T7. UPDATED INDIVIDUAL PARTICIPANT DATA META-ANALYSIS CONFIRMS LOWER LEVELS OF THE GLIAL MARKER TSPO IN PSYCHOSIS PATIENTS

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Methods: This meta-analysis follows the PRISMA guidelines and a protocol has been published in PROSPERO. A systematic search was performed using the databases PubMed, EMBASE, Cochrane, and PsycINFO. Eligible RCTs were identified and no restriction was made regarding diagnosis or publication date. Statistical analysis was based on a random effects model from which forest plots were generated. Effect sizes were reported as the standardized mean difference (SMD) with 95% confidence intervals (CI). Results were presented stratified by four exposure categories, namely < 6 weeks, 6–16 weeks, 16–38 weeks, and ≥ 38 weeks. Outcome measures include mean change from baseline in total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) and triglyceride levels.

Results: The search strategy identified 1144 citations. Of these, 746 abstracts were excluded as being off-topic. A total of 398 full-text articles were assessed for eligibility and 135 RCTs fulfilled the inclusion criteria. Preliminary results show an overall significant association between olanzapine and mildly elevated triglyceride levels (SMD 0.40, 95% CI 0.02–0.77), risperidone and elevated LDL levels (SMD 0.07, 95% CI 0.01–0.13) and clozapine with elevated total cholesterol and triglyceride levels (SMD 0.59 95% CI 0.26–0.02 and SMD 0.44 95% CI 0.35–0.53, respectively). Final results stratified by exposure category will be presented at the SIRS congress.

Discussion: The preliminary findings of this meta-analysis build upon previous literature and do confirm an association between the use of an antipsychotic drug and changes in lipid parameters. However, changes in the different lipid parameters do not seem to be consistent for each antipsychotic. Tentatively, we may suggest that the duration of exposure to an antipsychotic drug is correlated to the extent of lipid abnormalities. It should be noted that the majority of included studies had a short study duration (< 6 weeks). Monitoring over short periods might give misleading results. Furthermore, literature suggests that the role of lipids should not be seen independently, and interplay exists between lipid metabolism and changes in weight. For example, previous studies suggest that there is a positive association between increases in triglyceride levels and increases in weight, and that once weight has stabilised, triglyceride levels decrease. Further analysis should focus on including longer-term studies in which changes in body weight in relation to changes in lipids should be taken into account. We expect the findings of this study to be of clinical relevance in the management and monitoring of antipsychotic treatment. The knowledge of whether duration of exposure is asso-

T8. ANTIPSYCHOTIC TREATMENT AND EYE MOVEMENT ABNORMALITIES IN SCHIZOPHRENIA

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Methods: Individual participant data were obtained from PET studies that 1) used a second generation TSPO radioligand, 2) reported distribution volume (VT) values in brain in patients with psychosis as compared to healthy controls, and 3) reported TSPO affinity type of all participants. The outcome measure was VT in frontal cortex (FC), temporal cortex (TC) and hippocampus (HP). Bayes factors (BF) were applied to examine the relative support for higher, lower, or no-change of TSPO levels in patients compared to healthy controls.

Results: Individual participant data from seven studies were included, amounting to 99 patients with first-episode psychosis or schizophrenia and 109 healthy control subjects. In all regions investigated, BF showed moderate to strong support (BF > 5) for lower VT in patients as compared to no difference, and strong support (BF > 10) for higher VT compared to patients. Mean patient-control differences in standardized VT values were -0.41 for FC (95%CI -0.67 to -0.15, p = 0.0022), -0.38 for TC (95%CI -0.64 to -0.12, p = 0.0048) and -0.53 for HIP (95% CI -0.79 to -0.27, p = 0.0001). The mean change in standardized VT due to medication was 0.10 for FC (CI95% -0.10 to 0.30, p = 0.615), -0.08 for TC (CI95% -0.32 to 0.48, p = 0.666) and 0.08 for HIP (CI95% -0.46 to 0.30, p = 0.682). No association was observed between VT and disease duration or symptom levels (all p > 0.526).

Discussion: In this updated IPD meta-analysis including two new datasets, we found moderate to strong support for lower TSPO in psychosis patients compared to control subjects. In vitro data has shown a lack of correspondence between TSPO and pro-inflammatory activation, also recently confirmed in a post-mortem study in schizophrenia. Hence, based on the present results no firm conclusions can be made regarding the pro- versus anti-inflammatory status of glial cells in psychosis patients. Additional work is needed to understand the biological relevance of the observed lower TSPO in patients.
Methods: Eighty-five patients with schizophrenia were recruited and free-viewing, fixation stability and smooth pursuit tests were performed. First, multiple regression analysis was performed using the obtained parameters as the dependent variables, antipsychotics, illness severity, and duration of illness as independent variables. Secondly, patients were grouped into tertiles by antipsychotic dose (CPZ equivalents), then we conducted a group comparison with each parameter between the three groups.

Results: A multiple linear regression was calculated to predict each parameter based on CPZ equivalents, illness severity and duration of illness. There was no significance in the free-viewing and fixation stability test after Bonferroni correction. In smooth pursuit test, a significant regression equation was found with the horizontal gain (F (1.81) = 15.1, p < 0.00, R2 = 0.15) and vertical gain (F (1.81) = 12.5, p = 0.02, R2 = 0.12), and both were accounted only for CPZ equivalents. In a group comparison, there were significant effects of the horizontal gain (F (2.80) = 5.32, p = 0.07) and the vertical gain (F (2.80) = 3.31, p = 0.41), but both did not survive Bonferroni correction.

Discussion: It was found that antipsychotic treatment affects smooth pursuit eye movement. Eye movement abnormalities in schizophrenia can be a useful biomarker from previous studies, but the effects of antipsychotics must be considered.

T9. EPIGENETIC PROFILES IN SCHIZOPHRENIA DERIVED HUMAN INDUCED PLURIPOTENT STEM CELLS (hiPSCs) AND NEURONS

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Background: Schizophrenia (SCZ) is a severe psychiatric disorder affecting ~1% of the world’s population. It is largely heritable with genetic risk reflected by a combination of common variants of small effect and highly penetrant rare mutations. Chromatin modifications are known to play critical roles in the mediation of many neurodevelopmental processes, and, when disturbed, may also contribute to the precipitation of psychiatric disorders, such as SCZ. While a handful of candidate-based studies have measured changes in promoter-bound histone modifications, few mechanistic studies have been carried out to explore how these modifications may affect chromatin to precipitate behavioral phenotypes associated with the disease.

Methods: We applied an unbiased proteomics approach to evaluate the epigenetic landscape of SCZ in human induced pluripotent stem cells (hiPSCs), neural progenitor cells (NPCs) and neurons from SCZ patients vs. matched controls. We utilized proteomics-based, label free liquid chromatography mass spectrometry (LC-MS/MS) on purified histones from these cells and confirmed our results by western blotting in postmortem SCZ cortical brain tissues. Furthermore we validated our findings with the application of histone interaction assays and structural and biophysical assessments to identify and confirm novel chromatin ‘readers’. To relate our findings to a SCZ phenotype we used a SCZ rodent model of prepulse inhibition (PPI) to perform pharmacological manipulations and behavioral assessments.

Results: Using label free mass spectrometry we performed PTM screening of hiPSCs, NPCs and matured neurons derived from SCZ patients and matched controls. We identified, amongst others, altered patterns of hyperacetylation in SCZ neurons. Additionally we identified enhanced binding of particular acetylation ‘reader’ proteins. Pharmacological inhibition of such proteins in an animal model of amphetamine sensitization ameliorated PPI deficits further validating this epigenetic signature in SCZ.

Discussion: Recent evidence indicates that relevance and patterns of acetylation in epigenetics advances beyond its role in transcription and small molecule inhibitors of these aberrant interactions hold promise as useful therapeutics. This study identifies a role for modulating gene expression changes associated with a SCZ epigenetic signature and warrants further investigation in terms of how this early gene expression pattern perhaps determines susceptibility or severity of the SCZ disease trajectory.

T10. BIOMARKERS IN TREATMENT-RESISTANT SCHIZOPHRENIA; THE BITS STUDY (A STUDY PROTOCOL)

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Background: Approximately 30% of patients diagnosed with schizophrenia do not respond to conventional antipsychotic therapy, however, around 30% of these patients will respond to treatment with clozapine. The remaining clozapine non-respondent patients can be defined as ultra-treatment resistant. Special characteristics (biomarkers) may be found in this subgroup of ultra-treatment resistant patients. Recent evidence points to a central role of altered immunological and anti-inflammatory response in schizophrenia. Studies have found that antipsychotic medication affect the immune system and alter levels of different cytokines, but no clear relation between the effect on cytokine levels and improvement in symptoms has been documented. Also increased permeability of the blood brain barrier (BBB) have been linked to psychosis, and a dysfunctional BBB may lead to structural changes in the white matter and neurochemical changes (glutamatergic abnormalities) in CNS. The longitudinal course of BBB alterations in psychosis and how this may influence changes in neuronal structure and function and relate to fluctuation in symptoms have not been examined. The aim of this study is to establish a database with the purpose of identifying biomarkers for treatment resistant schizophrenia (TRS), containing measures of psychopathology and function, treatment variables, brain imaging data, immunological markers from blood and cerebrospinal fluid, BBB-permeability and genetic material. The database will consist of a group of ultra-treatment resistant patients and a group of patients responding to clozapine matched on sex, age and duration of illness (~3 years).

Specific aims:
• evaluate the permeability of BBB and characterize the immunological profile in blood and CSF
• examine the structure of grey and white matter, and the content of glutamate in specific brain areas
• characterize the psychopathology and the level of function
• collect blood-samples for genetic testing

Hypothesis
• Ultra-treatment resistant patients will have an increased inflammatory pattern in blood level cytokines compared to reference levels and clozapine responding patients
• Ultra-treatment resistant patients will have increased BBB permeability and altered levels of cytokines in the CSF
• Patients with altered CSF level of cytokines will have more pronounced structural and neurochemical brain changes
• In some patients, the BBB permeability and the CSF level of cytokines will be altered during the follow up period along with symptom fluctuation and these alterations will correlate with changes in white matter
• BBB-permeability and CSF levels of cytokines will be stable in patients stable on clozapine

Methods: The study is a naturalistic longitudinal study including patients with TRS. We plan a thorough examination twice with a three months interval and ultra-treatment resistant patients will be compared with patients.