Discussion: Our results using a novel machine learning approach suggest that an ensemble of cognitive, early environmental and genetic features can predict schizophrenia with significant accuracy. Our results also give key information on cognitive and environmental factors that can be targeted in early identification programs and offer novel insights about genetic loci that may be prioritized in future investigations of the pathophysiology of the disease. However, the near chance-level predictive ability of the genetic modality alone calls for the implementation and testing of more complex models of interaction between multiple risk factors.

O9.5. ABERRANT DOPAMINE SYSTEM FUNCTION REVERSED BY THE OREXIN RECEPTOR ANTAGONIST TCS1102 IN A RODENT MODEL OF SCHIZOPHRENIA

Stephanie Perez*[,1], Daniel Lodge[1]
[1]*University of Texas Health Science Center at San Antonio*

Background: Aberrant regulation of dopamine system function is thought to contribute to psychosis in schizophrenia patients; however, the brain regions associated with this dysregulation have not been conclusively demonstrated. We have recently demonstrated that medium spiny neurons in the nucleus accumbens (NAc) receive convergent input from the ventral hippocampus (vHipp) and paraventricular nucleus of the thalamus (PVT). Furthermore, inactivation of either the vHipp or PVT is sufficient to reverse aberrant dopamine system function in rodent models of schizophrenia. Using, chemogenetic experiments we now provide conclusive evidence that the thalamic input to the NAc plays a role in the regulation of dopamine neuron activity. These data demonstrate that the vHipp and thalamus (specifically the PVT) work in concert to regulate VTA dopamine neuron population activity. Such data are important as they provide evidence that thalamic abnormalities may contribute to the aberrant dopamine system function observed in schizophrenia and suggest that the PVT may be a novel site for intervention in psychosis. To examine this, we explored the orexin system, which is known to provide a dense innervation of the PVT.
Methods: Pregnant Sprague Dawley (SD) rats were treated on gestational day (GD) 17 with either methylazoxymethanol acetate (MAM; 22 mg/kg, i.p.) or saline. For Poly I:C, pregnant dams were treated on GD12 (7.5 mg/kg Poly I:C or saline). Male pups weaned on post-natal day 21 in groups of 2–3 until adulthood (>60 days). For chemogenetic experiments, normal SD rats were bilaterally micro-injected with AAV2 vectors (Addgene) expressing hm3D(Gq)(pAAV-h8yn-HA-hm3D(Gq)-mcherry; 0.5µL) into the PVT or mPFC. Control rats were administered the viral vector lacking the hm3D encoding gene. Prior to testing, CNO (0.75ul; 300uM) was injected into the nucleus accumbens. In vivo extracellular recordings were performed to measure dopamine neuron activity in the VTA. Spontaneously active VTA dopamine neurons were recorded using previously established electrophysiological criteria.
Results: NMDA activation of the PVT induces a significant increase in VTA dopamine neuron population activity. MAM- and Poly I:C-treated rats (both verified rodent models of schizophrenia) consistently display aberrant VTA dopamine neuron population activity, which is restored by pharmacological inactivation of the PVT with TTX. Chemogenetic activation of PVT neurons projecting to the mPFC do not affect VTA dopamine neuron activity; however, activation of PVT neurons projecting to the nucleus accumbens induces a significant increase in dopamine neuron population activity. This effect can be replicated in rats that receive microinjections of the endogenous orexin peptide A or B into the PVT. Consequently, dopamine neuron function can be restored in MAM-treated rats that received a systemic injection of the orexin peptide antagonist TCS 1102.
Discussion: We now demonstrate that orexin receptors are expressed on PVT neurons projecting to the NAc and may serve as a substrate for pharmacological manipulation of this pathway. Here, we provide evidence that both systemic and intracranial (PVT) administration of the orexin receptor antagonist, TCS1102, can normalize aberrant dopamine system function in a rodent model of schizophrenia. Collectively, these data suggest that targeting orexin signaling in the thalamus, specifically, the PVT, may represent a novel site of intervention for psychosis associated with schizophrenia.

O9.6. SPECIFIC SYMPTOMS IN ADOLESCENCE PREDICT PSYCHOSIS IN THE NORTHERN FINLAND BIRTH COHORT 1986

Juha Veijola*[,1], Tuula Hurtig[1], Graham Murray[2], Pirjo Mäki[1]
[1]*University of Oulu;* [2]*University of Cambridge*

Background: A number of psychological symptoms have been found to predict psychosis. Many studies have found no specificity to separate symptoms predicting non-psychotic psychiatric disorders from those predicting psychotic disorders. We were able to conduct prospective study comparing adolescent symptoms predicting non-psychotic psychiatric disorders and psychotic psychiatric disorders.
Methods: Members of the of the Northern Finland Birth Cohort 1986 were asked to fill in PROD-screen questionnaire at age 15–16 years. PROD-screen includes 21 items both measuring positive prodromal symptoms, negative prodromal symptoms and general symptoms.
We were able to follow 6,514 participants using Finnish Hospital Discharge Register detecting new hospital treated mental disorders till 23 years.
Results: The highest prevalence of positive symptoms in the PROD-screen were in the group of subjects who developed psychotic disorder (65% over the cut off) compared to subjects who developed non-psychotic disorder (36%; OR 5.7; 95%CI 2.1–15.4, $p<0.001$, adjusted for parents' psychiatric disorder, family structure, family SES, adolescent's cannabis use and gender), and to subjects without any disorder (27%; adjusted OR 6.5; 2.8–15.0, $p<0.001$). Respective figures for negative symptoms were 55% in the group of psychotic subjects compared to 30% in subjects with non-psychotic disorder (3.3; 1.4–7.7, $p=0.01$) and 24% in the 'healthy' (4.1; 1.9–8.6, $p<0.001$). When comparing separate symptoms in those having psychiatric hospital treatments, we found four positive symptoms and one negative symptom predicting specifically psychotic disorders.
Discussion: In this large prospective population sample both positive and negative symptoms in adolescence associated specifically with development of first episode psychosis.

O9.7. INDIVIDUALIZED LONG-TERM OUTCOME PREDICTION OF PSYCHOSIS IN AN OBSERVATIONAL STUDY: A MACHINE LEARNING APPROACH

Jessica De Nijs[1], Daniel P.J. van Opstal[1], Ronald J. Janssen[1], Wiepke Cahn[1], Hugo Schnack*[,2], GROUP Investigators
[1]*Brain Centre Rudolf Magnus, University Medical Center Utrecht;* [2]*University Medical Centre Utrecht*

Background: Schizophrenia and related disorders have heterogeneous outcomes. Predicting long-term psychosis outcome may be helpful in improving treatment decision making. The aim of our study was to develop and validate a long-term outcome prediction model of psychosis in individual patients. Many studies have shown that outcome is related to symptoms, demographic, clinical, cognitive, genetic and environmental data – at the level of correlations. We hypothesized that, using machine learning (ML), it is possible to predict individual long-term outcome based on patterns that are present in these data at baseline. Second, we test if variables that were recently found to be predictive of short-term outcome (European First Episode Schizophrenia Trial (EUFEST), Koutsouleris et al, 2016) can yield accurate long-term outcome predictions in our sample.

Methods: This study included 523 patients (mean (SD) age = 27.6 (7.4) year) from the Genetic Risk and Outcome of Psychosis study. The study extensively assessed patients at baseline, 3- and 6-year follow-up. Outcome was defined in two ways: 1) Symptomatic: being in remission (good outcome) or not in remission (poor outcome), according to the Remission Tool (i.e. a consensus definition which defines remission as maintaining core DSM symptoms, based on Positive and Negative Symptom Scale [PANSS] on a low level during ≥6 months); and 2) Functional, using Global Assessment of Functioning (GAF) scale, divided into good (GAF≥65) and poor (GAF <65) outcome. A support vector machine was trained to predict outcome based on (combinations of) the following sets of baseline data: PANSS, clinical and demographic variables, substance use, neurocognitive/ social cognitive tasks, premorbid adjustment, need of care items (CANSAS), extrapyramidal symptoms, genetic features, environmental variables; and the sets of predictors from 4- and 52-week GAF-based outcome prediction models from the EUFEST study. We trained full and leaner models, using recursive feature elimination (RFE). We tested performance of outcome prediction models using nested cross-validation, i.e., predicting outcome in patients not part of the training set.
Results: 6-year functional outcome (i.e. GAF status) was best predicted by a multi-modal model based on baseline PANSS, CANSAS, clinical and demographic variables, using RFE: 75% of the patients was correctly predicted. Significant predictions using single-modal models were obtained for baseline PANSS (62.7%), clinical (60.9%) and CANSAS predictors (58.0%). For functional outcome (GAF) at 6 years, also baseline PANSS, clinical and CANSAS related features produced highest accuracies (61.1%, 63.1% and 59.3% resp.). Classification of symptomatic and functional outcome at 3 years yielded comparable results. Replication using the best scoring predictors of 4 and 52 weeks outcome in the EUFEST study resulted in accuracies of 61.5% and 56.5% for remission 3-year outcome; 61.6% and 61.0% for remission 6-year outcome; 60.1% and 57.7% for GAF 3-year outcome; 62.3% and 64.6% for GAF 6-year outcome.
Discussion: Our results show that predicting long-term symptomatic and functional outcome can be done with reasonable accuracies of up to 75%. Training a ML algorithm revealed that PANSS, clinical and need of care features predicted our multiple endpoints best. Interestingly, EUFEST predictors included these three types of data as a main part of best performing predictors. We showed that these short-term outcome predictors are, to certain extent (up to 65%), also predictive of long-term outcome. Our study is a promising step in pursuit of personalized medicine applicability in mental care institutes. However, our model needs replication in independent samples.

O9.8. STRESS AND COGNITIVE FUNCTION AMONG INDIVIDUALS AT CLINICAL HIGH-RISK FOR PSYCHOSIS: FINDINGS FROM THE NAPLS COHORT

Alexis Cullen*[,1], Kristin S. Cadenhead[2], Jean Addington[3], Carrie E. Bearden[4], Tyrone Cannon[5], Barbara A. Cornblatt[6], Daniel Mathalon[7], Thomas H. McGlashan[5], Diana O. Perkins[8], Larry Seidman[9], William S. Stone[10], Ming Tsuang[2], Scott W. Woods[5], Elaine F. Walker[11]
[1]Institute of Psychiatry, Psychology & Neuroscience, King's College London; [2]University of California, San Diego; [3]University of Calgary; [4]University of California, Los Angeles; [5]Yale University; [6]Zucker Hillside Hospital; [7]University of California, San Francisco; [8]University of North Carolina, Chapel Hill; [9]Harvard Medical School; [10]Harvard Medical School, Beth Israel Deaconess Medical Center; [11]Emory University

Background: Accumulated evidence from non-human animal studies suggests that the prominent deficits in memory and executive function that characterise individuals with psychosis may, at least in part, be due to the effects of stress on the brain regions that support these functions. However, studies of patients with established psychosis have yielded inconsistent findings with regards to the relationship between stress and cognition, and research in high-risk populations is notably lacking. Utilising data from the North American Prodrome Longitudinal Study 2 (NAPLS 2), we aimed to further elucidate the relationship between stress (daily stressors, life events, and childhood trauma) and cognitive function in clinical high-risk (CHR) individuals and healthy controls (HC). We additionally explored the role of potential mediators [hypothalamic-pituitary-adrenal (HPA) axis function] and moderators (group status, sex, family history of illness).
Methods: The sample comprised 885 participants (CHR=646; HC=239) who completed measures of stress and cognitive function at the NAPLS 2 baseline assessment. Stress measures included the Daily Stress Inventory and a modified version of the Psychiatric Epidemiology Research Interview Life Events Scale, both of which provided continuous measures of stress exposure (number of events) and distress (subjective feelings of distress). Participants were also interviewed using the Childhood Trauma and Abuse Scale to determine any exposure to childhood trauma (abuse, neglect, and bullying occurring prior to age 16 years). Basal HPA axis activity was determined via salivary cortisol samples obtained at the baseline assessment and standardised scores from selected subtests from the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) were used to derive two cognitive domain scores (memory and executive function). To examine relationships between stress and cognitive domain scores, linear regression analyses were performed on standardised variables.
Results: Daily stressor exposure, daily stressor distress, and life event exposure exhibited negative quadratic (i.e., inverted U-shaped) associations with both memory and executive function ($P < 0.01$ for all). In contrast, the reverse pattern (i.e., a negative linear relationship and a positive quadratic relationship) was shown in the model for life event distress and memory domain scores ($P < 0.01$) whilst trauma history showed only a trend-level association with poorer memory performance ($P = 0.084$). These relationships, which did not differ across CHR and healthy control groups, were largely unchanged after adjusting for demographic factors and salivary cortisol. Exploratory analyses suggested that trauma exposure and a family history of psychosis may moderate the relationship between daily stressors/ life events and cognitive function.
Discussion: In this large sample of predominately CHR individuals, we observed that the association between stress and cognition is complex and differs across stressor types. The negative quadratic associations that we observed for daily stressor exposure, daily stressor distress, and life event exposure imply that whist lower levels of stress may facilitate memory and executive function, there may be a negative impact on cognition when these stressors become more frequent and distressing. Interventions aiming to minimise stress exposure and promote effective coping strategies might feasibly improve cognition in CHR individuals.

O10. Oral Session: Risk Factors

O10.1. DISORGANIZED GYRIFICATION NETWORK PROPERTIES DURING THE TRANSITION TO PSYCHOSIS

André Schmidt*[,1], Tushar Das[2], Daniel Hauke[1], Fabienne Harrisberger[1], Lena Palaniyappan[2], Stefan Borgwardt[1]
[1]University of Basel; [2]University of Western Ontario

Background: There is urgent need to improve the limited prognostic accuracy of psychopathology-based classifications to predict the onset of psychosis in clinical high-risk (CHR) subjects for psychosis. However, as yet no reliable biological marker has been established to differentiate CHR subjects who will develop psychosis from those who will not. This study investigated abnormalities in graph-based gyrification connectome in CHR subjects and patients with first-episode psychosis (FEP) and tested the accuracy of this systems-based approach to predict the transition to psychosis among CHR individuals.