

2D L-COSY at 7T Detects Glutamate, Glutamine, Glutathione and GABA in Patients with Schizophrenia

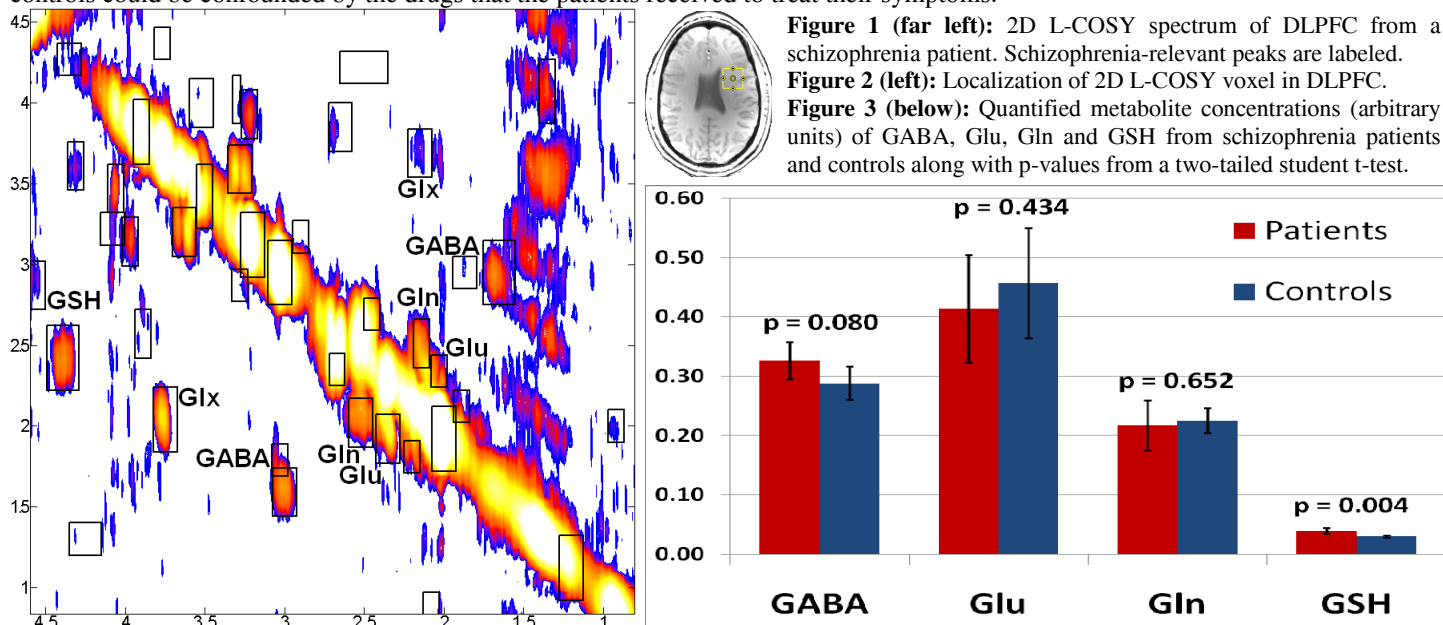
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Introduction: Irregularities in cortical glutathione (GSH) synthesis and glutamatergic neurotransmission have been correlated with increased clinical symptoms in schizophrenia (1). These metabolites are subject to spectral overlap with other metabolite resonances, and therefore difficult to detect and quantify using conventional 1D magnetic resonance spectroscopy (MRS) techniques or at lower field strengths. The recently-implemented 7T 2D L-COSY technique (2) has demonstrated promising reliability in detecting these and other resonances *in vivo* in the human brain and could prove effective in assessing the disease and monitoring treatment response. The primary goal of this study was to assess the metabolic differences in schizophrenia patients, particularly in GSH, glutamate (Glu)/glutamine (Gln), and γ -aminobutyric acid (GABA) (3), using the 2D L-COSY technique at 7T.

Materials & Methods: Twelve subjects – six schizophrenia patients and six age-matched controls (ages 19-29, all male) were scanned with the 7T L-COSY sequence at 7T. A $2.5 \times 2.5 \times 2.5$ cm³ voxel was placed in the dorso-lateral pre-frontal cortex (DLPFC) by registering a T₁-weighted image to a brain atlas for machine-guided localization. The other scan parameters for the L-COSY were as follows: 20/2000 ms TE/TR, 2048 F₁ points with 4000 Hz F₁ bandwidth, 64 Δt_1 increments of 0.4 ms, 8 averages for a total scan time of about 17-minutes. The raw data was post-processed offline in MATLAB and metabolite concentrations were computed using a volume integral method (3). The quantified metabolite values were normalized with respect to integral of the 3.0 ppm creatine diagonal peak.

Results & Discussion: Figure 1 shows a typical L-COSY spectrum from a schizophrenia patient and figure 2 shows the corresponding voxel in the DLPFC region. Figure 1 also shows the integral regions used for signal quantification for each of the measured metabolites. Coefficients of variation (CVs) in control subjects were 8% for GABA, 20% for Glu, 9% for Gln and 13% for GSH indicating a low variability in these metabolites as measured by L-COSY. Figure 3 shows the mean values for GABA, Glu, Gln and GSH cross peaks (with respect to creatine) for schizophrenia patients and controls. The error bars indicate standard deviation for each metabolite. P-values from a two-tailed student t-test are shown above each column of figure 3 and they indicate significantly higher GSH in the DLPFC of schizophrenia patients (p-value = 0.004). 2D L-COSY detected other metabolites other than those that were the primary focus of this study. Among these, lactate (Lac) was also found to be significantly elevated among the patient group, with a p-value of 0.038. Though these results are promising, the differences in GSH and Lac levels between schizophrenia and controls could be confounded by the drugs that the patients received to treat their symptoms.



Conclusion: 2D L-COSY was able to successfully detect a number of metabolites with suspected correlation to schizophrenia. Future applications of the 2D L-COSY could be to monitor the effect of various treatments for schizophrenia and correlate these findings with the progression of symptoms and performance in psychiatric evaluations.

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References: 1. Matsuzawa et al. PLoS One 2008; 3:e1944. 2. Verma et al. JMRI 2013 *in press*. 3. Costa et al. Crit rev Neurobiol 2004;16(1-2):1-23. 4. Govindaraju et al. NMR in Biomed 2000; 13:129-153