Comparison of Cerebral Glutamate and GABA in Schizotypal Personality Disorder using Spectral Editing and 2D Correlated Spectroscopy

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Introduction: Schizotypal personality disorder (SPD) is characterized by difficulties with social interaction coupled with odd behavior and thinking that is part of the schizophrenia spectrum disorders[1]. Studies have shown that SPD is closely related to schizophrenia (SZ) from a genetic, cognitive, and neurobiological perspective however little has been explored in this less severe form of psychosis[2]. Numerous studies have shown that γ-amino butyric acid (GABA) and glutamate (Glu) are altered in SZ[3] however to this date no studies have examined the role of these important neuorotransmitters in SPD. Magnetic resonance spectroscopy (MRS) can non-invasively measure brain chemistry including GABA and Glu. Unfortunately, due to the strong j-coupling between other molecules, their peak resonances overlap one another making them difficult to separate and quantify. Several MRS techniques have been developed to overcome this problem: By using frequency-selective refocusing pulses, the MEGA-PRESS can spectrally edit for GABA[4]. For glutamate, the TE-averaging method has been shown to be effective[5]. An alternative method is two-dimensional correlated spectroscopy (2D COSY) which utilizes a three-slice selective (ss) RF-pulse sequence: 90sst1-90ss-90ss-Acq(t2) creating a dataset that is a series of one dimensional (1D) spectra with traditional time readout (t2) but each with increments in delay (t1) inserted before the terminal readout 90° RF pulse[6,7]. Two-dimensional Fourier transformation (FT) of t1 and t2 produces a 2D spectrum whereby j-coupling between protons in molecules results in cross-peaks that allow for unambiguous identification of different metabolites.

Objective: The goal of this study was to measure GABA and Glu cerebral concentrations in SPD using both spectral editing and 2D MRS techniques and compare the results of the two methods. These results will provide the first evidence of GABA and Glu alterations in SPD.

Methods: Four neuroleptic-naïve SPD subjects and four age- and IQ-matched healthy controls (all male, ages 41-54) were recruited for this study. SPD diagnosed using DSM-IV criteria. All subjects were consented under local IRB approval and scanned on a 3T MRI scanner (Siemens Verio). The following protocol was then acquired in the left and right superior temporal gyrus (STG) using a voxel size of 20 x 30 x 20 mm (12 mL). The rationale for using the STG is that structural imaging studies[8] have shown changes in SPD in this location. The following methods have been used: 1) Conventional PRESS: TE = 30 ms, TR = 2 s, bandwidth = 2 kHz, 2048 complex data points, weak water suppression, and 128 averaged acquisitions. Unsuppressed water spectrum with the same parameters but without water suppression and 16 averages was also acquired. Total scan time: 4.8 minutes 2) TE-averaging: initial TE = 30 ms, with 32 TE increments of 10 ms, TR = 2 s, bandwidth = 2 kHz, 2048 complex data points, and 4 averaged acquisitions per TE. The TE averaging technique will be applied: all 1D spectra acquired at increasing TE values are co-added by the scanner to generate a single free induction decay signal, which upon Fourier transform edits the spectrum for optimization of glutamate signal. Scan time: 4.3 minutes. 3) MEGA-PRESS: TE = 70 ms, TR = 2s, bandwidth = 2 kHz, 1024 complex data points, and 128 averaged acquisitions acquired both on and off resonance whose difference spectrum will give the GABA edited sequence used for quantification. Scan time: 8.53 minutes. 4)COSY: 64 t1 increments with increments size of 0.8 ms in giving an indirect spectral width of 1250 Hz, TR 1.5 s, RF carrier frequency at 2.0 ppm, weak water suppression using WET, spectral width=2000 Hz, 8 averages per increment, and 1024 data points will be acquired. Scan time: 12.5 minutes. PRESS data was analyzed using LCmodel. Glu quantification will be undertaken on the peaks at 2.35 and Glx, a combination of Glu and Gln, at 3.75 ppm as seen in Figure 1. Similarly GABA at 3.0 ppm as well as Glx at 3.7 and 2.3 ppm will be quantified. Both spectral editing data were processed and suitable resonances quantified on the Syngo software provided by scanner manufacturer (Siemens AG, Erlangen, Germany). 2D COSY data was post-processed using Felix 2007 where crosspeak volumes was measured including location (F2, F1 in ppm), amplitude, and volume normalized to the Cr crosspeak amplitude and volume, respectively. 2D COSY measurements include Glu and GABA as well as other metabolites.
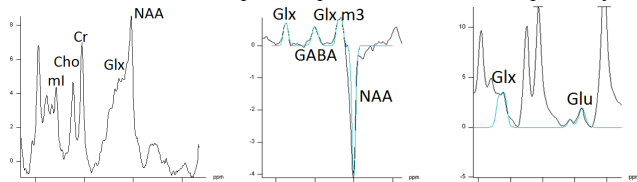

Figure 1. Representative 1D MRS of SPD. Left: PRESS MRS Middle: MEGAPRESS editing for GABA Right: TE-averaging for Glu
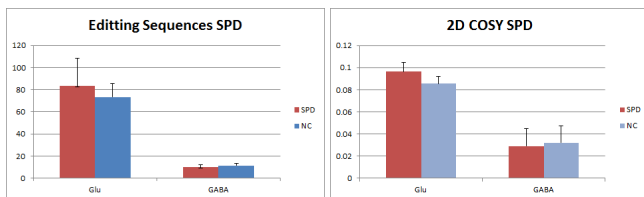
Figure 2. Glu and GABA Measures in SPD. Left: Results from spectral editing sequences. Right: Results from 2D COSY. SPD results in red, normal controls (NC) in blue.
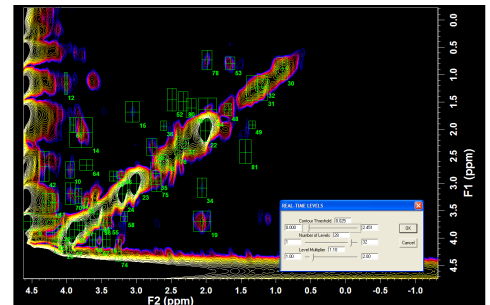

Figure 3. Representative 2D COSY of STG of SPD. Green ROIs show crosspeak identification. Inset shows threshold parameters.

Results and Discussion: The GABA measurements in the conventional PRESS voxel all had a Cramer-Rao lower bound (CRLB) that exceeded 20%, and was thus unreliable. For Glu, 25% of the total spectra acquired also failed CRLB limits of less than 20% thus demonstrating the need for spectral-editing and/or 2D methods. Representative GABA and Glu edited spectra are shown in Figure 1 and the results tallied in Figure 2. Similarly 2D COSY results for GABA and Glu are shown. Both spectral editing and COSY methods demonstrate the same results of increased Glu and decreased GABA in the STG of SPD subjects when compared with controls. The coefficients of variance were similar between the two methods as well demonstrating that 2D COSY could potentially be used in place of the individual spectra editing techniques. Most importantly, 2D COSY allows for the measurement of many other metabolites as shown by the multiple regions of interest in Figure 3. Additional resonances such as membrane phospholipids (glycerophosphorylcholine, phosphocholine) and peptides such as glutathione were also measured and have been shown to also play a role in SZ[3].

Conclusion: The results of comparison show that while 1D spectral editing can measure each of the metabolites using sequences such as MEGA-PRESS, 2D COSY can acquire all of these measurements in a single scan that is less time consuming than applying individual pulse sequences for each individual metabolite.

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