GABA and Glutamate abnormalities in the superior temporal gyrus and their association with electrophysiological abnormalities in schizotypal personality disorder and schizophrenia

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BACKGROUND: Many studies indicate the superior temporal gyrus (STG) shows volumetric reductions in schizotypal personality disorder (SPD) and in schizophrenia (SZ), reductions that in first episode SZ progress after onset [1]. Moreover, electrophysiology studies using P300 and mismatch negativity (MMN) event-related potentials (ERPs) show reductions in SZ that correlate highly with the extent of structural MRI volumetric abnormalities and, in the case of MMN, show concomitant progression of abnormalities in first episode SZ [2]. Data also indicate the gamma band oscillation (GBO, ~40 Hz) elicited by the auditory steady state response paradigm (ASSR) has a prominent origin in the STG [3].

Despite this extensive body of data about SZ and SZ spectrum abnormalities there have been, to our knowledge, no magnetic resonance spectroscopy (MRS) studies in SPD and SZ of STG voxels measuring GABA and glutamate (Glu) metabolites, the neurotransmitters used by inhibitory neurons and pyramidal neurons whose interaction is responsible for the GBO. Therefore the first aim of this study is to measure glutamate and GABA using conventional and spectral editing MRS methods in the superior temporal gyrus in SPD, SZ, and controls and compare the concentrations of these metabolites with electrophysiology measures.

METHODS: To determine the feasibility and promise of MRS in these disorders, four neuroleptic-naïve SPD subjects, six chronic SZ, and four age- and PSES-matched healthy controls (HC) (all subjects male, ages 41-54) were recruited for this study from a well-characterized cohort of patients where full DSM-IV criteria were met for SPD and SZ. The following protocol was then acquired in the left STG (Figure 1) using a voxel size of 20 x 30 x 20 mm (12 mL): PRESS TE=30ms, TR=2s, BW=2 kHz, 2058 pts 128 avgs and 16 avg water reference; MEGA-PRESS TE=70 ms, TR=2s, BW=2 kHz, 1024 pts, and 128 avg acquired both on and off resonance whose difference spectrum will give GABA. PRESS data was analyzed using LCmodel [4] providing the primary measure of Glu where Cramer-Rao lower bound (CRLB) < 20% was achieved for all subjects. Similarly, GABA was also analyzed using LCmodel and a GABA specific basis set [5] using the same CRLB criteria.

Figure 1. Left STG voxel location in three planes

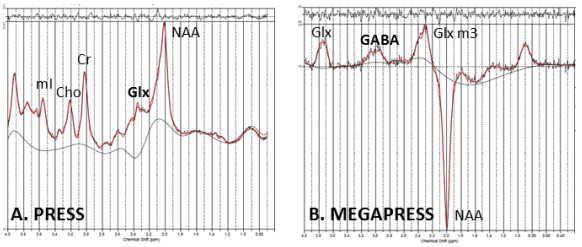

Figure 2. Representative PRESS (left) and MEGAPRESS spectra from LSTG

RESULTS/DISCUSSION: The ASSR data from 4 male DSM-IV SPD and 4 male age-matched HC showed a left GBO ASSR PLF deficit to 40Hz stimulation. The GBO PLF was highly correlated with the Left STG MRS data in both SPD and HC subjects. The PLF decreased with increasing Left STG Glu (rho= -0.9, p<0.04) and increased with increasing GABA (rho = 0.64, p<0.1) as shown in Figure 2. This is supportive dysfunction based on GABA disinhibition and the resulting increased glutamatergic excitation. Findings were similar in the medicated chronic SZ, which had a finer grain topographic analysis. The ASSR PLF was measured at 58 electrodes in 6 chronic SZ and 4 HC and then, for analysis, collapsed into regions of left and right Temporal, ParaCentral and Lateral based on a larger sample (24 chronic SZ, 24 HC). In this larger sample the maximum SZ PLF deficits were highly left-lateralized There was a strong association between the Left temporal 40 Hz GBO ASSR in chronic SZ and the LC Model Glutamate and MEGA-PRESS GABA concentrations in the Left STG. The predicted association for Left STG MRS Glu values and the Left Temporal and Left ParaCentral ASSR PLF for SZ and HC was observed in in significant inverse (negative) correlation (rho =-.66, p<0.019). Pearson r values were also significant. The predicted direct (positive) and significant correlation between Left STG GABA and the ASSR PLF in both Left Temporal and ParaCentral electrodes for SZ and HC was found (rho = 0.55, p = 0.049). We note the dispersion of the SZ GABA values and of the ParaCentral PLF allowed a within SZ group measurement without the distortion of a "ceiling effect" for Glu (where all values are high) and a "floor effect" for the PLF (all values are low). Indeed within the SZ group, Left STG MRS GABA and the Left Para-central PLF values are highly correlated, rho = 0.771, p = 0.036.

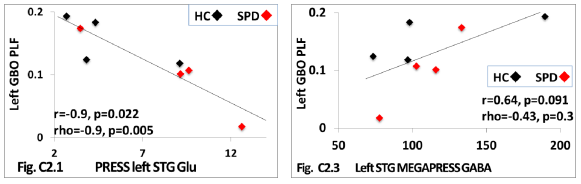

Figure 3. Correlation of Left GBO PLF with Glu (left) and GABA (right)

CONCLUSION: These data demonstrate associations between ASSR and MRS values in SZ, an association also found in the SPD subjects, who show a genetic relationship to SZ. Of note, in the never neuroleptic-medicated SPD, ASSR and MRS STG values paralleled our findings in the medicated SZ, suggesting the SZ data were not artifacts of medication. These data are consistent with our prediction, based on our GABA-Glutamate imbalance hypothesis, that both SPD and SZ would show a reduced ASSR PLF that would be associated with both a reduced GABA and increased Glu, a finding compatible with pyramidal cell disinhibition and GBO disruption.

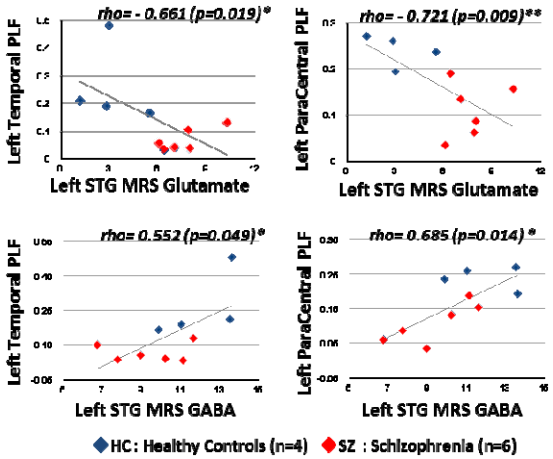

Figure 2. Correlation of left temporal PLF (left) with Glu (top) and GABA (bottom) and left paracentral PLF (right) with Glu (top) and GABA (bottom)/

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