## O4.2. HERITABILITY AND CORRELATION TO SCHIZOPHRENIA SPECTRUM DISORDER OF GLUTAMATE AND OTHER NEUROMETABOLITE LEVELS IN ANTERIOR CINGULATE AND LEFT THALAMUS: A REGISTER BASED MAGNETIC RESONANCE TWIN STUDY

Christian Legind*[,1], Brian Broberg[2], Rene Mandl[3], Rachel Brouwer[3], Simon Anhøj[4], Rikke Hilker[4], Maria H. Jensen[4], Philip McGuire[5], Hilleke E. Hulshoff Pol[6], Birgitte Fagerlund[7], Egill Rostrup[8], Birte Glenthoj[4]

*[1]Psychiatric Center Glostrup; [2]Center for Neuropsychiatric Schizophrenia Research; [3]University Medical Center Utrecht; [4]Center for Neuropsychiatric Schizophrenia Research and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, Copenhagen University Hospital, Mental Health Center Glostrup,[5]Institute of Psychiatry, Psychology & Neuroscience, King's College London; [6]Brain Center Rudolf Magnus, University Medical Center Utrecht; [7]Center for Neuropsychiatric Schizophrenia Research, Psychiatric Center Glostrup, Mental Health Services Capital Region of Denmark, University of Copenhagen and The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH); [8]Center for Neuropsychiatric Schizophrenia Research, & Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, Psychiatric Center Glostrup, University of Copenhagen, & Glostrup University Hospital*

**Background:** Glutamatergic changes in schizophrenia may precede dopaminergic alterations leading to psychopathology as part of a dopaminergic pathway, or they may represent a distinct pathophysiology. It is unknown if these glutamatergic alterations are due to genetic influences, although findings in gene studies implicate the NMDA receptor. Higher levels of glutamate and glutamine have been reported in the thalamus of patients with schizophrenia, while studies of the anterior cingulate cortex (ACC) have reported increased, decreased, and unaltered levels compared to healthy controls.

By studying discordant mono- (MZ) and dizygotic (DZ) twins it is possible to estimate heritability and correlation to disease in the same population. This kind of study has only been done once on glutamate levels, but no heritability estimates were reported.[1] A study of older healthy twins found N-acetyl aspartate (NAA), choline (Cho), creatinine (Cr), and myo-inositol (MI) levels to be heritable in posterior cingulate cortex.[2] Of these metabolites, NAA has generally been found to correlate negatively with schizophrenia. Here we present our final results on heritability, and correlation to liability for schizophrenia spectrum disorder (ICD-10 F2x.x) of the neurometabolite levels in the ACC and the left thalamus.

**Methods:** By linking The Danish Twin Register and The Danish Psychiatric Central Research Register, 25 complete MZ and 21 complete DZ twin pairs con- or discordant for schizophrenia spectrum disorder (ICD 10 F2x.x) and 29 complete MZ and 20 complete DZ healthy control pairs were included. Thirteen additional twins were scanned without their siblings. Spectra of glutamate, Glx, NAA, Cho, Cr and MI were obtained by [1H]-MR spectroscopy at 3 tesla and analyzed by using LCModel. Additive genetic, common environmental and unique environmental effects on metabolite levels were calculated by structural equation modeling with openMX software. The best fitting model was determined by the Akaike Information Criterion.

**Results:** In the ACC heritability estimates were significant for glutamate (29%), Glx (31%), NAA (39%), Cho (38%), Cr (37%) and MI (33%). In the left thalamus we found significant estimates of heritability for glutamate (16%), Glx (31%), Cho (60%), and of common environment for Cr (29%). A significant positive correlation to schizophrenia spectrum liability was found for glutamate in the left thalamus ($r=0.16$; $p = 0.03$), and negative correlations were found for NAA ($r = -0.16$; $p = 0.02$) and Cr ($r = -0.25$; $p = 0.006$) in the ACC. For glutamate in the thalamus and Cr in the ACC the significant correlation to disease was due to overlapping genetic effects influencing both metabolite and disease.

**Discussion:** In this the first study to estimate heritability of glutamate levels in the brain, the primary findings are that glutamate levels in both the ACC and the left thalamus are heritable, and in the left thalamus also correlated to disease with a significant genetic overlap. This emphasizes glutamate levels in the left thalamus as a potential endophenotypic marker for schizophrenia. NAA and Cr were negatively correlated to disease in the ACC, which could point to disturbances of neuronal health and metabolism. For Cr an overlap of genes influencing both metabolite levels and disease suggests Cr as a possible candidate endophenotype.

**References:**

1. Lutkenhoff ES, van Erp TG, Thomas M a, Therman S, Manninen M, Huttunen MO et al. Proton MRS in twin pairs discordant for schizophrenia. Mol Psychiatry 2010; 15: 308–18.

2. Batouli SAH, Sachdev PS, Wen W, Wright MJ, Suo C, Ames D et al. The heritability of brain metabolites on proton magnetic resonance spectroscopy in older individuals. Neuroimage 2012; 62: 281–289.

## O4.3. INCREASED CEREBRAL BLOOD FLOW AFTER SINGLE DOSE OF ANTIPSYCHOTICS IN HEALTHY SUBJECTS DEPENDS ON DOPAMINE D2 RECEPTOR DENSITY PROFILES EVALUATED WITH PET AND MRNA EXPRESSION DATA.

Pierluigi Selvaggi*[,1], Mattia Veronese[1], Peter CT Hawkins[1], Ottavia Dipasquale[1], Gaia Rizzo[2], Alessandro Bertolino[3], Juergen Dukart[4], Fabio Sambataro[5], Steven CR Williams[1], Federico Turkheimer[1], Mitul Mehta[1]

*[1]Institute of Psychiatry, Psychology and Neuroscience, King's College London; [2]Imanova Ltd., Centre for Imaging Sciences, Hammersmith Hospital; [3]University of Bari 'Aldo Moro'; [4]Translational Medicine Neuroscience and Biomarkers, F. Hoffmann-La Roche Ltd, Basel, Switzerland; [5]University of Udine*

**Background:** Previous studies measuring cerebral blood flow (CBF) with magnetic resonance sequences like Arterial Spin Labelling (ASL) showed that patients with schizophrenia (SCZ) have increased CBF in basal ganglia and reduced blood flow in cortical areas like the prefrontal cortex. It is still not clear whether these abnormalities are related to antipsychotic treatment or rather they reflect a disease trait independent from medication. Interestingly, administration of single dose of antipsychotics in healthy volunteers produce marked functional effects that are in the same region reported as altered in SCZ. These effects are thought to depend on dopamine D2 receptor (D2R) blockade, although their relationship with antipsychotic pharmacodynamics has not been fully established yet. In fact, the haemodynamic nature of CBF measures makes difficult to interpret drug effects in terms of altered neurotransmission function. Here, we tested whether CBF changes induced by different antipsychotics mirror receptor distribution profiles of D2R. We evaluated the correlation of CBF variation with receptor density as measured with PET and brain mRNA expression extracted from the Allen Human Brain Atlas (ABA).

**Methods:** Forty-two healthy male subjects were enrolled in a double blind, randomized, placebo-controlled, crossover study. Participants were randomized in two equal parallel groups to receive a single dose of antipsychotic/placebo in three separate sessions. In Group 1 placebo, olanzapine 7.5mg (OLA) or haloperidol 3mg (HAL) were administered before the MRI scan. In Group 2 participants received placebo, 0.5mg (lowRIS) or 2mg (highRIS) of risperidone. Regional CBF was assessed with pseudo-continuous ASL (pCASL) sequence. For each antipsychotic, a paired T-test was performed in SPM12 with global CBF values as covariate of no interest.

A template image of dopamine D2 receptor density was derived from 6 PET scans in healthy volunteers using the high affinity D2/D3 antagonist ligand [18F]-Fallypride. Brain mRNA expression values for DRD2 gene (coding for D2R) were extracted from the ABA dataset by using the MENGA toolbox. CBF contrast images and the [18F]Fallypride BPND template were segmented into 83 ROIs by using the Desikan-Killiany Atlas. The regional changes in CBF against placebo (ΔCBF) were compared with regional BPND values and gene expression maps using multivariate correlations.
**Results:** For all antipsychotics, CBF changes in each ROI were directly proportional to [18F]Fallypride non displaceable binding potential (BPND) values (OLA R2= 0.24, HAL R2= 0.61, lowRIS R2= 0.54, highRIS R2= 0.52, all p<0.001) and DRD2 mRNA expression levels (OLA R2= 0.04, HAL R2= 0.15, lowRIS R2= 0.19, highRIS R2= 0.20, all chance likelihood <2%).
**Discussion:** In the present study, we were able to show that the CBF increase induced by antipsychotic is directly proportional to D2R concentration in the brain, as indexed by PET BPND maps and mRNA expression levels. Interestingly, the association strength between ΔCBF and brain receptor distribution profiles mirrored differential D2R affinity between the tested drugs. Overall, these results indicate that CBF increases after administration of a single dose of antipsychotics actually reflect known pharmacodynamics profile of these compounds. In addition, these results further reinforce previous evidence suggesting the role of D2R blockade as a mechanism behind increased CBF induced by antipsychotics. Finally, CBF is ultimately a functional marker and this work is important in bridging the considerable gap between the pharmacokinetic and pharmacodynamic effects of compounds with unclear brain functional effects like antipsychotics.

## O4.4. DOES POLYGENIC RISK SCORE FOR SCHIZOPHRENIA MODERATE THE MOMENTARY AFFECTIVE AND PSYCHOTIC REACTIONS TO DAILY-LIFE STRESSORS?

Lotta-Katrin Pries*[,1], Sinan Guloksuz[2], Claudia Menne-Lothmann[1], Jeroen Decoster[3], Ruud van Winkel[3], Dina Collip[1], Philippe Delespaul[1], Marc De Hert[4], Catherine Derom[5], Evert Thiery[6], Nele Jacobs[7], Marieke Wichers[8], Boris Klingenberg[1], Ozan Cinar[1], Bochao Lin[9], Jurjen Luykx[9], Bart Rutten[1], Jim van Os[10]
*[1]Maastricht University Medical Centre; [2]Maastricht University Medical Centre, Yale School of Medicine; [3]Maastricht University Medical Centre, University Psychiatric Centre KU Leuven; [4]University Psychiatric Centre KU Leuven; [5]Centre of Human Genetics, University Hospitals Leuven, Ghent University Hospitals, Ghent University; [6]Ghent University Hospital; [7]Maastricht University Medical Centre, Open University of the Netherlands; [8]Maastricht University Medical Centre, University of Groningen, University Medical Center Groningen, Interdisciplinary Center Psychopathology and Emotion Regulation; [9]Brain Center Rudolf Magnus, University Medical Center Utrecht; [10]Maastricht University Medical Centre, Brain Center Rudolf Magnus, University Medical Center Utrecht, King's College London, King's Health Partners, Institute of Psychiatry*

**Background:** Studies using the event sampling method (ESM), a structured diary technique measuring subjective experiences and emotional fluctuations in daily life, have consistently shown that individuals reporting psychotic experiences display a heightened emotional reactivity to minor stressors—a neuropsychological mechanism that likely contributes to the development and perpetuation of psychotic experiences. Except a few undersized non-replicated candidate-gene studies showing an association between genetic variations and elevated momentary stress reactivity, genetic underpinnings of emotion reactivity to momentary stressors have not been investigated. Therefore, by leveraging a large general population twin dataset of ESM, we aimed to investigate—for the first time—whether the polygenic risk score (PRS) for schizophrenia moderates stress reactivity (psychotic experiences (PE) and negative affect (NA) in response to momentary stress).
**Methods:** Data were derived from a general population adolescent and young adult twin sample. The total sample included 638 participants (Monozygotic = 202, Dizygotic = 436). ESM variables were randomly measured at 10 times/day over 6 consecutive days. For the main analyses, we assessed ESM information on PE (suspiciousness, loss of control, racing thoughts, pervasive thoughts, difficulties to express thoughts), NA (feeling lonely, anxious, listless, down, guilty), and event-related stress (pleasantness of the most important event since last entry); and for additional explorative analyses we assessed social stress (participants were asked with whom they are (e.g. nobody or family) and to rate the pleasantness of the social situation). PRS were trained on the results from the Psychiatric Genetics Consortium-2 SZ. Multilevel regression analyses, taking into account of multiple observations nested within twins who were clustered within family, were used to analyze the moderating effects of PRS (at p-value < 0.05) on the relationship between momentary stress and NA or PE. All analyses were adjusted for age, sex and 2 principle components.
**Results:** There were significant main effects of momentary stress (event stress: b = 0.065, p < 0.001, 95% CI = 0.048, 0.082; social stress: b = 0.128; p < 0.001; 95% CI = 0.111, 0.145) on PE. However, neither the main effects of PRS on PE nor the interaction between PRS and momentary stress on PE were significant. The analysis with NA as dependent variable indicated main effects of momentary stress (event stress: b = 0.096; p <0.001; 95% CI = 0.081, 0.111; social stress: b = 0.180; p < 0.001; 95% CI = 0.164, 0.197), but no main effect of PRS. There was a significant negative interaction between PRS and both event-related stress (b = -0.016; p = 0.024; 95% CI = -0.031, -0.002) and social stress (b = -0.017; p = 0.024; 95% CI = -0.031, -0.002) on NA.
**Discussion:** This is the first study investigating the influence of molecular genetic risk for schizophrenia on momentary stress reactivity, measured using an ecologically valid diary method. These results suggest that PRS for schizophrenia does not have an effect on psychotic stress responses, while increased genetic risk for schizophrenia showed a buffering effect on the association between momentary stress and NA. It is possible that individuals with high PRS for schizophrenia might have emotional response deficits, a characteristic of the clinical phenotype. Alternatively, these individuals might have been less accurate in self-evaluating momentary stress, attributing high values to stressors that genuinely do not have an impact on their emotion regulation. Future studies, investigating both clinical and general populations, are required to elucidate the impact of PRS on stress reactivity.

## O4.5. INVESTIGATING GENETIC PROFILES ASSOCIATED WITH 'REAL WORLD' CLINICAL OUTCOMES IN PSYCHOSIS: A RETROSPECTIVE COHORT STUDY

Emma Francis*[,1], Olesya Ajnakina[2], Marta Di Forti[2], Robin Murray[2], Robert Stewart[2], Conrad Iyegbe[2]
*[1]South London and Maudsley NHS Foundation Trust; [2]Institute of Psychiatry, Psychology & Neuroscience, King's College London*

**Background:** The Clinical Record Interactive Search (CRIS) database provides anonymised data from the full electronic health records of all patients at the South London and Maudsley NHS Foundation Trust, a large provider of secondary mental health care. We have previously shown how the large volumes of available CRIS data pertaining to outcomes can be mined and integrated with patient data collected by historical research interview. The applications of this futuristic translational research model are yet to be fully explored. The aim of this study is to determine whether transcriptomic