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Background: There is considerable interest in identifying biomarkers of antipsychotic response in schizophrenia, and brain glutamate is one key candidate.

Methods: In a series of 1H-MRS studies, we have investigated the relationship between brain glutamate and antipsychotic response. This includes cross-sectional studies in patients with early psychosis, and chronic schizophrenia. Longitudinally, within the OPTiMiSE consortium, we examined whether glutamate levels in first-episode psychosis (FEP; n = 72, <2 weeks antipsychotic medication) predict psychopathology after subsequent administration of oral amisulpride for 4 weeks. Finally, in an ongoing study in treatment-resistant schizophrenia, we investigate whether glutamate levels prior to clozapine initiation predict the degree of symptomatic response after 12 weeks of clozapine treatment.

Results: The cross-sectional study in early psychosis found elevated glutamate in the anterior cingulate cortex (ACC) in patients who had reached remission compared to those who had not (T(30) = 3.02, P = .005). ACC glutamate level was positively associated with the severity of negative symptoms (r = .42; P = .017) and negatively associated with global functioning (r = .47; P = .007).

Our first cross-sectional study in chronic schizophrenia detected an elevation in ACC glutamate in treatment-resistant schizophrenia (TRS) compared to healthy volunteers (T(14) = 2.80, P = .01), which was not apparent in treatment responders (T(16) = 0.29, P = .77). The subsequent larger study found higher ACC glutamate levels in TRS than in treatment-responsive patients (T(35) = 2.34, P = .025).

In the OPTiMiSE FEP cohort at baseline (prior to amisulpride treatment), ACC glutamate was positively correlated with the PANSS general score (r = .26; P = .03) and negatively correlated with the personal and social performance (PSP) score (r = −.34; P = .006). Baseline glutamate in the ACC (r = −.38; P = .004) and thalamus (r = −.42; P = .003) were negatively correlated with PSP score after 4 weeks amisulpride. Baseline thalamic glutamate negatively correlated with the longitudinal reduction in the PANSS positive (r = −.35; P = .009) and total (r = −.28; P = .04) scores after 4 weeks amisulpride. An interim update on the ongoing clozapine study will also be provided.

Conclusion: This series of studies has returned consistent findings that elevated ACC glutamate is associated with poor response to antipsychotics, more severe symptoms, and social dysfunction. Brain glutamate may relate to the magnitude of response to subsequent antipsychotic treatment.

SA84. PROTON MAGNETIC SPECTROSCOPY SHOWS ELEVATED STRIATAL CHOLINE LEVELS IN DRUG-NAIVE PATIENTS WITH FIRST-EPISTODE PSYCHOSIS

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Background: Cytokines released by microglia has been hypothesized to cause aberrant astrocyte signaling which in turn may result in glutamate dysfunction. Elevated choline is proposed to reflect glial activation. To study our hypothesis that untreated, first-episode psychosis would affect levels of choline and glutamate, we conducted a magnetic resonance spectroscopy study in the striatum.

Methods: We enrolled 19 age, gender, and parental socioeconomic status matched healthy controls (HC) and patients with first-episode psychosis (FEP) as part of our study. One HC and 5 FEP patients who did not have good quality spectral data were not included in the analysis. Imaging was performed on a 3T head-only scanner (Magnetom Allegra, Siemens Medical Solutions, Erlangen, Germany) with a circularly polarized transmit/receive head coil. A series of sagittal, coronal, and axial T1-weighted anatomical scans (gradient-recalled echo sequence, TR/TE = 2500/80ms, flip angle= 70°, 5mm slice thickness, 1.5mm gap, 512x512 matrix) were acquired for voxel placement. MRS data were collected from a voxel in the left striatum (1.8x1.8x1.8cm). Following manual shimming, water-suppressed spectra were acquired using the point-resolved spectroscopy sequence (PRESS; TR/TE = 2600/80ms; 1200 Hz spectral bandwidth; 1024 points; number of averages = 512). Eight unsuppressed water average were also obtained. MRS data were analyzed in jMRUI. Spectra were quantified with respect to water in the time domain using the AMARES algorithm. Exclusion criteria of Cramer Rao Lower Bound >20% was used and had to exclude 2 HC based on CRBL for glutamate. Group differences in metabolites were examined with analysis of covariance (ANCOVA) using disease state as between-group factor and smoking and gray matter fraction as covariates. Positive and negative symptoms were assessed using Brief Psychiatric Rating Scale (BPRS). Partial correlations were used to examine the relationship between BPRS scores and metabolites.

Results: There were no differences between age, sex, and socioeconomic status between patients with FEP and HC. We found elevated choline levels in comparisons between FEP and HC groups, (P = .011 and F = 4.583, FEP mean = 0.235, SD = 0.036, HC mean = 0.200, SD = 0.026), after controlling for packs per day and gray matter fractions. There was no difference between the groups, with respect to other metabolites Glx (glutamate+glutamine), Cr, and NAA. In patients with first-episode psychosis, Glx was negatively correlated with BPRS scale positive symptom (r = −.42; P = .021).

Conclusion: The elevated choline in the FEP group may reflect the increased membrane turn over from glial cells, which supports the hypothesis of neuroinflammation as a possible etiology of schizophrenia. Antipsychotics have shown to inhibit the microglial activation in animal models, making a case for earlier treatment of untreated psychosis to prevent the downstream effects of inflammation.

SA85. WHITE MATTER CONNECTIVITY AS A PREDICTOR OF RESPONSE TO ANTIPSYCHOTIC TREATMENT: A DIFFUSION CONNECTOMETRY STUDY IN UNMEDICATED PATIENTS WITH SCHIZOPHRENIA

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Background: A number of studies have reported decreased white matter integrity in patients with schizophrenia, but little is known the relationship between white matter alterations and response to antipsychotic treatment.

Methods: We enrolled 30 unmedicated patients with schizophrenia in a 6-week longitudinal trial with risperidone, a commonly used antipsychotic medication. Symptom severity was assessed with the Brief Psychiatric Rating Scale (BPRS). We obtained diffusion-weighted images before treatment was started. Thirty diffusion sampling directions spanning the whole sphere were acquired twice and concatenated (in plane resolution 2.2 mm, slice thickness 2.2 mm, b-value 1000 s/mm², 5 b0 images). Motion and eddy current correction were performed with the FSL EDDY tool. Diffusion data were then reconstructed in MNI space using q-space diffeomorphic reconstruction to obtain the spin distribution function, with a sampling length ratio of 1.25. Group diffusion connectometry was performed to examine the relationship between connectivity and clinical response after 6 weeks of treatment (defined as BPRS total baseline − BPRS total week 6) / BPRS total at baseline ×