Quantitative Measurement of N-acetylaspartyl Glutamate (NAAG) at 3 Tesla Using TE-Averaged PRESS Spectroscopy and Lineshape Deconvolution

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Introduction: Measuring NAAG in the human brain by ^{1}H magnetic resonance spectroscopy (^{1}H MRS) is challenging because of its low concentration and overlap with other signals. Short echo time PRESS spectroscopy is currently the most popular method for measuring NAAG levels in vivo [1]. NAAG concentrations are largely determined by the acetyl proton signal at 2.04 ppm, which is the most prominent NAAG signal in ^{1}H MRS measured by short echo time. However, this signal is separated by only ~ 0.04 ppm from the corresponding signal of N-acetyl aspartate (NAA) [2]. Thus, in most clinical studies, it is difficult to differentiate the two signals, and this method is further hampered by the contamination signals near 2.04 ppm that arise from molecules such as glutamate and the macromolecule MM20. This study attempted to quantitatively detect NAAG by combining TE-averaged PRESS [3] with lineshape deconvolution. Tikhonov regularization [4] was introduced to restrain the noise amplification associated with lineshape deconvolution. The deconvoluted data were further denoised with the line-broadening window functions that were optimally determined by Cramer-Rao Lower Bound (CRLB), and then were fitted with the commonly used Voigt function to quantify NAAG.

Methods: All experimental data were collected on GE 3 T Excite scanners (GE Medical Systems, Waukesha, WI) using a quadrature head coil. Spectral data were acquired from the voxels dominated by the white matter ($2.0\times2.0\times4.5\text{cm}^3$). They were placed in the right frontal white matter, directly adjacent to the rostral anterior cingulate cortex. TE-averaged spectra were acquired with 32 different echo times (NA = 4 for each echo time). TE was started at 35 ms and increased by 6 ms for each of the 31 following echoes. The reference scans of unsuppressed water were collected immediately after spectral data acquisition and were repeated 16 times for averaging. All spectra were sampled with a bandwidth of 5 kHz and 4096 data points. Raw data were saved and processed offline with programs developed in-house. The conventional deconvolution has the solution:

$$X(t_i) = A^{-1}(t_i)Y(t_i), \qquad [1]$$

Where $X(t_i)$ and $Y(t_i)$ are the deconvoluted data and the original data, respectively, and $A^{-1}(t_i)$ is the inverse of the reference signal $A(t_i)$. Both $A(t_i)$ and $Y(t_i)$ contain noise errors that propagate into $X(t_i)$ by Eq. 1. These noise errors will be significantly amplified at the time points where $A(t_i)$ nears singular. Eq. 1 may thus not be a desired solution, as the resultant spectrum bears much more noise after deconvolution processing than before it. One of the solutions needed to solve the problem of noise amplification in Eq. 1 is to apply regularization, which can result in the following equation:

$$X(t_i) = \frac{1}{A(t_i)+\lambda}Y(t_i). \qquad [2]$$

λ is a positive regularization parameter to be determined later. After the lineshape deconvolution, the spectral fitting was carried out in the frequency domain from 1.8 to 2.2 ppm, using Levenberg-Marquardt non-linear algorithm. The model function consisted of two Voigt-type peaks with identical T^*_2 and was denoted by F:

$$F(t_n) = \sum_{j=1,2} c_j \exp(-\alpha t_n - \beta t_n^{\,2})\exp(i\omega_j t_n + \varphi). \qquad [3]$$

The subscript j represents NAA (j=1) and NAAG (j=2); t_n stands for the digitized time point. The parameters, c, α, β, ω, and φ, are signal amplitude, Lorentzian decay factor, Gaussian decay factor, frequency and phase, respectively. The fitting program, developed using IDL, used the graphic user interface (GUI) to initialize the fitting parameters. Therefore, the fitting could be started with different initial parameters, in order to search for the best fit with a minimal CRLB.

Results and Discussions: LCModel analysis [5] of short echo time (30 ms) spectra shows individual signals for NAAG, glutamate, and macromolecule MM20 (Fig. 1). Those signals strongly overlap with each other near 2.04 ppm. It is therefore expected that determination of NAAG using the short-TE proton spectra could be biased by glutamate and macromolecule signals. To avoid this problem, a spectral editing technique was recently developed [6] that used a highly selective editing pulse. In vivo TE-averaged PRESS spectrum (Fig. 2a) shows the clean baseline and that the acetyl peak of NAAG is clearly visible after the lineshape deconvolution. For quantification of NAAG, the sub-spectrum of the acetyl proton signals of NAA and NAAG from 1.8 to 2.2 ppm was fitted to the model function comprising two Voigt type peaks (Fig. 2b), yielding the NAAG-NAA ratio (0.192 ± 0.025 from twelve young subjects). Poor spectral resolution and the interference of overlapping signals, including the interfering macromolecule signals, are major factors that affect quantification of in vivo metabolites, particularly the weakly represented metabolites such as NAAG. Here, we used TE-averaged spectroscopy and lineshape deconvolution to solve those problems, in order to quantitatively detect NAAG. It was demonstrated that the glx-3 and macromolecule signals were effectively suppressed by TE-averaged spectroscopy and spectral resolution was enhanced by the regularized lineshape deconvolution without significantly sacrificing SNR. Quantitative detection of NAAG is therefore feasible and practical at 3T by using TE-averaged PRESS spectroscopy and regularized lineshape deconvolution.

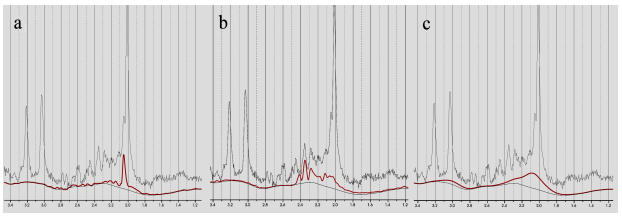

Figure 1. LCModel analysis of a short echo time spectrum yielded the fitted baseline, spectrum of NAAG (a), glutamate (b), and macromolecule MM 20 (c).

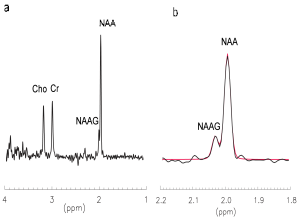

Figure 2. (a):An in vivo lineshape-deconvoluted TE-averaged spectrum. (b): the two Voigt-type peaks (red line) were fitted to the experimental spectrum from 1.8 to 2.2 ppm (black line).

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