LCModel Accuracy Testing for N-Acetyl Aspartyl Glutamate Measurement using Phantom Study

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INTRODUCTION: NAAG levels play a critical role in various diseases including Alzheimer's disease, schizophrenia and amyotrophic lateral sclerosis (ALS), *etc* [1-3]. Even though accurate measurements of *in vivo* NAAG levels are important in defining disease severity and monitoring of treatment outcome, there has been a lack of reliable quantification using MRS. Structurally, NAAG consists of N-acetyl aspartate (NAA) with a peptide bond to glutamate (Glu). This makes it difficult to differentiate NAAG from NAA and Glu by in vivo 1H MR spectroscopy (MRS). In the NAAG spectrum, the N-acetyl protons are separated by only 0.03 ppm from the corresponding NAA resonance. There are two strategies to approach the quantification of NAAG. The first one is to take advantage of this frequency difference by J-editing with the MEGA-PointResolved Spectroscopy (PRESS) technique [4]. The second one is a deconvolution algorithm such as LCModel with spectra at high fields, good field homogeneity, and stability [5]. In this study, we performed a phantom study to determine the accuracy the accuracy of NAAG measurement using LCModel.

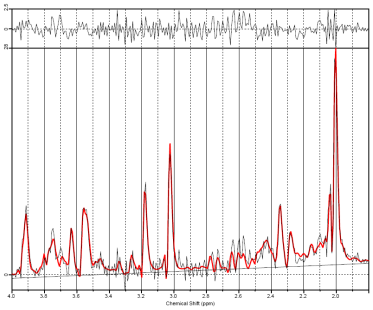

Figure 1 A typical LCModel results

Table 1 Metabolite Concentrations of the Phantoms

Phantom Number	Metabolites (mM/kg)	
	Glu	NAAG
1	5.84	0.42
2	15.46	0.64
3	7.74	0.86
4	3.8.	1.28
5	11.70	1.69

Note. – Metabolite names: Glu (Glutamate), NAAG (N-Acetyl Aspartyl Glutamate), Concentration : Asp (1.00), Cre (7.93), GPC+PCh (2.00), GABA (1.00), Gln (3.04), mI (7.02), NAA (10.00), Scyllo (0.11), Tau (1.01), Lac (0.50)

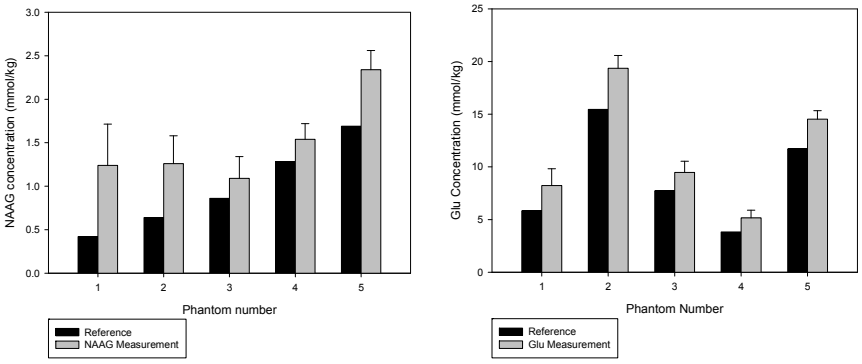

Figure 2 LCModel measurement and reference concentration of NAAG (a) and Glu (b)

MATERIALS AND METHODS: Chemical shift imaging (CSI) data was acquired from a 3T MRI (Siemens MAGNETOM Trio) with an acquisition-weighted elliptical phase-encoding scheme 16 x 16 matrix, slice thickness 16mm, FOV 240 x 240 mm, VOI 120 x 120 mm, 1024 data points acquired with 2000 Hz spectral width, 30 msec TE, TR 1500 msec, two averaging, 50 FWHM Hamming filter and CHESS water suppression. 5 phantom cases with different concentrations of Glu, NAAG, and a constant concentration of other 10 metabolites have been fabricated (Table 1). Five repetitive trials of the phantoms were scanned with the same CSI sequence at one-day intervals to figure out the reproducibility and the accuracy of the measurement. For quantitative analysis, spatially transformed data was processed offline using LCModel Version 6.2-1A. Figure 1 presents the fitted result of LCModel for typical phantom data. Metabolite measurements with Cramér–Rao lower bounds (CRLB) below 20%, SNR of more than 5 and linewidth below 0.15 FWHM (ppm) have been used. Absolute quantification was estimated by calibrating the measured spectral resonance area with the known concentration of a reference solution (NAA+NAAG) [6]. The accuracy of estimated measurements was evaluated using the Bland-Altman method.

RESULTS: Figure 2 shows the LCModel measurement and reference concentration of NAAG (a) and Glu (b). Contrary to Glu measurement, NAAG measurement results show distinct overestimations especially when they are below about 1mM/kg, even though tight CRLB bound (below 20%) was used. 95% confidence interval of the subtracting estimated measurements from actual measurement of NAAG metabolite (3~5 phantoms) are -0.57 ~ 0.18 (Bland-Altman method). In addition, as SNR of spectra increases, measurement accuracy also increases.

DISCUSSION AND CONCLUSION: It was found that as the concentration of NAAG becomes smaller (especially below 1mmol/kg), the overestimation bias in measuring the NAAG gets stronger. NAAG concentration range is known as 0.6 ~ 2.7 mmol/kg [4]. If NAAG measurement is below 1.0mmol/kg, it would be negligible. In conclusion, the results presented in the paper clearly demonstrate that concentration and CRLB need to be considered simultaneously for NAAG measurement without specialized MR spectroscopy sequence.

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