Glutamate and Glutamine Discrimination via Constant Echo Time Difference Spectroscopy

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Introduction

The study of Glutamate (Glu) is important in understanding the function of the human brain. Glu is the major excitatory neurotransmitter in the brain, and consequently is involved in neurodegenerative disease and psychiatric disorders. Glutamine (Gln) is also important as Glu is converted to Gln in glia after being used as a neurotransmitter. The Gln is then transported back to the neurons and converted back to Glu. The quantification of Glu and Gln in spectroscopy can be problematic, as these coupled systems exhibit complex spectra and, because of similar molecular composition, comparable resonant frequencies, inhibiting their discrimination at lower field strengths. Several techniques have been proposed to detect either Glu or Gln or both, including multiple quantum filtering (1), editing techniques (2), and J-resolved spectroscopy (3). However, these methods are generally not used clinically, with most localization accomplished with basic PRESS and STEAM sequences. This work proposes a simpler technique, based on constant echo time (TE) PRESS difference spectroscopy (4). The method relies on strongly coupled signal modulation at constant TE. By varying the two echo times, TE1 and TE2, the signal variation for a particular resonance can be maximized such that the difference between the two spectra displays only the metabolites that exhibit this variation. Consequently, singlet and other overlapping resonances can be removed in the subtraction spectrum, while maintaining all signals in the addition of the two spectra. The signal variation in TE space for Glu and Gln at 4.7 T is such that this particular method produces a subtraction spectrum with only the Glu MN peaks at 2.06-2.14 ppm visible, and other resonances, including the NAA singlet (2.02 ppm) and Gln MN multiplet (2.13-2.15 ppm) removed. This work investigates this method with simulation as well as phantom and in vivo experiments.

Methods

Theoretical simulations were performed to determine the Glu and Gln spin response to the PRESS sequence using an in-house numerical simulation program developed by Thompson (5). The program was run for a range of TE1 and TE2 values (5-200 ms), and peak areas were calculated for each spin group (A, MN and PQ), resulting in TE space area maps. From the maps, optimal time points were chosen along a line of constant TE (155 ms) to maximize the Glu MN signal variation while simultaneously minimizing the Gln MN variation. These timings (TE1 = 125 ms, TE2 = 30 ms subtracted from TE1 = 80 ms, TE2 = 75 ms) were then used in the phantom and in vivo measurements. All experiments were performed at 4.7 T using a quadrature birdcage coil for transmission and reception. A set of cylindrical phantoms containing various amounts of Cho, Glu and Gln was used to determine the efficacy of the subtraction method. Also, a phantom containing physiological ratios of NAA, Glu, Gln, Cr and Cho was constructed to resemble in vivo conditions. In each case, the time points from the simulation were used in the PRESS sequence, with a voxel size of 10 mm^3 and 256 averages. Similar experiments were performed on healthy volunteers. The voxel was placed in parietal gray matter to ensure maximal Glu concentration, with a voxel size of 15 mm^3 and 512 averages.

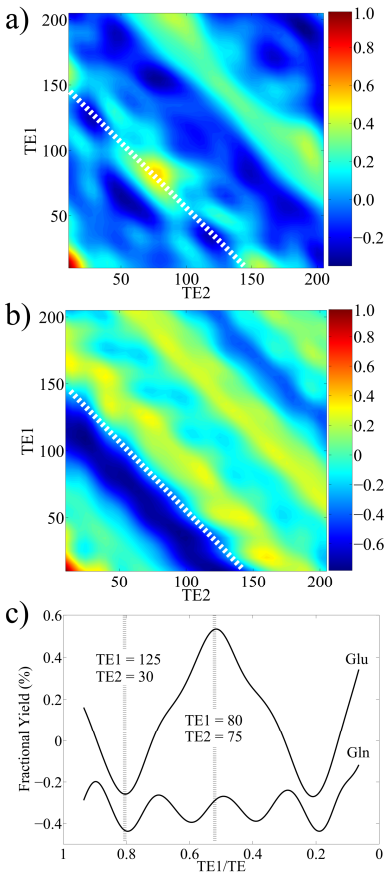

Figure 1: TE space area maps for a) Glu MN and b) Gln MN. c) Graph of area for Glu MN and Gln MN along the line TE = 155 ms (dotted line in a and b).

Results

The TE space area maps produced by the simulator for Glu MN and Gln MN are shown in Fig 1a and b, respectively. The constant TE line with greatest signal variation (TE=155 ms) is denoted by the dotted white line. Note the large variation in Glu compared to Gln. An area graph of the TE=155 ms line is shown in 1c. The time points chosen for the subtraction experiments are illustrated by vertical dotted lines. Based on the simulations, 96% of the Glx MN resonance is due to Glu, proving the validity of the subtraction technique. Figure 2 shows simulated spectra using the two time points (top: TE1 = 80 ms, TE2 = 75 ms, middle: TE1 = 125 ms, TE2 = 30 ms) for Glu (solid) and Gln (dashed). The subtraction spectrum is shown at the bottom. Note the large remaining signal from Glu in the MN region (2.06-2.15 ppm) and minimal Gln, as well as a large reduction in the Glx PQ peak (2.35-2.41 ppm). Figure 3 shows demonstrative phantom (left panel) and in vivo (right panel) spectra using the subtraction technique. The three spectra in each panel are at the same timings as in Figure 2. The subtraction spectra for the phantom and in vivo cases have been magnified 3 and 6 times, respectively. Both subtraction spectra exhibit similar lineshapes in the Glx MN range, displaying a strong, and remnant Glu MN resonance. In addition, the myo-inositol peak at 3.58 ppm maintains a large signal in both subtraction spectra, and therefore has variation patterns that produce reasonable results at these time points.

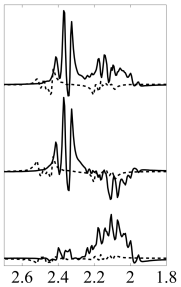

Figure 2: Simulated spectra at (TE1,TE2) ms top: (80, 75), middle: (125, 30), bottom: subtraction.

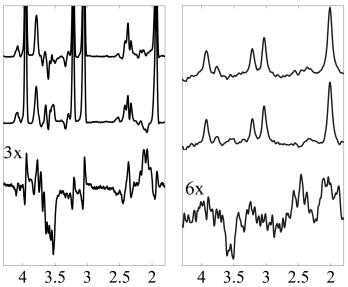

Figure 3: Phantom (left) and in vivo (right) spectra at similar timings as Fig. 2. The bottom spectra have been magnified as illustrated.

Discussion

These results show that at a constant TE of 155 ms, the large signal variation in Glu MN and much lower Gln MN variation due to varied PRESS echo asymmetry allow discrimination between the two metabolites using a PRESS subtraction spectroscopy method in phantom and in vivo experiments. Typically, the Glx PQ multiplet is used for quantification because of the large and relatively unobstructed signal. However, the signal variation at 4.7 T for Glu PQ is insufficient for successful subtraction spectroscopy. This technique may also be applied to other metabolites such as myo-inositol (as seen above), aspartate, and the ABX group of NAA. The method is particularly useful when other signals contaminate the signal of choice. The procedure is straightforward and only requires a common PRESS sequence with some prior knowledge of coupled spin signal variation. This powerful technique requires no changes to the standard PRESS sequence except for inter-echo times, and is therefore readily available for clinical use.

References

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