Extraction of glutamate from the GABA edited spectra

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

Introduction: Glutamate and γ-aminobutyric acid (GABA) are the primary excitatory and inhibitory neurotransmitters in the CNS, respectively. 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). Usually, glutamate or GLX (GLU + GLN) is measured in a separate scan using glutamate editing or short-TE methods. Due to the time constraint of many clinical studies, it is highly desirable to acquire both glutamate and GABA in a single scan. At 3 Tesla, separation of glutamate from Glx is usually difficult because of spectral overlap and strong J couplings. Here we used full density matrix simulation to investigate the effects of a spectral editing pulse used in GABA detection at 3 Tesla (1) on the J evolution of glutamate, glutamine and NAA. It was found that the GABA editing pulse (1), which also irradiates the glutamate and glutamine H3 protons, causes a significant spectral separation between glutamate H4 and glutamine H4 resonances. The contribution to the resonances in the 2.2-2.4 ppm region from the aspartyl moiety of NAA is also reduced at the relatively long echo time used in GABA editing. Our results showed that it is possible to extract glutamate signal using linear combination spectral fitting of the GABA spectra.

Methods: The updated GAMMA(2) was obtained from http://scion.duhs.duke.edu/vespa/gamma and used to simulate the effects of the GABA editing sequence for a spectroscopy voxel of 2 x 2 x 4.5 cm^3. The effects of RF shapes, crusher gradients and various coherence pathways were fully simulated (3). Simulations consisted of 64 by 64 locations in the transvere plane over an area of 8 cm by 8 cm to fully cover the spectroscopy voxel and its surrounding volume. In a subloop every average encompasses an average of 8 x 8 x 8 spatial substeps in the three voxel dimensions to simulate the effects of the gradient crushers. The spatial step (Dxyz_cm) in the subloop was calibrated to give a 180 phase change over the sum of the four crushers: Dxyz_cm = 0.5 / (4.0 * crushStrength_Hz * crushLength_s). The basic spatial step Dxyz was incremented in eight steps to cover all possible signal coherence path combinations of the four crushers in the PRESS sequence. The simulated signals were normalized according to the number of proton spins in the metabolites. Chemical shifts and J couplings for the metabolites were obtained from ref. (4). Both spectra, with the GABA editing pulse on and off, were simulated to obtain the difference spectrum.

Ten volunteers were scanned on a 3 Tesla whole body scanner (GE, Milwaukee, WI, 14M4 platform). A spectroscopy voxel (2 cm x 2 cm x 4.5 cm) was placed immediately superior to the ventricles. The GABA editing pulse sequence was modified from a standard PRESS sequence (1). NS = 512, TR/TE = 1500/68 ms, NEX = 2. The editing pulse (14.4 ms, γB1max = 160 Hz) has a top-hat frequency profile with a bandwidth spanning the 2.2 ppm – 0.6 ppm range (1) covering both GABA β-H2 and the M4 macromolecules. The GABA editing pulse was switched on and off during even- and odd-numbered scans. A total of 512 edited and non-edited FID pairs were acquired for a total of 26 minutes. The non-edited and the difference spectra were fitted with a Levenberg-Marquardt non-linear fitting program in IDL (ITT Visual Information Solutions, White Plains, NY, USA). The non-edited scan was fitted with simulated reference signals for NAA (NAA1 for the coupled spins and NAA2 for the singlet, respectively), creatine (CRE), choline (CHO), myo-inositol (MIO), glutamate (GLU), glutamine (GLN), and scyllo-inositol (SCI). The difference spectrum was fitted with the subtracted reference signals (edited - non-edited for a positive GABA signal) for NAA1, NAA2, GLU, GLN, and GABA1 (the triplet at 3 ppm). The fitted amplitudes for glutamate in both spectra were normalized by the fitted amplitude of creatine. The theoretical editing efficiency for glutamate was calculated from the first time point of the non-edited simulated time domain signal and the difference of the edited and the non-edited simulated time domain signals.

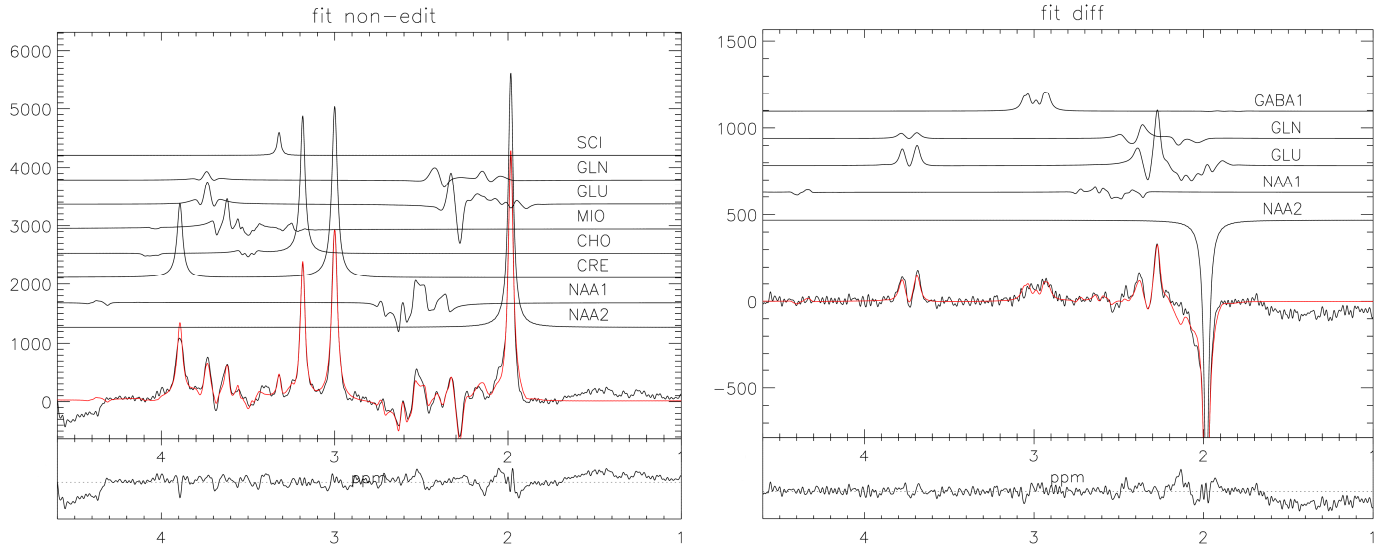

Figure 1. Non-edited spectrum in the left panel and the difference spectrum in the right panel. Fitted reference spectra are shown above and residuals below.

Results and Discussion: From the GAMMA simulation the yield of glutamate was found to be 0.2306 in the unedited spectrum and 0.0851 in the difference spectrum resulting in a theoretical editing efficiency loss of 2.71. From the 10 subjects the glutamate to creatine ratio measured using the non-edited spectra is 2.35 ± 0.35 (mean ± SD) and 2.54 ± 0.17 (mean ± SD) using the difference spectrum after the theoretical editing efficiency correction. The measured loss in editing efficiency for glutamate compared with the non-edited spectrum is a factor of 2.50, close to the above theoretical value of 2.71. However the deviation in the glutamate to creatine ratio for the non-edited scans of 15% is more than twice as high as the deviation obtained from the difference spectrum of 6.8%. The more reliable glutamate measurement in the difference spectrum is most likely because of the significantly reduced contribution from the aspartyl moiety of NAA to the 2.2-2.4 ppm region (as seen in the right panel of Fig. 1), and reduced correlation of the fitted glutamate signal in the difference spectrum with other metabolites. The editing pulse placed at 1.91 ppm only slightly affected the spin evolution of the aspartyl moiety of NAA. As a result, the NAA aspartyl CH_2 protons were largely canceled in the edited spectrum. Therefore, the difference GABA spectrum is more suitable for simultaneous determination of glutamate using the GABA editing sequence. Transverse relaxation and water referencing will be addressed in the future for absolute quantification of glutamate.

References: 1. Sailasuta P. et al, Proc ISMRM 9:1011 (2001). 2. Smith SA et al, J. Magn. Reson. 106a, 75-105, (1994). 3. de Beer R et al, Meas. Sci. Technol. 22 (2011) 114022 (9pp). 4. Govindaraju V et al, NMR Biomed 13 129-153 (2000).