psychiatric symptoms that are difficult to treat with regular medications. Treatment of the underlying genetic disease can cure the associated psychiatric symptoms or help regular medications work better. Discovery of rare genetic diseases in psychiatric patients would reveal specific treatment options, and give information about the chances of other family members being affected. In this study, we test the hypothesis that psychiatric populations are enriched for pathogenic variants associated with selected treatable inborn errors of metabolism (IEMs).

Methods: Using targeted next-generation sequencing, we screened schizophrenia (n=1132), bipolar (n=719) and major depressive disorder (n=195) patients for variants in genes associated with Niemann-Pick disease type C (NPC), Wilson disease (WD), homocystinuria (HOM) and acute intermittent porphyria (AIP), and compared the frequency of known and predicted pathogenic variants found to 123 136 samples from the gnomAD consortium.

Results: Our study is the first to explore the prevalence of NPC, WD, HOM and AIP gene variants in well-defined psychiatric cohorts. Among 2046 cases (male, n=1116; female, n=940), carrier rates of 0.93%, 0.98% and 0.20% for NPC, WD and HOM were observed, respectively. The carrier rate for NPC was marginally enriched in the SCZ cohort (1.15%) compared to general (95% CI, 0.007 – 0.201; p=0.084) and comparison (95% CI, 1.967 – 5.227; p=5.16e-05) populations. AIP affected rate of 0.29% was observed across the entire psychiatric cohort relative to the general (95% CI, 0.001 – 0.006; p=3.47e-13) and comparison (95% CI, 1.572 – 10.044; p=0.012) populations, an almost 300x enrichment in comparison to what is expected in the general population.

Discussion: An enrichment of known and predicted pathogenic variants associated with NPC and AIP was found in the psychiatric cohort, especially in SCZ patients. The results of this proof-of-principle study support that rare genetic disease variants, such as those associated with treatable IEMs, may contribute to the pathogenesis and treatment responsiveness of psychiatric disorders. Discovering genetic diseases in psychiatric patients will shift how health care is delivered to these vulnerable patients by addressing underlying conditions rather than masking symptoms with medications, and has the potential to especially help patients who don’t respond to regular psychotropic medications. Further studies screening large psychiatric cohorts for pathogenic variants in a large panel of treatable IEM genes will reveal the full impact of such disorders for psychiatric patients.

F196. DIFFERENTIAL EFFECTS OF MGLU5 RECEPTOR BLOCKADE ON BEHAVIOR, SCHIZOPHRENIA-RELEVANT GENE EXPRESSION AND NEURONAL ACTIVATION PATTERNS FROM DEVELOPMENT TO AGING MICE

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Background: The glutamate system is implicated both in schizophrenia and mood disorders. Mice lacking metabotropic mGlu5 receptors (mGlu5 KO) display schizophrenia-like abnormalities. Additionally, mGlu5 antagonists represent promising alternative anxiolytics/antidepressants. However, the underlying age-specific molecular/cellular mechanisms are only partially understood. We aimed at identifying molecular alterations associated with a genetically induced mGlu5 deletion, which results in a schizophrenia-like phenotype. Additionally, we investigated age-specific effects of mGlu5 antagonists on emotional behaviour and c-fos activation.

Methods: For analysis of mRNA and protein levels we performed Real-time RT-PCR and Western blot investigations in the hippocampus and prefrontal/frontal cortex (PFC/FC) of mice with a genetic deletion of the metabotropic glutamate receptor 5 (mGlu5), addressing key components of the GABAergic and glutamatergic systems. Additionally, we used classical behavioral tests for determining anxiety- and depression-like changes triggered by the mGlu5 antagonist 2-Methyl-5-phenylethynyl)pyridine (MPEP). Finally, we used profiling of c-Fos expression, as marker of neuronal activity, induced by MPEP from postnatal day 16 (P16) to adulthood (P90).

Results: mGlu5 knockout (KO) mice showed a significant reduction of reelin, GAD65, GAD67 and parvalbumin mRNA levels, which is specific for the PFC/FC, and that is paralleled by a significant reduction of protein levels in male KO mice. We also analysed the main NMDA and AMPA receptor subunits, namely GluN1, GluN2A, GluN2B and GluA1, and observed that mGlu5 deletion determined a significant reduction of their mRNA levels, as well as the hippocampus, with differences between the two genders. We measured age-specific alterations in emotional behaviour of mGlu5 KO mice, with marked increase of anxiety during aging. There was a remarkably conserved activation of the paraventricular nucleus of the hypothalamus, implicated in stress regulation, by MPEP at all investigated ages, whereas the extended amygdala was specifically activated in adulthood only.

Discussion: Our data suggest that neurochemical abnormalities impinging the glutamatergic and GABAergic systems may be responsible for the behavioral phenotype associated with mGlu5 KO animals and point to the close interaction of these molecular players for the development of neuropsychiatric disorders such as schizophrenia. These data could contribute to a better understanding of the involvement of mGlu5 alterations in the molecular imbalance between excitation and inhibition underlying the emergence of a schizophrenic-like phenotype and to understand the potential of mGlu5 modulators in reversing the deficits characterizing the schizophrenic pathology.

F197. PROMOTING MYELIN REPAIR RESCUES MICE FROM SCHIZOPHRENIA-LIKE BEHAVIOR INDUCED BY SOCIAL ISOLATION

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Background: Although pathological and genetic evidence suggest that oligodendrocyte (OL) or myelin deficits are associated with schizophrenia, the contribution of OL/myelin deficits to its etiology has not been clearly dis- sected, because OL/myelin abnormalities may be a concomitant phenomenon during the pathogenesis of schizophrenia.

Methods: Using olig2 ablation specifically in OLs (olig2 CKO) mice, we detected myelin development status and animal behaviors under normal condition or subjected to social isolation. We also examined the therapeutic effect of FDA-approved compounds, like quetiapine (an APD) or clemastine (a histamine antagonist) on animal behaviors.

Results: Our results demonstrated that deleting of olig2 led to impaired development of OLs and myelin deficit from postnatal day14 (P14) to P56, preferentially in cerebral cortex, and these young adult Olig2 KO mice showed anxiety-like behavior, motor skill learning deficit and cognitive deficit. Moreover, Olig2 CKO mice exhibited earlier social avoidance behavior than the WT littermates under prolonged social isolation, indicating that myelin deficit may enhance risk of schizophrenia upon environmental stress attacking. Interestingly, enhancing oligodendrocyte generation and myelin repair by quetiapine or clemastine successfully reversed the above phenotype.

Discussion: Taking together, promoting myelin repair may present a new therapeutic strategy against schizophrenia.

F198. EFFECTS OF CANNABINOIDs ON A HUMAN OLIGODENDROCYTE CULTURE: IMPLICATIONS FOR SCHIZOPHRENIA

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