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N-acetyl-aspartate levels correlate with intra-axonal compartment parameters from diffusion MRI

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ABSTRACT

Diffusion MRI combined with biophysical modeling allows for the description of a white matter (WM) fiber bundle in terms of compartment specific white matter tract integrity (WMTI) metrics, which include intra-axonal diffusivity (D_{axon}), extra-axonal axial diffusivity ($D_{e||}$), extra-axonal radial diffusivity ($D_{e\perp}$), axonal water fraction (AWF), and tortuosity (α) of extra-axonal space. Here we derive these parameters from diffusion kurtosis imaging to examine their relationship to concentrations of global WM *N*-acetyl-aspartate (NAA), creatine (Cr), choline (Cho) and *myo*-Inositol (mI), as measured with proton MR spectroscopy (^{1}H-MRS), in a cohort of 25 patients with mild traumatic brain injury (MTBI). We found statistically significant ($p < 0.05$) positive correlations between NAA and D_{axon}, AWF, α, and fractional anisotropy; negative correlations between NAA and $D_{e\perp}$ and the overall radial diffusivity ($D_\perp$). These correlations were supported by similar findings in regional analysis of the genu and splenium of the corpus callosum. Furthermore, a positive correlation in global WM was noted between D_{axon} and Cr, as well as a positive correlation between $D_{e||}$ and Cho, and a positive trend between $D_{e||}$ and mI. The specific correlations between NAA, an endogenous probe of the neuronal intracellular space, and WMTI metrics related to the intra-axonal space, combined with the specific correlations of $D_{e||}$ with mI and Cho, both predominantly present extra-axonally, corroborate the overarching assumption of many advanced modeling approaches that diffusion imaging can disentangle between the intra- and extra-axonal compartments in WM fiber bundles. Our findings are also generally consistent with what is known about the pathophysiology of MTBI, which appears to involve both intra-axonal injury (as reflected by a positive trend between NAA and D_{axon}) as well as axonal shrinkage, demyelination, degeneration, and/or loss (as reflected by correlations between NAA and $D_{e\perp}$, AWF, and α).

Introduction

Diffusion MRI (dMRI) is the imaging method of choice to probe white matter (WM) microstructure. To date, diffusion tensor imaging (DTI) has been the primary dMRI technique used to conduct *in vivo* investigations of WM microstructural integrity (Basser, 1995; Jones, 2010). DTI quantifies the Gaussian part of the probability distribution of molecular displacement in terms of the overall diffusion tensor from which derived metrics such as the mean, axial, and radial diffusivities (MD, $D_{||}$, and $D_\perp$), and fractional anisotropy (FA) are derived. DTI metrics have been shown to be significantly altered in multiple pathologies (Horsfield and Jones, 2002; Jones, 2010). In addition, over the past decade several techniques have been proposed to assess the non-Gaussian part of the diffusion displacement distribution (Alexander et al., 2002; Jensen and Helpern, 2010; Liu et al., 2004; Maier et al., 2004; Özarslan et al., 2013; Tuch, 2004; Wedeen et al., 2005). In particular, diffusion kurtosis imaging (DKI), a clinically feasible non-Gaussian method (Jensen and Helpern, 2010; Jensen et al., 2005; Lu et al., 2006),

Abbreviations: α, tortuosity; AWF, axonal water fraction; Cho, choline; Cr, creatine; CSF, cerebral spinal fluid; CSI, chemical shift imaging; DAI, diffuse axonal injury; D_{axon}, intra-axonal diffusivity; $D_{e||}$, extra-axonal axial diffusivity; $D_{e\perp}$, extra-axonal radial diffusivity; DKI, diffusion kurtosis imaging; $D_{||}$, axial diffusivity; $D_\perp$, radial diffusivity; dMRI, diffusion MRI; DTI, diffusion tensor imaging; EAS, extra-axonal space; FA, fractional anisotropy; FOV, field of view; GM, gray matter; ^{1}H-MRS, proton magnetic resonance spectroscopy; IAS, intra-axonal space; $K_{||}$, axial kurtosis; $K_\perp$, radial kurtosis; MD, mean diffusivity; mI, myo-inositol; MK, mean kurtosis; MNI, Montreal Neurological Institute; MP-RAGE, Magnetization Prepared RApid Gradient Echo; MTBI, mild traumatic brain injury; NAA, *N*-acetylaspartate; ROI, region of interest; TE, echo time; TR, repetition time; VOI, volume of interest; WM, white matter; WMTI, white matter tract integrity.

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has shown promise in several brain pathologies (Jensen and Helpern, 2010; Steven et al., 2014).

The growing list of clinical studies using both DTI and DKI demonstrates the high sensitivity of their empirical diffusion parameters to microstructural changes in WM integrity. However, such *empirical* measures only provide an indirect characterization of microstructure. Their physical meaning in terms of specific tissue properties still remains uncertain. Indeed, it is imperative to distinguish between mathematical models representing the diffusion signal (*e.g.*, the cumulant expansion (Kiselev, 2010), mono-, bi-, and stretched exponential models (Assaf and Cohen, 1998; Bennett et al., 2003; Niendorf et al., 1996), and mean apparent propagator (Özarslan et al., 2013)) and true biophysical models taking into account actual neuronal structure as described below for WM. The former (*e.g.*, DTI and DKI) are applicable in all brain voxels and do not make assumptions about the underlying microstructure, whereas the latter are specifically tailored to model the effects of microstructure on diffusion in certain regions of the brain. Hence, such biophysical models are especially useful to gain insight into the underlying pathological processes and to increase the pathophysiological specificity.

In modeling WM diffusion, the common practice has been to model axons as zero radius, infinitely long, impermeable tubes and cylinders (Assaf and Basser, 2005; Assaf et al., 2004; Kroenke et al., 2004) or sticks (Behrens et al., 2003). Another common assumption is to neglect the water exchange through the myelin sheath surrounding axons. As a result, the diffusion signal in the WM contains at least two components, which correspond to the intra- and extra-axonal spaces. While these assumptions seem plausible and form the basis for most current diffusion models of WM in the brain (Alexander et al., 2010; Assaf and Basser, 2005; Assaf et al., 2004; Basser et al., 2007; Jespersen et al., 2007; Nilsson et al., 2013; Panagiotaki et al., 2009, 2012; Wang et al., 2011; Zhang et al., 2012), further validation remains warranted.

Based on the assumptions of a two non-exchanging compartments model, we recently showed 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 $b = 0$ are sufficient to discern between intra- and extra-axonal water, and allow for the description of compartment specific white matter tract integrity (WMTI) metrics from the diffusion and kurtosis tensor (Fieremans et al., 2010, 2011). Specifically, as shown in Fig. 1, these include intra-axonal diffusivity (D_{axon}), extra-axonal axial and radial diffusivities ($D_{e\parallel}$ and $D_{e\perp}$), axonal water fraction (AWF), and tortuosity (α) of extra-axonal space (Sen and Basser, 2005). To date, WMTI metrics have been preliminarily applied to several brain conditions and shown to provide useful information about plausible biophysical mechanisms (Benitez et al., 2014; Fieremans et al., 2013; Hui et al., 2012; Lazar et al., 2014).

The purpose of the current study is to examine the *in vivo* relationship between these WMTI parameters and concentrations of the metabolites *N*-acetylaspartate (NAA), creatine (Cr), choline (Cho), and *myo*-Inositol (mI) measured using ^{1}H-MRS. Our results could help clarify their meaning and shed light on the validity of the assumptions typically made when modeling the diffusion signal in WM. In particular, we hypothesized that NAA, as an endogenous probe of the neuronal intracellular space (Kroenke et al., 2004), would correlate specifically with the WMTI parameters related to axonal density and diffusion *inside* the axons.

The relationship between FA and NAA, Cr, and Cho has been evaluated in the WM of healthy adults in a previous study which showed that NAA concentrations explained most of the variance in FA (Wijtenburg et al., 2012). Here, we evaluate the relationship between DTI, DKI, model-specific WMTI parameters, and ^{1}H-MRS metabolites (NAA, Cr, Cho, and mI absolute concentrations) in a cohort of patients with mild traumatic brain injury (MTBI). This cohort has already been compared to age-matched controls using DTI (Grossman et al., 2013), DKI (Grossman et al., 2013), and ^{1}H-MRS (Kirov et al., 2013a,b). By combining the results from both diffusion and spectroscopy measurements in MTBI, we aim (i) to investigate the specificity of diffusion parameters for ^{1}H-MRS-detectable metabolites and (ii) to elucidate specific biophysical mechanisms that influence structural and metabolic changes following MTBI.

Methods

Subjects

Approval for the study was obtained from the Institutional Review Board of the New York University School of Medicine and all participants provided informed written consent. Twenty-five adult patients with MTBI (20 male, 5 female; mean age = 33.6 years ± 11.2) prospectively recruited in our previous studies (Grossman et al., 2013; Kirov et al., 2013a) were examined retrospectively. Patients had been included if they were within 1 month following injury (mean interval = 21.2 days ± 14.3) and classified with MTBI using diagnostic criteria developed by the Mild Traumatic Brain Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine (Esselman and Uomoto, 1995). Enrollment was permitted only in cases in which there existed no other history of brain damage or disorders of the central nervous system, no history of systemic illness, and no history of alcoholism or drug dependency. Patient demographics and clinical data are summarized in Table 1. Nineteen patients had an emergency room Glasgow Coma Scale score of 15, five had a score of 14, and one had a score of 13. Conventional MRI scans showed in each of four patients the separate presence of a right frontal convexity arachnoid cyst, a nonspecific focus of T2 hyperintense signal in the left frontal lobe white matter, a stable right cerebellopontine angle arachnoid cyst, and left temporal lobe encephalomalacia.

Data acquisition

DKI and ^{1}H-MRS were performed on a 3 T Magnetom Tim Trio whole-body scanner (Siemens, Erlangen, Germany) as previously described (Grossman et al., 2013; Kirov et al., 2013a) within the same or next day of each other. The DKI-protocol included a 2D T2-weighted

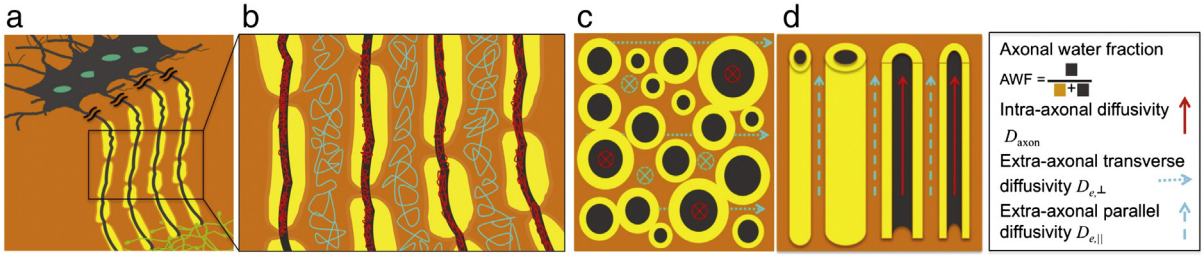

Fig. 1. The WMTI model for compartment specific cellular diffusivity: (a) a white matter fiber bundle is composed of cylindrical axons surrounded by a myelin sheath; (b) the diffusion signal reflects restricted water molecule movement in both intra-axonal (red) and extra-axonal (cyan) space; (c) transverse and (d) parallel cross-sections illustrate the metrics used to estimate this activity which are summarized by the model parameters legend.