Phase-Adjusted Echo Time (PATE)-Averaging: Application for glutamine resolution at 3.0 Tesla

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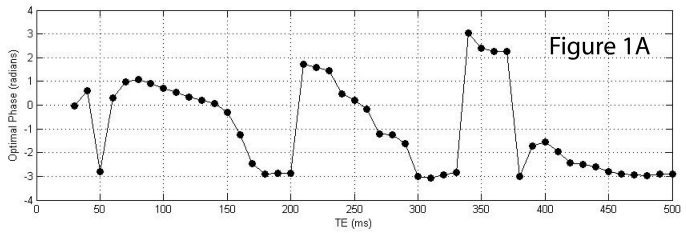
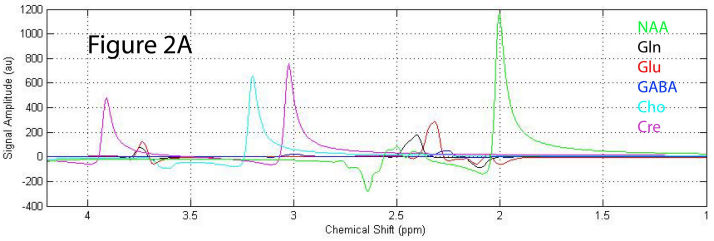
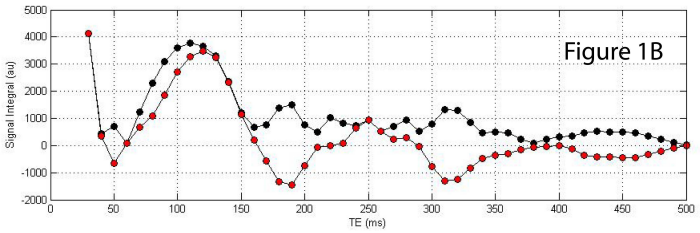
Introduction: Several proton (^{1}H) magnetic resonance spectroscopy (MRS) studies have reported abnormal glutamatergic neurotransmission in psychiatric disorders including schizophrenia (**1**) and acute mania (**2**). For such studies, the reliable separation of Gln from Glu resonances is of critical importance as impaired glutamatergic neurotransmission may be associated with altered glutamate (Glu) and/or glutamine (Gln) concentration. However, substantial spectral overlap of Gln peaks with Glu and N-acetyl aspartate (NAA) resonances occurs with conventional ^{1}H MRS performed at clinical static magnetic field strengths ($B_0 \leq 3.0$ T). Glu resolution can be improved through an approach known as echo-time (TE)-averaging ^{1}H MRS (**3**), which involves the averaging of multiple TEs. That method retains the central line of a Glu 2.35 ppm pseudo-singlet at the expense of strongly suppressing the phase-modulated Gln resonances. Here we report a processing method that we have termed phase-adjusted TE (PATE)-averaging for retrieving Gln signals from a TE-averaged ^{1}H MRS dataset. PATE-averaging applies an optimal zero-order phase factor to each TE step prior to signal averaging. Preliminary simulation and *in vivo* data are presented here to demonstrate the potential utility of the technique.

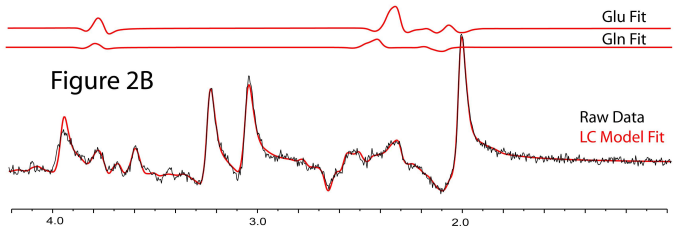
Methods: MATLAB (The MathWorks, Natick, MA) was used to simulate Gln, Glu, γ-amino butryic acid (GABA), choline (Cho), creatine (Cre) and NAA spectra using density matrix theory ($B_0 = 3.0$ T; TE = 30 - 500 ms; ΔTE = 10 ms). Simulations assumed ideal spin excitation (-Iy) followed by a non-selective double spin echo. Chemical shifts and spin-spin (*J*) coupling constants were taken from precedent literature (**4**). Spectra were generated using physiologic concentration ratios ([Glu]:[Gln]:[Cho]:[Cre]:[NAA] = 8:4:2:8:10) and a realistic *in vivo* line broadening factor was applied to all spectra. In addition, a T_2-weighting filter was applied along the TE dimension using previously reported metabolite T_2 relaxation times (**5,6**). The Gln T_2-relaxation time filter was assumed to match that of Glu (**6**). All 48 TE-stepped Gln spectra were subjected to a zero-order phase loop (-179 to 180 degrees) with peak integration over the 2.41 - 2.49 ppm chemical shift region calculated for each phase factor. The optimal TE-specific phase yielded maximum signal area. ***In vivo* Measurements:** Six subjects were scanned twice on consecutive days using a 3.0 Tesla Siemens (Erlangen, Germany) Trio whole body MRI system. TE-stepped ^{1}H MRS data were acquired from a 22.5 mL voxel positioned bilaterally on the anterior cingulate cortex (TR/TE = 2000/30 - 500 ms; ΔTE = 10 ms; NEX = 8). *In vivo* data were processed using phasing parameters determined from simulation and fitted using Linear Combination (LC)-Model (**7**) with a simulated PATE-averaged basis set. The PATE-averaged test-retest performance was compared with standard PRESS data acquired from the same voxel (TR/TE = 2000/30 ms; NEX= 128). The PRESS Cre signal area was used to normalize metabolite peak areas derived from both techniques and test-retest reliability was determined by the group mean coefficient of variation (CV; 100*standard deviation (SD) /mean).

Results and Discussion: The TE-specific optimal phase for maximizing the Gln peak integral (2.41 - 2.49 ppm) is plotted in Figure 1A. The Gln peak area following application of the optimal phase at each TE is plotted in Figure 1B (black dots) together with the corresponding phase-unadjusted Gln peak area (red dots). Figure 2A shows simulated PATE-averaged data for six metabolites with color-coding used to identify each separate spectrum.. That data were reconstructed using the TE range of 50 - 230 ms as the averaging of these phase-adjusted TE steps yielded efficient suppression of the overlapping Glu and NAA methylene resonances. A PATE-averaged dataset acquired *in vivo* is presented in Figure 2B, together with the composite LC Model fit and individual Glu and Gln fits. Gln measurement test-retest reliability was calculated as 19 ±25% and 8 ±7% for PRESS and PATE-averaging, respectively. Glu measurement test-retest reliability was calculated as 7 ±7% and 9 ±6% for PRESS and PATE-averaging, respectively. Processing of TE-averaged ^{1}H MRS datasets using PATE-averaging approaches may help improve Gln quantification while maintaining Glu measurement reliabilit. Gln resolution is achievable in ~10 minutes using the parameters outlined in the present study (TE = 50 - 230 ms). PATE-averaging and the targeting of other metabolite resonances (e.g. GABA) currently is under investigation, and comparison with existing methods (**8**) will help put the findings into context.









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