Background: The response to antipsychotic treatment in patients with psychosis is difficult to predict on the basis of the patient’s clinical features. As a result, patients are generally treated in a similar way, even though their response can vary dramatically. Recent neuroimaging studies suggest that the pattern of brain abnormalities in patients with psychosis may vary in relation to treatment response. However, in many of these studies, patients had already been treated, and it was unclear if this had contributed to the findings.

Methods: In Optimise we obtained a structural Magnetic Resonance Imaging data from n=203 minimally treated patients at their first presentation for a psychotic episode. All patients then started treatment with standard doses of amisulpride. After 4 weeks, 56% were in symptomatic remission.

Results: We identified brain neoplasms in 3 patients, but the most common radiological findings were non-specific white matter T2-weighted hyperintensities (n=48); cavum septi pellucidi (n=34); and arachnoid cysts (n=9). Cortical thickness, surface area, and gyrification were measured using FreeSurfer (1). Preliminary analyses applying machine learning to these measures at baseline indicated that symptomatic remission at 4 weeks could be predicted with an accuracy of 64%.

Discussion: These findings suggest that radiological assessment can identify abnormalities that require an alternative to conventional treatment in a minority of patients. In most patients with psychosis, neuroimaging abnormalities may be better detected using statistical approaches, and these have greater potential for the stratification of patients according to future antipsychotic response.

31.4 GENETIC, IMMUNOLOGICAL AND BIOCHEMICAL MARKERS OF TREATMENT RESPONSE IN SCHIZOPHRENIA

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Background: One of the major shortcomings in the current treatment of schizophrenia is that we have no valid criteria in clinical practice to decide which antipsychotic treatment should be chosen first. This is why we need to define a blood-based biological signature of treatment response that can be easily tested at patient bedside and would also help to identify molecular mechanisms of treatment response by determining biological changes associated with symptom improvements.

Methods: Through a European consortium on Optimization of Treatment and Management of Schizophrenia in Europe (FP7, OPTiMiSE), we conducted a clinical trial on treatment response with Amisulpride in 500 subjects with first episode psychosis. For each patient, biological samples (DNA, RNA, plasma and serum) have been collected before treatment and during follow-up visits at weeks 4, 10 and 22, to measure biological changes associated with treatment initiation and with symptoms improvements. We combined multiple high-throughput technologies for transcriptome, genome, metabolome, proteome analyses before and after treatment.

Results: The transcriptome analysis conducted on 10,683 genes expressed in peripheral mononuclear cells identified significantly more genes differentially expressed after treatment in 112 patients who will be in remission after 4-weeks treatment than in 51 non-remitters. Using interaction network analysis, we identified biological pathways affected by Amisulpride. For some genes, the expression level was significantly correlated with symptom improvement. Moreover, some genes were already differentially expressed before treatment between remitters and non-remitters, suggesting they might be used to predict treatment outcome. In addition, we identified genetic variations associated with gene expression level and thus may explain individual difference in treatment response.

In parallel, as recent biological data have suggested a preponderant role of innate and adaptive immune system in the vulnerability to schizophrenia or in antipsychotic treatment response (Fond et al., 2015), we paid a particular attention to the analysis of inflammatory markers and the presence of auto-antibodies in patients’ sera. Circulating autoantibodies against glutamatergic N-methyl-D-aspartate receptor (NMDAR-Ab) have been reported in up to 10% of patients with psychotic disorders. In our study, we demonstrated the advantage of using cutting-edge methods to ascertain the presence of NMDAR-Ab in seropositive patients that cannot be clinically identified (Jezequel et al., 2017). Indeed, the only clinical characteristics found in NMDAR-Ab seropositive patients, was the high frequency of female patients, the presence of mild neurologic symptoms and signs of antipsychotic intolerance. In addition, using an advanced statistical classification algorithm, we defined clinically-based subgroups of patients who had specific cytokine signature associated to remission after 4-weeks of treatment, suggesting that these markers may be used to predict treatment response.

Discussion: Altogether, our multilevel biological approach resulted in the identification of promising biomarkers, which may be used both to predict drug response and remission in first psychosis episode.

32. DIGGING DEEPER IN THE PROTEOME OF SCHIZOPHRENIA

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Overall Abstract: Advances in genomics and transcriptomics have yielded novel insights for the pathophysiology of schizophrenia, moving the field forward by providing new substrates for the development of treatment strategies. Interestingly, this has led to a large gap in knowledge in the field, as the impact of genomic variability or alterations in transcript expression is dependent on the next level of gene expression. While proteomics has lagged behind other disciplines in schizophrenia research, several groups are utilizing proteomics approaches to answer and answer the largest possible questions in translational schizophrenia research. Proteomics has evolved as a field very quickly, going beyond the characterization of expression levels of one or a few proteins. With precise quantification of protein expression and degradation, characterization of post-translational modifications as well as the detection of low abundant proteins as putative biomarkers, we will show several different state-of-the-art proteomics approaches applied to the schizophrenia substrate. James Meador-Woodruff (University of Alabama at Birmingham) will provide a brief overview of the field, and present new data showing abnormalities of lipid and carbohydrate modifications on receptor proteins in schizophrenia, as well as abnormal levels of key enzymes associated with these abnormal protein modifications. Robert McCullumsmith (University of Cincinnati, USA) will add pivotal information on the long-standing synaptic hypothesis of schizophrenia by depicting the PSD95 interactome in normal and schizophrenia brain, connecting the excitatory postsynaptic proteome to Big Data analytics. The other two speakers will show how translational proteomics data can be used to develop clinical biomarkers. Dr. Mariana Fioramonte will present how the use of the latest tools in proteomics can tell us more about brain proteomics and protein interactomics. Finally, David Cotter (Royal College
of Surgeons, Ireland) will show that proteins associated to the complement system present in the blood plasma of adolescent subjects experiencing psychosis can be predictive broadly in the vulnerability of adult psychiatric disorders. This symposium provides relevant on the biological and biochemical aspects of schizophrenia and proposes potential applications that might be, after adjustments and validations, implemented in the clinic in the future, towards a personalized medicine concept.

32.1 MECHANISMS OF ABNORMAL POSTTRANSLATIONAL PROTEIN PROCESSING IN SCHIZOPHRENIA BRAIN

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Background: Molecular disturbances of neurotransmitter systems have long been held to be a core feature of the pathophysiology of schizophrenia. Despite years of study of neurotransmitter associated protein expression at multiple levels of gene expression, reports of abnormal neurotransmitter receptor transcript, protein, and signaling complex expression in schizophrenia brain have often been conflicting. These inconsistencies led us to reconsider neurotransmitter-based hypotheses of schizophrenia not as a problem of receptor number, or as a defect of neurotransmitter systems, but rather as a dysregulation of central cellular processes regulating the intracellular distribution of signaling proteins. Our working hypothesis is that a fundamental dysregulation of intracellular processes exists in schizophrenia, resulting in abnormal assembly, trafficking, and intracellular targeting of many key proteins involved in neurotransmission and other critical cellular functions. Previous studies have shown the important roles posttranslational lipid and carbohydrate modifications play in targeting receptors, transporters, and other proteins between intracellular compartments and the synapse, and in the lateral translocation of such molecules between lipid microdomains at the distal end of forward trafficking pathways. Accordingly, we have predicted that abnormal posttranslational lipid and/or sugar modification of proteins by occurs in schizophrenia. We have previously reported changes in extent of N-linked glycosylation as well as of the lipid modifications palmitoylation and N-myristoylation on target proteins in schizophrenia brain. In an ongoing project to elucidate mechanisms of these changes, we have studied expression patterns of key enzymes associated with these posttranslational modifications.

Methods: Using well characterized samples of postmortem brain from schizophrenics and matched comparison subjects, we assayed transcript expression of enzymes associated with posttranslational protein modifications by lipids and carbohydrates using microarrays and qPCR. Next, we assayed protein expression of a subset of enzymes using western blot analyses. To determine the brain cell specificity of protein changes, we used laser capture microdissection (LCM) of neuronal and glial cells to harvest specific cell populations from postmortem brains, and developed and validated a capillary electrophoresis system for ultra-low quantity protein quantification in 500 ng of protein obtained from these cells. We have validated that we can reliably harvest cortical neuronal subtypes and astroglia, are able to measure 4 proteins simultaneously in samples from these cells lines, and are currently collecting cells to extend these findings into cell-specific studies to determine if the changes we have found in posttranslational modification proteins are widely specific or specific to given subpopulations of brain cells.

Discussion: These data support our earlier findings of altered patterns of the posttranslational modifications of both glycosylation and lipid modification of proteins in the cortex of schizophrenia. By identifying changes in both mRNA and protein expression of key enzymes associated with these posttranslational modifications, we have begun to elucidate potential mechanisms of these earlier observations. One of the challenges that has plagued schizophrenia research for decades is that many different neurotransmitter and neurochemical systems have been implicated and studied in this illness, and reconciling this large literature is challenging. These many changes in numerous different systems suggest, however, that rather than schizophrenia being a disorder of a given neurotransmitter system, it is rather a disturbance of core intracellular processes that underlie regulation of multiple neurochemical systems. The machinery associated with posttranslational modifications of proteins is a possible substrate that could reconcile prior abnormalities identified in myriad systems. We have proposed that a fundamental defect in the brains of those affected with this illness is abnormal assembly, trafficking and receptor dynamics of many different proteins in schizophrenia that is due mechanistically to abnormal posttranslational modifications that influence intracellular targeting and trafficking of proteins between subcellular compartments. Dysregulation of lipid and glycan modification of proteins are likely candidates for such a process, and these present data begin to elucidate the mechanisms from which these abnormalities occur.

32.2 ABNORMALITIES OF SYNAPTIC PROTEOMES IN SCHIZOPHRENIA

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Background: The human brain is comprised of billions of neurons that form networks of connections within and between brain regions. These connections facilitate neuropsychological events that underlie learning and memory, critical aspects of cognitive function often perturbed in neuropsychiatric illnesses. Neuronal signaling is mediated by fast and slow transmission events, encompassing receptors, ligands, ions, enzymes, and other substrates. These elements are spatially arranged in subcellular microdomains, facilitating juxtaposition of proteins that coordinate various biological processes. For example, synaptic transmission is modulated via release of neurotransmitter into the synaptic cleft, where receptors are activated and the postsynaptic cell modulated via electrical and chemical signals. The pre- and postsynaptic compartments include highly specialized protein clusters, with elegant and complex regulatory mechanisms that traffic proteins to and from these zones. In particular, postsynaptic densities...