulcus where the treatment was delivered. Correlations between these measures and the decrease of AVH after rTMS treatment were computed.
Results: Study 1: Comparison of the parallel and crossover studies revealed distinct results for each study design; placebo has a significant effect size in the parallel studies but not in the crossover studies. In meta-analysis of the parallel studies, the 45° position coil showed the highest effect size. Finally, the 5 studies that reported a significant superiority of active rTMS over sham rTMS in AVH treatment were generally those for which weak or no placebo effect was observed on average. Study 2: Correlations between the clinical efficacy of rTMS and the temporal target SCD or the GMD were significant. However no correlation between rMT and GMD or SCD in the motor cortex region was observed.
Conclusions: These results support the idea that the treatment efficacy could be related first to the placebo effect and second to the depth of the temporal target. These results fundamentally inform the design and the method of further controlled studies, particularly with respect to studies of rTMS in the treatment of AVH.
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S31.4 A three dimensional symptom structure of schizophrenia is linked to specific structural and functional brain changes

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Background: Eugen Bleuler described schizophrenia as a dissociation of highest order brain functions, i.e. cognition, emotion and volition. It is unclear, however, how the respective phenomenology can be explained by disorders of the working brain. In the last 2 decades, performance in various neuropsychological tasks was correlated with large scale brain network dysfunctions. In recent years, however, also typical schizophrenic symptoms used to diagnose the disorder were matched to structural and functional brain changes. In particular, auditory verbal hallucinations and formal thought disorders were linked to structural and functional abnormalities of the language system. However, movement and communicative motor abnormalities were associated with gray and white matter abnormalities in the motor system, while abnormal limbic structures were found in patients with severe emotional dysregulation indicating further neurobiological pathways to behavioral dimensions in schizophrenia.
Methods: Symptom patterns were assessed in a group of 47 patients with schizophrenia spectrum disorders and 44 healthy controls with the Positive and Negative Syndrome Scale and the Bern Psychopathology scale for psychotic disorders (BPS). The BPS is a neurobiologically informed clinical rating, which allows severity ratings on three behavioral dimensions (language, affectivity and motor). The patient group was stratified according to the symptom severity (severe, mild, no) in each dimension. Whole brain resting state cerebral blood flow (CBF) and voxel-based morphometry were compared between patient subgroups and controls.
Results: Each symptom dimension was be associated with distinct functional and structural (GM) changes with minimal overlap of the findings. Behavioral alterations in the language dimension were linked to increased CBF in Heschl's gyrus, and to reduced GM volume of Broca's and Wernicke's area. Altered affectivity in terms of paranoid experience of threat or power was linked to increased CBF in amygdala, and to GM changes in the ventral striatum. Finally, abnormalities of motor behavior were linked to decreased CBF in the anterior cingulate cortex, and to GM changes in the supplementary motor area.
Conclusions: Investigating behavioral alterations in three schizophrenia dimensions identified distinct regional CBF and GM changes in the language, limbic and motor brain circuits, with minimal overlap. The results suggest different pathophysiological pathways to a limited number of specific symptom dimensions in schizophrenia.

S32. Excitation/inhibition balance disturbances in schizophrenia: from circuits to large-scale networks

S32.1 Inhibitory and disinhibitory GABAergic interactions in the hippocampus of schizophrenics

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Background: Schizophrenia is a neurodevelopmental disorder in which the ingrowth of an excitatory fiber system from the basolateral amygdala (BLA) is suspected of acting as a "trigger" for the onset of this disorder during late adolescence and early adulthood. Based on a combination of postmortem and rodent modeling studies, these glutamatergic excitatory fibers have been postulated to contribute to the dysfunction of GABAergic interneurons within a discrete locus of the trisynaptic pathway defined as the stratum oriens (SO) of sectors CA3/2. GABAergic interneurons at this site receive direct BLA projections and probably play an important role in the regulation of information processing along the trisynaptic pathway. Postmortem studies have demonstrated abnormal expression of GAD67, a key marker for GABAergic function, as well as important genes associated with the regulation of the electrical properties of interneurons.
Methods: Using a rodent model specifically designed to test hypotheses regarding GABA neuron dysfunction in the hippocampus of schizophrenics, the influence of BLA fibers has been stimulated by the stereotaxic infusion of picrotoxin in the stratum oriens of sector CA3/2 where GABA neuron somata are the exclusive neuronal subtype. The influence of these fibers on the electrical properties of GABA cells in the SO of CA3/2 has been analyzed using single cell recordings.
Results: The influence of BLA fibers on these GABA cells is mediated, in part, by kainate-sensitive glutamate receptors (KARs). By adding kainate to the bath, a paradoxical decrease in firing rate, together with a dramatic increase in after-hyperpolarizing (AHPs) currents was observed. When the GluR5 antagonist UBP 296 is added, a further increase in the amplitude of AHPs was recorded in interneurons. Subunits of inotropic KARs (GRIK1, 2 and 3 = GluR5, 6 and 7 subunits, respectively) mediate incoming BLA activity and contribute to the firing rate and amplitude of after-hyperpolarizing (AHP currents) recorded in individual inhibitory basket neurons. An upregulation of an AHP dependent potassium channels (HCN3 = Ih) that regulates GABA neuron firing contributes to a highly significant increase in the amplitude of AHP currents in inhibitory interneurons. Changes in the expression of these various genes may influence the ability of GABA cells at this locus to provide normal or abnormal modulation of the trisynaptic pathway. Both postmortem studies and rodent experiments have suggested that there may be two functional types of interneurons involved in this circuit: ones that are inhibitory in nature and suppress pyramidal neuron firing and ones that provide GABA-to-GABA disinhibitory interactions with these inhibitory cells that suppress inhibitory neuron firing. Evidence from these experiments suggest that changes in KARs containing GluR 6 subunits may influence the activity of both types of GABA cell through postsynaptic receptor-mediated mechanisms on both subtypes of interneuron. On the other hand, KARs containing GluR 5 subunits may be involved in regulating a pre-synaptic GABA-to-GABA modulation of inhibitory GABA neurons at this locus.
Conclusions: Both postmortem studies and rodent experiments have suggested that there may be two functional types of interneurons involved in the SO-CA3/2 circuit: ones that are inhibitory in nature and suppress pyramidal neuron firing and ones that provide GABA-to-GABA disinhibitory interactions with these inhibitory cells that suppress inhibitory neuron firing. Evidence from these experiments suggests that changes in KARs containing GluR 6 subunits may influence the activity of both types of GABA cell through postsynaptic receptor-mediated mechanisms on both subtypes of interneuron. On the other hand, KARs containing GluR 5 subunits may be involved in regulating a pre-synaptic GABA-to-GABA modulation of inhibitory GABA neurons at this locus. Taken together, these studies suggest that an imbalance in the activity of inhibitory and disinhibitory GABA neurons may play a role in the generation of abnormal oscillatory rhythms in patients with schizophrenia.
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S32.2 Genetic evidence for the disruption of excitatory and inhibitory signalling in schizophrenia

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Background: Evidence that disruption of synaptic signaling contributes to schizophrenia pathophysiology has emerged from studies of de novo and large, rare copy number variants (CNVs) (Kirov *et al.*, 2012; Szatkiewicz *et al.*, 2014); rare disruptive and de novo single nucleotide variants and indels (Fromer *et al.*, 2014; Purcell *et al.*, 2014); and more recently from GWAS and common alleles (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). These studies consistently highlight neurotransmitter receptors and associated protein complexes isolated from excitatory glutamatergic synapses. While deficits in inhibitory GABAergic signaling have long been

hypothesised to contribute to schizophrenia, evidence supporting the direct involvement of GABA has as yet not been compelling.
Methods: Autosomal CNV data were collated for 11,355 cases and 16,416 controls from three separate studies: the International Schizophrenia Consortium (ISC); the Molecular Genetics of Schizophrenia (MGS); and a UK study of individuals diagnosed with schizophrenia and taking the anti-psychotic clozapine (CLOZUK) (International Schizophrenia Consortium, 2008; Levinson *et al.*, 2011; Rees *et al.*, 2014). A circumscribed set of annotations related to CNS function were collated and tested for enrichment in case CNVs, controlling for known confounds and differences between studies.
Results: We show for the first time that CNVs from individuals with schizophrenia are enriched for genes involved in GABAergic neurotransmission, providing novel evidence for the disruption of inhibitory signaling in the disorder. Strong, independent associations were also evident for postsynaptic complexes derived from glutamatergic synapses. These sets of genes did not entirely account for the enrichment of CNVs in cases, suggesting that subcellular processes beyond those currently ascribed to GABAergic and glutamatergic complexes remain to be identified.
Conclusions: Consistent with non-genetic reports of GABAergic deficits in schizophrenia, our findings now show that disrupted GABAergic signaling is of direct causal relevance rather than a secondary effect or due to confounding. Additionally, we independently replicate and greatly extend previous findings of CNV enrichment among genes involved in glutamatergic signaling. Given the strong functional links between the major inhibitory GABAergic and excitatory glutamatergic systems, our findings converge on a broad, coherent set of pathogenic processes.

S32.3 Schizophrenia and NMDA receptor deficiency: rebalancing excitation/inhibition disturbances

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Background: Rodent microdialysis studies have shown increases in extracellular glutamate (Glu) in the medial prefrontal cortex (MPFC) following acute administration of ketamine or PCP [1–3]. In schizophrenia (ScZ), proton MRS studies of the same brain region show elevated total-tissue glutamatergic compounds, Glu or glutamine (Gln) or their combination, Glx [4–8] in unmedicated patients. Ketamine studies in healthy human subjects further support this picture by demonstrating acute increases in MPFC total-tissue Glu or Gln [9–11]. Together, these findings raise the question of potential disturbances in excitation/inhibition balance in the illness, possibly arising from NMDA receptor deficits.
Methods: This question is addressed using proton MRS studies with the PRESS J-editing method at 3T that generates simultaneous acquisition of Glx and GABA. Studies using this approach in the MPFC in subjects at ultra-high risk (UHR) for psychosis, in ScZ, and in ketamine administration to healthy subjects are summarized. These provide data to assess concurrent alterations in Glx and GABA.
Results: In UHR subjects, GABA and Glx were found to be 11-12% elevated in MPFC [12]. In ScZ, 30% elevations in the two measures were found in this brain region [8]. In ketamine administration, both compounds increased and returned to baseline on the same time scale, attaining maximal increases of 17% in Glx and 11% in GABA. In addition to these significant mean elevations, GABA and Glx were correlated across subjects ($R = 0.57$; $P = 0.006$ within the UHR group; $R = 0.89$, $P < 0.001$ in the ScZ patients). Correlations did not differ between patient and control groups.
Conclusions: These data suggest a significant disturbance in excitation/inhibition balance in Scz, even before onset of the full clinical syndrome. The ketamine data suggest this disturbance and its rebalancing may be related to NMDA receptor deficits, and that it may occur as rapidly as on the time scale of minutes. The mechanism (s) of excitation/inhibition rebalancing at elevated neurotransmitter levels might include increased Glu neurotransmission stimulating GABA release, or upregulation of GABA-Glu cycling through enzyme-catalyzed biochemical reactions, or both. Increased net synthesis is indicated by these data, since detection of changes in MRS outcome measures require changes in total-tissue concentration and not merely redistribution of neurotransmitters between compartments. Smaller elevations of GABA and Glx in UHR than in ScZ might be related to averaging over subjects some of whom never convert to psychosis. Under ketamine administration, smaller elevations might be due to limitations on the short-term rate of stimulated neurotransmitter synthesis. Significant elevations in GABA and Glx without alterations in GABA-Glx balance suggest powerful homeostatic mechanisms that act to restore excitation/inhibition balance, even at the abnormal levels seen in these studies.
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S32.4 Neural oscillations and e/i-balance parameters across the schizophrenia spectrum: insights from magnetoencephalography (MEG)

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Background: Neural oscillations and their synchronization may represent a versatile signal to realize flexible communication within and between cortical areas. By now, there is extensive evidence to suggest that cognitive functions depending on coordination of distributed neural responses are associated with synchronized oscillatory activity, suggesting a functional mechanism of neural oscillations in cortical networks. In addition to their role in normal brain functioning, there is increasing evidence that altered oscillatory activity may be associated with certain neuropsychiatric disorders, such as schizophrenia, that involve impaired cognition and behaviour. Dysfunctional oscillations may arise due to anomalies in the brain's rhythm generating networks of GABA (γ-aminobutyric acid) interneurons and deficits in NMDA-receptor functioning.
Methods: I will present data obtained with Magnetoencephalography (MEG) in chronically medicated ScZ patients ($n = 20$), unmedicated patients with first-episode (FE) ScZ ($n = 20$) and a group ($n = 40$) of participants at ultra-high risk (UHR) for psychosis. In addition, a group of healthy volunteers were recruited who were administered a subanesthetic dose of Ketamine. MEG signals were analyzed with Morlet-wavelets and a dynamical imaging of coherent sources (DICS) beamformer and transfer-entropy was computed between sources as an index of effective connectivity.
Results: Resting-State Data: FE-ScZ patients and UHR-participants revealed an increase in resting-state neural oscillations and connectivity in the gamma-frequency range in a network including hippocampus, temporal gyrus and thalamus which correlated with the strength of positive symptoms. This upregulation was not present in chronic ScZ-patients.
Task-related MEG-responses: MEG-data were analysed for ERF-responses and oscillatory power at sensor and source-level during the presentation of Mooney faces, a visual stimulus which requires the grouping of stimulus elements into coherent object representations. Similar to chronic ScZ-patients, the amplitude of 60-120 Hz power was significantly reduced at illness-onset although the impairment was less pronounced. In addition, the analysis of M100, M170 and M250 components revealed increased responses in FE-ScZ patients while in chronic patients reductions in all components were observed.
MEG-data during Ketamine: Neural oscillations were recorded in a group of 15 healthy volunteers during the administration of a sub-anaesthetic dose of ketamine (0.006 mg/Kg) and a placebo saline solution in a within-subject design. MEG-data were recorded during the presentation of a sinusoidal grating at rest. The acute administration of ketamine lead to an upregulated gamma-band activity both at rest and during visual processing in health controls. This is possibly

mediated by a shift in the excitation/inhibition balance in favour of excitation of pyramidal cells due to hypofunctioning NMDA-receptors.
Conclusions: The analysis of MEG-data reveals distinct pattern of neural responses in FE-ScZ patients and UHR-participants which is supported by elevated, spontaneous gamma-band activity as well as increased amplitude of ERF-responses which were not observed in chronically medicated ScZ-samples. This pattern of MEG-activity at illness onset is consistent with the effects of the NMDA-R antagonist Ketamine on MEG-parameters in healthy volunteers, suggesting that aberrant glutamatergic neurotransmission may underlie the increased excitability of neural circuits.

S33. Negative symptoms: why they are so important and yet so difficult to treat?

S33.1 Reduction of negative symptoms with the rehacop in chronic patients with schizophrenia

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Background: Cognitive remediation (CR) improves cognition in patients with schizophrenia, but its effect on other relevant factors such as negative symptoms and functional outcome has not been extensively studied
Methods: In this hospital-based study, 84 inpatients with chronic schizophrenia were recruited from Alava Hospital (Spain). All of the subjects underwent a baseline and a 3-month assessment that examined neurocognition, clinical symptoms, insight, and functional outcome according to the Global Assessment of Functioning (GAF) scale and Disability Assessment Schedule from World Health Organization (DAS-WHO). In addition to receiving standard treatment, patients were randomly assigned either to receive neuropsychological rehabilitation (REHACOP) or to a control group. REHACOP is an integrative program that taps all basic cognitive functions. The program included experts' latest suggestions about positive feedback and activities of daily living in the patients' environment.
Results: The REHACOP group showed significantly greater improvements at 3 months in the areas of neurocognition, negative symptoms, disorganization, and emotional distress compared with the control group (Cohen's effect size for these changes ranged from d = 0.47 for emotional distress to d = 0.58 for disorganization symptoms). The REHACOP group also improved significantly in both the GAF (d = 0.61) and DAS-WHO total scores (d = 0.57). Specifically, the patients showed significant improvement in vocational outcomes (d = 0.47), family contact (d = 0.50), and social competence (d = 0.56).
Conclusions: CR may be useful for the reduction of negative symptoms and functional disability in schizophrenia. These findings support the integration of neuropsychological rehabilitation into standard treatment programs for patients with schizophrenia.

S33.2 Changes in dimensions of negative symptoms differentially predict self-rated and observer-rated functional outcomes following cognitive remediation

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Background: The nature of cognitive remediation treatment response is variable across studies. Effects beyond cognition are considerably smaller on functioning and on positive or negative symptoms. Emerging research indicates the structure of negative symptoms is more variable than previously considered, but these effects have not been examined following cognitive remediation.
Methods: Community dwelling adults with schizophrenia ($N = 68$) were assessed before and after 12 weeks of cognitive remediation on cognition, symptoms (PANSS), and observer-rated everyday outcomes (Specific Levels of Function Scale; SLOF). Participants also completed self-rated Quality of Life (QOL; Sheehan Disability Scale). Two dimensions of the PANSS negative symptom domain were examined. Expressive negative symptoms included blunted affect, poor rapport, and lack of spontaneity and flow of conversation. Experiential negative symptoms included emotional withdrawal, passive/apathetic social withdrawal, and active social avoidance. Assessments came from independent raters and scales.
Results: The two negative symptom domains were partially overlapping but shared only 25% variance. Both domains showed non-significant trends for significant improvement. Improvement in observer-rated social outcomes was predicted by improvements in both expressive negative symptoms (r = .37) and experiential negative symptoms (r = .30). However, self-rated improvement social QOL was more strongly associated with expressive (r = .31) than experiential improvements (r = .12). In contrast, patients' self-rated improvements in work/productivity were associated with experiential (r = .24) but not expressive negative symptoms. Again, observer-ratings of work/productivity were equally associated with expressive (.21) and experiential (.24) negative symptoms.
Conclusions: Dimensions of negative symptoms show small and similar improvements following cognitive remediation, with slightly larger improvement in expressive than experiential symptoms. The association of change in everyday outcomes as rated by observers appears to be equally associated with both dimensions of negative symptoms. However, patient self-ratings of their quality of life improvements were differentially associated with negative symptom domains. These findings have implications for the nature of the relationship between measures to assess change in treatment studies.

S33.3 Cognitive remediation can improve social functioning and symptoms in first episode schizophrenia

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Background: For schizophrenia patients cognitive deficits have become critical intervention targets due to their strong links to everyday functioning. Meta-analyses have reported that effects of cognitive remediation might go beyond improvement in cognition to include benefits for symptom reduction and improvements in functioning for chronic schizophrenia patients (McGurk *et al.*, 2007; Wykes *et al.*, 2011). However, little is known about the benefits of these potential treatments at critical intervention points in the early course of schizophrenia
Methods: A RCT compared cognitive remediation to another active intervention, healthy behavior training, in 61 patients (77% male, mean age = 21.9 years, and education of 12.3 years) with a first psychotic episode within the prior two years. Cognitive remediation combined approaches used in chronic schizophrenia by Bell *et al.* and Medalia *et al.*, drawn from neuropsychological rehabilitation and educational remediation fields. A social interactions bridging group was used to link cognitive training to community functioning. Participants trained with 22 computer programs focusing on attention, memory, and problem solving in 50 sessions over 6 months and then completed booster sessions with decreased frequency over the next 6 months. The UCLA Social Attainment Survey assessed changes in social functioning and the BPRS and SANS were used to assess changes in symptoms. The General Linear Mixed Models (GLMM) approach was used to examine the effects of cognitive training on social functioning and symptoms.
Results: From Baseline to 6 months: Cognitive remediation training as compared to healthy behavior training was associated with a significant increase in the trajectory over time of total social functioning on the UCLA Social Attainment Survey ($F(1,138) = 7.1$, $P < .01$). This effect seems to be mostly driven by the domains that deal with opposite dating relationships and peer relations ($F(1,138) = 11.1$, $P < .01$). Cognitive training also resulted in reduced BPRS positive symptoms, defined as combined reality distortion and disorganization ($P = .03$) and reduced negative symptoms as assessed with the BPRS score for blunted affect ($P = .03$) and SANS Global score for anhedonia ($P = .05$).The same general pattern held for the period from Baseline to 12 months.
Conclusions: The beneficial effects of cognitive remediation training, when combined with a bridging social interactions group intervention, extend to improvements in symptoms and social functioning in

recent-onset schizophrenia patients. These results suggest that cognitive remediation might have an impact in the early course of schizophrenia that reaches beyond cognition at a time that reduction of risk for chronicity is most critical. Future research might explore whether improvements in social functioning are mediated by improvements in cognition or symptoms.

S33.4 Cognitive remediation for negative symptoms of schizophrenia: a network meta-analysis

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Background: Cognitive remediation (CR) is a treatment targeting cognitive difficulties in people with schizophrenia. Recent research suggested that CR may also have a positive effect on negative symptoms. This meta-analysis investigates the effect of CR on negative symptoms.
Methods: Systematic search was used to identify all randomized-controlled trials of CR in people with schizophrenia reporting negative symptoms outcomes until May 2015. Levels of negative symptoms at baseline, post-therapy and follow-up, sample demographic and treatment length were extracted. Study methodological quality was assessed. Heterogeneity was addressed with I2 and Q statistic. Standardized mean change in negative symptoms was calculated and used as the main outcome.
Results: The search identified 40 studies reporting results for 2095 participants; 13 studies reported follow-up outcomes. Approximately 75% of the studies used the PANSS as a measure of negative symptoms. CR was associated with a reduction of negative symptoms (-0.39; 95% CI: -0.47, -0.30) at post therapy compared with treatment as usual and this effect was largely maintained at follow-up (-0.36; 95% CI: -0.51, -0.21). Drop-out rate between CR and TAU was comparable. Network meta-analysis confirmed CR was superior to TAU and TAU plus active control or adjunctive treatment. No evidence of publication bias was found.
Conclusions: Despite negative symptoms are not yet being considered a primary target for CR, this intervention can have small to moderate beneficial effects on this symptom cluster. Future research should explore more in detail the active mechanisms responsible for negative symptoms improvement and the relationship between cognitive and negative symptoms in people with schizophrenia

S34. Lifespan development of schizophrenia and how the treatments improve the outcomes

S34.1 MRI-BASED RISK STRATIFICATION IN CLINICAL HIGH-RISK INDIVIDUALS: STATE-OF-THE-ART AND CHALLENGES AHEAD

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Background: Recent meta-analyses on the single-subject neurodiagnostic separability of patients with schizophrenia from healthy volunteers have demonstrated classification accuracies between 70% and 80%. Although these findings point to robust neuroanatomical and neurofunctional surrogate markers or schizophrenia, it is doubtful that these surrogates (1) homogeneously subserve the disorder's diverse clinical phenotypes; (2) specifically demarcate the diagnostic borders between schizophrenia and affective psychoses, and (3) remain static throughout a lifespan of brain maturation and aging.
Methods: The talk will first focus on findings of structural heterogeneity observed across different schizophrenic symptom dimensions. Then, the impact of this heterogeneity on the neuroanatomical classification of patients with schizophrenia vs. healthy controls and patients with other non-affective psychoses and personality disorders will be discussed. Finally, the talk will investigate how these multiple disease surrogates may be linked to abnormal brain maturation and whether they can already be traced in the at-risk and prodromal phases of schizophrenia.
Results: (1) Separability of neuroanatomical patient subgroups in schizophrenia and (2) quantification of their presence in bipolar disorder, major depression and at-risk individuals, (3) predictive value of these patterns in estimating adverse mental-health outcomes in psychosis.
Conclusions: Neuroanatomical dysmaturation seems to be a core feature of the disorders that is present early in the course of the illness and may affect a subgroup of patients with pronounced negative symptoms and poor disease outcomes.

S34.2 Somatic comorbidity and its outcomes in schizophrenia during lifespan

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Background: Studies mainly relied on hospital or case-control data have well documented that individuals with psychoses, and especially with schizophrenia have increased rates of physical illnesses. They have two to four-fold higher mortality risk, and about 10 to 25 years shorter life expectancy compared with the general population. The aim of this study is to evaluate the prevalence of physical illnesses in individuals with schizophrenia or with other psychoses and among people without psychoses until the age of 46 years using complete outpatient and inpatient data from birth cohort.
Methods: The study is based on The Northern Finland 1966 Birth Cohort (NFBC 1966), which is a population-based prospective cohort concerning 12.058 live-born children in 1966 in the provinces of Lapland and Oulu. The study population consisted of 10.933 individuals, who were alive at the age of 16-years, and followed serially until the age of 46-years.The study population was divided into three groups: those having schizophrenia ($N = 228$) and those with other psychoses ($N = 240$) while individuals without psychosis ($N = 10.465$) formed the control group. The data was obtained from various national registers.
Results: Diseases of the blood and blood forming organs (prevalence in SCZ was 17% versus 10% in controls, $P < 0.001$), endocrine, nutritional and metabolic diseases (45% vs. 27%, $P < 0.001$), diabetes mellitus (7% vs. 3%, $P < 0.001$) and nervous diseases (33% vs. 25%, $P = 0.018$) were more common among individuals with SCZ compared with controls. Diseases of musculoskeletal system and connective tissue were less common in SCZ than among controls (28% vs. 41%, $P < 0.001$). People with other psychoses than SCZ had statistically significant association with all the diagnostic groups classified in ICD-10 except with neoplasms. Infections and parasitic diseases (prevalence in other psychoses was 44% versus 32% in controls, $P < 0.001$), diseases of the blood and blood forming organs (18% vs. 10%, $P < 0.001$), endocrine, nutritional and metabolic diseases (42% vs. 27%, $P < 0.001$) including diabetes mellitus (9% vs. 3%, $P < 0.001$), nervous diseases (40% vs. 25%, $P < 0.001$), diseases of the eye and adnexa (32% vs. 21%, $P < 0.001$), diseases of the ear and mastoid process (58% vs. 44%, $P < 0.001$), diseases of circulatory (50% vs. 37%, $P < 0.001$), respiratory (70% vs. 60%, $P < 0.001$) and digestive system (77% vs. 68%, $P = 0.004$), diseases of skin and subcutaneous tissue (23% vs. 16%, $P = 0.006$), diseases of musculoskeletal system and connective tissue (51% vs. 40%, $P = 0.004$) and diseases of genitourinary system (41% vs. 31%, $P = 0.003$) were more common among people with other psychoses than SCZ compared with controls.
Conclusions: A new finding is that not only people with schizophrenia but especially those with other psychoses show a greater occurrence of somatic diseases compared with those without psychosis. The increased occurrence of somatic comorbidity in other psychoses should be noted by medical professional, and further longitudinal studies are warranted to study its possible risk factors during lifespan.

S34.3 Long-term outcome of psychosis: modulation by environmental factors like exercise

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Background: Schizophrenia is a severe mental disorder leading to life-long disability in a substantial proportion of the sufferers. One of the

predictors for an unfavorable outcome is a cognitive deficit especially in the domain of episodic and working memory.
Methods: Furthermore, episodic memory deficits as measured by the VLMT are correlated to a volume loss especially in the left hippocampal formation.
Results: Interestingly, in mice running wheel improves synaptic plasticity as well as performance in the Maze test. Hence we have accomplished an initial study (Exercise I) comparing the effect of three months indoor cycling by means of clinical parameters, neuropsychology and brain measures in patients with multi-episode schizophrenia vs. healthy controls and patients playing table football. The patient group performing cycling revealed a volume increase of the hippocampal formation as measured with structural MRI, increase of the NAA/CRE ratio in the same brain region as measured with MRS and an improvement of the episodic memory domain.
Conclusions: In a follow-up study (Exercise II) physical exercise was combined with cognitive remediation leading to significant functional improvement as measured by GAF and SAS. However, after termination of the 3 months exercise package the functional improvement was lost after 3 months at 5 months follow up. Therefore, physical exercise seems to be a good means to induce, but necessarily maintain synaptic plasticity. Long-term studies are needed to study the possibilities to maintain exercise-induced synaptic plasticity, at least in a subgroup of patients. A possible design of such a study will be discussed during the presentation.

S34.4 Antipsychotic medication and outcomes in schizophrenia from a lifespan perspective

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Background: Antipsychotic medications play an important role in schizophrenia, and their efficacy in the relapse prevention and treatment of acute psychotic symptoms is clear-cut. However, data on their long-term use and impact on prognostic issues is limited, although some previous studies noted a high risk of relapse during the first two years after the first acute psychosis. Our aim was to study the characteristics and clinical course of medicated and unmedicated schizophrenia patients.
Methods: The study population consisted of schizophrenia patients from the Northern Finland 1966 Birth Cohort. Altogether 70 participants with a schizophrenic psychosis according to DSM-III-R were accepted for the current study. Use of antipsychotics was examined in the follow-up interview by asking about the subjects' medication history during the previous three months. The sample was divided into a non-medicated group ($n = 24$) and a medicated group ($n = 46$).
Results: Men were more likely non-medicated than women (63% vs. 50%). The non-medicated subjects were more often employed or unemployed and less often on a disability pension than the medicated subjects. Relapses during the follow-up were equally frequent between non-medicated and medicated subjects (47% vs 53%). Not having been hospitalised during previous five years, but not previous two years, before the interview predicted long-term successful antipsychotic withdrawal without relapse. Fifteen of the subjects in the non-medicated group (63%) and 9 in the medicated group (20%) were in remission.
Conclusions: The present results imply that there are some individuals with schizophrenic psychoses not using antipsychotic medication whose psychotic illness and clinical course are so favourable that they do not necessarily need medication permanently. Changes in the antipsychotic dosing should not be made too fast and the patient and relatives should be able to contact without delay if exacerbation of psychotic symptoms is suspected.

S35. Social (cognitive) functioning in schizophrenia: mechanisms, course and treatment

S35.1 Origins of social deficits in the psychosis phenotype

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Background: Social deficits are a core feature of psychotic disorders and are thought to emerge many years before first signs of illness. However, only few studies have been able to elucidate the extent and developmental progression of social deficits in the psychosis phenotype.
Methods: Data from the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort were analysed: social knowledge, practical judgment in social situations, level of social maturation, and the extent of development of moral conscience were measured at ages 4, and, 8; psychotic like experiences (PLEs) and psychotic disorder were ascertained at age 18 using a structured interview.
Results: Deficits in social knowledge and social judgment emerged more than a decade before symptoms (Effect size at age 4 = -0.26). Distinct developmental trajectories distinguished the PLEs and psychotic disorder groups: whereas deficits decreased from age 4 to 8 in the PLEs group (Effect size change = 0.26), they increased in the disorder group (Effect size change = -0.15).
Conclusions: The findings show that social deficits emerge early on in those experiencing psychotic symptoms in adulthood and also that different clinical outcomes follow distinct developmental trajectories. These findings suggest that the origins of psychosis include a developmental process evident from early childhood (age 4 years). Children who will grow up to develop a psychotic disorder experience increasing difficulties in understanding social situations and making practical judgments in social situations as they get older.

S35.2 The 20-year longitudinal trajectories of social functioning in psychotic disorders

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Background: Social deficits are a core feature of schizophrenia and common in other psychotic disorders. Nevertheless, only a few studies have systematically investigated the course of social impairment in psychotic disorders, yielding mixed findings. We will present new data on the 20-year differential longitudinal trajectories of social functioning in patients diagnosed with psychotic major depressive disorder, psychotic bipolar disorder and schizophrenia.
Methods: We used data from the Suffolk County Mental Health Project (New York, US), a county-wide study of first-admission patients with psychotic disorders ($n = 485$) followed over a 20-year period and a non-psychotic comparison group ($n = 262$). Social functioning was assessed at 6 months, 2, 4, 10 and 20 year after first admission. Latent Class Growth Analysis was applied to establish latent trajectories of social functioning across and within diagnoses. Regression analyses were used to examine how these latent trajectories were associated with premorbid functioning scores in childhood, early- and late adolescence.
Results: Four latent trajectories with stable life-course trajectories of 'Preserved', 'Mildly Impaired', 'Severely Impaired', and 'Profoundly Impaired' social functioning were identified. Differences between these trajectories were already evident in childhood, with the two most impaired trajectories starting to diverge from each other in early adolescence. Specifically, those with the lowest social functioning during childhood showed the lowest social functioning over the course of 20 years.
Multiple trajectories were represented within each disorder, however relatively more participants with schizophrenia were in the more impaired trajectories and relatively more with mood disorders were in the better functioning categories. Social functioning at 20-years was significantly worse in the three lowest trajectory classes (all $P < .001$) compared to Never Psychotic individuals.

Conclusions: The current results demonstrate four surprisingly stable functional trajectories that differ quantitatively in severity across psychotic disorders. However, social functioning also varied widely within disorders, which suggests a need for continuous representation of social outcomes.
Our findings indicate that a large group of individuals admitted to hospital with psychotic disorders have lifelong, stable social impairment. These findings highlight the importance of detailed assessment of social functioning and emphasize the need for targeted, transdiagnostic treatment interventions aiming to preserve and improve social functioning.

S35.3 Trust vs. paranoia: the dynamics of social interaction in early and chronic psychosis

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Background: Psychosis is associated with severe social dysfunction. Impaired trust and a insensitivity to positive social cues of others have been shown to impact negatively upon social interactions of adults with chronic psychosis. However, the tendency to trust and to cooperate changes from adolescence to adulthood. As such, the early stages of psychosis might present a window of opportunity to foster trust and social sensitivity. To elucidate this we investigated interpersonal trust and its impact on social interactions in early and chronic psychosis.
Methods: Two multi-round trust games with a pre-programmed cooperative and unfair game partner were used to assess differences in trust in response to positive and negative social partner behaviour. The sample consisted of 79 patients with psychosis (39 early and 40 chronic cases) and 140 controls. Associations between group status and trust (amount invested) were analyzed by means of multilevel random regression analyses. In addition, we investigated the associations between trusting behaviour and psychotic symptoms in the patient groups.
Results: Patients with early and chronic psychosis did not differ in their basic trust (initial investments) towards others but both groups showed lower trust than controls ($P < 0.01$). Patients with early psychosis increased their trust towards similar levels as controls ($P = 0.37$) during cooperative interactions. Patients with chronic psychosis, in contrast, showed lower trust than patients with early psychosis and controls (both $P < 0.01$). The three groups did not differ in their levels of (basic) trust towards the unfair game partner. There were no significant associations between (basic) trust and symptom levels in early or chronic psychosis patients.
Conclusions: Regardless of illness phase and symptom levels, psychosis is associated with compromised (basic) trust towards others. Suggestive of a higher sensitivity for positive social signals, early psychosis patients increased their levels of trust towards levels of controls in response to a cooperative partner. In line with earlier research, chronic psychosis was specifically associated with an insensitivity to cooperative others. The loss of basic trust paired with insensitivity to positive social signals may aggravate social dysfunction in chronic illness stages. The findings suggest that early illness stages present a window of opportunity for interventions that aim to keep the behavioural flexibility towards others intact.

S35.4 Oxytocin for schizophrenia: a randomized controlled trial

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Background: Both human and animal studies have found that the neuropeptide oxytocin (OXT) is involved in regulating affiliative behaviors, including sexual behavior, mother–infant and adult–adult pair-bond formation. Social dysfunction is among the most disruptive outcomes of schizophrenia. Intranasal OXT administration has been reported to have pro-social effects in patients with autism spectrum disorders and with schizophrenia. The aim of this study was to examine the effectiveness of intranasal administration of OXT alone, and of OXT combined with social skills training in the treatment of social dysfunction in patients with schizophrenia.
Methods: Using a 2X2 design, we conducted a randomized, double blind, placebo-controlled, 3 week trial testing the effect of intranasal OXT (24IU X3/d) or placebo in combination with social skills training or supportive psychotherapy. Subjects were 51 patients with schizophrenia or schizoaffective disorder with significant impairment of their social abilities, stabilized on anti-psychotics. The primary outcome measure was a structured assessment of social interaction, done by video-taping interviews with subjects and then having raters blinded to treatment status assessing the quality of the social interactions, specifically focusing on gaze to experimenter's face, vocalization (patient's vocal output, positive/negative tone, and fluent speech) and affect, body tone, movements, and other non-verbal signals. Secondary outcome measures included PANSS and the PENN Emotion recognition tasks.
Results: Of the 51 patients randomized, 48 completed the study (23 in the oxytocin and 25 in the placebo group). Analysis of the primary outcome measure did not show significant effects of oxytocin in any of the variables rated (all P values > 0.05). However, the following variables did show non-significant improvement in patients receiving drug compared to placebo during the social interaction: positive affect, effect size (ES) = 0.20, negative affect ES = 0.53, fluency of conversation was found in the PENN-CNP emotion battery tasks, nor in the PANSS scales (all P values > 0.05).
Conclusions: Although changes were not statistically significant, oxytocin improved affect, reduced tension and improved fluency of social interactions at effect sized of mild-moderate amplitude, and it is conceivable that larger sample sizes will yield statistically significant findings. These variables might reflect subtleties of social interaction not reflected in PANSS scores. The results of the published studies of add-on oxytocin vs placebo for schizophrenia are heterogeneous with both positive and negative findings. We conclude that before further studies are performed, individual patient meta-analyses of all add-on oxytocin studies in schizophrenia should be performed.

PL36. Feeding from bedside into bench, and back to bedside: towards better understanding of schizophrenia

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Abstract: The diagnostic boundaries defined by current diagnostic systems are being challenged by recent advances in the genetic architecture of psychiatric disorders. The field of psychiatry is now moving towards a "dimensional" approach to understanding mental disorders, based on specific phenotypes with defined biological etiology and pathophysiology. We have built an infrastructure to conduct preclinical and clinical studies seamlessly to seek the goal of early diagnosis and intervention for psychotic and mood disorders. Study participants are characterized at the levels of clinical psychiatry and psychology. Then, we study the patients, according to molecular and/or cellular phenotypes obtained from their cells via biopsies, in combination with brain imaging and other physiological studies that provide the information at the circuitry level. In the clinical study domain, we explore correlations among molecular, cellular, circuitry, and behavioral characteristics. Mechanistic link among these characteristics at the different levels is addressed by using animal models in which we use cutting-edge methodologies of molecular and circuitry interventions in pathological trajectories. In summary, we aim to clarify common pathophysiological pathways for the mental conditions downstream of a wide variety of etiopathogenesis. My talk here will include the following topics: 1) Utility of nasal biopsy: genome-wide epigenetic study and a novel, non-invasive brush swab approach. 2) Combination of stem cells, brain imaging, neuropsychology, and animal models: elucidating the role for specific phosphorylation of DISC1 protein in neurodevelopment and cognitive function. 3) Perspectives: how are preclinical and clinical studies integrated to address clinical and scientific questions?

S37. Second chance: what would senior schizophrenia researchers do if they could start over again?

S37.1 A schizophrenia research plan as psychiatry merges with neurology

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Background: This will be a discussion of the future of research on schizophrenia.
Methods: A listing was made of research on schizophrenia that would be carried out if I were just starting my career.
Results: The research would include the following:
I would look for a 3 or 4 year program that would allow me to do one year of neurology; one year of neuropathology; and one year of intensive clinical work working with patients with schizophrenia and bipolar disorder. Primary position: I would look for a fulltime clinical position in the psychiatric unit of a major medical center with an inpatient unit and a large number of admissions of individuals with serious mental illnesses (SMI). The medical center should also have a strong infectious disease department that was willing to collaborate on research. I would take responsibility for a large number of SMI, starting with their first admission, and would follow them indefinitely. On all patients I would obtain a detailed childhood history of pet exposure and infectious diseases. Serum, CSF, neurological, MRI, and DTI would be obtained prior to beginning treatment and thereafter every 3 years and/or at the time of any relapse. This patient cohort would be used to accomplish three goals: 1. Identify infectious agents that are involved in the etiology. 2. By linking patient symptoms to MRI and DTI findings over time, establish the neuroanatomical pathways involved with specific symptoms. 3. Carry out treatment trials of anti-inflammatory and anti-infective agents. Insofar as I had research funds available to support other research activities I would support the following: 1. A postmortem brain bank similar to the Stanley Brain Bank 2. A longitudinal study of children similar to the Avon Longitudinal Study being carried out in England 3. Epidemiological research on schizophrenia, especially including immigrant studies (e.g., collect serum for antibody studies prior to, then again after, immigration. I would also support detailed studies of geographic areas thought to have unusually high or low prevalence of schizophrenia.). Research areas of low priority would include genetic studies and perinatal studies of schizophrenia. For example, I would not again undertake the study of monozygotic twins.
Conclusions: If I were starting my research over, I would focus on some of the same and some different issues.

S37.2 On recovering from a delusion

Robin Murray*[1]

[1]*Institute of Psychiatry, KCL*

Background: I spent too much time investigating minute differences on brain structural and functional imaging between people with schizophrenia and control subjects, imagining that these were pathognomonic of what we then thought was a discrete disease. Now we know that these deviances are largely a reflection of non-specific factors (e.g., lower IQ, exposure to antipsychotics or illicit drugs), and that schizophrenia is a syndrome with multiple risk factors, genetic and environmental
Methods: N/A
Results: I wish I had moved into epidemiology earlier than I did, and in particular into the role of social risk factors which were largely ignored in the first two decades of my academic life. I am glad to have recovered from my early Kraepelinian delusion that schizophrenia is a deteriorating disorder but sadly this notion continues to mesmerise many biological researchers, and does untold harm to patients. If I had my time over I would use long-term outcome studies to publicise the fact that 10 years after onset, more than half the people diagnosed as schizophrenic have no psychotic symptoms.
Conclusions: I am most interested in aetiology, and here genetics and epigenetics are moving fast. Therefore if I were starting out now I would train in genomics, and go on to examine gene-environmental interactions. My bet is that different environmental risk factors (e.g., child abuse; cannabis use) will interact with quite different genes. This knowledge will give us a range of different approaches to treatment and ultimately to prevention.
If I wasn't clever enough to do this I would study pathogenesis and in particular neurochemical imaging Learning Chinese would probably also be a good idea.

S37.3 Possibilities and pitfalls - reflections on 42 years in academic psychiatry and lessons for a suggested repeat performance

Eve Johnstone*[1]

[1]*The University of Edinburgh*

Background: I worked from 1968 until 2010 in psychiatry, most of the time as an academic, with an emphasis on research in schizophrenia. Overall it seemed to me to go well. Could I do it again, starting now?
Methods: My initial aim of finding a cure for schizophrenia may have failed but at least the idea that there is nothing wrong with the brains of people with schizophrenia is not now seriously advanced. I focused on imaging work, treatment trials and large clinical studies and these went well but other areas which I was fortunate to avoid but which did look good for a while turned out to be false dawns. Successful progress depends on choosing the right area but avoiding blind alleys is just as important. There is much to be said for deriving research ideas from what you see in clinical reality and avoiding areas which do not fit with your clinical experience. What would I do if I had the chance to do it again? I do not think I can ask any more of imaging. The kind of trials I did are difficult now because the level of inpatient care required is not easy to achieve but it is important to keep up with advances and possibilities.
Results: The possibility that attracts me is that stem cells can be derived from affected people with minor genetic anomalies and can be grown in dishes where the weaknesses of their synaptic function may be visualised and at least potentially the effect of relevant drugs upon these weaknesses examined. As far as psychosis is concerned this is a future hope rather than a present reality but I think it may be realised. If I could work for even 10 more years I would like to be peripherally involved. I could not do the lab work but involvement would allow me to do what I probably do best, to harness the assets of my environment to do the right assessments in the right patients and engage with families to include affected and unaffected members in studies which can be very long term. With the right questions, studies of this kind may well yield a very great deal.
Conclusions: Until we find a cure, clinical studies of an experimental kind are an area which will not become a 'false dawn' but they have to be tied to the right scientific advances.

S37.4 A personal retreat and advance

William Carpenter*[1]

[1]*The University of Maryland School of Medicine*

Background: Personal engagement in research concerned with schizophrenia began in 1968. The acquisition of knowledge and understanding related to persons with schizophrenia has been central in my career as investigator, research leader/administrator and journal editor. Much has changed and developed over these years, but advance in knowledge is slow.
Methods: Introspection to address how I wish I had done my work. Thought experiment to anticipate future work assuming a new career start.
Results: In retrospect, progress related to my work could have been accelerated with less reliance on publications and more advocacy. Anticipation of future is based on domains of pathology as clinical phenotypes, deconstruction at more fundamental levels, and emphasis on new paradigms integrating resilience and compensatory mechanisms in therapeutic discovery and secondary prevention of psychoses.
Conclusions: Progress has been unnecessarily slow. This can be fixed. Schizophrenia is not a target for discovery. Alternative paradigms are essential and are not restricted to pathophysiology.

S38. Global perspectives on stigma in the clinical high risk state for psychosis: new empirical advances

S38.1. Risk of psychosis, mental illness stigma and suicidality

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Background: Young people at risk of psychosis are also at greater risk of suicide. The stigma and discrimination associated with mental illness may contribute to this suicide risk. An argument to support this hypothesis is that many consequences of stigma, e.g., social isolation or hopelessness, are predictors of suicidality. Furthermore labeling processes and the experience of stigma as a stressor that exceed individual coping resources begin during the at-risk phase. However, empirical data on this issue are lacking.
Methods: In a longitudinal study in Switzerland, the level of perceived public stigma, self-labeling as "mentally ill", stigma-related stress and suicidal ideation were assessed by self-report measures among 172 young people at risk of psychosis. The measures were re-administered to participants after one year.
Results: Findings on self-labeling and stigma variables at baseline as predictors of suicidality, both at baseline and after one year, will be presented.
Conclusions: The role of self-labeling and stigma-related stress for suicidality is compatible with diathesis-stress models of suicidality. Our findings have implications for early intervention and suicide prevention for young people at risk. If our results are corroborated by future studies, such programs should take labeling and stigma processes into account in order to reduce suicide risk.

S38.2 Self-perceptions of having a mental illness and relationship with help - seeking from Brazilian and UK community samples of young people at-risk of psychosis

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Background: The recognition that attenuated symptoms and significant disability typically precede onset of frank psychosis has led to early intervention strategies that target help-seeking individuals in the prodromal phase of illness that precedes onset of psychotic disorder. Previous research has shown that self-identification as being mentally ill among a non-clinical sample of adults was associated with subsequent help-seeking behaviour. Little is known about how young people perceive their own identity in relation to having a mental illness alongside the development of such psychotic symptoms. This study examines self-identity in relation to mental illness and relationship with help-seeking among community samples of young people at-risk of developing psychotic disorder.
Methods: Data were collected on self-identification in relation to mental illness, mental health service use and intended help-seeking from two existing, ongoing prospective cohorts in the UK and in Brazil. Participants were recruited from primary schools. Participants come from enriched community cohorts (including a greater than average proportion of young people at risk of developing psychotic disorders) in Greater London ($n = 550$) and a similar cohort of young people in Brazil ($n = 1{,}500$).
Results: Findings on the relationship between self-identity in relation to mental illness, mental health service use and intended help-seeking, will be presented.
Conclusions: Perceptions of mental illness and self-identity among young people at risk of psychosis who do not yet use clinical services could be important for future help-seeking. Future research should investigate the stability of self-perceptions over time in relation to the development of mental illness and how this is related to long term help-seeking and mental health service use among young people.

S38.3 Stigma of people at clinical high risk state for psychosis in a Chinese population

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[1]The University of Hong Kong

Background: Research and clinical services for people at clinical high risk of psychosis is developing in Hong Kong. Social implications of this diagnostic label remain a concern as stigma remains a major issue in the Chinese population. We conducted a cross-sectional survey designed to examine public stigma towards people at clinical high risk of psychosis in Hong Kong when compared with other diagnoses.
Methods: Four vignettes depicting individuals suffering from the clinical high risk state for psychosis, schizophrenia, depression and psychotic-like-experiences were presented and participants were asked to complete a self-administered questionnaire to assess seven aspects of stigma.
Results: Overall, the stigma associated with the clinical high state for psychosis is less than that of schizophrenia, but higher than the stigma associated with depression or psychotic-like-experiences. Stigma was also associated with gender, age, education level, occupation and having had a previous visit to mental hospital.
Conclusions: The study explored the potential stigma associated with the identification of the clinical high risk state for psychosis in comparison with other mental disorders in a Chinese population. That stigma was elevated in the clinical high risk state for psychosis when compared with depression or psychotic-like experiences indicates that this identification may be associated with greater stigma in Chinese populations. Further implications for cultural differences that stigma may take in Asia will be discussed in conjunction with their implications for clinical services and research for individuals at clinical high risk state for psychosis.

S38.4 Stigma related to initial self-identification of being 'at high risk for psychosis' vs. a 'non-psychotic disorder' in individuals at clinical high-risk for psychosis

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Background: The clinical high risk state for psychosis syndrome (CHR) offers substantial potential benefits in terms of early identification and treatment for at-risk youth. Early treatment might lead to decreased symptoms, thus leading to reduced symptom-related stigma. However, stigma of the clinical high risk state for psychosis designation might also initiate further stigma. An unresolved issue is that the relative stigma associated with symptoms, as opposed to the label of risk (i.e., attending a specialized CHR clinic), is not known. Differentiating the relative impacts of these sources of stigma is critical in order to best minimize stigma associated with CHR identification.
Methods: Stigma assessments were conducted with 100 clinical high risk state for psychosis individuals as part of a major, NIH-funded longitudinal study at Columbia University Medical Center, Harvard University Medical Center, and Maine Medical Center from 2011 to present. Labeling-related measures adapted to the CHR group included measures of internalized stigma and shame associated with attending a specialized CHR clinic. Parallel stigma measures to assess stigma associated with CHR symptoms were also administered. In the first presentation of findings from this study, these measures will be examined in relation to symptoms of anxiety and depression, adjusting for core CHR symptoms (e.g., attenuated psychotic symptoms).
Results: Relative levels of stigma associated with the label of risk (i.e., attending a specialized CHR clinic) vs. the levels of stigma due to CHR symptoms and experiences will be presented. A recently published pilot study indicated that CHR participants described less stigma associated with attending CHR services than they did due to

symptoms; if corroborated in this study, this could ameliorate one major potential barrier to the adoption of CHR identification worldwide. Further, findings illustrating the relationship between stigma associated with the label of risk vs. stigma of symptoms and their associations with anxiety and depression will be presented.
Conclusions: Both stigma of attending a specialized CHR clinic and stigma of symptoms contribute to the experience of CHR individuals. Determining whether label-related and symptom-related stigma are associated with symptoms enhances our understanding of how different forms of stigma might differentially impact CHR individuals. Furthermore, delineating if one or both forms of stigma are salient to the experience of CHR individuals is essential to designing interventions to reduce potential risk of stigma at identification. These findings have potential implications for guiding implementation of CHR services both in the United States and worldwide.

S39. Clinical and neurobiological impact of physical exercise interventions in schizophrenia

S39.1 Changes in brain connectivity after endurance training in schizophrenia

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Background: It has been shown that learning a new skill leads to structural changes in the brain. However, it is unclear whether it is the acquisition or continuous practicing of the skill that causes this effect and whether brain connectivity of patients with schizophrenia can benefit from such practice.
Methods: We examined the effect of 6 months exercise on a stationary bicycle on the brain in patients with schizophrenia and healthy controls. Biking is an endemic skill in the Netherlands and thus offers an ideal situation to disentangle the effects of learning vs practice. The 33 participating patients with schizophrenia and 48 healthy individuals were assigned to either one of two conditions, i.e., physical exercise or life-as-usual, balanced for diagnosis. Diffusion tensor imaging brain scans were made prior to and after intervention. In addition, cardiovascular fitness, oxygen uptake, BMI and IQ were assessed.1
Results: We demonstrate that irrespective of diagnosis regular physical exercise of an overlearned skill, such as bicycling, significantly increases the integrity, especially of motor functioning related, white matter fiber tracts whereas life-as-usual leads to a decrease in fiber integrity.2 in patients, a decrease in positive symptoms over time significantly correlated with fractional anisotropy improvement over time. There were no significant associations of fractional anisotropy with body mass index, heart rate at rest, heart rate at maximum, and IQ in both groups, and with other PANSS scores and with chlorpromazine dosage in the patients.
Conclusions: Thus, regular training on a bicycle improves the brain network and learning of a new – and often complicated- skill is not required for this training to be beneficial. Moreover we find that mental health outcome in patients recuperated after the period of exercise; specifically, alleviation of positive symptoms and increasing white matter integrity seemed to go hand-in-hand. Interestingly, a growing body of evidence suggests possibly direct contributions of activation of fiber bundles to changes in white matter.3 Our findings imply that exercise of an overlearned physical skill improves brain connectivity in patients and healthy individuals. This has important implications for understanding the effect of fitness programs on the brain in both healthy subjects and patients with schizophrenia.
References:
1. Scheewe *et al*. Eur Neuropsychopharmacol 2014.
2. Svatkova *et al*. Schizophr Bull 2015.
3. Mandl *et al*. Frontiers of Hum Neurosci 2013.

S39.2 The impact of endurance training on brain structure and function in schizophrenia patients

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Background: Structural and functional brain alterations as well as cognitive deficits are well-documented findings in schizophrenia patients. Cognitive impairments affect the long-term outcome of schizophrenia and are the main contributors to disability. Despite their clinical impact, however, no effective options are available to treat them sufficiently. Aerobic endurance training has been shown to have effects on brain plasticity, gray and white matter volume as well as functional connectivity measures and on cognitive functioning.
Methods: 21 chronic schizophrenia patients and 21 age- and gender-matched healthy controls underwent 3 months of aerobic exercise (endurance training, 30 min, 3 times per week). 21 additionally recruited schizophrenia patients played table soccer (known as "foosball" in the USA) over the same period. After 6 weeks of endurance training or table soccer, all participants commenced standardized cognitive training with a computer-assisted training program. Clinical symptoms, thorough neuropsychological testing and multimodal neuroimaging with 3D-volumetric T1-weighted sequences as well as task-based fMRI and DTI were performed on a 3 T MR scanner at baseline and after the 3-month intervention and 3 additional training-free months.
Results: In summary, a 3-month endurance training program combined with CR therapy for the last 6 weeks of the intervention period had positive effects on everyday functioning in multiepisode schizophrenia patients. Deficits improved from medium to mild as assessed with the GAF. Negative symptoms, short- and long-term verbal memory and cognitive flexibility also improved with endurance and cognitive training. We could demonstrate grey matter volume increase in the left temporal lobe in schizophrenia patients undergoing endurance training. A non-endurance and coordinative training stimulus like playing table soccer led to a clearly distinct pattern of grey matter alterations in schizophrenia patients. There were no effects of the intervention on brain networks in schizophrenia patients. *Conclusions*: Aerobic exercise interventions can be feasible and effective interventions for schizophrenia and help to disentangle the underlying brain pathology of the disorder.

S39.3 An exercise intervention for patients with antipsychotic-resistant schizophrenia

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Background: Aerobic and other forms of exercise appear to offer benefits for patients with schizophrenia, in the domains of symptoms of psychosis, depression, cognitive function, and perhaps partial amelioration of smaller than expected volume of the hippocampus. The feasibility of implementing exercise programs for patients that are poorly responsive to antipsychotics, and the potential benefits need further investigation.
Methods: Seventeen chronic refractory schizophrenia inpatients were enrolled in a 12-week exercise intervention trial that included aerobic and resistance training. Symptom severity was assessed with the PANSS, exercise physiological assessments included body mass index (BMI), resting heart rate (RHR), blood pressure (BP), VO2 Max). Memory functioning was studied with the Hopkins Verbal Learning Test Revised. MRI data (3D structural MRI, 3 T) were ascertained at baseline and 12 weeks.
Results: Mean total PANSS scores declined from 95.6 to 78.8 ($P < 0.001$), however changes in medication also occurred during the inpatient stay. A small improvement in mean BMI was seen (28.3 to 27.2, $P = 0.03$). Measures of RHR, BP and VO2 Max were not statistically different at 12 weeks. A small increase in total hippocampal volume was observed after 12 weeks of exercise (1.5%,

$P = 0.02$). Of interest, improvement in verbal memory was positively associated with change in left entorhinal cortex thickness ($P = 0.01$), but not with left hippocampal volume.
Conclusions: Although seriously mentally ill, patients were able to participate in an exercise program as part of an inpatient stay. Symptomatic improvement occurred, although the attribution to milieu, medication, or exercise cannot be determined in this naturalistic study. The relationship between change in entorhinal cortex thickness and improved memory function suggests that some aspects of neuroplasticity in schizophrenia are exercise-sensitive, and may have functional consequences.

S39.4 Translational evidence of the impact of exercise on brain structure and function in animal models and healthy humans

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Background: Increasing evidence suggests a beneficial effect of exercise in schizophrenia but both the underlying mechanisms and the real world implications of these studies deserves further examination.
Methods: Longitudinal rodent neuroimaging (including structural and spectroscopy studies) and a combination of activity measurement in real life with functional and structural neuroimaging in humans.
Results: Exercise (wheel running) in rodents specifically enhances hippocampal volume in a process that interacts with neurogenesis. Negative effects of high caloric ("Cafeteria") diets are partially reversed by exercise in our rodent model. In humans, relationship between walking in urban and rural environments are mapped onto stress processing, reward processing and brain structure.
Conclusions: Our data suggest mechanisms for hippocampal volume enhancement that should support a beneficial effect of sports interventions in schizophrenia.

S40. Zooming in on the synapse in schizophrenia

S40.1 Role of lifespan expression trajectories in psychiatric disease onset

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Background: Adolescence and early adulthood marks the onset of many psychiatric and neurological disorders. These disorders are known to have strong genetic components and so it is unclear why they would not become apparent as soon as the mutated genes are expressed. Though the developmental processes in the cortex are known to continue until early adulthood, it remains unclear whether these changes are directly related to disease aetiology. A greater understanding of the molecular processes involved in these late developmental processes should help clarify how genetic susceptibility contributes to the characteristic ages of onset of these disorders.
Methods: We examined the complex changes in the synaptic proteome and transcriptome trajectories throughout the lifespan of both mice and humans. We performed label-free relative quantification of PSD preparations from the forebrain of mice aged throughout the transition to adulthood. Furthermore we generated a microarray dataset with 186 samples using the Illumina platform to comprehensively maps the developmental changes which occur in the mouse brain throughout the murine lifespan.
Results: A critical species-conserved time window was identified which links susceptibility genes to the onset of rare and common psychiatric and neurological disorders. Evidence was found linked age dependent changes in synapses to changes in psychiatric and neurological disease susceptibility genes.
Conclusions: Age-linked changes in expression of synapse associated genes may be the primary mechanism timing the vulnerability of teenagers and young adults to the onset of monogenic and polygenic brain disorders. We suggest that novel therapeutics for psychiatric diseases might act to stabilise the normal age-associated genomic and synaptic changes that occur in young adults.

S40.2 Proteomic analysis of the postsynaptic density in the major psychoses schizophrenia and bipolar disorder

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Background: The PostSynaptic Density (PSD) is a highly organized structure, attached to the postsynaptic neuronal terminal, comprised of a complex network of cytoskeletal scaffolding and signaling proteins that facilitate the movement of receptor and signaling complexes. Candidate genes and signaling mechanisms, that converge on and act through it, include NMDA, AMPA and mGLU receptors. We enriched for the PSD and conducted proteomic analysis of this fraction in order to test the hypothesis of altered protein expression and pathways within the PSD in schizophrenia and bipolar disorder.
Methods: We have used a combination of pre-fractionation methods to enrich for the PSD in the anterior cingulate cortex in schizophrenia, bipolar disorder and control tissue obtained from the Stanley Medical Research Institute. Liquid chromatography-mass spectrometry was used to quantify differential protein expression and to investigate the relevance of antipsychotic treatment for these findings. Validation methods were utilized to characterize differential protein expression of the PSD.
Results: Quantitative investigation of the PSD fraction revealed between 700 and more than 2000 protein identifications. Pathway analysis of the significantly differentially expressed proteins revealed involvement of proteins with functions linked to mitochondrial function, calcium signaling, endocytosis, long-term potentiation, and protein translation through mTOR and EIF2 signaling in these disorders.
Conclusions: This is the first study to characterize the differential protein expression within the PSD in schizophrenia and bipolar disorder. Our data display the PSD associated proteins in schizophrenia and bipolar disorder, and they converge to suggest that the regulation of synaptic plasticity within the PSD is a basis to the disorders and a potential target for new treatments.

S40.3 Dysregulated intracellular targeting and synaptic abnormalities of receptor proteins in schizophrenia

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Background: Reports of abnormal neurotransmitter receptor expression in schizophrenia brain have often been conflicting. These inconsistencies have led us to reconsider neurotransmitter-based hypotheses of schizophrenia not as a problem of receptor number, or as a defect of neurotransmitter systems, but rather as a dysregulation of central cellular processes regulating the intracellular distribution of signaling proteins. Our overarching hypothesis is that a fundamental dysregulation of intracellular processes exists in schizophrenia, resulting in abnormal assembly, trafficking, and intracellular targeting of many key proteins involved in neurotransmission and other critical cellular functions, in turn resulting and abnormal synaptic expression of these proteins in schizophrenia brain.
Methods: We have developed a series of tools to study this question in human postmortem brain, including the development and extensive validation of subcellular compartments including endoplasmic reticulum (ER), Golgi, synapses, and multiple endosomal compartments; proteomics; and assays of posttranslational protein modifications associated with subcellular targeting and trafficking including N-linked glycosylation, palmitoylation, and prenylation. Using well-characterized paired samples of postmortem frontal cortex from patients that had schizophrenia and comparison subjects, we have studied this question of abnormal intracellular receptor processing in schizophrenia giving rise to synaptic changes, focusing on both glutamatergic and GABAergic receptor proteins.
Results: We have identified a complex pattern of both glutamate and GABA receptor abnormalities in schizophrenia, demonstrating in particular subcellular abnormalities of receptor expression and

handling. These data have revealed abnormal cellular processing of receptors including abnormal expression levels of NMDA, AMPA, and GABA receptor subunits in subcellular compartments including the ER, early endosome, and synapse itself; as well as abnormal glycosylation and palmityolation modifications of NMDA, AMPA, and GABA receptor subunits. These findings, taken together, are consistent with accelerated exit from the endoplasmic reticulum and Golgi, as well as increased forward trafficking and abnormal intracellular targeting of receptor complexes in schizophrenia. Finally, we have identified putative abnormalities of insertion, expression, and regulation of AMPA and GABA receptor complexes at the synapse.
Conclusions: We propose that a fundamental defect in the brain in schizophrenia is abnormal assembly, intracellular targeting and trafficking, and receptor dynamics of receptor complexes, which in turn give rise to abnormal synaptic expression of neurotransmitter receptors.

S40.4 Focusing on synaptosomal and mitochondrial proteomes from schizophrenia postmortem brains

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Background: Although synaptic dysfunction is well documented in schizophrenia, we still need to identify proteins and metabolites that drive this dysfunction. Also, we want to understand if energetic imbalances we have been observing in postmortem brains are directly associated to synaptic defects.
Methods: We have enriched synaptosomal and mitochondrial proteins from the corpus callosum and two other cortical areas collected postmortem from schizophrenia patients and controls in an attempt of connecting the energy function to synaptosomal changes. Following this line of thought, we evaluated the energetic function from a glutamate hypothesis perspective by treating oligodendrocytes, astrocytes and neuronal cell lines with the NMDA receptor antagonist MK-801.
Results: Signaling (e.g., calmodulin) and structural (e.g., Clathrin) proteins were found differentially expressed in synaptosomes. The mitochondrial fraction also presented differences that confirm previous findings (e.g., oxidative stress-related). Aiming to connect data from both cellular compartments, MK801-treated cells were evaluated at proteome level and did present specific dysfunctions in energy metabolism.
Conclusions: Postmortem and MK801-treated cells data suggest that defective synapses may be the target or trigger energetic dysfunctions. This still need to be investigated further, warranting new roads to be traveled in the understanding of the molecular underpinnings of schizophrenia.

S41. Microglia in schizophrenia

S41.1 Microglial activity in schizophrenia: PET data in the prodrome and the effects of antipsychotic treatment

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Background: Schizophrenia is associated with elevated markers of microglia in post mortem and PET studies. Furthermore elevated levels of pro-inflammatory cytokines such as IL-6 that are released by activated microglial have been linked to the onset of schizophrenia. However it is unknown whether microglial activation develops as a consequence of illness, and/or treatment with antipsychotic drugs, or if microglial activation is intrinsic to the development of the disorder.
Methods: Antipsychotic-naïve people with prodromal-type symptoms who met clinical ultra high risk of psychosis criteria, and patients with established schizophrenia were compared with age and sex-matched controls. All subjects (total $N = 56$) received PET imaging with [11C]-PBR28, a high affinity, second generation PET tracer that provides an in vivo index of microglial activity. Levels of IL-6, TNF-alpha and symptoms were measures in the clinical groups. To determine the effects of antipsychotic treatment on microglial density and morphology rats (>6 per group) received sustained release chronic haloperidol treatment and were compared with vehicle control in either naïve or lipopolysaccharide induced inflammatory conditions.
Results: [11C]-PBR distribution volume ratio was elevated in both the ultra high risk (effect size, $d = 1.2$, $P = 0.004$), and in schizophrenia (effect size, $d = 1.7$, $P < 0.001$) groups relative to controls in cortical gray matter, including the frontal and temporal cortices. There was a significant positive correlation between [11C]-PBR28 distribution volume ratio and symptom severity ($r = 0.730$, $P < 0.01$). Antipsychotic treatment was associated with a reduction in microglial density in both naïve ($P = 0.002$) and inflammatory ($P = 0.001$) conditions.
Conclusions: These data provide evidence for increased cortical microglial activity prior to the onset of psychosis and antipsychotic treatment, extending previous data showing cytokine elevations in first episode and prodromal psychosis to show CNS involvement and link this to symptoms. Antipsychotic treatment reduces microglial markers, indicating that antipsychotic exposure does not explain the elevation in microglial activity seen in schizophrenia.

S41.2 Maternal immune activation increases inflammatory cytokine expression in the offspring's brain without overt signs of microglia anomalies

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Background: Prenatal exposure to infectious or inflammatory insults can increase the risk of developing schizophrenia. At least a subset of patients with schizophrenia displays signs of brain inflammation that is characterized by increased expression of inflammatory markers and microglia activation. It remains debatable, however, whether these long-term inflammatory changes may stem from early-life immune exposures such as maternal infection.
Methods: We used a well-established mouse model of maternal exposure to the viral mimetic poly(I:C) to test the hypothesis that early-life immune exposure can lead to long-lasting alterations in inflammatory mediators and microglia activation. The prenatal poly(I:C) administration model has been demonstrated to induce multiple brain and behavioral abnormalities relevant to schizophrenia, and therefore, it provides a valid model system to explore the link between enduring inflammatory processes and neuronal pathologies relevant to the disorder.
Results: We found that maternal immune activation during pregnancy led to brain region-specific abnormalities in inflammatory cytokine expression in the adult offspring: It increased IL-1β in the hippocampus as well as IL-1β and TNF-α in the ventral midbrain, whereas it did not change the cytokine profiles in other brain areas such as the prefrontal cortex or striatum. Intriguingly, the increase in hippocampal IL-1β expression was associated with pre- and post-synaptic deficits, whereas altered IL-1β and TNF-α levels in the ventral midbrain were paralleled by abnormal expression of dopaminergic markers such reduced dopamine transporter (DAT) density. Detailed analyses of microglia phenotypes using microglia-specific cellular markers (Iba1 and CD68) and morphological assessments (microglia cell soma size and ramification) showed that prenatal immune activation did not change the density or activation statuses of these cells.
Conclusions: Our data thus show that maternal immune activation can cause long-term inflammatory and neuronal abnormalities in the absence of overt microglia abnormalities. Future attempts to identify the mechanisms underlying the development of infection-induced inflammatory and neuronal abnormalities should thus go beyond the possible role of altered microglia functions.

S41.3 Increased inflammatory markers associated with astrogliosis in the midbrain in schizophrenia

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Background: Previously, we have found a higher microglia density and increased expression of cytokines in post mortem prefrontal cortex

(PFC) from a subgroup of individuals with schizophrenia (40%). Individuals with schizophrenia who also had increased expression of inflammatory cytokines displayed an exacerbated neuropathology, including decreased levels of antioxidant defense molecules, increased GFAP mRNA, hypertrophic astrocyte morphology, and reduced brain grey matter volume, particularly in the superior frontal gyrus, relative to individuals with schizophrenia with low levels of inflammatory cytokines and unaffected controls. Here we asked if cytokines were increased in the midbrain of people with schizophrenia.
Methods: The substantia nigra was dissected from 60 µm thick hemisected fresh frozen midbrain tissue and the total RNA extracted using Trizol was converted to cDNA. Quantitative real-time PCR (qPCR) for genes of interest (IL6, SERPINA3, IL1B, IBA1 and GFAP) were normalized to a geomean of 3 housekeeper genes (ACTB, TBP, UBC)..
Results: We detected robust increases in IL6 and SERPINA3 mRNAs in the midbrain of people with schizophrenia compared to controls ($p \leq 0.001$). IL1β and IL6ST were also elevated in schizophrenia ($P < 0.05$). Additionally, increased levels of GFAP correlated positively with both SERPINA3 and IL6 mRNAs (both $r = 0.36$).
Conclusions: Our data suggest that increases in inflammatory and acute-phase like mRNAs (SERPINA3) extend to the midbrain. Thus, even in adults with chronic schizophrenia, many individuals have elevated cytokines associated with markers of neuropathology such as increased cytokines and astrogliosis. These changes would suggest that prior immune challenges or current immune challenges may have a direct impact on dopamine neurotransmission in schizophrenia.

S41.4 Neuroinflammation at different stages of schizophrenia: a PET study of microglial activation

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Background: Neuroimaging studies in schizophrenia (Sz) have identified dynamic structural abnormalities in select frontal and temporal regions (including hippocampi) at early illness stages. However, the underlying neurobiology involved remains unclear. Recently, elevated neuroinflammatory processes have been identified in individuals with schizophrenia, including activation of microglia (the brain's inflammatory cells) and identification of inflammatory cytokines. We sought to identify an inflammatory signature across stages of schizophreniform psychoses and to assess the relationship to brain structural measures.
Methods: Activation of microglia was quantified using [11C]-(R)-PK11195 PET (positron emission tomography) in 12 recent-onset patients, 10 chronic patients and 14 age-matched controls. Time-activity curves were extracted for each voxel and normalised by the ratio of injected activity to participant weight. Parametric images of binding potential (BPND) were generated using linear graphical analysis. T-tests were performed for each voxel to test for group differences in BPND. Within significant clusters, BPND was assessed for correlations with grey matter volume (assessed with MRI), illness duration and symptom severity.
Results: BPND was significantly lower in recent-onset patients relative to controls in widespread brain regions ($P = .043$). A trend towards decreased BPND in the frontal pole and planum temporale was found in recent-onset compared to chronic patients ($P = .08$). BPND was positively correlated to illness duration ($r = .611$, $P = .004$) and symptom severity ($r = .487$, $P = .021$) and negatively correlated to grey matter volume ($P < .01$).
Conclusions: We found suppressed microglia activation in recent-onset patients with schizophrenia, suggesting early illness involves altered microglial function. We also found that increases in microglial activation were associated with greater illness duration, symptom severity and regional volume loss. These findings suggest that alterations in microglia accompany brain and clinical changes. Further studies are exploring the role of glutamate, which has a modulating influence on microglial activity.

S42. Back to the hippocampus: investigating hippocampal abnormalities in early psychosis

S42.1 Evidence of hippocampal change in adolescents reporting psychotic experiences: a population-based MRI study

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Background: The hippocampus has frequently been implicated in the pathophysiology of schizophrenia, and more recently extending to the first episode of Psychosis (FEP) with reduced volumes identified in the patient groups compared to control samples. White matter (WM) abnormalities of the fornix, the main input /output circuitry of the hippocampus, have also been reported in schizophrenia and FEP studies yet the underlying mechanisms relating to the structural underpinning of the disease remain unclear and in particular if similar patterns of hippocampal change are present in adolescents who report subclinical psychotic experiences – a known vulnerability group for later severe psychopathology, including psychotic illness. We employed hippocampal volume measures using automated volumetrics (Freesurfer) and constrained spherical deconvolution (CSD) based deterministic fibre tractography to assess the hippocampal circuitry extending to the fornix in adolescents reporting psychotic experiences.
Methods: A population-based, case-control study of 25 adolescents aged 13-16 years who reported psychotic experiences and a matched sample of 25 young people who did not report psychotic experiences drawn from a sample of 212 young people recruited from primary schools in Dublin and Kildare, Ireland.T1 weighted anatomical high resolution imaging and high angular resolution diffusion imaging (HARDI) data were used to conduct quantitative anatomical volumetric evaluations of the hippocampal white matter (WM) including the subfield divisions of the subiculum and CA1 and the fibre pathways of the fornix and tracts passing through the hippocampus.
Results: Compared with controls, adolescents who reported psychotic experiences showed WM differences bilaterally in volume of the complete hippocampi and more specifically in the subiculum and CA1 subfield partitions of the structure. Subtle patterns of change were identified bilaterally in the fornix while tracts running through the hippocampal body appeared well preserved. The presence of PE also significantly predicted decreased hippocampal volumetric.
Conclusions: In a population-based study of adolescents reporting psychotic experiences, we found a number of bilateral volumetric differences in the whole hippocampal measures and more specifically in the subiculum and CA1 subfields of the structure. The hippocampal circuitry showed patterns of change localised bilaterally to the more anterior regions of the fornix while tractography measures revealed the preservation of white matter tracts passing through the hippocampal body. These findings suggest that subtle structural changes to WM microstructure are not merely a consequence of disorder but may index vulnerability to psychosis even at a very early age.

S42.2 Age-dependent patterns of aberrant brain structure in youth with psychosis spectrum symptoms

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Background: Structural brain abnormalities are prominent in schizophrenia, with reductions in hippocampal volume among the most consistent findings. However, it is unclear when abnormalities emerge in the disease process, and if these abnormalities are present in association with less severe psychosis-spectrum (PS) symptoms in youth. Here we sought to investigate the structural brain

abnormalities in youth with PS symptoms, and determine how these differences related to age and symptom severity.
Methods: The Philadelphia Neurodevelopmental Cohort (PNC) is a prospectively accrued population-based sample of nearly 10,000 youths who received a structured psychiatric evaluation. A subsample of 1,601 youths age 8-22 underwent 3 T magnetic resonance imaging. Here we report the volumetric analysis of high-quality T1-weighted structural imaging data from 391 of these subjects identified through structured interview as having psychosis-spectrum features (PS), and 400 typically developing comparison subjects without significant psychopathology (TD). Regional volumes were estimated with an advanced multi-atlas regional segmentation procedure. Voxelwise analyses were conducted using regional analysis of volumes in normalized space (RAVENS maps). Nonlinear effects of age were examined using penalized splines within a general additive model. In addition to the categorical analysis comparing PS and TD, we evaluated dimensional effects of PS symptom severity summarized using factor analysis.
Results: Compared to the TD group, the PS group had diminished whole brain gray matter (GM) volume and expanded white matter (WM) volume. Notably, these differences were larger at older ages, with a significant nonlinear age by group interaction for GM ($P = 1.6$x10-5) and WM ($P = 6.6$x10-8). Importantly, a separate sample of PNC youth with psychiatric symptoms outside of the psychosis spectrum ($n = 591$) did not exhibit significant GM or WM differences, suggesting abnormalities were specific to the psychosis spectrum. Voxelwise analyses revealed multiple clusters of significant (cluster-corrected $P < 0.01$) GM volume reduction that was maximal in the hippocampus and surrounding medial temporal structures, and also present in ventromedial prefrontal cortex, orbitofrontal cortex, posterior cingulate, dorsolateral prefrontal cortex, and superior parietal cortex. Notably, higher severity of PS symptoms was associated with greater volume reduction in bilateral hippocampus and adjacent parahippocampal gyrus, as well as the precuneus.
Conclusions: These results from a large community-based sample of PS youth demonstrate that structural brain abnormalities commonly reported in adults with psychosis are present by mid-adolescence in youth with subclinical PS symptoms. The especially prominent volume reductions in hippocampus, correlating with symptom severity, are concordant with findings in schizophrenia but to our knowledge have not been previously linked to PS symptoms in a population-based sample. As hippocampal volume loss may be a downstream consequence of increased glutamate and hypermetabolism, our results suggest interventions targeting this mechanism might profitably begin in youth with subclinical symptoms.

S42.3 Hippocampal shape analysis yields new clues about symptom progression in youth at ultrahigh risk for psychosis

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Background: Hippocampal abnormalities have been widely studied in those at ultrahigh risk (UHR) for psychosis. However, there have been inconsistent findings concerning hippocampal morphology prior to and during the transition to psychosis, and little is known about how specific subregions are related to the symptom progression.
Methods: A total of 38 UHR and 42 healthy controls underwent a 3 T MRI scan as well as structured clinical interviews. Shape analysis of hippocampi was conducted with FSL/FIRST vertex analysis to yield a localized measure of shape differences between groups. A subgroup of the sample (24 UHR and 24 controls) also returned for a 12-month clinical follow-up assessment.
Results: The UHR group exhibited smaller hippocampal volumes bilaterally and shape analysis revealed significant inversion in the left ventral posterior hippocampus in the UHR group. Greater inversion in this specific subregion, was related to elevated symptomatology at baseline and increased positive and negative symptoms 12-months later.
Conclusions: Abnormalities in hippocampal subregions appear to reflect underlying pathogenic processes. These findings suggest that examining shape may provide an important new perspective for our conception of brain alterations in the prodromal period.

42.4 Longitudinal changes in hippocampal volume in adolescents with psychotic symptoms – relationship to functioning, co-morbid disorder and stressful life events

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Background: Recent evidence of excessive exposure of the brain to stress, mediated through the neurotoxic effects of cortisol and possible neuroinflammatory processes, may cause a developmental disturbance impacting both brain structure and function. General population studies have suggested that childhood adversity may be associated with development of psychosis. Together with the evidence that early life maltreatment results in structural hippocampal changes, the involvement of the hippocampus in psychosis appears ever more feasible.
Hippocampal abnormalities and memory deficits are frequently implicated as core components in the deficits of episodic memory and emotional learning seen in schizophrenia. This is a key point that advocates for focused early interventional strategies for vulnerable adolescents with psychotic experiences. Adolescence appears to be a critical window during which early intervention may benefit people at risk of schizophrenia.
Objectives: We aimed to quantify clinical measures and presence of stressful life events in relation to automated structural hippocampal volumetrics at baseline and follow up after a period of two years.
Methods: A longitudinal population-based, case-control study of 25 adolescents aged 13-16 years who reported psychotic experiences and a matched sample of 25 young people who did not report psychotic experiences drawn from a sample of 212 young people recruited from primary schools in Dublin and Kildare, Ireland.
Combined clinical assessments and MRI T1 weighted high resolution quantitative anatomical volumetric of the hippocampal white matter assessments conducted at baseline and two year follow-up timeframes.
Results: We found significant group-differences ($P < 0.05$) at baseline between adolescents reporting psychotic experiences compared with matched controls on bilateral hippocampal volumetrics; measures of global functioning; the presence of stressful life events and the presence of Axis1 disorder. Longitudinal analyses are being conducted and will describe changes in hippocampal structure over a two-year period in relation to functioning, comorbid disorder and stressful life events.
Conclusions: In this population-based study of adolescents reporting psychotic experiences, we describe the importance of longitudinal assessments and quantify both clinical and anatomical measures to accurately profile symptomology and associated hippocampal structure among adolescents reporting psychotic experiences. This will allow further elucidation of the trajectory to psychosis among young people at risk.

PHARMACEUTICAL PIPELINE

Drug development strategies for schizophrenia using a novel PDE10 a 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 prepulse 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 1 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 Cmax, AUC, and Cmin. 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.

Can pharmacogenetics improve drug discovery? Insights from a naturalistic study and a randomized controlled trial for schizophrenia treatment outcomes

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Background: Most clinical trials that move past pre-clinical stages fail in phase II of human testing. To decrease attrition in early phases, a potential role of pharmacogenetic testing (Roses, 2004) has been suggested. By screening for likely non-responders, these tests would reduce the required sample size, saving time and resources, and aiding in bringing effective treatments to the market. However, the feasibility and efficacy of these tests in predicting response and adverse side-effects are not clear. Thus, we are conducting (1) a naturalistic study and (2) a randomized controlled trial to examine the effectiveness of pharmacogenetic testing. In particular, we are investigating the tests' utility in predicting treatment outcomes of schizophrenia patients receiving antipsychotics.
Methods: The naturalistic study sample consists of patients: (1) starting or switching to a new psychotropic medication, (2) experiencing inadequate response, or (3) suffering from significant and persistent side-effects. Currently, the sample includes 4018 patients, of which 398 are diagnosed with schizophrenia or schizoaffective disorder. Patients were genotyped using a panel of genetic markers from major liver enzyme genes (e.g., CYP2D6, CYP2C19). Patients were categorized as poor (PM), intermediate (IM), extensive (EM) or ultra-rapid metabolizers (UM) for each enzyme and were assessed at baseline, four and eight weeks for: (1) Treatment response (CGI), (2) adverse side-effects (UKU), and (3) depressive symptoms (BDI). Our preliminary analysis examined the association between metabolizer status with treatment response and baseline side-effect severity.
Results: Patients were categorized by metabolizer status: CYP2C9 (PM: 2.7%, IM: 26.1%, EM: 71.2%), CYP2C19 (PM: 3.3%, IM: 20%, EM: 72.6%, UM: 3.6%) and CYP2D6 (PM: 2.7%, IM: 26.1%, EM: 84.5%). CYP2C9 metabolizer status was nominally associated with weight gain ($P = 0.006$), with IM gaining more weight than EM. Additionally, CYP2C19 metabolizer status was associated with lassitude ($P = 0.044$), with EM experiencing greater lassitude compared to IM. No other associations were observed in relation to side-effect severity. Metabolizer status was not associated with treatment response ($P > 0.05$).
Discussion: Our current findings suggest that pharmacogenetic tests may be useful for predicting side-effect severity. However, these findings are preliminary; we are currently in the process of collecting follow-up treatment response and side-effect severity information.
Moreover, to investigate the efficacy of pharmacogenetic tests in schizophrenia treatment, we are currently conducting a double-blind, randomized controlled trial (Trial ID: NCT02573168). This trial will assess the utility of the GeneSight pharmacogenetic test (AssureX Health) in predicting change in schizophrenic symptoms and side-effect severity (e.g., weight gain, dyskinesias) over 12 months. This trial promises to serve as a further proof-of-principle that pharmacogenetics can be used to identify non-responders and reduce the costs of clinical trials, allowing drugs with genuine therapeutic benefit to reach patients in need.

Randomized, double-blind, placebo-controlled, phase 3 study of encenicline as pro-cognitive treatment in patients with schizophrenia on chronic stable atypical antipsychotic therapy

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Background: Patients with schizophrenia suffer from significant cognitive impairments [1], which significantly affect quality of life, even when positive and negative symptoms are optimally treated. Encenicline is a selective α7 nicotinic receptor agonist. Phase 2 studies were positive, leading to two follow-up Phase 3 studies [2]. The primary objective of this study was to assess the efficacy and safety of once-daily encenicline tablets as a pro-cognitive treatment versus placebo in stable patients with schizophrenia.
Methods: NCT01716975 was a randomized, double-blind, placebo-controlled, parallel-dosing, 26-week, Phase 3 study to evaluate the efficacy and safety of once-daily encenicline tablets (0.9 and 1.8 mg) versus placebo. Eligible male and female subjects aged 18–50 years with a diagnosis of schizophrenia of at least 3 years' duration were assigned to treatment in a 1:1:1 ratio, after successful completion of a 14- day single-blind placebo run-in period. The co-primary efficacy endpoints were cognitive function, as measured by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) Neurocognitive Composite Score, and patient function, as measured by the interview-based Schizophrenia Cognition Rating Scale (SCoRS). Both tests were administered during the screening visit (Day -14, which preceded the placebo run-in period), and on Days 1 (pre-dose), 28, 56, 84 and 182. The Day 1 MCCB and SCoRS scores represent the baseline for each of the efficacy evaluations. Safety and tolerability were determined by clinical and laboratory assessments.
Results: 1147 subjects were screened and 766 subjects were randomized; 46.2% subjects were enrolled from sites located in the United States. The effects of encenicline versus placebo on cognition (as measured by the MCCB Neurocognitive Composite Score) and function (as measured by SCoRS), as well as safety and tolerability results, will be presented.
Discussion: The results of this Phase 3 trial support the efficacy and favorable safety and tolerability of encenicline for the treatment of

cognitive impairment in schizophrenia. Together with a separate Phase 3 study using the identical study design, this is the largest database of pro-cognitive schizophrenia treatment to date.
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A phase 2 study of PF-02545920 (PDE10A inhibitor) in adjunctive treatment of outpatients with sub-optimally controlled symptoms of schizophrenia

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Background: PDE10A exhibits high expression in medium spiny neurons in core nuclei of the basal ganglia; inhibition of PDE10A increases concentrations of cyclic nucleotides, increasing activation of the medium spiny neurons that serve as the major cortical inputs to basal ganglia circuits. PF-02545920 is an inhibitor of PDE10A in development for the adjunctive treatment of suboptimal response in schizophrenia. PF-02545920 was shown to enhance the cAMP signaling produced by D2 receptor blockade, resulting in synergistic effects of PF-02545920 with currently used antipsychotic agents in a number of preclinical assays that are predictive of D2 antagonist antipsychotic activity.
Methods: This study was a 12-week, randomized, outpatient, parallel group, double blind comparison of PF-02545920 5 mg and 15 mg, and placebo dosed BID in the adjunctive treatment of subjects with stable schizophrenia who demonstrated a suboptimal response to a stable dose of antipsychotic monotherapy and other psychotropic medications. The primary efficacy endpoint was change from baseline to Week 12 in PANSS Total score. The secondary efficacy endpoints included the change from baseline to Week 12 in the PSP, PANSS Positive, Negative, and General subscales, PANSS derived Marder factor scores, and CGI-S. The CGI-I total score at Week 12 was also evaluated. A linear mixed effect repeated measures model with fixed effects for treatment, time (visit), baseline value of PANSS Total and investigator site, and a random effect for subject, were used to analyze the change from baseline for the PANSS Total. Secondary endpoint change from Baseline analyses were conducted as described for the primary endpoint.
Results: A total of 240 subjects were assigned to study treatment, of which 78 subjects received PF-02545920 5 mg BID, 82 subjects received PF-02545920 15 mg BID, and 80 subjects received placebo. Among the 240 subjects who were treated, 116 subjects discontinued from the study, of which 8 subjects discontinued due to treatment-related AEs. A majority of the subjects (41.4%) who discontinued were discontinued due to study termination by the sponsor. Study termination was decided based on the results of the interim analysis, which showed a lack of efficacy of study drug. For the primary comparison of change from baseline in PANSS Total score at Week 12, the difference in response to placebo was not statistically significant for either of the PF-02545920 groups, and results numerically favored placebo by a 2-3 point improvement over both doses of PF-02545920. The secondary endpoint results were generally consistent with the primary analysis. Observed concentrations of PF-02545920 were generally as expected based on previous clinical studies with PF-02545920. The most frequent treatment-emergent AEs were sedation and somnolence, more common in the PF-02545920 15 mg group (14 subjects) than in the PF-02545920 5 mg and placebo groups (9 subjects each). The combined all causality incidence of EPS AEs was more common in the PF-02545920 15 mg group (8 subjects) than in the PF-02545920 5 mg and placebo groups (0 subjects each). The overall AE profile was consistent with that observed in prior studies. No notable differences between the treatment groups were observed in vital signs or ECG results.
Discussion: Overall, no statistically significant improvements over placebo were observed in either PF-02545920 treatment group in the efficacy endpoints assessed. The study was stopped for futility based on the Bayesian predictive probability of PF-02545920 being superior to placebo at the end of study being $< 40\%$ for both doses. Adjunctive treatment with PF-02545920 at doses of 5 mg and 15 mg BID was generally safe and well tolerated in the subjects with stable schizophrenia evaluated in this study.

The open translational science in schizophrenia project: Janssen clinical trial and NIH data together in an open-science collaboration

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Background: The OPTICS Project is a pilot initiative designed to provide a forum for true translational science based on Janssen clinical trials made publicly available to qualified investigators and NIH data from related observational studies and trials in schizophrenia made available through the National Institutes of Health (dbGaP).
This effort is distinct from other initiatives in that it is a time-limited proof of concept for an open-science analytic collaboration based on both clinical trial and observational data sources; it is not the development of a data resource to be used in perpetuity.
Aims: The aim of this project is to conduct a pilot to demonstrate the value of an open-science approach using pharmaceutical clinical trial and federally-funded observational data to:
1. Advance efficacy and safety of medicines for schizophrenia;
2. Increase understanding of schizophrenia, including disease natural history, subtypes, and etiologies; and
3. Contribute to the development of analytic and design methods for disparate data types, including novel statistical methods and research designs.
Methods: Members of the project's advisory board include researchers from Yale University School of Medicine, Rutgers University, Harvard T. H. Chan School of Public Health, the National Institute of Mental Health (Genomics Branch), and Janssen Pharmaceutical Research & Development. The role of the board is to manage the project and adjudicate the scientific merit of initial proposals and long abstracts submitted at the conclusion of the analysis period.
Data: Collections of Janssen's paliperidone clinical trials ($N = 17$ trials – the 'OPTICS Bundle' on the Yale Open Data Access Project (YODA) site) and NIH genetic/genomic data about schizophrenia ($N = 10$ studies, the 'OPTICS Collection' on the NCBI Database of Genotypes and Phenotypes (dbGaP) site) are being used for these analyses.
Process: An open invitation has been issued to researchers worldwide to collaborate in the analyses. All researchers must: 1) meet the data access and use requirements of the data holders; 2) agree that Intellectual property generated from this project will be dedicated to the public and free for everyone to use; and 3) agree that all publications related to this project will first be published in the OPTICS volume.
Collaborations are encouraged across industry, industry-academic, and outside the usual silos (e.g., econometrics, business modeling, computer science, etc.). OPTICS provides a workspace (web-based) in which such collaboration can occur. Groups with similar methods and/or research topics are encouraged to work together.
The Harvard Catalyst Clinical and Translational Science Center has issued an RFA to provide funding for Harvard-affiliated researchers.
Note that this is not the establishment of a data repository with a common data model for use in perpetuity; instead, it is a time-limited open-science collaboration.
Results: At the conclusion of the analysis period (Q1 2017), researchers will meet to discuss results and prepare the publication. Participants who have completed analyses will be invited to attend a meeting at which results are presented and discussed. Groups with similar strategies or research topics will be encouraged to integrate efforts in combined or companion manuscript(s). All results passing peer review will be published in an open-access online journal. Finally, the pilot will be evaluated with the goal of replicating it for other neuropsychiatric disorders.
Discussion: This is the first time data about the natural history of the disorder and data from clinical trials of therapies is available to researchers in one place. The ability to analyze these datasets together enables researchers to address questions about the disease, therapies, and analytic methods in ways not possible before now.

Evenamide (NW-3509), a putative antipsychotic, targets abnormal electrical activity and glutamatergic abnormalities in improving psychotic symptoms in patients with schizophrenia in a phase II, placebo-controlled trial

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Background: Current antipsychotics provide inadequate and short-lived benefits in patients with schizophrenia, and switching from a 1st- or 2nd-generation antipsychotic to another 2nd generation does not confer additional benefits. Although D2 blockade is mandatory for the improvement of positive symptoms, approximately 30% of patients relapse while on therapeutic doses of D2-blockers. Chronic D2 blockade caused by these 5HT2-D2 inhibitors may be associated with dopaminergic hypersensitivity in the mesolimbic cortex that undermines the efficacy of these drugs. The mechanism underlying this "Super-sensitivity psychosis" is not understood. D2-blockers antagonize the protective effect of dopamine on kindling in the mesolimbic system, decrease latency to kindling in rats, and lower seizure thresholds.
Marketed antipsychotics, or those in development, do not counteract the abnormal electrical hyperactivity in the cortex and hippocampus, or abnormal glutamatergic transmission implicated in schizophrenia. Aberrant electrical activity and subsequent increase in dopaminergic hypersensitivity lead to repeated limbic kindling and worsening of psychotic symptoms.
Evenamide (NW-3509), a new generation antipsychotic, acts through pathways not targeted by current treatments or other putative antipsychotics. It is associated with a functional, voltage-gated blockade of cortical neuronal sodium channels that normalizes aberrant cortical and hippocampal electrical activity, and consequently inhibits abnormal glutamate release.
Methods: The antipsychotic effects of evenamide were evaluated in animal models of impaired sensory motor gating and information processing (pre-pulse inhibition), where impairment was either spontaneous, or induced by amphetamine or NMDA-receptor antagonists (MK-801 or PDP) or stress (sleep deprivation). Evenamide was evaluated as monotherapy, and also when sub-threshold doses were given in conjunction with sub-threshold doses of various antipsychotics. In addition, evenamide was also evaluated as monotherapy in animal models of aggression (resident-intruder paradigm), compulsive behaviors (marble-burying test), depression (tail-suspension test), and cognitive impairment (novel object recognition test) induced by natural forgetting or by scopolamine.
Results: In the above models, evenamide was effective at doses of 0.5 mg/kg ip to 5 mg/kg po (effective plasma concentrations exceeded 20 ng/mL). In healthy volunteers, single doses of 1-20 mg were evaluated and plasma concentrations of 40 ng/mL were achieved. A Phase 2, placebo-controlled study in patients with schizophrenia, experiencing breakthrough symptoms while on adequate doses of risperidone or aripiprazole, is ongoing, in which evenamide is being evaluated as add-on therapy at doses of 15-25 mg bid as add-on therapy for reducing positive symptoms and psychotic worsening.
Discussion: Despite lack of interactions with any neurotransmitter, transporter, or major enzymes, Evenamide improves positive and negative symptoms, cognition, hostility, depression, and information processing in animal models, independent of whether the impairment was produced by perturbing dopaminergic, glutamatergic, serotonergic or cholinergic systems, or by extreme stress. Evidence of antipsychotic efficacy of Evenamide as an add-on to antipsychotics would revolutionize development of novel antipsychotics that would target aberrant electrical activity, and glutamatergic transmission in patients with schizophrenia. Furthermore, it would offer patients and physicians a completely new therapeutic option that would allow them to continue on their current medication by adding a treatment with a totally new and different mechanism.

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