Systematic Error in the Measurement of [GABA]/[Cr] Ratio Using Methyl Resonance of Creatine

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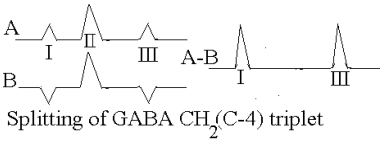
Purpose: GABA is a very important inhibitory neurotransmitter, which is present at a very low concentration in the brain (~1 mM). Special spectral editing is necessary at clinical field strengths in order to detect GABA by magnetic resonance spectroscopy. J-difference spectroscopy is a very efficient way of spectral editing GABA signal and is widely used. It is a common practice to report [GABA]/[Cr] ratio by measuring the areas under the 3.01 ppm CH_2 (C-4) GABA peak in the edited spectrum and the 3.03 ppm CH_3 creatine (Cr) peak in the unedited spectrum. We show that this way of measuring [GABA]/[Cr] ratio will introduce a systematic error, and we propose the use of the 3.93 ppm CH_2 Cr peak for this purpose.

Methods: Both phantom and *in vivo* scans were performed using a 3 tesla whole body Siemens Total Imaging Matrix Trio system with a circularly polarized transmit/receive head coil. The phantom consisted of a solution of GABA and Cr, each having a 10 mM concentration. MEGA PRESS scans were performed by prescribing a 1×1×1 cm^3 voxel in the phantom and 2×2×2 cm^3 voxel in the sensorimotor cortex in *in vivo* scans. A water based interleaved navigator was implemented as well in the *in vivo* scans to assess subject motion, and discard motion corrupted part of data. The scan parameters were TR=2700 ms, TE=68 ms, editing pulse frequency = resonance frequency of the GABA CH_2 (C-3) resonance. Macromolecule correction was done in the *in vivo* scan by (i) placing the off-resonance pulse symmetrically opposite of the 1.7 ppm macromolecule resonance, and (ii) running a metabolite nulling scan. The areas of the 3.01 ppm GABA peak (I_{GABA}) in the final edited spectrum, 3.03 and 3.93 ppm Cr peaks (I_{Cr}) in the spectra prior to subtraction were measured and the [GABA]/[Cr] ratios were determined using the formula $\frac{[GABA]}{[Cr]} = \frac{H_{Cr} \times I_{GABA}}{H_{GABA} \times I_{Cr} \times EE}$, where EE is the editing efficiency, and H_{Cr} and H_{GABA} are the number of protons in the Cr and GABA resonances respectively. H_{GABA} = 2 for GABA CH_2 resonance, and H_{Cr} = 3 and 2 respectively for Cr CH_3 and CH_2 resonances respectively. Appropriate T1 and T2 corrections were applied.

Results: For the phantom scan, [GABA]/[Cr] ratios using CH_3 and CH_2 resonances of Cr were calculated to be 0.62(18) and 0.95(18) respectively. Since the real ratio of GABA and Cr in the phantom was 1.0, this confirms that selection of the peak corresponding to CH_2 resonance is necessary to obtain the [GABA]/[Cr] ratio. Using the Cr CH_3 and CH_2 resonance peaks, the [GABA]/[Cr] ratio at the sensorimotor cortex, for 10 subjects data, were determined to be 0.13(2) **and 0.15(3)** respectively. Absolute quantification was also performed by running a water unsuppressed scan and performing voxel segmentation for tissue composition correction; the concentration of Cr and GABA were calculated to be 11.2(1) and 1.40(25) mM respectively using Cr CH_3 resonance, and **9.7(1) and 1.37(24) mM** respectively using Cr CH_2 resonance.

Discussion: The difference between spectra obtained with the editing pulse at the resonance frequency of GABA CH_2 (C-3) resonance (A) and with the pulse at a different frequency (B), yields in the edited spectrum (A-B). The total area under the peaks I and III in the edited spectrum gives a measure of GABA intensity. The standard practice is to use the area under the CH_3 resonance of Cr as a measure of its intensity. However, this way of getting Cr concentration will be an overestimate, since the same peak will also contain GABA (II of the triplet). Theoretically, $I_{CH3} = \frac{3 \times I_{CH2}}{2} + I_{II}$, where, I_{CH2}, I_{CH3}, and I_{II} are areas under the Cr CH_3 and CH_2 resonances, and peak II respectively (ignoring small difference in T2 of CH_2 and CH_3 resonances). Using the CH_3 resonance for Cr will result in an error in the measure of [GABA]/[Cr] by systematically under-estimating the value of the ratio. This can easily be rectified by measuring the area under the peak from the CH_2 resonance of Cr. In addition, using a fixed assumed concentration of Cr (as is done in many studies) will introduce the same systematic error in the absolute quantification of GABA. In our *in vivo* study, we used a scan without water suppression to measure both Cr and GABA levels in individual subjects. Thus, variation of Cr content from individual to individual does not affect single subject GABA measurement.



Splitting of GABA CH_2(C-4) triplet

Conclusion: This study demonstrates that use of Cr CH_3 resonance peak in GABA editing using J-difference spectroscopy systematically underestimates [GABA]/[Cr] ratio; this systematic error will possibly be different in populations with compromised GABA concentration which could seriously compromise studies. It is recommended to use the CH_2 resonance peak for this same purpose.

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