Evaluation of Anatomic Variation in Macromolecule Contribution to the GABA Signal using Metabolite Nulling and the J-editing Technique at 3.0 T

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Background: Dysregulation of the inhibitory amino acid neurotransmitter system of γ-aminobutyric acid (GABA) has come under a great deal of scrutiny due to its potential key role in the pathophysiology of a variety neuropsychiatric disorders, including schizophrenia, major depressive disorder, generalized anxiety disorder, and substance abuse. Currently, ^{1}H MRS is the only noninvasive technique that offers the possibility to study changes in brain GABA concentrations *in vivo*. However, the GABA 3.0-ppm C^4H resonance that is detected using available "editing" techniques has been shown [1] to be overlapped by a resonance due to mobile macromolecules (MM), which has a coupling partner at 1.7 ppm, just 0.2 ppm upfield from the GABA C^3H ppm resonance, and is, therefore, co-edited with GABA to varying degrees depending on the editing method. Failure to correct for this MM contamination can confound interpretation by overestimating the true brain GABA concentrations. Since the degree of MM contamination of the edited GABA signal depends on the frequency selectivity of the editing pulses, which, in turn, depends on chemical shift dispersion and B_o field strength, we undertook this study to estimate the magnitude and extent of the anatomic variation of the contamination of brain GABA by MM at 3.0 T for the J-editing technique.

Methods: Scans were acquired for 6 healthy volunteers, 3 males and 3 females, ages 25.9 ± 2.7 years. For each subject, two back-to-back MRS acquisitions were performed. First, GABA spectra uncorrected for MM contamination were recorded, as previously described [2], from 19.6 cm^3 voxels localized in occipital lobe (OCC), anterior cingulate cortex (ACC), and dorsolateral prefrontal cortex (DLPFC) on a GE 'LX' 3T MR system, using the standard J-editing technique [1], with TE/TR 68/1500 ms and an 8-channel phased-array head coil. Second, without moving the subjects, short-tau inversion-recovery (STIR) or "metabolite nulling" was then immediately implemented as described below to record the spectra of the MM resonance at 3.0 ppm. For MM detection, the standard J-editing sequence was preceded with a nonselective 180° adiabatic spin inversion pulse, followed by an inversion-recovery delay (TI) of 525 ms that had been experimentally determined *in vivo* (**Fig. 1**) to allow the slower-relaxing GABA and other major metabolite resonances to reach the zero-crossing point in the rotating frame of reference, and then implementing the J-editing sequence exactly as it had been for GABA detection. Three quantities, 1) the MM to internal water ratio, 2) the $GABA_T$ (GABA plus MM) to internal water ratio, and 3) the MM to $GABA_T$ ratio, were evaluated and compared across the 3 brain regions using repeated measures ANOVA.

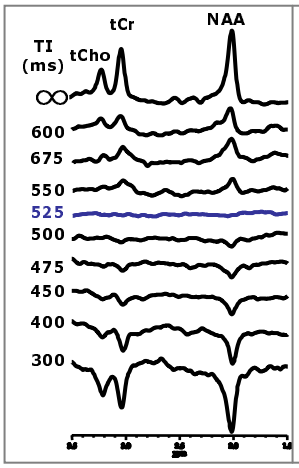


Fig. 1: *In vivo* of STIR for optimal TI determination.

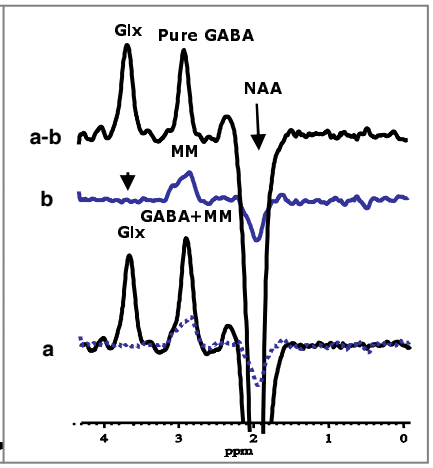
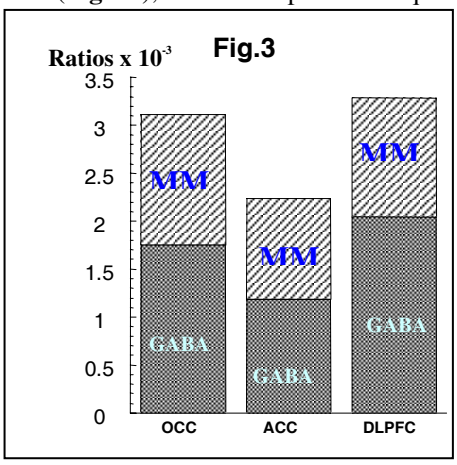


Fig. 2: *In vivo* determination of MM contamination using J-editing.

Results: Representative GABA and MM editing results are shown in **Fig. 2**, which demonstrate that a spectrum acquired with STIR **off** consists an MM-uncorrected GABA resonance and a glutamate+glutamine (Glx) resonance (**Fig. 2a**), whereas a spectrum acquired with STIR **on** yielded only the faster-relaxing MM resonance (**Fig. 2b**), which would have fully relaxed for the value of the TI that was optimal for nulling GABA and the other metabolites. Subtracting these two spectra yielded the MM-corrected GABA spectrum (**Fig. 2a-b**).The ratio of $GABA_T$/Water showed significant anatomic variability (OCC: 3.11 ± 0.46 x 10^{-3}, ACC: 2.24 ± 0.57 x 10^{-3}, DLPFC: 3.29 ± 0.67 x 10^{-3}; p = 0.03), as did MM/Water (OCC: 1.36 ± 0.21 x 10^{-3}, ACC: 1.06 ± 0.21 x 10^{-3}, DLPFC: 1.25 ± 0.18 x 10^{-3}; p = 0.02). However, the ratio MM/$GABA_T$ was relatively stable across regions (OCC: 0.44 ± 0.10, Acc: 0.49 ± 0.13, DLPFC: 0.41 ± 0.17; p = 0.58). **Fig. 3** shows the relative contributions of MM and GABA corrected for MM to the total uncorrected $GABA_T$ across the three brain regions.



Conclusions: While $GABA_T$ and MM signal showed significant anatomic variation across these regions ($p < 0.05$), the contribution of MM to $GABA_T$ was relatively stable, ranging from 41% to 49%, a non-significant regional variation. This range of MM to $GABA_T$ value at 3.0 T is similar to the value of about 40% determined at 2.1T [1], suggesting similar MM contributions to the edited GABA signal at the two slightly different fields. In summary, our results provide an estimate for MM contribution to $GABA_T$ signal that can be expected with a GE 3T scanner using the methods of our study.

References: [1] Rothman DL et al., *Proc. Natl. Acad. Sci. USA* **90**:5662–5666 (1993). [2] Shungu DC, et al., *Proc. Intl. Soc. Mag. Reson. Med.* ***14****:488 (2006)*