NAA spectroscopy correlates with intra-axonal compartment parameters from diffusion MRI

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PURPOSE: Diffusion MRI (dMRI) is the imaging method of choice to probe white matter (WM) microstructure. Diffusion tensor imaging (DTI), while very fast, has a deficiency: by treating tissue as a single compartment, it cannot discern between intra- and extra-cellular water. We have recently shown that, for a single WM fiber bundle, a minimum set of two shells in q-space (i.e. two nonzero b-values in each direction), together with b=0 is sufficient to discern between intra- and extra-axonal water, and allows for the description of WM in terms of compartment specific WM tract integrity (WMTI) metrics.[1,2] In particular, these include intra-axonal diffusivity (D_{axon}), extra-axonal axial and radial diffusivity ($D_{e\parallel}$ and $D_{e\perp}$), axonal water fraction (AWF), and tortuosity (α) of extra-axonal space (**Figure 1**). The purpose of the current study was to examine the relationship between these WMTI parameters and concentrations of the neurochemicals n-acetylaspartate (NAA), creatine (Cr), choline (Ch), and myo-Inisotol (mI) measured *in vivo* using ^{1}H-MRS on a cohort of patients with mild traumatic brain injury (MTBI). In particular, we hypothesized that NAA, as an endogenous probe of the neuronal intracellular space[3], would correlate specifically with the WMTI parameters related to the intra-axonal space. Target audience: MRI physicists and clinicians interested in gaining insight into microstructure using clinically feasible MRI methods.

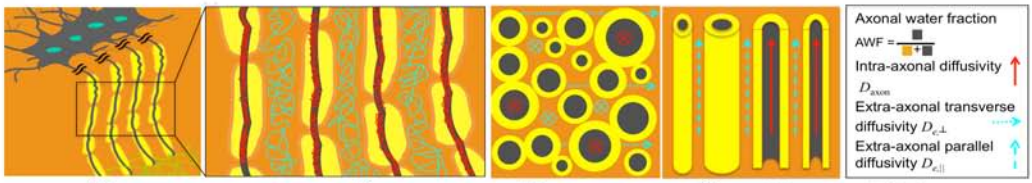

Figure 1: WM fiber bundle model and its derived WM tract integrity (WMTI) parameters[1,2]: (a) a fiber bundle is composed of cylindrical axons, each surrounded by a myelin sheath; (b) the diffusion signal consists of restricted diffusion in the intra-axonal space (IAS, red), and hindered diffusion in the extra-axonal space (EAS, cyan); the WMTI parameters used are explained in the legend and illustrated in (c) the transverse and (d) parallel cross-sections (xs).

METHODS: Twenty-five adult patients with MTBI (20 male, 5 female; mean age 33.6 yrs ± 11.2) were recruited within an average of 21.2 days ± 14.3 since injury in accordance with diagnostic criteria of the American Congress of Rehabilitative Medicine[4] and underwent MRI on a Siemens 3T scanner (Magnetom Trio, A Tim System) using diffusional kurtosis imaging (DKI) and ^{1}H-MRS as previously discussed elsewhere.[5-7] The study was IRB approved and all participants provided informed written consent. Differences between patients and controls were already identified in prior studies using this data.[5-7] DTI and DKI parametric maps were calculated[8] and used to derive WMTI parametric maps.[2] The fractional anisotropy (FA) maps were non-linearly registered to the MNI FA template and the transformations were applied to all WMTI parametric maps using FSL.[9] A rectangular region of interest (ROI) was drawn on the MNI T1 template that corresponded to the ROI employed for the ^{1}H-MRS measurements and used to extract mean values from each WMTI parametric map. The ^{1}H-MRS measurements were then correlated with the mean values for each WMTI parameter and assessed using Pearson correlation coefficients and corresponding *p* values.

RESULTS: ROI analysis demonstrated significant ($p < 0.05$) positive correlations between NAA and D_{axon}, AWF, α, and FA and negative correlations between NAA and $D_{e\perp}$ and radial diffusivity ($D\perp$) while no correlations were found for $D_{e\parallel}$, mean and axial diffusivity, and mean, radial, and axial kurtosis. The plots and regression lines for these results are shown in **Figure 2**. No significant correlations were found between any diffusion metrics and other metabolites (Cr, Ch, and mI).

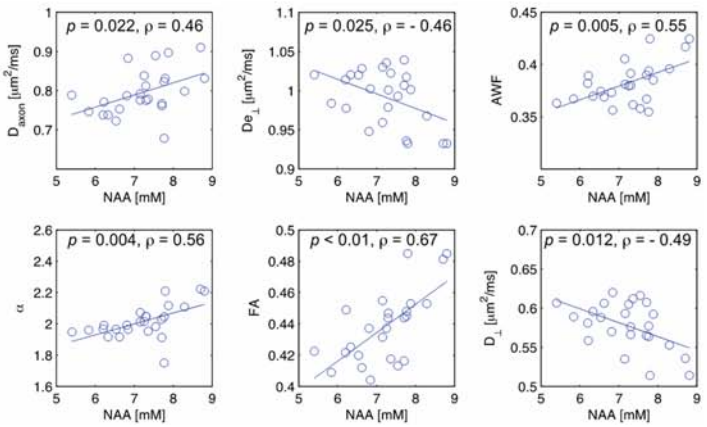

Figure 2: Plots showing significant ($p < 0.05$) correlations and corresponding Pearson coefficients (ρ) between NAA and WMTI and DTI parameters.

DISCUSSION: The observed correlations between ^{1}H-MRS and DTI metrics (FA and $D\perp$) in MTBI patients are similar to those found in a previous study in healthy controls.[10] Furthermore, as the WMTI diffusion model allows for disentangling the diffusion signal into intra- and extra-axonal diffusion[1,2], we investigated the specificity of WMTI parameters with respect to neurochemical changes measured with MRS. As expected, we found correlations between NAA and D_{axon}, $D_{e\perp}$, AWF, and α, while no such correlations existed between NAA and $D_{e\parallel}$, a marker for extra-axonal diffusivity along the axon bundle, nor with any other metabolites that are present in both compartments. Hence, these relationships may serve as an in vivo validation of the two-compartment model of intra- and extra-axonal diffusion. In addition, combining these two modalities may also help provide insight about subtle underlying disease processes: changes in NAA appear to involve a complex relationship with both acute intra-axonal injury (implied by correlations with D_{axon}) and axonal shrinkage, degeneration, and/or loss (implied by correlations with $D_{e\perp}$, AWF, and α), which might be consistent, in part, with the fact that NAA also influences many downstream processes important to subcellular architecture such as plasma osmolarity and myelin synthesis.[11,12] Further work is needed to elucidate how this information can be used to understand tissue damage and predict outcome.

REFERENCES: [1]Fieremans, E., *et al. NMR Biomed.* 23, 711-724 (2010). [2]Fieremans, E., *et al. Neuroimage* 58, 177-188 (2011). [3]Kroenke, C.D., *et al. Magn. Reson. Med.* 52, 1052-1059 (2004). [4]Esselman, P. C., et al. *Brain Inj.* 9, 417-424 (1995). [5]Grossman, E. J. *et al. Am. J. Neuroradiol.* 34, 951-957 (2013). [6]Kirov, I.I., *et al. J. Neurol.* 260, 242-252 (2013). [7]Kirov, I.I., *et al. J. Neurotrauma* 30, 1200-1204 (2013). [8]Tabesh, A., *et al. Magn. Reson. Med.* 65, 823-836 (2010). [9]Smith, S. M. *et al. Neuroimage* 31, 1487-1505 (2006). [10]Wijtenburg, S. A., *et al. Neuroimage* 66C, 161-168 (2012). [11]Chakraborty, G., *et al. J. Neurochem.* 78, 736-745 (2001). [12]Baslow, M.H. *Neurochem. Res.* 28, 941-953 (2003).