Spectral Alignment Improves GABA Measures in Schizotypal Personality Disorder

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Introduction: Schizophrenia (SZ) is a devastating disorder that affects about 1% of the general population. It is generally agreed that the lack of integration of processing components, including sensory, motor, and higher cognition are the most common features. Disruption of communication between neuronal groups via gamma band oscillations (GBO) may play a role in the symptoms. It has been shown *in vitro* that the neurotransmitters γ-amniobutyric acid (GABA) and Glutamate are involved in the regulation of GBO [1,2]. The auditory cortex is one of the key ROIs where GBO abnormalities have been measured as the auditory steady-state response (ASSR) [3]. Estimation of GABA in the human brain has been made possible with MRS and spectral editing techniques like MEGA-PRESS [4,5]. A reliable measurement of GABA in the auditory cortex could reveal its role in GBO abnormalities in SZ and Schizotypal Personality Disorder (SPD). This is often complicated by low SNR of the GABA resonance and difficulty to shim in the region of interest (ROI). In addition, grey matter volume loss characteristic of SZ and SPD further reduces the GABA signal that arises from neuronal cell bodies and complicates voxel placement in this region.

Objective: The goal of this study was to improve the methods of estimating GABA in the human brain with the MEGA-PRESS MRS sequence. Since the MEGA-PRESS spectrum is the result of the difference between an on resonance and off resonance spectrum, even small misalignments of frequency and phase between these two spectra may produce significant artifacts and skew the absolute metabolite concentration estimation. LCModel, which estimates the absolute concentration of MRS metabolites [6] accounts for frequency shifts and phase correction in the difference spectrum, but not the frequency and phase alignment of the on and off resonance spectra. The reproducibility and correlation of GABA measures with EEG measures are considered with and without frequency and phase alignment prior to LCModel processing.

Methods: Four healthy subjects and four subjects DSM-IV classified with Schizotypal Personality Disorder (SPD) underwent a protocol consisting of MR imaging and spectroscopy. The MR component was performed in a 3T MR scanner (Siemens TIM Verio). Structural MRI for localization and segmentation of MRS voxels, used the MP-RAGE sequence with TR/TE = 1800/3.4 ms, TI=1100, FA = 7º, FOV = 25.6cm2, 176 contiguous axial slices, voxel size 1x1x1 mm. The MRS single voxel was placed on the left Superior Temporal Gyrus (STG) over the auditory cortex. The MEGA-PRESS sequence used TE =68 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. The left STG was voxel size 20 x 30 x 20 mm (12 mL). Electrophysiology measurements were also taken with an EEG to measure the left paracentral ASSR at 40Hz, which quantifies the GBO that may be disrupted in SPD subjects. Five subjects underwent the protocol again on a second day to assess the reproducibility. The LCModel GABA estimate from the MEGA-PRESS difference spectra automatically generated by the scanner are compared to the estimate from difference spectra generated by a method that aligns the on and off resonance spectrum. This algorithm zero fills the Free Induction Decay (FID), applies a FFT, and finely adjusts the frequency and phase offset between the on and off resonance spectra. The spectra are aligned at the Cr peak at 4 ppm to minimize the signal and create a flat baseline in the 3.9 ppm to 4.2 ppm region of the difference spectrum (boxed in Figure 1). Finally, an inverse FFT is applied and the FID is truncated down to the initial length. Both the original difference spectra and the difference spectra aligned with this method were processed in LCModel.

Figure 1: MEGA-PRESS spectra on resonance in blue (top), off resonance in blue (middle), and difference (bottom).

Results and Discussion: With the additional spectral alignment step, the GABA estimate showed less variation between scans. For the five subjects that were scanned twice, the RMSD Coefficient of Variation of the GABA concentration between two sets of scans reduced from 0.25 with the original difference spectrum from the scanner to 0.21 with the finely aligned difference spectrum. The average percent change of GABA without alignment of 16% dropped to 9.8% with the alignment. Since the true GABA concentrations in the brain for each subject is unknown, the correlation between the GABA estimate to the EEG electrophysiology measurements in this region of the brain is assessed. The left ASSR at 40Hz and the GABA concentration without spectral alignment resulted in a Pearson's correlation with R of 0.42 and p-value of 0.31. With the spectral alignment step, this resulted in a Pearson's R of 0.71 and the p-value of 0.048.

Figure 2: Correlation between GABA in the left STG and the auditory steady-state response (ASSR) with alignment (right) and without alignment (left); Healthy controls are shown in black and SPD subjects are in red

Conclusion: The results suggest that performing an additional fine spectral alignment can improve reproducibility for this type of MRS data. This may be particularly useful in correcting difference spectra from brain ROI that have shown significant volume loss have reduced SNR and movement artifacts. The correlation with the left ASSR at 40 Hz associated with GBO in this brain region appears to have improved and became statistically significant. This method may be utilized in the future to obtain a more reproducible estimation of the *in vivo* GABA concentration in the brain.

References: [1]McNally, JM, et al. Neuroscience (2011) [2]McNally, et al. Current Psych. Rep. (2013) [3]Kwon, JS, et al. Arch. of Gen. Psych. (1999) [4]Mescher, M., et al. NMR in Biomed. (1998) [5]Mullins, PG., et al NeuroImage (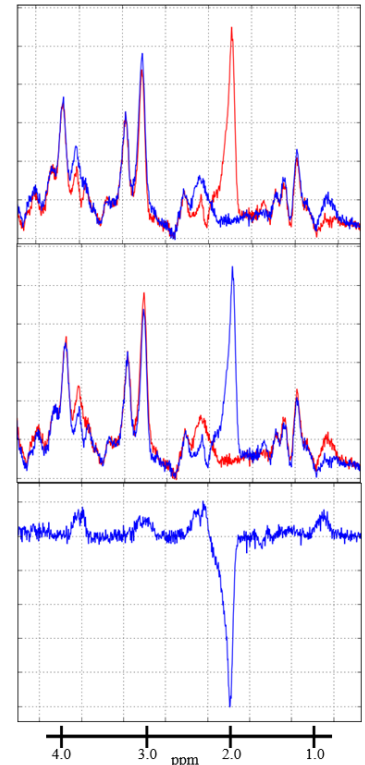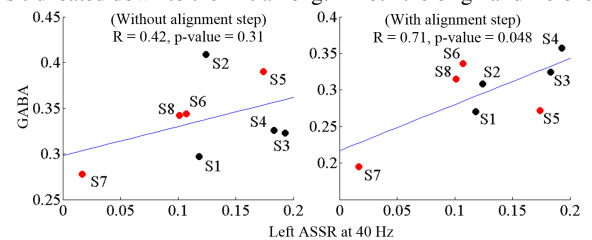2012). [6]Provencher, SW. MRM (1993)