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White matter tract integrity metrics reflect the vulnerability of late-myelinating tracts in Alzheimer's disease☆

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ABSTRACT

Post-mortem and imaging studies have observed that white matter (WM) degenerates in a pattern inverse to myelin development, suggesting preferential regional vulnerabilities influencing cognitive decline in AD. This study applied novel WM tract integrity (WMTI) metrics derived from diffusional kurtosis imaging (DKI) to examine WM tissue properties in AD within this framework. Using data from amnestic mild cognitive impairment (aMCI, n = 12), AD (n = 14), and normal control (NC; n = 15) subjects, mixed models revealed interaction effects: specific WMTI metrics of axonal density and myelin integrity (i.e. axonal water fraction, radial extra-axonal diffusivity) in late-myelinating tracts (i.e. superior and inferior longitudinal fasciculi) changed in the course of disease, but were stable in the initial stages for early-myelinating tracts (i.e. posterior limb of the internal capsule, cerebral peduncles). WMTI metrics in late-myelinating tracts correlated with semantic verbal fluency, a cognitive function known to decline in AD. These findings corroborate the preferential vulnerability of late-myelinating tracts, and illustrate an application of WMTI metrics to characterizing the regional course of WM changes in AD.

1. Introduction

Alzheimer's disease (AD) and its associated cognitive and functional declines are hypothesized to arise from the preferential vulnerability of late-myelinating areas. Specifically, post-mortem studies have shown that brain regions that are "last in," or that myelinate later in development, are typically "first out," or the most vulnerable to aging and the first areas to manifest neurodegenerative pathology (Braak and Braak, 1996). In vivo neuroimaging studies using diffusion tensor imaging (DTI) have supported this observation. DTI uses the micron-scale displacement of water to probe the microstructural integrity of brain white matter (WM) (Basser and Pierpaoli, 1996). Briefly, the directional variability of water diffusion in WM is indexed by fractional anisotropy (FA), where higher FA values imply greater directional coherence of WM fiber bundles. Consistent with post-mortem findings, prior studies show that compared to controls, AD patients have lower FA values in late-myelinating regions relative to early-myelinating areas (Choi, 2005; Gao et al., 2011; O'Dwyer et al., 2011a; Stricker et al., 2009). While this effect could be largely attributable to myelin breakdown, conflicting observations in the larger DTI literature on AD suggest that the mechanisms and the course of these changes are likely complex and synergistic (i.e. involving both Wallerian degeneration and myelin breakdown; O'Dwyer et al., 2011a; Sexton et al., 2011).

The ambiguous pathogenic interpretation of these DTI results is partly due to the limited specificity of FA, which is affected by several factors such as myelination, axon density or diameter, and intravoxel incoherence of fiber orientation (Beaulieu, 2002; Schmierer et al., 2007). In AD, gliosis as well as myelin and axonal loss may influence FA values (Gouw et al., 2008). Thus, FA by itself is insufficient to disentangle the individual contributions of each degenerative process. Alternatively, simultaneously assessing changes in multiple diffusion indices could provide more insight into underlying AD pathology (Acosta-Cabronero

Abbreviations: AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment; AWF, axonal water fraction; CP, cerebral peduncle; D_{axon}, intrinsic axonal diffusivity; $D_{e,\parallel}$, axial extra-axonal diffusivity; $D_{e,\perp}$, radial extra-axonal diffusivity; DKI, diffusional kurtosis imaging; DTI, diffusion tensor imaging; FA, fractional anisotropy; ILF, inferior longitudinal fasciculus; NC, normal control; PLIC, posterior limb of the internal capsule; SLF, superior longitudinal fasciculus; WM, white matter; WMTI, white matter tract integrity.

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et al., 2010; Bosch et al., 2012; Gold et al., 2010; Liu et al., 2011; O'Dwyer et al., 2011b; Shu et al., 2011). It has been proposed, for example, that radial diffusivity reflects myelin loss (Budde et al., 2008; Klawiter et al., 2011; Song et al., 2002), while axial diffusivity suggests axonal damage (Budde et al., 2008; Song et al., 2003). Should a change in radial diffusivity, but not in axial diffusivity, be observed, one might infer that myelin loss rather than axonal damage has occurred. However, radial diffusivity has also been found to indicate axonal loss (Klawiter et al., 2011). Thus, like FA, radial and axial diffusivities are informative, but have limited specificity to distinct neurodegenerative processes.

Furthermore, because of its assumption of Gaussian water diffusion, DTI is restricted in its ability to fully exploit all of the information available from diffusion MRI. Diffusional kurtosis imaging (DKI) is a clinically feasible extension of DTI that examines the additional contribution of non-Gaussian diffusion effects known to occur in the brain as a result of its microstructural complexity (Jensen and Helpern, 2010; Jensen et al., 2005). DKI provides both the diffusion and kurtosis tensors, from which all of the DTI-compatible metrics, such as the mean, radial and axial diffusivities are obtained, as well as the mean, radial and axial kurtoses, which quantify the diffusional non-Gaussianity. This added information can potentially improve the characterization of subtle tissue microstructural changes in neurodegenerative diseases, such as AD.

Nonetheless, such empirical diffusion measures only provide an indirect characterization of microstructure, making their physical meaning in terms of specific tissue properties uncertain. To overcome this limitation of pathological non-specificity, recent developments in the field of diffusion MRI have focused on biophysical modeling of the diffusion MRI signal to allow for more precise in vivo detection of subtle changes in biological tissue. In line with this effort, several advanced models have been proposed to interpret the diffusion MRI signal in brain WM (cf. Fieremans et al., 2011; Panagiotaki et al., 2012). In particular, our group has proposed a method that relates DKI-compatible metrics directly to WM microstructure using a specific WM model (Fieremans et al., 2011). This WM model applies to WM regions with highly aligned fiber bundles, and partitions water into two compartments, an intra-axonal space and an extra-axonal space. The fraction of diffusion MRI–visible water in the intra-axonal space represents the axonal water fraction (AWF). In addition, the diffusion metrics for the two compartments can be separately calculated. We refer to these WM model-derived parameters as WM tract integrity (WMTI) metrics, since they are most applicable to well-defined WM tracts. In addition to the AWF, the WMTI metrics include the intrinsic axonal diffusivity (D_{axon}), the radial extra-axonal diffusivity ($D_{\mathrm{e},\perp}$), and the axial extra-axonal diffusivity ($D_{\mathrm{e},\parallel}$).

The WMTI metrics are by design more directly related to the microstructure than empirical DTI and DKI parameters. The AWF and $D_{\mathrm{e},\perp}$ are sensitive to demyelination and axonal loss, whereas the axial compartment diffusivities, D_{axon} and $D_{\mathrm{e},\parallel}$, are specifically sensitive to structural changes along the axon bundle in the intra-axonal space (e.g., due to axonal beading (Fieremans et al., 2012c; Hui et al., 2012)) and in the extra-axonal space (e.g., due to gliosis, loss of oligodendrocytes, extracellular inflammation), respectively. As a result, D_{axon} and $D_{\mathrm{e},\parallel}$ are both far less sensitive to changes in myelin and axonal geometry transverse to the axon bundle, a finding that is consistent with our recent analysis of healthy human development data (Fieremans et al., 2012a). In addition, recent biophysical modeling (Fieremans et al., 2012a, 2012b, 2012c) suggests that the AWF may be most affected by axonal loss, while $D_{\mathrm{e},\perp}$ is most indicative of myelin integrity, with an elevated value being indicative of myelin breakdown. Currently, these are provisional interpretations that require further investigation. One such effort underway is a histological validation of these metrics in a mouse model of demyelination that is currently under review (cf. Falangola et al., 2012).

Of particular relevance to AD, we reported in a clinical study that the WMTI metrics demonstrated high sensitivity and diagnostic accuracy in detecting WM changes through the course of AD (Fieremans et al., 2013). The transition from normal aging to the amnestic mild cognitive impairment (aMCI) stage was characterized by increased radial extra-axonal diffusivity ($D_{\mathrm{e},\perp}$), consistent with widespread myelin breakdown, whereas a decrease in AWF occurred later in the disease from aMCI to AD, as would result from a reduction in axonal density. Moreover, our initial voxelwise analysis suggested that these extra-axonal changes appeared to preferentially occur in late-myelinating tracts earlier in the disease, whereas the AWF declined in both late- and early-myelinating tracts in the later stages. Although these initial findings provide qualitative support of the vulnerability of late-myelinating tracts in AD, a quantitative analysis that explicitly compares regions previously defined as early- or late-myelinating in prior studies of cognitive aging and AD (Brickman et al., 2012a; Stricker et al., 2009) would provide a more rigorous test of this hypothesis.

The purpose of this study was to apply WMTI metrics to clarify the tract-specific changes in WM tissue properties, using cross-sectional data from demographically similar groups of subjects that simulate the course of AD. We hypothesized that late-myelinating tracts would degenerate through the course of AD in contrast to relatively stable early-myelinating tracts, using the WMTI metrics to investigate whether these changes resulted from degeneration in axonal or myelin integrity. We further expected that these WMTI metrics in late-myelinating tracts would be associated with semantic verbal fluency, a cognitive function known to decline through the course of AD (Henry et al., 2004) and facilitated by late-myelinating regions (Brickman et al., 2006; Chen et al., 2009).

2. Materials and methods

2.1. Subjects and procedures

Subjects were recruited from the New York University (NYU) Alzheimer's Disease Center to undergo a full clinical research evaluation per Uniform Data Set procedures for Alzheimer's Disease Centers (Morris et al., 2006), and an MRI brain scan. Diagnoses were rendered by consensus and followed research criteria: NC subjects (n = 15) had no evidence of dementia or MCI and had a Clinical Dementia Rating (CDR) global score of 0; aMCI subjects (n = 12) were deemed to be in the precursor stage to AD dementia as defined by having a self- and/or informant-reported memory complaint, memory impairment based on performance that was at least −1.5 standard deviations below the Wechsler Memory Scale — Revised normative mean for age on Logical Memory-II or other memory subtests, CDR = 0.5, and no dementia (Petersen, 2004); AD subjects (n = 14) were given a diagnosis based on the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition; (American Psychiatric Association, 2000) and the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria for probable AD (McKhann et al., 1984), CDR ≥ 0.5 (range 0.5–2.0), and were not deemed to have any medical, neurological, or psychiatric conditions that could otherwise account for the dementia. The three groups did not statistically differ in demographic characteristics (Table 1). Nonetheless, due to the sensitivity of the WMTI metrics and diffusion MRI metrics in general (Sullivan and Pfefferbaum, 2006) to age, age was included as a covariate in all analyses. Supplementary Table 1 presents the subjects' raw scores on the neuropsychological tests from the Uniform Data Set.

Although all three groups reported histories of vascular risk factors or events that have been identified in the literature as contributors to the pathogenesis of AD (Kalaria et al., 2012), for the subjects in this study, these factors were not deemed to be the primary etiology for the observed cognitive impairment per consensus diagnosis. The extent to which the current clinical and research criteria preclude definitive conclusions regarding the relative contributions of vascular and neurodegenerative pathologies is a current topic of interest (Kling et al., 2013) that unfortunately cannot be directly addressed in this study. Nonetheless, as the groups in this study did not statistically differ in self-reported