Automated Whole-Brain N-Acetylaspartate 1H MR Spectroscopic Quantification

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Purpose: N-acetylaspartate (NAA) is the second most abundant amino acid in the human brain (~0.1% of wet weight)[1]. Whole-brain NAA (WBNAA) [2] measurements from the entire head address concerns[3] in localized proton MR spectroscopy (1H-MRS) such as: voxel repositioning errors in serial studies, long acquisitions, and susceptibility to T1 and T2 changes in disease. However, WBNAA quantification is complicated by the combination of small NAA signals with large underlying lipid signals. It has hereto been done by manual phasing and NAA peak-region definition, followed by integration[4], rendering it susceptible to operator and baseline biases. We describe a novel automated method that fits a whole-head 1H spectrum with the full spectral model (NAA plus other1H-MRS visible "nuisance" metabolites), together with a baseline estimate to overcome these biases. We compare the performance of the previous with the proposed WBNAA quantification methods in a cohort of young healthy adults.

Methods: Fifteen healthy adults: 8/7 men/women, 25-41 y/o (33.3±5.3) were recruited under IRB approved protocol. All MRI and WBNAA measurements were taken at 3T (Trio, Siemens). NAA peak areas were manually quantified as described previously[2,4]. Automated WBNAA fitting was implemented in the Vespa[5] software package. Vespa-Simulation calculated NAA, Glu, Gln, tCho, tCr and mI basis functions using a full density matrix model with sequence RF pulses and timings to account for all (non-)linear phases accumulated during acquisition.

Automated spectral processing/fitting was done in Vespa-Analysis. A standard set of processing and spectral fitting parameters were applied as: (i) an HLSVD-Pro algorithm to remove residual water signals at and above 4.0 ppm; (ii) a 1 Hz Gaussian apodization; (iii) processed spectra were fitted using the automated algorithm previously described by Soher et al. in[6]. For a robust estimate of the NAA peak area, our metabolite basis set for the parametric fit included Glu, Gln, tCr, tCho and mI model-functions, as shown in Fig.1 that were treated as "nuisance signals" simplifying the use of wavelet filtering to account for non-parametric residual baseline signals.

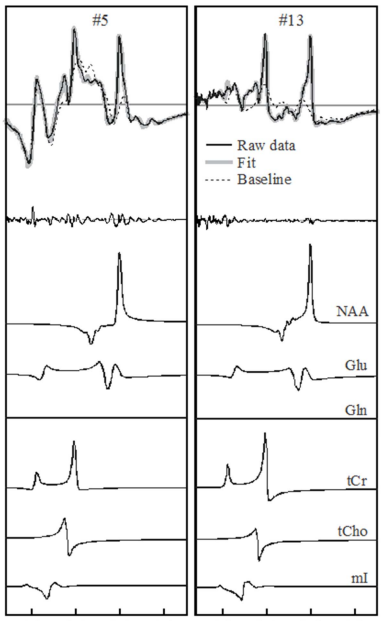

Figure 2: Automated fit of WBNAA data for two subjects.

Results: Fitting results (experiment, fit and baseline) for two subjects are shown in Fig.1 (top). Residuals (experiment-fit) in Fig.1 (middle) demonstrate quality of the fit. Manual integration used previously, did not provide such quality-control feedback. Basis functions used in the fit are shown in Fig.1 (bottom). WBNAA results for all subjects and both methods are plotted in Fig.2. The WBNAA estimated means of the two post-processing methods were not significantly different (12.76 versus 12.86 mM; p=0.691) according to a paired sample t-test. The CVs were not statistically different either (p=0.336). The fitted line widths, another data quality metric, ranged from 8.4 to 12.5 Hz with fairly similar performance.

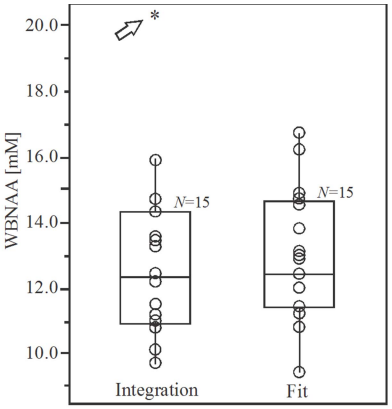

Figure 1: Box plots with 1st, 2nd (median), and 3rd quartiles (box), ±95% (whiskers) and outliers (*) WBNAA distributions for manual (left) and automated (right) methods

Discussion: This study demonstrates a robust, automated, operator bias-free, spectral fitting method for WBNAA quantification in the presence of: (i) spectrally varying phase, (ii) variable baseline contributions from residual water/lipids; (iii) "nuisance" metabolite signals; and (iv) semi-random global breathing/motion B0 shifts. Compared to the already established[2-4] performance of the simple manual phase/integration method the two methods yield nearly identical mean WBNAA (~1% apart), with SDs that are not statistically different. The automated approach also: (i) removes the need for expert operators; and yields quality control metrics, e.g., (ii) Cramer Rao bounds; (iii) (experiment-fit) residuals; and, (iv) metabolites' line width. These advantages are demonstrated in Fig. 2, where an outlier (indicated by arrow) was captured correctly by the automated fitting approach. Future improvements may include: removal of Gln from the nuisance metabolite basis set, the exclusion of corrupted WBNAA signal averages before fitting, or a method that simultaneously fits all signal averages to minimize nuisance signal variance effects.

Conclusion: Computer fitted whole-head 1H-MRS yields WBNAA distribution similar to manual spectral region integration but without a need for expert operators and yields quantitative reliability metrics: : Cramer-Rao bounds, residuals and line widths.

References: 1. Birken DL, Neurosci Biobehav Rev 13:23-31(1989); 2. Gonen O, MRM 40:684-9(1998); 3.Rigotti DJ, AJNR 28:1843-9(2007); 4.Rigotti DJ, AJNR 32:1011-5(2011); 5.Soher BJ, http://scion.duhs.duke.edu/vespa/project; 6.Soher BJ, MRM 40:822-31(1998)