More global whole-brain free water group differences, however, did not reach statistical significance, which may indicate some regional specificity to these changes early in development. Nonetheless, the NHP MIA model complements the human schizophrenia literature, in which extracellular free water increases have been repeatedly identified. Ultimately, these data provide validation of the clinical relevance of the NHP MIA model and improve our understanding of neuroimmune mechanisms in the development of psychiatric disorders, particularly schizophrenia.

O2.7. A NEUROPROTEOMICS-CENTERED APPROACH TO UNDERSTAND AND REVEAL BIOMARKERS TO SCHIZOPHRENIA

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Background: Schizophrenia affects over 20 million people worldwide through a wide range of symptoms. As an incurable disorder, the disease management is normally based in antipsychotics, which may present severe side effects and does not work properly to half of the patients. This is mainly because we lack in understanding the molecular basis of the disease, impairing the development of new and more effective medication.
Methods: Here, we employed a neuroproteomics-centered approach to unravel molecular the underpinnings of schizophrenia as well as reveal protein biomarkers associated to antipsychotic effectiveness. For that, we have been using mass spectrometry-based proteomics to studying brain tissue collected postmortem from patients and mentally healthy controls, in vitro pre-clinical models such as cell lines and iPSC-derived cerebral organoids. Specific biological processes found in human samples which may be targeted by novel medication have been studied in pre-clinical models using genetic tools. Moreover, blood plasma collected in vivo from patients before and after antipsychotic medication (risperidone, olanzapine and quetiapine).
Results: At first, postmortem brain tissue proteomics from seven different brain regions led us to investigate in vitro the role of the above-mentioned biological processes in cultured oligodendrocytes treated with MK-801 and antipsychotics, to learn more about biochemical processes that may be involved in schizophrenia. iPSC-derived cerebral organoids, neurons and astrocytes were also investigated in terms of proteome dysregulations associated to the disease. Proteomic findings in postmortem brains and pre-clinical models have led us to investigate specific biological processes associated to the disease such as energy and mitochondrial metabolism, spliceosomal machinery, myelination and tripartite synapses. These may be targeted by novel medication. Additionally, we revealed blood plasma proteins, which are potential candidates to clinical implementation in the personalized choice of the correct antipsychotic to each patient.
Discussion: Neuroproteomics may be a powerful asset to reveal novel biological processes in the investigation of complex human disorders as schizophrenia. This has been contributing to knowledge that may lead to more effective medication and potential biomarkers for clinical use.

O2.8. DOWNREGULATION OF NPAS4 IN PARVALBUMIN INTERNEURONS AND COGNITIVE DEFICITS IN A DEVELOPMENTAL MOUSE MODEL OF SCHIZOPHRENIA

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Background: Dysfunction of prefrontal parvalbumin interneurons (PV-I) is recognized to contribute to the cognitive deficits observed in schizophrenia. A current hypothesis suggests that developmental hypofunction of NMDA receptors expressed on PV-I leads to aberrant maturation of the prefrontal GABAergic system, persistent disruption of PV cell connectivity, long-lasting disinhibition of excitatory pyramidal cells, and, consequently cortical over-excitation. However, the molecular links between NMDA receptor hypofunction and dysfunction of PV-I in schizophrenia remain unclear. Recently, human- and rodent-based studies have suggested a potential involvement of the brain specific transcription factor Npas4 to the molecular abnormalities and symptoms of schizophrenia.
Methods: To further investigate the role of Npas4 in aspects of schizophrenia we used the ketamine developmental mouse model of NMDA receptor hypofunction in conjunction with transgenic mice lacking Npas4 specifically in PV-I. We used multiple behavioral tests to assess for abnormalities in cognitive functions, emotional regulations and general activity. We also performed immunofluorescent staining and used Western Blot analyses to test for changes in expression of Npas4 in prefrontal PV-I and in markers of changes within the excitatory/inhibitory balance.
Results: We showed that perinatal exposure to ketamine, a NMDA receptor antagonist, reduces the level of Npas4 expression specifically in PV-I of the prefrontal cortex of mice, which is associated with prefrontal-dependent cognitive deficits. Using a transgenic Cre-Lox approach in mice, we demonstrated that Npas4-dependent dysfunction of PV-I is responsible for deficits in prefrontal-dependent cognitive functions and for abnormal expression of molecular markers indicative of excitatory/inhibitory imbalance in the prefrontal cortex, including Nptx2, Egr1 and GluR4.
Discussion: Our data show for the first time that the brain specific transcription factor Npas4 may be an important molecular mediator of the effects of developmental NMDA receptor hypofunction on PV-I dysfunction, thereby contributing to cognitive deficits. These findings provide a potential novel therapeutic target to rescue the cognitive impairments of schizophrenia that remain to date unresponsive to treatments.

O3. ORAL SESSION: DRUG-INDUCED PSYCHOSIS: MECHANISMS AND IMPLICATIONS

O3.1. ASSOCIATION OF EXTENT OF CANNABIS USE AND ACUTE INTOXICATION EXPERIENCES IN A MULTI-NATIONAL SAMPLE OF FIRST EPISODE PSYCHOSIS PATIENTS AND CONTROLS

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Background: FEP patients who use cannabis experience more frequent intoxication experiences compared to controls. It is not clear whether this is consequent to patients being more vulnerable to the effects of cannabis use or to their heavier pattern of use. We aimed to determine whether extent of use predicted psychotic-like and euphoric intoxication experiences in FEP patients and controls and whether this differs between groups.