Background: Present pharmacological treatment approaches in schizophrenia rest on "neuroleptic" drugs, all of which act as antagonists at dopamine D2/D3 receptors but additionally display major variability in their binding capacity to neurotransmitter receptors (Van Os & Kapur 2009). At present, the choice of any particular drug does not rest on any principled criteria: Once individual treatment has been started, therapeutic efficacy is monitored clinically, and a switch to a different drug is initiated when clear improvements remain absent after a few weeks. It is presently not possible to predict in advance which patients will respond well to a particular drug and who will experience little or no benefit (Case et al. 2011; Kapur et al. 2012).

For instance, clozapine and olanzapine are often prescribed after other antipsychotics have shown to be ineffective in patients with schizophrenia or related disorders due to their pronounced side-effects. Both drugs, clozapine and olanzapine, share certain pharmacodynamic properties with comparatively low affinity towards dopamine D2-receptors, but very high affinity towards muscarinic receptors – a unique constellation that distinguishes them from other common antipsychotics. Importantly, previous studies have shown that a subgroup of schizophrenia patients might particularly benefit from these properties (Raedler et al. 2003, Scarr et al. 2009).

Here, we present an ongoing observational study (COMPASS) which builds on these observations and addresses the question whether functional readouts of dopaminergic and muscarinic systems in individual patients could enable personalised treatment predictions. Guided by the dysconnection hypothesis of schizophrenia (Stephan et al., 2009), which postulates aberrant interactions between NMDA receptors and neuromodulators like dopamine/acetylcholine, the COMPASS study adopts a neuromodeling approach. The focus is on EEG/fMRI paradigms and computational models with empirically demonstrated sensitivity for altered function of NMDA, dopamine and muscarinic receptors, respectively.

Methods: To detect even small effect sizes, the study aims to recruit N=120 patients with schizophrenia who begin treatment with, switch to, or augment medication with olanzapine or clozapine. If possible, a replication sample (an additional N=120) will be recruited, too. Patients will be examined +/- 96h relative to treatment onset. Data acquisition encompasses the following measurements: Clinical interview, EEG (working memory, reward learning under volatility, auditory MMN under volatility, "resting"-state), MRI (optional; fMRI during auditory MMN under volatility, "resting"-state, and structural imaging), blood samples (genetic and biochemical analyses). After 2 and 8 weeks a clinical follow-up is conducted.

Results: The study is ongoing.

Discussion: The EEG/fMRI data will be analysed by computational models that infer functional states of glutamatergic, dopaminergic, and cholinergic systems (for review, Stephan et al. 2015). Model parameter estimates will serve as features in machine learning analyses of treatment prediction (Brodersen et al. 2014).

If successful, this proof-of-concept study will lead to clinically useful tests for predicting the efficacy of clozapine/olanzapine prior to or during very early treatment. This could have a significant impact on clinical management as it would enable predicting, at an early stage, the therapeutic benefit for individual patients. Our neuromodeling approach to individual predictions may thus provide a principled basis for treatment decisions, help spare side-effects and enable informed switches in treatment strategy.

S24. IS IT FEASIBLE TO PREDICT LONG-TERM METABOLIC OUTCOMES IN PSYCHOSIS USING BIOLOGICAL PROFILING AT BASELINE?

Conrad Iyegbe*[,1], Lauren Allen[2], John Lally[2], Marta DiForti[3], Robin Murray[2], Fiona Gaughran[2]

[1]Department of Psychological Medicine; [2]Department of Psychosis Studies; [3]Centre for Social, Genetic and Developmental Psychiatry

Background: Antipsychotic medications are widely prescribed for the treatment of psychotic disorders but carry a variable propensity to increase weight. Thus metabolic dysfunction is the primary cause of premature death in psychosis patients. A system-based approach to understanding the molecular mechanisms behind metabolic dysfunction can potentially provide scope for tailored interventions and alternative treatment pathways that avert such risks on an individual basis. The aim of this study is to identify transcriptomic predictors of high Body Mass Index (BMI) and blood glucose in first episode and chronic psychosis patients.

Methods: 100 first-episode and 100 chronic cases of psychosis meeting ICD-10 criteria (F20-29 and F30-33) were recruited as part of 2 independent studies from 3 NHS Trusts: South London and Maudsley (SLAM), Oxleas and Sussex. Cases were ethnically mixed and aged between 18–65. All participants gave informed consent for biological sampling and a range of physical health assessments. Blood glucose was measure using HbA1c while height and weight data were also taken and used to calculate BMI. For FEP subjects biological measures were taken at baseline, 3 months and 12 months post recruitment. RNA samples were collected at the baseline timepoint via PAXgene blood tubes and interrogates, using the Illumina HumanHT-12.v4 beadchip array. Samples were run at the National Institute for Health Research's (NIHR) Biomedical Research Centre for Mental Health (BRC-MH) at the Institute of Psychiatry, Psychology and Neuroscience. A total of 4756 probes passed a stringent quality control across the 200 samples.

Results: Quantitative data on BMI and hba1c levels were used to assess the predictive efficacy of variables grouped by source (ie. clinical, demographic, technical and transcriptomic features) in first episode psychosis patients. All the predictor categories were included in the initial model, although individual categories were then dropped one at a time. This leave-one-out strategy allowed the direction, impact and relative contribution of the different feature classes to be assessed. Gene-expression and clinical features were consistently associated with the lowest Mean Squared Error after 100 iterations of K-fold cross-validation and after 11 different values of the alpha parameter across 500 imputed datasets. Hba1c or BMI was used as the clinical predictor, depending on whether Hba1c or BMI was used as the target variable. Unattributed surrogate variables derived from surrogate variable analysis (n=6) were analysed within the technical feature set. Having established that gene expression has inherent value as a predictor of metabolic status the same analytical steps were repeated for the discretised versions of these traits (ie. diabetes and obesity). Top-ranking gene transcripts were compared between the quantitative and discretised models. Rank lists of transcripts were subsetted to allow the power distribution across ordered transcripts to be profiled.

Discussion: The top performing transcripts identified are undergoing validation analysis in the chronic sample. Results will be conveyed in terms of sensitivity and false positive rates (ie. the area under the Receiver Operating Characteristic curve). We will undertake further validation through trajectory analysis of gene-expression profiles in followed-up patients.

S25. COGNITIVE REMEDIATION THERAPY AND ITS EFFECTS ON BDNF SERUM LEVELS

Rafael Penades*[,1], Irene López-Vílchez[2], Rosa Catalán[2], Barbara Arias[3], Clemente García-Rizo[4], Guillem Masana[4], Miquel Bernardo[2]

[1]Hospital Clinic Barcelona, Universitat Barcelona, IDIBAPS, CIBERSAM; [2]Hospital Clínic Barcelona, Universitat Barcelona; [3]Universitat Barcelona; [4]Hospital Clínic Barcelona

Background: Brain-derived neurotrophic factor (BDNF) has been proposed as a biomarker of schizophrenia and, more specifically, as a biomarker of cognitive recovery. Unfortunately, it has only been tested once with cognitive remediation treatment (CRT).

Methods: A randomized and controlled trial (NCT02341131) with 70 schizophrenia outpatients and 15 healthy volunteers was conducted. The participants with schizophrenia were randomly assigned to either CRT or the control group. All the participants were assessed in terms of cognition,