Diffusion Weighted Spectroscopy of NAA in Multiple Sclerosis: Studying the Microstructure, Macrostructure and Organization of Axonal Tracts in the Corpus Callosum

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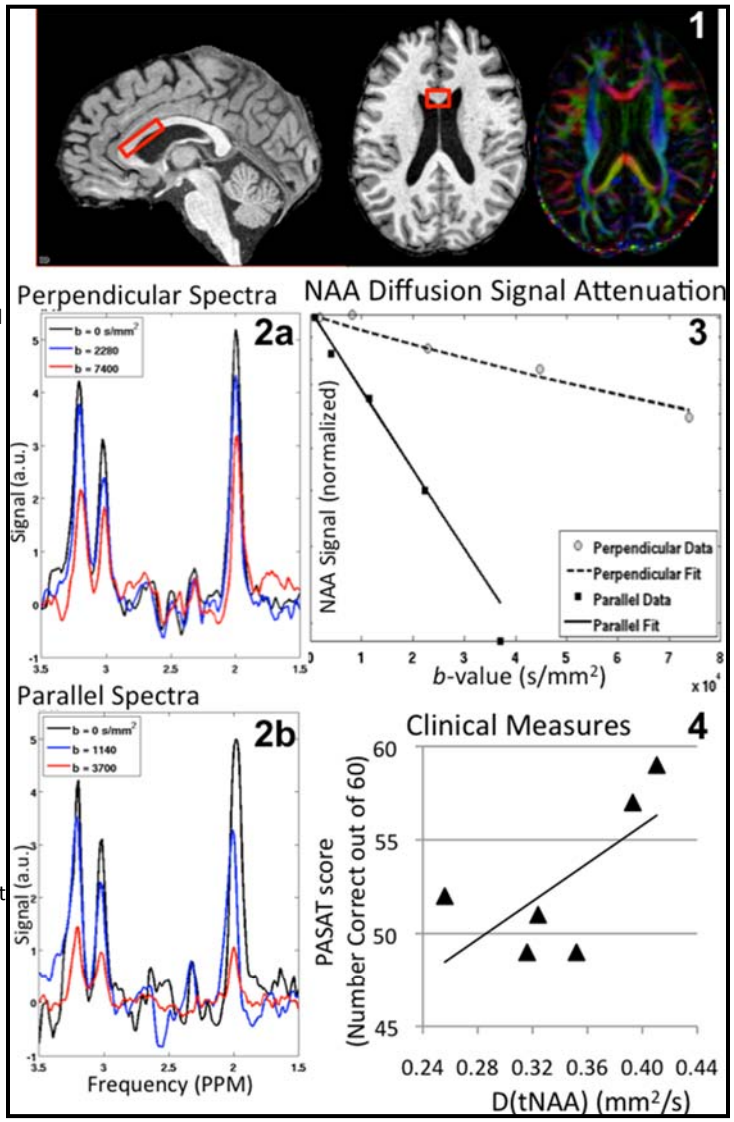
Target Audience: Physicists and neuroscientists interested in brain microstructure and compartmentation and clinicians who study neurodegeneration.

Purpose: Diffusion weighted spectroscopy (DWS) combines features of both diffusion tensor imaging (DTI) and MRS, allowing measurement of the diffusion properties of intracellular metabolites. As such, it may be sensitive to disruption of tissue microstructure within neurons and might consequently serve as a useful marker of axonal integrity and reversible damage in multiple sclerosis (MS). Previous work comparing patients with MS to healthy controls demonstrated lower NAA diffusion parallel (||) to axon tracts in the corpus callosum (CC), even in the setting of higher water diffusion in the same direction [*1*]. In order to better characterize axonal damage in the CC in MS and improve the reliability of DWS of NAA for longitudinal analysis of MS patients, we applied a modeled analysis of NAA diffusion in the CC that incorporates DTI eigenvector analysis to maximize microstructural information [*2*] from DWS.

Methods: 6 MS patients were scanned on a 3T MRI system (Philips Medical Systems, Best, NL) with transmit body-coil and an 8-channel receive head coil. For each volunteer, a T_1-weighted structural scan (3D MPRAGE), a DTI scan and DWS spectra from a 3.6 cm^3 volume of interest (VOI) in the anterior CC (VOI = 3.0(AP) x 1.5(RL) x 0.8(FH) cm^3) were collected (see Fig. 1). The T_1-w images were used for voxel positioning and tissue segmentation. The segmented VOI mask was applied to the DTI to derive the primary eigenvector (e_1) for each DTI voxel within the VOI. NAA diffusion measurements were obtained by incorporating bipolar diffusion gradients within a point-resolved spectroscopic sequence (PRESS [*3*], TE = 110 ms, Δ = 55 ms, δ = 22 ms, TR = 3 cardiac cycles (triggering using PPU), spectral width 1.5 kHz, 1024 sample points). Diffusion weighting was applied in 2 directions (1 ∥ and 1 perpendicular (⊥) to the longitudinal axis of CC fibers) with 5 *b*-values (*b*-values ⊥ = 0, 822, 2280, 4480, 7400 s/mm^2, *b*-values ∥ = 0, 411, 1140, 2240, 3700 s/mm^2) (see Fig. 2). Spectra were acquired with frequency-selective excitation/dephasing water suppression - RF pulse was optimized to retain enough water signal for zero-order phase correction and a reliable NAA signal for zero- and 1st-order phase correction prior to spectral averaging. 80 spectra were averaged for each *b*-value/direction combination (acquisition time ~30 min) and quantified with LCModel [*4*]. LCM-derived NAA+NAAG concentrations are referred to as total NAA (tNAA).



In order to derive a robust measure of the diffusion coefficient of tNAA in the cytoplasm D(tNAA), the DWS data were fit to a model [*2*] (see Fig 3) where the CC within the VOI is viewed as a curved cluster of cylinders with distributions of diameters, and angular dispersion of individual axons. This model is based on several assumptions: 1) diffusion times are long compared to the gradient pulses [*5*]; 2) in WM, tNAA is primarily in the axonal cytoplasm and neuronal cell bodies are sparse; 3) diffusion in cylinders can be decomposed into the components of molecular displacement ∥ and ⊥ to the tube wall [*6*]; 4) axonal diameters in the antCC are distributed similarly across subjects as described by [*7*]; and 5) the macroscopic curvature of the CC through the VOI can be described by DTI-derived e_1s from within the VOI. Spectra phasing, frequency-drift correction, fitting and modeling programs were written in MATLAB (Mathworks, Inc., Natick, MA).

Results: For 6 stable MS patients (no relapses within at least 1 year), the mean D(tNAA) in the antCC was 0.35 mm^2/s (range 0.25-0.52). Interestingly, there was a trend toward a correlation of D(tNAA) with the PASAT score (p=0.12), a measure of cognitive impairment – those patients with the highest NAA diffusion had the best PASAT scores (see Fig 4).

Discussion & Conclusion: By modeling the CC as a cluster of cylinders with macroscopic curvature and microscopic angular dispersion distribution, DWS measurements made ∥ and ⊥ to the long axis of those cylinders can be combined to yield D(tNAA) values that more accurately reflect the organization of the many fibers that make up a spectroscopy voxel. An additional advantage of these measurements is that they can be performed at clinical field strength (3T) and with standard MR equipment. Further work will investigate the directionality of the diffusion components measured with this model as well as the usefulness of this approach for longitudinal monitoring of neurodegeneration in MS.

References: [1] E. T. Wood *et al.*, *J Neurosci* **32**, 6665–6669 (2012). [2] I. Ronen *et al.*, *Proc ISMRM*, p1833 (2012). [3] H. E. Kan *et al.*, *MRM* **67**, 1203–1209 (2012). [4] S. W. Provencher, *MRM* **30**, 672–679 (1993). [5] P. van Gelderen *et al.*, *JMR* **103**, 255–260 (1994). [6] L. Avram *et al.*, *NMR Biomed* **21**, 888–898 (2008). [7] F. Aboitiz *et al.*, *Brain Res* **598**, 143–153 (1992).