In-Vivo Detection of Human Brain GABA* in Frontal Cortex, Thalamus and Hippocampus by J-Difference Spectroscopy at 3T

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Introduction

γ-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the brain [1], and altered GABA levels and/or GABA turnover rates have been implicated in a range of neurological and psychiatric disorders [2,3]. At a concentration of ~1 mM in cortical grey matter (GM) in humans, GABA lies at the lower sensitivity limit of standard clinical 3T MR scanners. To circumvent low sensitivity, surface receive coils have been employed most frequently for the detection of GABA, but when also used to transmit, surface coils are limited to parietal and occipital lobes due to the possibility of overheating the lenses and furthermore, are not optimal for investigating deep brain structures or sampling whole brain. We have implemented MRS sequences and developed data correction techniques that enable GABA* detection with standard quadrature volume coils in frontal cortex, thalamus, and hippocampus, areas where in-vivo concentrations have either been infrequently or altogether unreported.

Methods

20 normal volunteers were studied in accordance with procedures approved by the Vanderbilt University Institutional Review Board. All experiments were performed on a 3T Philips Achieva scanner (release 1.2.2) with the standard T/R 30.0 cm diameter quadrature volume coil. GABA* (GABA, homocarnosine, macromolecule) data were acquired using the MEGA-PRESS pulse sequence [4] from mostly gray matter voxels located in the frontal cortex (n=20), thalamus (n=2) and hippocampus (n=2) with 2.5 second recycle delays. Acquisition times for frontal, thalamus and hippocampal voxels with average volumes equal to 10.5 mL, 4.3 mL, and 1.3 mL, respectively, were 11 (frontal and thalamus) and 26 minutes (hippocampus). 2000 complex points were sampled with 2 kHz receiver bandwidth. Prior to FFT, J-difference time-domain spectra were apodized with a 4 Hz exponential function. Selective inversion pulse durations were 15.64 ms sinc-center pulses (64 Hz bandwidth). The carrier frequency was maintained within ~2 Hz using the manufacturer ^1H_2O navigator based frequency drift compensation option. Pulse sequences were modified to allow acquisition and storage of single phase-cycled shots; fids were retrospectively corrected for frequency and phase errors to compensate for susceptibility induced shifts and generic carrier frequency update errors. Time-domain data were corrected using nonlinear time-domain fitting to one or more singlets, depending on signal to noise, or by an iterative alignment of data blocks.

Results and Discussion

A representative frontal lobe difference spectrum is shown in Figure 1 and intensity ratios (n=20) with respect to Cho, Cre, NAA (sampled from control acquisitions), and the co-edited GLX+GSH doublet at ~3.75 ppm are 0.080 (0.16), 0.056 (0.011), 0.041 (0.011), 0.62 (0.14), respectively. Intensities of GABA* and the GLX+GSH doublet represent the average of wing intensities. These ratios are provided as a reference for quick comparison only and not intended as a substitute for quantitative concentration estimates. While it is generally possible to select relatively large (~10 mL) volumes containing mostly gray matter in the frontal lobe, voxel dimensions are constrained in structures such as the thalamus and hippocampus. Representative spectra (Figure 2) from these regions were acquired from 4.3 and 1.3 mL (pulse bandwidth defined as fwhm) voxels, respectively. The doublet splitting from the thalamus spectrum is 13 Hz, and the hippocampal counterpart is 12 Hz, both slightly less than the nominal splitting of ~14 Hz. Smaller than expected splittings have also been reported from Terpstra et al. [5]; we suspect these deviations result from incomplete alignment of single transients which can result from insufficient single shot signal to noise (small voxels) or improper lineshape models (shim dependent). Nevertheless, the GABA* doublet is consistently observed and is usually accompanied by the expected co-edited doublet (pseudo) at ~3.75 ppm (GLX+GSH). The intensity ratios of GABA to Cre, Cho, NAA and (GLX+GSH) is notably increased in thalamus spectra (n=2). More data is necessary to confirm this trend or identify it as a statistical anomaly, but it is noteworthy that the intensity ratios of GABA to Cre, Cho and NAA are approximately doubled in this region. The co-edited macromolecule peak at 1.0 ppm confirms spectral quality and it is readily apparent that GABA* is increased relative to this peak as well in the thalamus. Hippocampus intensity ratios are more similar to frontal cortex, but spectral quality is decreased relative to frontal cortex and thalamus data, which were acquired in less than half the time (from ~3-8 times larger voxels). The necessity of robust frequency and phase alignments is especially acute in the thalamus and the hippocampus, and for single shot signal to noise ratios achievable on our scanner, alignment based on fitting to one singlet is no longer feasible. Hence, more prior knowledge or an iterative block alignment approach must be taken, albeit at a heavy data analysis time penalty, to acquire GABA* from the thalamus and hippocampus. These preliminary results illustrate the feasibility of attaining quality GABA* data from frontal (mostly) gray matter and thalamus with a standard clinical research scanner and, although not explicitly quantified, suggest GABA* concentrations are approximately 2 times higher in the thalamus than the frontal cortex.

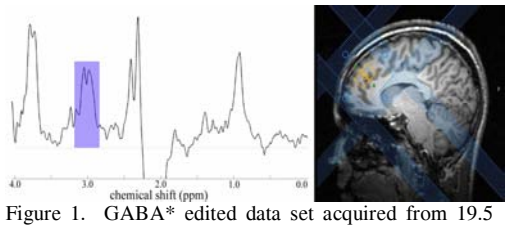

Figure 1. GABA* edited data set acquired from 19.5 mL voxel located in the anterior cingulate cortex (256 shots).

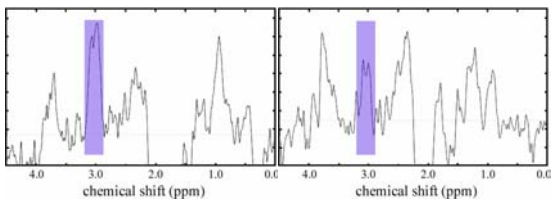

Figure 2. GABA* spectra from the thalamus (left) and hippocampus (right)

References

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