5:45 PM
THE NEUROBIOLOGY OF NEGATIVE SYMPTOMS AND THE EFFECT OF GLYCINE REUPTAKE INHIBITORS

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Background: Negative symptoms can affect up to 60% of patients with schizophrenia. Their severity is predictive of poor outcomes. Avolition (reduced motivation to initiate or persist in goal-directed behaviour) is a critical component of negative symptoms in schizophrenia and has been hypothesised to drive clinical features of apathy, asociality, and alogia. Recently, four major components have been identified that transform reward information into behavioural responses: 1) hedonics; 2) reward prediction and wanting combined with reinforcement learning; 3) cost-benefit analysis; and 4) ability to generate and execute goal-directed action plans necessary to achieve the valued outcome.

Methods: Animal models were used to investigate the in vitro and in vivo effects of bitopertin (a glycine reuptake inhibitor [GRI] under phase 3 investigation for the treatment of predominantly negative and suboptimally controlled positive symptoms of schizophrenia) and a close analogue of bitopertin on different components of motivation typically dysfunctional in schizophrenia, particularly in patients with negative symptoms.

Results: Bitopertin modulated rat ventral tegmental area dopaminergic neuronal firing (a crucial process for reward prediction and reinforcement learning) and attenuated deficits in motivated behaviour induced by decreased dopaminergic neurotransmission in rats. In non-human primates, bitopertin enhanced accuracy in the delayed match-to-sample task, a dorsolateral prefrontal cortex paradigm, implying a positive effect on working memory (a crucial component of executive function). Furthermore, GRIs alleviated deficits in attentional-set shifting (an index of cognitive flexibility) in rats induced by subchronic phencyclidine (PCP) treatment. GRIs also alleviated social interaction deficits in rats induced by subchronic PCP treatment or by isolation rearing in combination with early post-natal PCP treatment.

Discussion: These results support the hypothesis that improved NMDA receptor function may be a valuable strategy for the treatment of avolition in patients with negative symptoms.

6:00 PM
THE ROLE OF OLIGOPEPTIDASES IN SCHIZOPHRENIA – TRANSLATIONAL EVIDENCE FROM HUMAN TO ANIMAL RESEARCH

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Background: Oligopeptidases are a class of enzymes that cleaves peptides but not proteins. The first two oligopeptidases described were Nuclear-Distribution protein nudE-like 1 (Ndel1) and Prolyl-oligopeptidase (POP), besides the Angiotensin-I Converting Enzyme (ACE). Later, Ndel1 was showed to be the binding partner of DISC1, a gene associated to schizophrenic (SCZ) susceptibility. In the first study to evaluate the Ndel1 enzyme activity in human, we found a significantly lower Ndel1 activity in SCZ patients compared to healthy controls (HC) plasma (Gadelha et al., J Psych Res 2013). To extend the investigation of oligopeptidases in SCZ, we also examined the POP and ACE activities in human plasma, as these enzymes also share the same natural substrates with Ndel1. Cognitive enhancing properties of POP inhibitors and the ACE involvement in cognition and behavior were demonstrated by others using animal models. Few studies have suggested altered ACE levels in cerebrospinal fluid of SCZ patients. However, we are the first to validate the correlation of the enzymatic activity with SCZ in both human patients and animal models.

Methods: 92 SCZ patients were compared to 105 HC. POP and ACE activity in human plasma samples were measured by fluorimetric assays, using FRET specific peptide substrate. ACE transgenic mice were evaluated in cognitive tasks.

Results: POP activity in human plasma was null for all samples. The ACE enzymatic activity was significantly higher in SCZ patients compared to HCs (F=0.16, p<0.001) and, among patients, this higher activity was correlated with the PANSS disorganized/cognitive dimension (Spearman’s rho=–0.224 p=0.037). No correlation of ACE enzymatic activity to gender and age in the whole sample, and of duration of illness and dose of antipsychotics among SCZ patients were observed. Titration of ACE gene using transgenic mice allowed demonstrating a significant cognitive impairment due to higher ACE activity.

Discussion: Our results show convergent evidence suggesting that higher ACE enzymatic activity levels could be associated to cognitive/disorganization symptoms in SCZ. Furthermore, ACE inhibitors have been showed to improve cognitive measures in animal models and to delay demenia progression in humans. Previous results with Ndel1 showed a lower enzymatic activity levels among hebephrenic and treatment-resistant SCZ patients, which usually present more prominent cognitive disturbances and disorganization symptoms, pointing towards the same direction of ACE results. Final validation of the full range of behavioral characteristics of ACE transgenic mice and genetic and cognitive evaluation of our patients and controls samples is being conducted. Overall, these results support a potential involvement of oligopeptidases in SCZ.

Oral Presentations
GENETICS AND EPIDEMIOLOGY
Chairperson: Dan Rujescu
Tuesday, 8 April 2014
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A POPULATION-BASED LONGITUDINAL STUDY OF SERUM INTERLEUKIN-6 AND C-REACTIVE PROTEIN IN CHILDHOOD AS PREDICTORS OF PSYCHOSIS AND DEPRESSION IN YOUNG ADULT LIFE

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Background: A potential role of early-life infection and inflammation in the aetiology of schizophrenia is supported by clinical epidemiological, experimental healthy volunteer and animal model research. Recently, cytokine mediated communication between the immune system and the brain has been implicated in the pathophysiology of both schizophrenia and depression. This is supported by meta-analyses reporting increased serum interleukin (IL) 6 and C-reactive protein (CRP) in first episode psychosis, acute psychotic relapse and depression. However, due to their cross-sectional design these studies cannot ascertain whether increased IL-6/CRP is a cause or consequence of illness. Longitudinal studies of systemic inflammatory markers and subsequent risk of psychosis are lacking, and those of depression are limited in number with inconsistent results. In a longitudinal design we predicted that higher levels of systemic inflammatory markers (IL-6 and CRP) in childhood would increase the risks of developing psychosis and depression in the future.

Methods: We used data from approximately 4500 individuals from the general population-based Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort. IL-6 and CRP was measured in non-fasting serum samples obtained at age 9 years. The outcomes of psychotic experiences and psychotic disorder were measured by the face-to-face semi-structured psychotic-like symptoms interview (PLIKS) at age 18 years. Depression was measured in two ways: a clinical interview and a questionnaire so as to allow internal replication. The sample was divided into thirds according to tertiles of the IL-6 and CRP distributions in all individuals with these measurements at age 9 years (irrespective of their status at the end of follow-up). We used logistic regression to calculate the odds ratios (ORs) and 95% confidence intervals (CI) for developing psychiatric outcomes at age 18 years among individuals in the middle and top, compared with the bottom third of inflammatory marker distribution at age 9 years. Linearity
of association was tested by inspection of the OR over the thirds of the inflammatory marker distribution. Regression models were adjusted for age, sex, body mass index, ethnicity, social class, past psychological and behavioural problem, and maternal post-natal depression.

Results: At age 18 years, 101 participants reported psychotic experiences (4.0%), 35 met the criteria for psychotic disorder (1.4%), and 423 met the criteria for depression (13.2%) (all based on clinical interviews). Participants in the top third of IL-6 values compared with the bottom third at age 9 years were more likely to develop psychotic experiences at age 18 years (adjusted OR 1.81 [95% CI 1.01 to 3.28]. The risks of psychotic disorder and of depression at age 18 years were also increased with higher IL-6 at baseline; adjusted OR 2.40 [95% CI 0.87 to 6.62] and 1.55 [95% CI 1.13 to 2.14], respectively. In addition, the associations between serum IL-6 at age 9 years and the risks of psychotic experiences and depression at age 18 years were consistent with a dose-response relationship. The results remained virtually unchanged using the questionnaire measure of depression.

Discussion: Higher levels of the systemic inflammatory marker IL-6 in childhood is associated with the risk of subsequent psychosis and depression. Processes in the inflammatory pathway may be therapeutic targets for these disorders. Inflammation might explain the high comorbidity between cardiovascular disease, diabetes, schizophrenia and depression.

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ANTICIPATING AND EXPERIENCING PLEASURE IN SCHIZOPHRENIA: A NEW PARADIGM
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Background: Anhedonia in schizophrenia is generally defined as “a loss of the ability to feel pleasure”. Anhedonia predicts transition to diagnosis in an ultra-high risk group and poor functional outcomes in schizophrenia. Debate surrounding conflicting results in the literature has held back the development of targeted interventions. Despite reporting low levels of pleasure in questionnaires, individuals with schizophrenia seem to experience similar levels of pleasure as controls when asked “in the moment”. One explanation may be a specific deficit in anticipating pleasure whilst the experience of pleasure in direct response to a positive stimulus (consummatory) is intact. The aim of the study was to develop a new computer task which measured both anticipatory and consummatory pleasure using the same methodology and stimuli.

Methods: A healthy control group (n=16) and a group of individuals with schizophrenia (n=39) completed a newly developed computer task. The participants firstly give consummatory ratings of valence and arousal for positive and negative images and neutral images. The participants learn associations between 4 images and cues as part of a learning paradigm. The participants then produce anticipatory pleasure ratings of these 4 images in response to the cues alone. Participants also completed measures of mood, pleasure and symptoms. To assess consistency the computer task was repeated within two weeks.

Results: The consummatory ratings in the computer task were highly consistent in the clinical (average r=0.85, p<0.001) and the control (average r=0.91, p<0.001) groups. Anticipatory ratings were consistent only in the control group (average r=0.67, p<0.06) with the clinical group showing larger discrepancies while anticipating the same stimuli at different time points. In the clinical group mood and symptoms correlated with anticipatory ratings (p<0.1). As expected, there were no significant differences in the consummatory ratings between the groups. In contrast to the hypothesis there was also no difference found in anticipatory ratings. A within-groups analysis revealed a pattern in both groups of participants anticipating pleasure to high pleasure images and over-anticipating pleasure to low pleasure images from the consummatory phase. This pattern appears in more ratings in the clinical group.

Discussion: The consummatory ratings made during the computer task are consistent. The anticipatory ratings are consistent only in the control group. Anticipatory fluctuations in the clinical group are influenced by mood and symptoms. There is no “in the moment” pleasure deficit in schizophrenia. No difference in anticipatory pleasure was seen in contrast to the hypothesis. However, a pattern of emotional blunting is observed which is particularly pronounced in the clinical group. A reduced ability to distinguish high pleasure from low pleasure when anticipating could be linked to the low motivation and apathy reported in schizophrenia. A targeted intervention which heightened emotional experience and awareness when anticipating events may be beneficial.

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COMMON AND RARE RISK VARIANTS IMPLICATE PAK SIGNALING IN THE MOLECULAR ETIOLOGY OF SCHIZOPHRENIA
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Background: The emerging genetic architecture of schizophrenia includes a spectrum of risk variation from rare mutations of large effect, to many common risk variants of small effect. Highly penetrant risk mutations, although rare, may be particularly important in facilitating dissection of molecular etiology to gain biological insight in model systems.

Methods: We conducted a gene-based analysis of large (>100kb), rare copy number variants (CNVs) in the Wellcome Trust Case Control Consortium 2 (WTCCC2) schizophrenia sample of 1,564 cases and 1,748 controls all from Ireland, and further extended the analysis to include an additional 5,196 UK controls. We performed a replication analysis in a European dataset including 3,111 cases and 2,267 controls and in a further UK bipolar dataset of 2,243 cases and 10,295 independent controls. We confirmed this finding in an extended sample including 11,707 psychosis cases and 21,000 controls. CNVs were validated across arrays, through haplotype analysis and by sequencing of CNV breakpoints. We tested this family by common variant analysis in the Psychiatric Genomics Consortium 2 (PGC2) Schizophrenia Dataset (>38,000 cases and >110,000 controls).

Results: We found association with duplications at chr20p12.2 (P=0.007) and some evidence of replication in large independent European schizophrenia (P=0.052) and UK bipolar disorder case-control cohorts (P=0.047). A combined analysis of Irish/UK subjects including additional psychosis cases (schizophrenia and bipolar disorder) identified 22 carriers in 11,707 cases and 10 carriers in 21,204 controls (meta-analysis CMH P value = 2×10^-4 (odds ratio (OR)=11.3, 95% CI=3.7, ∞). Nineteen of 22 cases and 8 of 10 controls carried duplications starting at 9.68Mb with similar breakpoints across samples. By haplotype analysis and sequencing we identified a tandem ~149kb duplication overlapping the gene p21 Protein-Activated Kinase 7 (also called PAK5) indicative of a single ancestral duplication event. We confirmed the breakpoints in 8/8 carriers tested and found co-segregation of the duplication with illness in two additional family members of one of the affected probands. P21-activated kinases (PAKs) are a family of serine/threonine protein kinases, regulated by the Rho family of small G proteins and involved in multiple intracellular signaling pathways. Six PAK genes are expressed in human and based on their regulatory functions are classified into Group I (PAK1-3) and Group II (PAK4-6) members. Group I PAKs are activated by RAC-PAK signaling to promote axon connectivity, and synapse formation, in the developing brain in a pathway regulated by another schizophrenia risk gene DISC1. Group II members are less investigated, but PAK7 knockout mice are viable with no obvious developmental abnormalities. PAK6/PAK7 double knockout mice show behavioral and learning deficits suggesting functional redundancy between these isoforms. PAK6 maps to one of the common risk loci identified in the PGC2 dataset (p=4.9×10^-8). Finally, in a co-immunoprecipitation experiment we confirmed interaction between PAK7 and DISC1 in synaptoneurosomal preparations from full mouse brain at post-natal day 8-10.

Discussion: We identified a rare, inherited mutation with a common founder contribute to psychotic risk in the European population. This implicates PAK7 a gene from a family of 6 p21-activated kinases involved in the development/regulation of synaptic networks and regulated by DISC1. We report provisional evidence confirming interaction between PAK7 and DISC1 suggesting a potential signalling mechanism in the molecular etiology of psychosis.
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