Improvements on extraction of glutamate and glutamine from GABA editing spectra at 3 Tesla

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Target Audience: MR spectroscopists with interests in GABA, glutamate, glutamine, and spectroscopic quantification and simulation.

Introduction: Glutamate and γ-aminobutyric acid (GABA) are the primary excitatory and inhibitory neurotransmitters in the CNS. Both are believed to be involved in a variety of psychiatric and neurological disorders. GABA can be measured using proton MRS with a PRESS-based two step editing sequence (1). Due to the time constraint of many clinical studies, it is highly desirable to acquire glutamate, glutamine and GABA in a single scan. In this study we show the extraction of the glutamate, glutamine, and GABA signals from GABA editing experiments using a novel fitting routine, while taking advantage of the partial spectral separation of glutamate and glutamine by the GABA editing pulse placed at 0.7-2 ppm. We fitted a linear combination of simulated metabolite signals to the un-edited and difference signals simultaneously using the same set of parameters. Data from 141 GABA editing experiments performed on normal volunteers were analyzed. The high SNR afforded by averaging the large number of spectra also allowed in vivo validation of metabolite chemical shifts and J coupling constants.

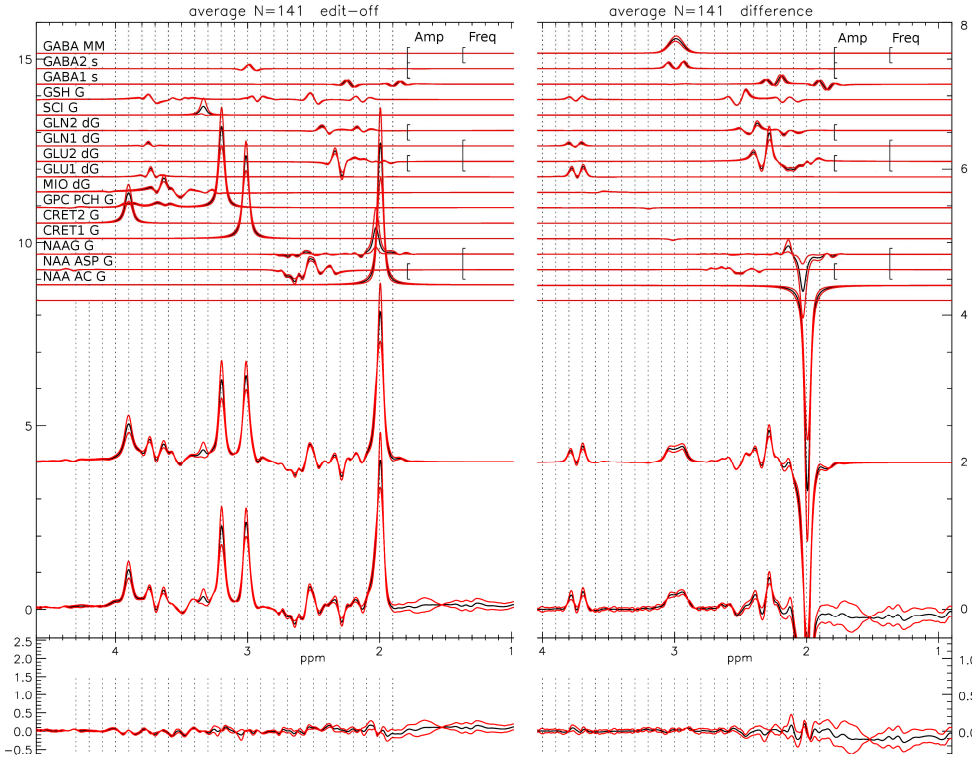

Figure 1. The average of the 141 simultaneous fits of the edited and difference signals. Black lines are the average, red lines twice the standard deviation. The label G denotes parameter values from Govindaraju, s for GABA set2, and dG from R.A. de Graaf. Square braces show sharing of a single parameter in the fit.

Methods: An updated GAMMA (2) was obtained from duke.edu (3) and used to simulate the effects of the GABA editing sequence. The effects of RF shapes, crusher gradients and various coherence pathways were fully simulated (4,5). The simulated signals were normalized according to the number of proton spins in the metabolites/moieties. Chemical shifts and J couplings for the metabolites were obtained from Govindaraju (6) and R.A. de Graaf (7, email). 141 volunteers were scanned on a 3 Tesla whole body scanner (GE, Milwaukee, WI, 14M4 platform). The spectroscopy voxel was placed immediately superior to the ventricles, NS = 768, TR/TE = 1500/68 ms, NEX = 2. The GABA editing pulse (1) covers both GABA β-H2 and the M4 macromolecules, it was switched on and off during even- and odd-numbered scans. A total of 384 edited and non-edited FID pairs were acquired for a total of 20 minutes. The non-edited and the difference spectra were fitted simultaneously using a Levenberg-Marquardt non-linear fitting program written in IDL (ITTVIS). The fit was performed using simulated reference signals for; NAA (NAA1 for the coupled spins and NAA2 for the singlet), NAAG, creatine (CRE, 1/2 creatine and 1/2 phospho-creatine(7)), choline (CHO 1/3 phosphocholine (PCH) and 2/3 glycerophosphocholine (GPC) (7)), myo-inositol (MIO), glutamate (GLU), glutamine (GLN), scyllo-inositol (SCI), glutathione (GSH), and GABA. The GABA reference signal consists of two GABA moieties, GABA1 for spins between 1.7 and 2.4 ppm, GABA2 for spins at 3.0 ppm, and a macromolecular contribution (MM) modeled by a gauss line at 3.0 ppm with a linewidth of 14 Hz. Their relative amplitudes were determined by a fit of the GABA moieties with individual amplitudes to the difference spectrum only. In the simultaneous fit these amplitudes were fixed relative to each other for an optimum GABA reference signal. Two GABA chemical shift and J coupling parameters sets were tested, set 1 (Govindaraju 6) and set 2 (J_{23}= 7.35 Hz, J_{34}= 7.49 Hz, averaged values from ref. 6). The final simultaneous fit to the unedited and difference signals used an optimal combination of set2 and GABA/MM = 0.61 as determined by the optimal fit.

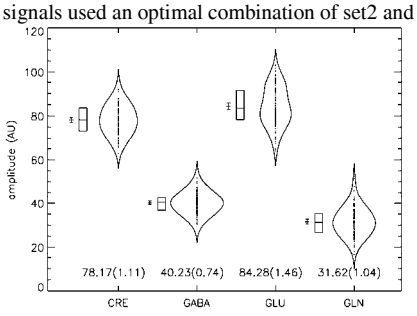

Figure 2. Violin plots for CRE, GABA, GLU, and GLN. Amplitudes are shown as mean and 2*stdev, median and first quartile, and the distribution of amplitude values.

Results and Discussion: Fitting using set2 resulted in an approximately equal amplitude for the GABA1 and GABA2 moieties (15.16 and 16.30 respectively) and an amplitude of 24.71 for the MM, for a MM fraction of 0.61. Fitting with the GABA parameter set of Govindaraju resulted in unequal GABA1 and GABA2 amplitudes, 15.14 and 27.19 respectively, caused by the residual central line in the GABA2 triplet in the difference spectrum. The MM amplitude from the Govindaraju parameter set of 17.24 amounts to a MM fraction of 0.29. Since the relaxation-weighted normalized concentration of the two GABA moieties should be approximately equal set2 was chosen for spectral quantification. The GABA/MM ratio of 0.61 is in close agreement with previous experimental results (0.56) using inversion recovery (8). In Fig.2 the distribution of the amplitudes of creatine, GABA, glutamate and glutamine are given using violin plots. The distributions of GABA, glutamine and glutamate are comparable to the distribution for creatine for the 141 experiments. Metabolite ratios (mean, (2*stdev),n=144) were determined to be GABA/CRE = 0.201 (0.009) (after MM correction), GLU/CRE = 1.08 (0.022), and GLN/CRE = 0.40 (0.036).

References: 1. Sailasuta P. et al, Proc ISMRM 9:1011 (2001). 2. Smith SA et al, J. Magn. Reson. 106a, 75-105, (1994). 3. http://scion.duhs.duke.edu/vespa/gamma 4. de Beer R et al, Meas. Sci. Technol. 22 (2011) 114022 (9pp). 5. Van der Veen, JW et al, Proc ISMRM 21:2032 (2013) 6. Govindaraju V et al, NMR Biomed 13 129-153 (2000). 7. R.A. de Graaf, in vivo NMR Spectroscopy,2nd ed. 8. van der Veen, JW et al Proc ISMRM 15:1399 (2007)