F8. SEARCHING FOR A STRATIFICATION MARKER FOR ANTIOXIDANT USE IN SCHIZOPHRENIA AND BIPOLAR DISORDER: A META-ANALYSIS OF MRS STUDIES OF ANTERIOR CINGULATE GLUTATHIONE

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Background: Glutathione [GSH] is a major intracellular antioxidant that disposes peroxides and protects neurons and glial cells from oxidative stress. In both schizophrenia and bipolar disorder, atypical levels of GSH has been demonstrated, particularly in the anterior cingulate cortex (ACC), though no consistent results have emerged due to limitations in sample size. Examining the state of GSH deficit in schizophrenia is a critical step when attempting to correct putative redox imbalance in this illness using agents such as N-Acetyl Cysteine (NAC). We conducted a meta-analysis to investigate the aberrations in GSH levels in the ACC of patients with schizophrenia and bipolar disorder measured using magnetic resonance spectroscopy (MRS).
Methods: Medline, Google Scholar, Ovid Online and EMBASE databases were searched for studies published until September 2017. Search terms included magnetic resonance spectroscopy, MRS, schizophrenia, psychosis, psychotic, bipolar disorder, glutathione, GSH. We included all 1H-MRS studies reporting GSH values for patients satisfying DSM or ICD based criteria for a primary psychotic disorder (SCZ) or bipolar disorder (BPAD) in comparison to a healthy controls (HC) group. We screened all identified abstracts, filtered studies that did not satisfy inclusion criteria, hand-searched references and contacted experts to locate further studies. We excluded studies that reported only on comorbid illnesses, did not compare patients and HCs, or failed to report data required to construct effect size metrics. After initial screening, a total of 261 patients and 185 controls were considered for the meta-analysis from the SCZ group; 464 patients and 245 controls were considered for the meta-analysis from the BPAD group. A random-effects, inverse-weighted variance model was used to calculate the pooled effect size. Mean values were extracted and verified independently. Effect sizes were computed based on excel macro, produced by Major Depressive Disorder Neuroimaging Database investigators.
Results: Contrary to our expectations, in SCZ, there were no significant differences in ACC GSH in patients compared to HC (RFX p= 0.74; 95% CI, -0.24 to 0.17; FFX p= 0.71; heterogeneity p = 0.58). In BPAD, there were highly significant differences in the ACC GSH, with patients having higher GSH concentrations than HC (RFX: p= 0.0003; 95% CI, 0.14 to 0.5; heterogeneity p=0.70). In the BPAD group, the mean effect size (SMD) was d= 0.32, indicating a small to medium sized difference. A network meta-analysis revealed significantly higher GSH levels in BPAD compared to SCZ (RFX p= 0.01; 95% CI, 0.08 to 0.63; SMD=0.36; heterogeneity p = 0.71). There were several methodological issues in the reported studies. Notably, most acquisitions were not optimized to collect GSH spectra; polymorphisms in the glutamate-cysteine ligase catalytic gene (GCLC) were not quantified in most studies; voxel placements were not standardized across the published studies; majority of patients were medicated, in various stages of illness.
Discussion: There are no major differences in concentration of ACC glutathione in the anterior cingulate cortex in patients with schizophrenia, though in bipolar disorder, GSH levels appear elevated. Given that GSH is the most readily accessible cortical redox marker in vivo, current status of MRS literature is insufficient to prepare for stratified therapeutics with antioxidants among patients with schizophrenia. Nevertheless, abnormalities in the redox system may be more pronounced in bipolar disorder compared to schizophrenia, and could serve to guide stratification in samples lacking diagnostic clarity (e.g. in First Episode Psychosis clinics).

F9. ALTERATIONS OF NEURONAL METABOLISM IN PATIENT SUBGROUPS AT ULTRA-HIGH RISK FOR PSYCHOSIS ACCORDING TO PACE CRITERIA – A 1H/31P-MR-SPECTROSCOPY STUDY

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Background: Glutamatergic dysfunction, deregulated mitochondrial metabolism and alterations of membrane phospholipids have been extensively investigated in schizophrenic illness by using in vivo magnetic resonance spectroscopy (MRS). Findings in the ultra-high risk (UHR) phase of psychotic illness, however, are still rare and inconsistent. Combining both 1H- and 31P-MRS, this study investigates these aspects in the different UHR patient subgroups as defined by PACE (Personal Assessment and Crisis Evaluation) criteria.
Methods: We applied 3 T chemical shift imaging (3D 31P-MRS, 2D 1H-MRS) and hippocampal single-voxel MRS in 69 neuroleptic-naïve UHR patients (age: 26.2 ± 6.2y; males 59.4% 41/69, attenuated symptoms (AS) n=50, BLIPS n=5, genetic risk (GR) n=8, AS+GR n=6; transition rate 17.2%, all transitions in the AS or BLIPS group) and 61 healthy controls (age: 25.2 ± 4.8y; males 54.1% 33/61). 11 metabolite markers were investigated (neuronal/mitochondrial metabolism: glutamate (Glu), N-acetyl-aspartate (NAA), phosphocreatine (PCr), and adenosine triphosphate (ATP); phospholipid synthesis: phosphomonoester/-metabolites (PME, Peth, Pch); phospholipids breakdown: phosphodiester/-metabolites (PDE, Gpeth, Gpch); astrocyte activation: myo-Inositol (mI)) in 5 brain regions (dorsolateral prefrontal cortex, DLPFC; dorsomedial prefrontal cortex, DMPFC; dorsal anterior cingulate cortex, dACC; mediodorsal thalamus, Th; and hipoocampus, Hip). Psychopathology was assessed using the CAARMS-Interview as well as PANSS, BPRS-E and SCL-90-R ratings. Statistical analysis included multi-and univariate ANOVA, Kruskal-Wallis-tests and correlation analysis.
Results: (i) In all UHR individuals (and also in the AS and BLIPS subgroup), NAA was reduced in the left Th. There was no alteration of Glu. While PCr was increased in the left DLPFC, left dACC (right trend) and in the right Hip, ATP was not different from controls. PME were decreased in the right Hip, PDE did not differ from controls. mI was found increased in the left Hip. (ii) In the GR subgroup PCr was increased in the bilateral Th. The PME metabolite Peth was decreased in the right Th. PDE were increased in the left dACC. mI was increased in the left Th.
Discussion: While the observed pattern of metabolite abnormalities in the AS and BLIPS risk group suggests a pathology that affects the left thalamus (NAA decrease), left DLPFC, dACC and bilateral Hip (left: PCr increase, PME decrease; right mI increase), the pathology of the GR group appears more focussed on the bilateral Th (bil. PCr increase, right PME decrease, left mI increase) and left dACC (PDE increase). The results suggest a functional disturbance of networks including the left DLPFC, dACC, bilateral Hip and Th, whereby the latter might be more an expression of a genetic risk profile.

F10. DIFFERENTIAL EXPRESSION OF MICRORNAS IN CEREBROSPINAL FLUID AND PLASMA SAMPLES IN SCHIZOPHRENIA

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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 /