^{1}H MRS Study of Metabolic Alternations in Schizophrenia at 7T

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PURPOSE: Schizophrenia (SCZ) is a chronic psychotic disease of high prevalence (0.5-1% of the world population), resulting in severe disability. Evidence suggests that SCZ involves alterations in glutamatergic transmission [1]. Metabolites associated with neuronal transmission may include the primary excitatory neurotransmitter, glutamate (Glu), and inhibitory neurotransmitters, γ-aminobutyric acid (GABA) and glycine (Gly). Magnetic resonance spectroscopy (MRS) provides a noninvasive tool for evaluating potential alterations of the metabolites for studying abnormalities in the glutamatergic transmission. Here we present ^{1}H MRS measurements of metabolites in anterior cingulate cortex (ACC) in SCZ patients vs. healthy subjects, obtained using previously-reported methods at 7T [3-4].

METHODS: ^{1}H MRS data were obtained from the ACC in 22 normal volunteers (NV) (11 male; 11 female; age of 44.3 ± 11.7) and 34 schizophrenic patients (SCZ) (18 male; 16 female; age of 44.0 ± 11.5), using point-resolved spectroscopy (PRESS) with echo times (TE) of 92 ms [3] and 150 ms [4] in a 7T whole-body MR scanner (Philips Medical Systems). Acquisition parameters included: voxel size = 30x20x15 mm^3, TR = 2.5 s, sweep width = 5 kHz, number of sampling points = 4096, and number of averages = 256. Spectral fitting was performed with LCModel software [5], using basis spectra calculated incorporating the volume localizing RF and gradient pulses of PRESS with published chemical shift and J-coupling constants [6]. Metabolite levels were calculated with respect to total creatine (tCr), assuming identical metabolites transverse relaxation times (T_2) between NV and SCZ. A two-tailed unpaired t-test with Welch's correction was performed to evaluate the statistical significance of metabolic differences between the control and patient groups.

RESULTS: Although the spectral resolution is improved with increasing field strength, the small signals of GABA and Gly remain extensively overlapped with neighboring large signals in short-TE MRS at 7T. We obtained complete separation among Glu, GABA and Gln using PRESS TE = 92 ms and between Gly and myo-inositol using PRESS TE = 150 ms. In-vivo spectra were well reproduced by spectral fitting, giving noise-level residuals and signal estimates with relatively small Cramér–Rao lower bound (CRLB) (Fig. 1). The group analysis showed that the concentration of N-acetylaspartate (NAA) was significantly lower ($p<0.0008$) in SCZ than NV (Fig. 2), in agreement with many prior MRS studies in neuropsychiatric disorders [7]. The Glu level was significantly decreased ($p<0.007$) in SCZ while the Gly level was significantly higher ($p<0.04$) in SCZ than in NV. The data showed a trend of reduced GABA in SCZ, but the difference was not significant ($p<0.18$). Total choline (tCho) was significantly lower ($p<0.04$) in SCZ. Gln was about the same ($p<0.5$) between the two groups.

DISCUSSION AND CONCLUSION: The current study reports alteration in Gly level in SCZ for the first time. Our observation of reduced Glu in SCZ is in agreement with a recent study by Stan et al. [8]. Increased levels of Gly would be expected to enhance NMDA receptor function while reduced Glu would reduce Glutamatergic function at the NMDA receptor and other ionotropic (AMPA, KA) and metabotropic glutamate receptors (mGluRs). These data may suggest selective reduction of glutamate transmission at non-NMDA glutamate receptors. We observed a trend of reduced GABA in SCZ in the ACC, in agreement with a report by Rowland et al. [9]. If the trend held up with a larger sample size and increased the power, GABA reduction could be explained by a mechanism that restores excitation and inhibition balance.

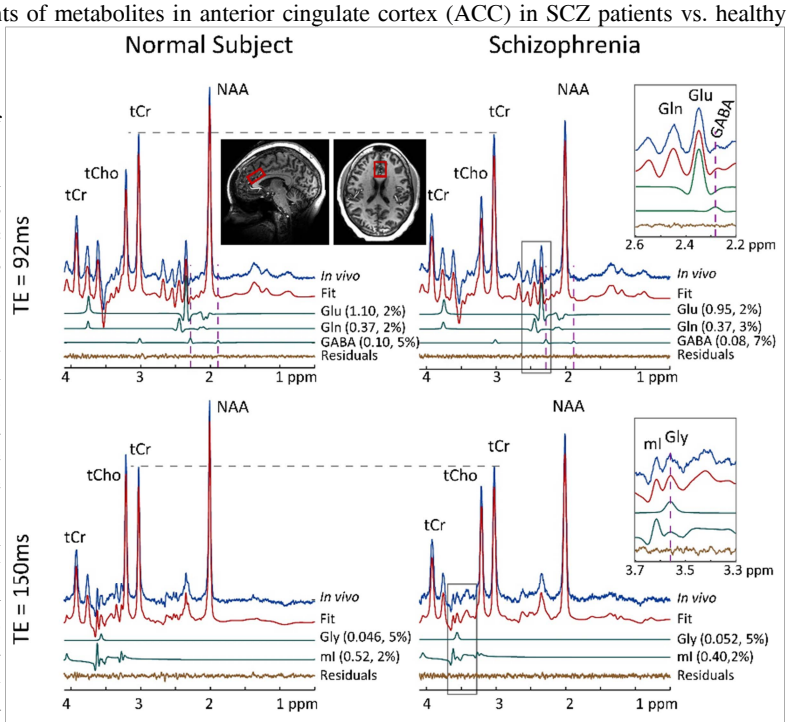

Fig.1: Representative *in vivo* spectra from the anterior cingulated cortex of a normal subject and a schizophrenia (SCZ) patient, obtained with PRESS TE= 92 ms and 150 ms at 7T, are shown together with LCModel fits, residuals and metabolites signals. The numbers in brackets are metabolite / tCr and CRLB. For data from SCZ, spectra within the box are magnified and shown on the right (2.2-2.6 ppm for TE =92ms, 3.3-3.7 ppm for TE = 150 ms).

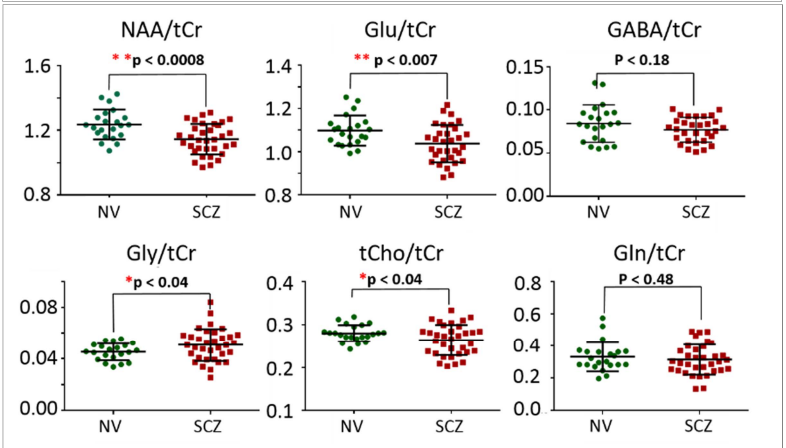

Fig.2: The ratios of metabolites and tCr levels are shown for normal subjects (NV) and schizophrenia patients (SCZ), together with p values from two tailed unpaired t-test. * for $p < 0.05$ and ** for $p < 0.01$.

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