Background: Genetic variants in miRNA genes and abnormalities in the concentration of microRNAs (miRNAs) in tissues and biological fluids have recently been associated with a diagnosis of schizophrenia. Most of these studies used post-mortem brain tissue or whole blood as the source of RNA. However, examination of microRNAs in cerebrospinal fluid (CSF) might provide an in vivo biomarker, more accurately reflecting expression level changes in the brain. To date, there are no studies that have investigated miRNA expression in CSF in patients with schizophrenia using small RNA-seq. In the past, our group had the opportunity of investigating the correlation between miRNA profiles in CSF and blood measured using microarray technology. Therefore, to expand our findings and use current cutting-edge technology, we measured miRNA profiles in CSF and plasma using small RNA-seq in a sample of patients with schizophrenia-spectrum disorder (SSD) diagnosis and healthy volunteers.
Methods: Twenty-two SSD patients and 17 healthy volunteers underwent a lumbar puncture and a blood draw. 15–25 cc of CSF and 5–10 cc of peripheral blood were obtained from each subject. CSF and peripheral blood samples were centrifuged. CSF and plasma samples were aliquoted into 1 mL cryovials, and stored at -80C degrees. Vesicular RNA was extracted from 1 mL of CSF and plasma samples following the protocol from the Qiagen exoRNA easy kit. The BioScientific NextFlex RNA sequencing kit was used for library construction. Sequencing was done on HiSeq2500. Samples that had at least 50,000 reads going to mature miRNA sequences were included in the analysis. Differential expression analyses were conducted in R using the DESeq2 package in Bioconductor.
Results: In the overall sample cohort, most subjects were male (66.7%), not Hispanic (81.0%) and black (48.7%). Mean age was 36.8 years (SD=12.3), There were no differences in age, sex, ethnicity or race between the patient and healthy control groups. In the patient group, 16 (72.7%) had schizophrenia, 5 (22.7%) had schizoaffective disorder and 1 (4.5%) had psychosis not otherwise specified. Differential expression (DE) analyses were conducted for 144 miRNAs in CSF and 354 miRNAs in plasma. After adjusting for multiple comparisons, DE analysis between patients and controls in CSF showed statistically significant higher levels in patients of miR-769-5p, miR-99b-3p, miR-107, miR-451a and miR-708-5. Similar analysis in plasma showed statistically significant higher levels in patients for miR-375, miR-204-5p, miR-942-5p, miR-6734-5p, miR-423-5p and miR-144-5p. Principal component analysis showed a clear separation between CSF and peripheral blood samples. Out of 443 miRNAs used to examine the relationship between CSF and plasma, 205 (46.3%) were detected in both plasma and CSF samples, 88 (19.9%) were detected only in CSF samples while 150 (33.9%) were detected only in plasma samples.
Discussion: Five miRNAs were upregulated in CSF samples and six were upregulated in plasma samples of SSD patients compared to healthy volunteers. There was no overlap in the statistically significant upregulated miRNAs between CSF and plasma samples. Therefore, miRNA profiles in CSF and plasma have important quantitative and qualitative differences that may make them excellent, but different, candidate biofluids for biomarker discovery.

F11. TRANSLATIONAL STUDY OF GRIN1, GRIN2A AND 2B GENE EXPRESSION IN PATIENTS WITH SCHIZOPHRENIA AND ANIMAL MODELS

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Background: Changes in glutamatergic system, specifically the ionotropic receptor N-methyl-D-aspartate (NMDAR), are involved in psychosis. NMDARs could be composed of two NR1 and two NR2 subunits. NR1 is one obligatory subunit and is the glycine binding site; and NR2 subunit contain the binding site for the neurotransmitter glutamate and have four different subtypes including NR2A-D. NR1 and NR2A-B are essential subunits of NMDAR, which are encoded by genes Grin1, Grin2A and Grin2B, and have been identified as candidate genes for psychiatric disorders. NMDARs dysfunction disrupts neural excitation and to contribute to the altered brain function underlying, especially in schizophrenia and other psychosis. The aims of this work were 1) to evaluate the expression of Grin1, Grin2A and 2B genes by qPCR of patients with first episode of schizophrenia compared with the siblings and controls; 2) to quantify the NR1 and NR2 subunits plasma concentrations by ELISA; 3) to evaluate the Grin1, Grin2A and 2B gene expression by qPCR in peripheral blood and animals brain tissue.
Methods: Participants will be 30 patients diagnosed with schizophrenia or schizophreniform disorder, including the shorter illness without substance addiction; those participants with siblings who agreed to participate (n = 30) and 30 controls, matched to patients by sex, age and education. Male Wistar rats were kept isolated (n = 10) or grouped (n = 10) from weaning for 10 weeks. After this period the animals were exposed to the Open Field and soon afterwards they were sacrificed, hippocampus and prefrontal cortex (PFC) were dissected to RNA extraction. RT-PCR was performed using probes and TaqMan mastermix to evaluate the mRNA expression. One-way ANOVA with a Bonferroni correction was used for statistical analysis.
Results: Humans: Regarding the glutamatergic system, none of the chosen genes were expressed in the studied sample. Animals: Isolated reared animals presented hyperlocomotion at the two first time bins (0–5 and 5–10 min) in periphery of the arena when compared to the grouped [0–5 min: $p = 0.025$; 5–10 min: $p = 0.002$], respectively. Decreased expression of Grin1 (31%), Grin2A (45%) and Grin2B (52%) were found in PFC of isolated animals when compared to grouped ($p < 0.05$), while no changes were found in the hippocampus.
Discussion: Changes in the expression of essential isoforms (NR1 and NR2) that make up NMDAR in PFC suggest abnormalities of glutamatergic neurotransmission in the pathophysiology of schizophrenia, corroborating recent studies. In addition, this study reinforces the validity of the social isolation rearing model from weaning with a better understanding of the mechanisms of NMDAR hypofunction and the influence of the environment on gene expression in this disorder.

F12. INFLAMMATORY BIOMARKERS AND COGNITION IN FIRST EPISODE PSYCHOSIS: GENDER DIFFERENCES

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Background: Cognitive impairment is considered a central feature of psychotic disorders, with an important impact on prognosis and functional outcome (Nuechterlein et al., 2011). Among the etiological explanations on psychosis, several hypotheses involving alterations in the immune /

inflammatory system have been proposed and recent research links these inflammatory processes with cognitive function, suggesting that the presence of inflammation is associated with poorer cognitive performance (Ribeiro-Santos et al., 2014, Cabrera et al., 2016). The study of the influence of gender on the possible association between inflammatory biomarkers and cognitive performance may favor the implementation of personalized treatments.
The aim of the study is to investigate the association between inflammatory biomarkers and gender-based cognition in a sample of first psychotic episode (FEP). A total of 92 patients with a FEP, 62 men and 30 women, recruited in five clinical centers were included. A neurocognitive assessment was performed and the expression of pro and anti-inflammatory mediators in peripheral blood mononuclear cells (PBMC) and plasma was measured.
Methods: In the neurocognitive evaluation the domains of attention, verbal and working memory and executive function were included. Other and clinical variables included the assessment of psychotic and affective symptoms, age, sex, educational level and socio-economic level. The expression of the proinflammatory mediators (NFκB, iNOS, COX-2, PGE2, NO-2 and TBARS) and anti-inflammatory (15d-PGJ2, PPARγ and IκBα) of the main intracellular inflammatory pathway was measured in PBMC and plasma.
Results: A correlation was made between inflammatory biomarkers and neurocognitive performance according to gender, and significant associations were selected to perform a subsequent hierarchical regression analysis. In the final model, only the expression of COX2 was associated with better performance in executive function in males (B = 0.504, p = <0.001) and the expression of NO2 to worse performance in working memory in women (B = -0.911; p = 0.010), after controlling the confounding factors. Men and women did not differ in any of the confusing variables.
Discussion: The expression of certain pro / anti-inflammatory components could have a differential effect according to the gender of patients with FEP. The expression of COX2 could be beneficial in the case of males, explaining part of the variability in executive function. On the contrary, the expression of NO2 could have a detrimental effect on working memory in women. The establishment of biomarkers linked to gender-based cognition could be useful for monitoring the course of cognitive decline and could guide treatment programs, providing tools to select a personalized approach.

F13. TOWARDS MOLECULAR INSIGHTS INTO PSYCHIATRIC DISORDERS USING AFFINITY PROTEOMICS

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Background: Numerous studies have shown a correlation between high autoantibody titers and subsequent autoimmune disease in patients with psychiatric disorders compared to healthy individuals. In this study we used a targeted affinity proteomics approach to investigate these autoantibody repertoires. We therefore obtained serum samples from patients diagnosed with various psychiatric disorders and compared these with samples of healthy volunteers. Additionally we used our approach to identify autoantibodies in post mortem brain tissue from patients diagnosed with schizophrenia.
Methods: In this study we utilized a well characterized cohort of patients with psychiatric disorder to study the autoantibody repertoire. From this sample set we analysed more than 600 serum in a first discovery approach. Based on the in-house screening and previous external published studies of autoantibodies within psychiatry we selected a set of 231 protein fragments from the Human Protein Atlas with a length of roughly 80 amino acids. With this selected panel we screened additional 130 post mortem brain tissue samples. Autoantibody profiling was performed using suspension bead array technology and IgG reactivity was measured in patients and controls.
Results: Our findings could indicate altered immune response in patients with psychiatric disorders compared to healthy controls. In our study we identified potential predictive autoimmune signatures. Those were presented with higher IgG reactivity in patients compared to healthy control samples.
Discussion: With our approach we were able to profile autoantibody repertoires in patients with psychiatric disorders. Additionally, we were able to use our approach to profile brain tissue using a multiplexed affinity proteomics approach. By further validating these putative autoimmunity targets, we could gain insights into the autoantigens associated to chronical mental illnesses.

F14. REDUCED DURATION MISMATCH NEGATIVITY ASSOCIATED WITH DECREASED GLUTAMATE+GLUTAMINE LEVEL IN SUBJECTS AT CLINICAL HIGH-RISK FOR PSYCHOSIS

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Background: Abnormal mismatch negativity (MMN), thought to be a putative marker of glutamatergic function, has been reported in non-Asian, first episode schizophrenia and clinical high-risk for psychosis (CHR) individuals as indicative of impairments in pre-attentive processes. However, reports of abnormal MMN in Asian populations are sparse, as well as its relationships to glutamate and γ–aminobutyric acid (GABA) levels in medial prefrontal cortex. The present longitudinal study explored MMN differences between CHR subjects who will and who will not remit, and its relationships with prefrontal glutamate and GABA levels.
Methods: All subjects participated in the ShangHai At-Risk for Psychosis (SHARP) program. CHR subjects met the criteria defined by the Chinese version of the Structural Interview for Prodromal Syndromes (SIPS). From the SHARP sample, 76 CHR subjects (41 male, age 18.63 ± 5.02 years) and 53 HC (31 male, age 17.72 ± 3.18 years) completed both MMN test and proton magnetic resonance spectroscopy (1H MRS) scans using a MEGA-PRESS sequence at their initial visit. CHR subjects were divided into remitted (37) and non-remitted (34) individuals based on their clinical symptoms and functional scores at a one-year follow up. Duration MMN amplitude was measured at electrodes F1/2, Fz, FC1/2, FCz, C1/2 and Cz. Concentrations of glutamate+glutamine (Glx) and GABA in the medial prefrontal cortex (mPFC) were quantified using the LCModel software (version 6.3-0I).
Repeated measures analysis of variance (ANOVA) with group (remitted CHR, non-remitted CHR and HC) as the between-group factor and electrodes (Fz, FCz and Cz) as the within-group factor were performed for the midline sites, and the ANOVA using F1/2, FC1/2 and C1/C2 with laterality (left and right hemisphere) as an additional within-group factor was performed for the lateral sites. Correlations of the dMMN amplitude (averaged over the 9 electrodes) and Glx and GABA concentrations were assessed by Pearson correlation tests for each group.
Results: There was a significant main effect of group ($F(2,121)=3.14$, $p<0.05$) for the midline fronto-central dMMN amplitude. Post-hoc tests showed that non-remitted CHR subjects had lower baseline dMMN amplitude (-4.75 ± 0.37μv) than HC (-5.92 ± 0.30μv, $p<0.05$), whereas dMMN in remitted CHR (-5.22 ± 0.36μv, $p=0.41$) was comparable to dMMN in HC. The main effect of group was marginally significant at lateral sites ($F(2,121)=2.83$, $p=0.06$). DMMN amplitude in non-remitted CHR (-4.67 ± 0.37μv) tended to be lower than those in HC (-5.76 ± 0.29μv,