In vivo GABA Measurement of Sensorimotor Cortex

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Introduction: Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the brain. Understanding the GABA distribution, in vivo, is very important to understand normal brain function. Abnormal GABA has been implicated in several neuropsychiatric disorders. Using a variant of MEGA point resolved spectroscopy (MEGA-PRESS) sequence with interleaved water scans to detect subject motion, GABA level of sensorimotor cortex was measured, where the spectroscopy voxel was identified from a functional MRI scan. In addition, using linear regression analysis, GABA concentration in cortical gray matter and white matter in the sensorimotor region were obtained.

Methods: MR scans were performed using a 3 Tesla Siemens whole body Tim-Trio scanner (Erlangen, Germany) with a CP head coil. Healthy volunteers were scanned with a MEGA-PRESS sequence (1) having water signal-based interleaved navigator (2) to assess and discard motion-corrupted data. A 20×20×20 mm^3voxel at the motor cortex was selected prior to the spectroscopy scan from the area of maximum activation (Siemens Neuro3D program) following an fMRI scan in which each subject performed self-paced bilateral finger tapping in a block interleaved 32 second ON and 32 second OFF pattern. The frequency of the editing pulse was alternated in an interleaved fashion between 1.9 and 1.5 ppm to minimize macromolecule contamination. A metabolite-nulling scan was also performed (TI = 650 ms) to account for any residual macromolecule contamination. Data were acquired in a shot by shot basis, and the first four measurements were ignored in order to ensure steady state magnetization. PRESS scans with and without water suppression were performed for absolute quantification following the editing scans. MRUI software was used for spectroscopy data analysis (3). [GABA]/[Cr] ratio was first obtained from the editing scans using the equation $\frac{[GABA]}{[Cr]} = \frac{(G^* - M)}{I_{Cr} \times EE}$, where G^* is the area under the 3.01 ppm GABA peak from the edited (subtracted) spectrum, M is the area under the macromolecule resonance peak at 2.99 ppm in the metabolite nulled spectrum, I_{Cr} is the area under the 3.95 ppm methylene peak of creatine, and EE is the editing efficiency. EE was obtained in a fashion similar to that by Terpstra et al (1) by comparing the unmodulated GABA signal relative to glycine from a PRESS scan with the edited GABA signal with respect to glycine from the same voxel of the same GABA-glycine phantom. Difference in *in vivo* T2 of the Cr methylene and of the C^4H GABA resonance was assumed to be negligible. Also, since the T1 of GABA is comparable with that of other metabolites (4) , the T1 difference between GABA and Cr was neglected. We have used the methylene resonance of Cr instead of the widely used methyl resonance (1, 5) in this calculation since, the use of methyl resonance can introduce a systematic error in the measurement of [GABA]/[Cr] ratio (6). The gray matter, white matter and CSF contribution to the voxel composition (f_{GM_vol}, f_{WM_vol} and f_{CSF_vol}) was performed by using the FAST segmentation algorithm (7) of the FSL software library (8) with the anatomical 3D MPRAGE as the base image, and applying a mask at the voxel location. Next [Cr] was calculated from the equation $[Cr] = \frac{(f_{GM} \times R_{H2O\_GM} + f_{WM} \times R_{H2O\_WM} + f_{CSF} \times R_{H2O\_CSF})}{S_{H2O\_obs}(1 - f_{CSF}) \times R_{Cr}} \times \frac{2}{\#H_{Cr}} \times [H_2O]$, where f_{GM}, f_{WM}, and f_{CSF} are fractions of gray matter, white matter and CSF water in the voxel, R_{H2O_GM}, R_{H2O_WM}, and R_{H2O_CSF} are the relaxation attenuation factors for water in different tissue types, S_{H2O_obs} is the area under the water peak in scan viii, R_{Cr} is the relaxation attenuation for creatine methylene resonance, $\#H_{Cr}$ (= 2) is the number of protons in Cr methylene, and $[H_2O]$ (= 55 M) is the concentration of pure water. f_{GM}, f_{WM}, and f_{CSF} were calculated as in Ref (9) using the volume fraction of GM, WM, and CSF in the voxel (f_{GM_vol}, f_{WM_vol} and f_{CSF_vol}). The GABA concentration, [GABA] was next determined by taking the product of [GABA]/[Cr] and [Cr]. Finally, a statistical regression analysis was performed as in Ref. (10) and the gray matter and white matter GABA concentrations were calculated by plotting [GABA] vs $f_{GM}/(f_{GM}+f_{WM})$; the GM and WM GABA concentration were estimated by extrapolating the regression line to $f_{GM}/(f_{GM}+f_{WM}) = 1$ and 0 respectively.

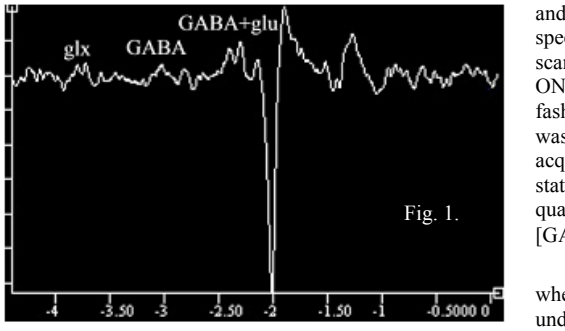

Fig. 1.

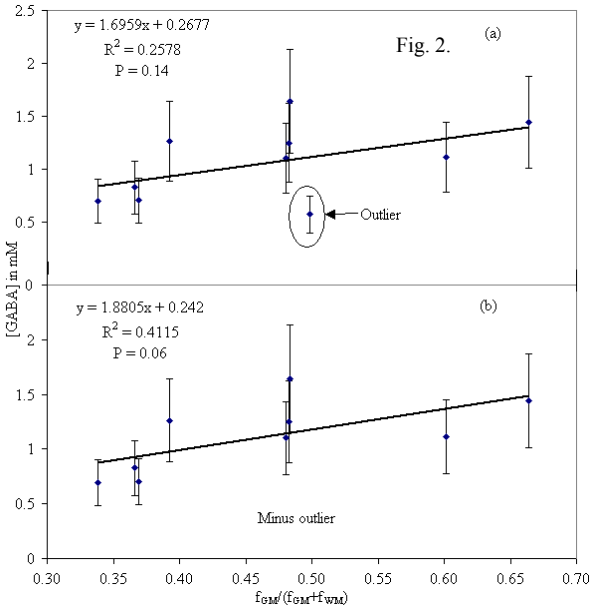

Fig. 2.

Results and Discussion: A representative single subject GABA edited spectrum is shown in Fig. 1. Plots of [GABA] vs $f_{GM}/(f_{GM}+f_{WM})$ are shown in Fig. 2. The results from this study are given in the Table. This study differs from some prior single voxel studies (11-14) in either having smaller voxel size (relevant for functional brain regions) or implementing segmentation in the data analysis and having stricter quality control criteria with respect to subject motion.

Conclusion: To the best of our knowledge, this constitutes the first single-voxel MR spectroscopy study to measure GABA in a fMRI defined region of the brain with spectral quality control with respect to subject motion, and accounting for possible gray/white matter dependence of GABA. This approach of functionally defining the region of interest using fMRI can be used in other cortical regions to obtain cortical and subcortical GABA concentrations in different brain regions.

%GM	%WM	%CSF	[GABA]/[Cr]	[Cr] (mM)	[GABA] (mM)	Gray Matter [GABA] (mM)	White Matter [GABA] (mM)
N = 10 (Age 38.4 ± 13.6 years)							
37 ± 7	52 ± 12	11 ± 8	0.15 ± 0.05	6.83 ± 0.63	**1.06 ± 0.35**	**1.97 ± 0.42**	**0.27 ± 0.08**
N= 9 (Age 39.1 ± 14.1 years) (After discarding the outlier)							
36 ± 7	51 ± 13	12 ± 7	0.16 ± 0.04	6.80 ± 0.62	**1.12 ± 0.33**	**2.12 ± 0.43**	**0.24 ± 0.08**

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