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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

Table 1
Demographic and medical history descriptive statistics for Normal Controls (NC), Amnestic MCI (aMCI), and Alzheimer's disease (AD) subjects (n = 41).

	NC (n = 15)	aMCI (n = 12)	AD (n = 14)	χ^2/ *F*-test	*p*-Value
	n (%)	n (%)	n (%)		
Demographics					
Age (yrs, mean ± SD)	77.54 ± 4.01	79.05 ± 7.23	78.30 ± 9.55	0.15	0.87
Female	10 (66)	6 (50)	8 (57)	0.78	0.68
Education (yrs, mean ± SD)	16.14 ± 2.51	15.08 ± 3.66	15.14 ± 2.83	0.54	0.59
Right handed	13 (87)	11 (92)	13 (93)	1.94	0.75
White race	14 (93)	10 (83)	12 (86)	4.46	0.62
Medical history					
Hypertension	8 (53)	8 (67)	4 (29)	3.95	0.14
Hypercholesterolemia	12 (80)	9 (75)	6 (43)	3.09	0.21
Diabetes	2 (13)	1 (8)	1 (7)	0.35	0.84
Thyroid disease	3 (20)	2 (17)	1 (7)	1.01	0.60
Cardiac arrest	2 (13)	3 (25)	1 (7)	2.01	0.37
Cardiac bypass	1 (7)	1 (8)	0 (0)	1.13	0.57
Stroke or TIA	1 (7)	1 (8)	1 (7)	0.03	0.99
Depression within the past two years	4 (27)	1 (8)	4 (29)	1.85	0.40

Note: TIA = Transient Ischemic Attack.

medical history (Table 1), we considered that any potential effects due to a vascular risk history are at least comparable across the groups.

2.2. MRI acquisition and image processing

MRI experiments were conducted on a 3 T TIM Trio MR system (Siemens Medical Solutions, Erlangen, Germany) with the parameters as previously reported (Fieremans et al., 2013). Briefly, the MR protocol included 3D T1-weighted imaging for anatomical reference using a magnetization prepared rapid acquisition of gradient echoes (MPRAGE) sequence, and diffusion imaging with three *b*-values (0, 1000, 2000 s/mm^2) along 30 diffusion encoding directions using a single shot twice refocused echo-planar sequence. In-house image processing software (diffusional kurtosis estimator, DKE; Tabesh et al., 2011; http://www.nitrc.org/projects/dke) was used for checking image quality, motion correction, and for estimating the diffusion tensor and diffusional kurtosis tensors. The tensors were then used to derive the DKI-acquired parametric maps of mean diffusivity (MD), axial diffusivity ($D_\parallel$), radial diffusivity ($D_\perp$), and fractional anisotropy (FA), mean kurtosis (MK), axial kurtosis ($K_\parallel$), and radial kurtosis ($K_\perp$), as well as the WMTI metrics (Fieremans et al., 2011).

As in prior imaging studies that compared the relative vulnerability of early- and late-myelinating tracts in aging and AD (Brickman et al., 2012a; Stricker et al., 2009), the regions of interest (ROI) were bilateral early-myelinating tracts (i.e. posterior limb of the internal capsule [PLIC], cerebral peduncle [CP]) and late-myelinating tracts (i.e. superior longitudinal fasciculus [SLF], inferior longitudinal fasciculus [ILF]) (see Fig. 1). Using FMRIB's Software Library (FSL, Analysis Group, FMRIB, Oxford, UK), the individual FA maps were non-linearly registered to the FMRIB58 FA template and resampled to the $1 \times 1 \times 1$ mm^3 Montreal Neurological Institute (MNI) 152 space. A mean FA map over all subjects was created. The tract ROIs were obtained from the Johns Hopkins University (JHU) WM atlas (Mori et al., 2005). The ROIs were thresholded to FA ≥ 0.4 to restrict further analysis to voxels consisting of single fiber orientations as necessary for the derivation of the WMTI metrics. Means and standard deviations over the ROIs were extracted for each WMTI metric. The means of the metrics from the left and right ROIs were calculated. In addition, the metrics for the PLIC and CP,

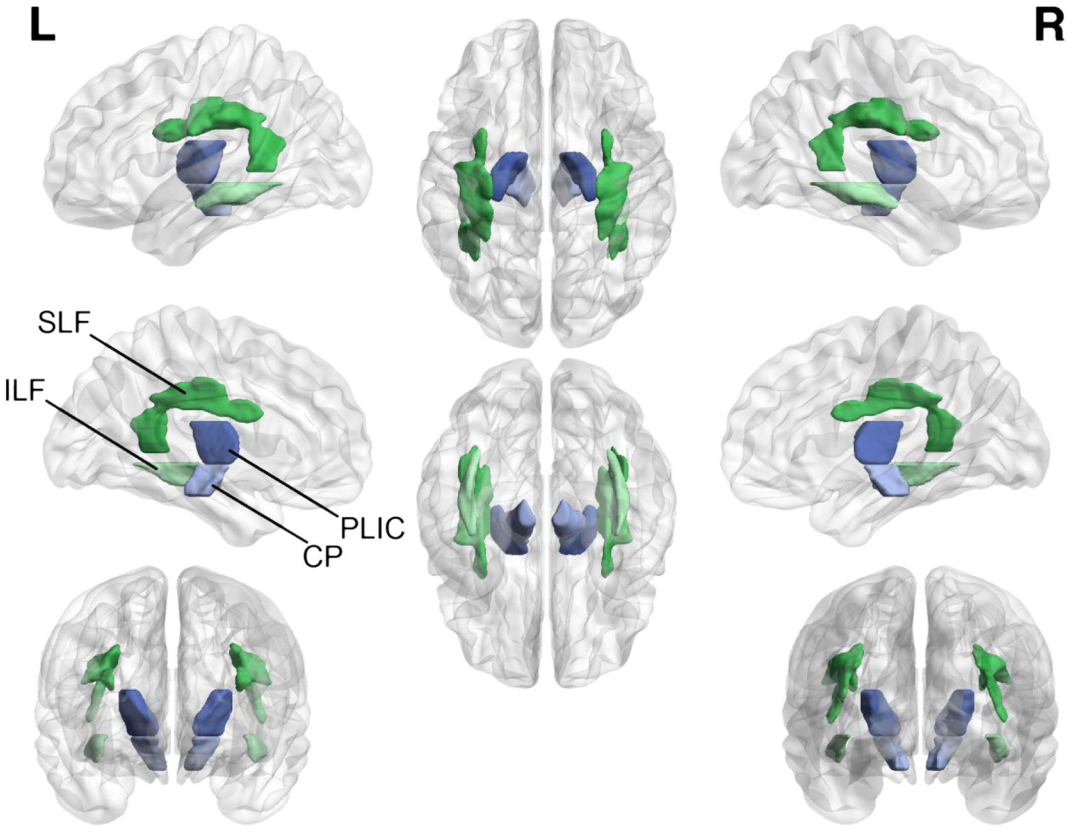

Fig. 1. Regions of interest, depicting the early-myelinating (blue) and late-myelinating (green) tracts. SLF = superior longitudinal fasciculus, ILF = inferior longitudinal fasciculus, PLIC = posterior limb of the internal capsule, CP = cerebral peduncle.

and for the SLF and ILF, were averaged to create composite early-myelinating and late-myelinating tract metrics.

2.3. Semantic verbal fluency

Semantic verbal fluency was assessed using the animal and vegetable tests. Subjects were asked to name as many animals as they could in 60 s, and vegetables in a separate 60-second trial. To facilitate interpretation and analyses, the raw total of correct responses for each test was converted to a *z*-score using normative data for age, sex, and years of education from the National Alzheimer's Coordinating Centers Uniform Data Set (Shirk et al., 2011), and an average *z*-score composite was generated for each subject. One AD subject did not complete these tests for unknown reasons. As expected, the three groups differed on this semantic verbal fluency composite *z*-score [$F(2, 37) = 14.24$, $p < 0.001$], with the AD subjects (-1.97 ± 1.11) scoring significantly lower ($p < 0.01$) than the NC (0.77 ± 1.22) and aMCI (-0.06 ± 1.77) subjects.

2.4. Statistical analyses

To test our a priori hypothesis, we conducted mixed model ANOVAs for each WMTI metric with between-group (i.e. NC, aMCI, AD) and within-group (i.e. early-, late-myelinating) factors, and with age as a covariate. That is, we tested whether there was a significant interaction effect between groups and regional WMTI metrics. Because of the relatively modest sample sizes in this preliminary study, we did not adjust the significance threshold for the four mixed models tested. We conducted Spearman's correlations (two-tailed) between the WMTI metrics of the late-myelinating tracts and semantic verbal fluency composite *z*-scores. To account for age, the age-residualized WMTI metrics were used, where age was regressed onto each metric. A conservative Bonferroni-corrected significance value was set to ($p < 0.05/4 = 0.0125$) to minimize Type I error from the multiple pairwise correlations between the four regional metrics and the semantic verbal fluency composite *z*-score. To identify which WMTI metric best correlated with semantic verbal fluency, Hotelling's *t*/Steiger's Z-tests for correlated correlations were conducted to statistically test for the relative strength of each correlation coefficient. Analyses were conducted using IBM SPSS version 20 (Armonk, NY).

3. Results

3.1. A decrease in AWF and an increase in $D_{e,\perp}$ occur primarily in late-myelinating tracts through the course of AD

Table 2 reports the summary statistics, while Fig. 2 depicts the results of the mixed models. In support of our first hypothesis, there was an interaction effect for AWF [$F(2, 37) = 3.89$, $p < 0.05$, $\eta^2 = 0.17$]; AWF in early-myelinating tracts did not differ across the groups, whereas AWF in late-myelinating tracts was lower in AD than in NC and aMCI. There was a within-group main effect for tract type [$F(1, 37) = 223.57$, $p < 0.001$, $\eta^2 = 0.86$]; AWF in late-myelinating tracts was significantly lower than AWF in early-myelinating tracts. The model for $D_{e,\perp}$ approached significance [$F(2, 37) = 3.05$, $p = 0.059$, $\eta^2 = 0.14$]; $D_{e,\perp}$ in early-myelinating tracts was higher in AD than NC, but $D_{e,\perp}$ in late-myelinating tracts was higher in AD than both NC and aMCI. There was a within-group main effect for tract type [$F(1, 37) = 192.77$, $p < 0.001$, $\eta^2 = 0.84$]; $D_{e,\perp}$ in LM tracts was significantly higher than in EM tracts. Per partial eta-squared values, these models have large effect sizes (Cohen, 1969; Richardson, 2011). In contrast, the mixed model was not significant for $D_{e,\parallel}$ [$F(2, 37) = 1.46$, *ns*]. The model for D_{axon} was significant [$F(2, 37) = 3.80$, $p < 0.05$, $\eta^2 = 0.17$], but there were no significant within- or between-group main effects.

3.2. Extra-axonal diffusivities correlate with semantic verbal fluency

Table 3 reports Spearman's correlations between the age-residualized WMTI metrics of the late-myelinating tract composites and the semantic verbal fluency *z*-scores for all the subjects. Semantic verbal fluency was correlated with the WMTI metrics of AWF and extra-axonal diffusivities (i.e. $D_{e,\parallel}$, $D_{e,\perp}$) in the expected directions. That is, worse semantic verbal fluency was associated with greater extra-axonal diffusivities and with lower AWF in late-myelinating tracts. However, semantic verbal fluency correlated more strongly with $D_{e,\perp}$ than with AWF [Hotelling's $t(37) = -4.28$, $p < 0.001$], and

Table 2
ANCOVA post-hoc results for normal control (NC), amnestic MCI (aMCI) and Alzheimer's disease (AD) subjects, controlling for age, for each regional WMTI metric (n = 41).

Metric	Region of interest	NC (n = 15)	aMCI (n = 12)	AD (n = 14)	NC v. aMCI	aMCI v. AD	NC v. AD
		Mean ± SD	Mean ± SD	Mean ± SD	*p*-Value	*p*-Value	*p*-Value
AWF	Early-myelinating	0.42 ± 0.02	0.42 ± 0.01	0.41 ± 0.03	0.77	0.20	0.65
	ICp	0.42 ± 0.02	0.42 ± 0.02	0.41 ± 0.03	0.95	0.58	0.86
	CP	0.42 ± 0.02	0.43 ± 0.01	0.41 ± 0.04	0.64	0.10	0.56
	Late-myelinating**	0.38 ± 0.03	0.37 ± 0.02	0.34 ± 0.04	1.00	0.02	0.02
	SLF**	0.40 ± 0.03	0.40 ± 0.03	0.37 ± 0.05	0.99	0.01	0.01
	ILF*	0.35 ± 0.03	0.34 ± 0.03	0.32 ± 0.04	1.00	0.08	0.05
D_{axon} [μm²/ms]	Early-myelinating	0.84 ± 0.05	0.86 ± 0.05	0.87 ± 0.08	0.72	1.00	0.58
	ICp	0.82 ± 0.07	0.84 ± 0.07	0.86 ± 0.09	0.90	0.81	0.37
	CP	0.87 ± 0.06	0.89 ± 0.03	0.87 ± 0.09	0.58	0.80	0.98
	Late-myelinating	0.88 ± 0.07	0.87 ± 0.05	0.83 ± 0.05	0.95	0.23	0.06
	SLF**	0.89 ± 0.08	0.87 ± 0.08	0.79 ± 0.09	0.97	0.04	<0.01
	ILF	0.88 ± 0.08	0.86 ± 0.04	0.87 ± 0.05	0.97	0.98	1.00
$D_{e,\parallel}$ [μm²/ms]	Early-myelinating**	2.16 ± 0.15	2.27 ± 0.08	2.29 ± 0.09	0.05	0.94	0.01
	ICp*	2.01 ± 0.14	2.11 ± 0.07	2.13 ± 0.09	0.09	0.96	0.02
	CP*	2.30 ± 0.17	2.43 ± 0.09	2.45 ± 0.11	0.07	0.94	0.02
	Late-myelinating**	2.17 ± 0.10	2.22 ± 0.06	2.29 ± 0.11	0.51	0.11	<0.01
	SLF	2.02 ± 0.08	2.05 ± 0.06	2.05 ± 0.09	0.84	0.98	0.59
	ILF**	2.31 ± 0.16	2.39 ± 0.12	2.53 ± 0.15	0.54	0.04	<0.01
$D_{e,\perp}$ [μm²/ms]	Early-myelinating*	0.93 ± 0.09	0.99 ± 0.09	1.04 ± 0.13	0.41	0.37	0.01
	ICp	0.83 ± 0.08	0.88 ± 0.09	0.91 ± 0.13	0.61	0.64	0.08
	CP**	1.02 ± 0.11	1.10 ± 0.10	1.16 ± 0.16	0.39	0.29	<0.01
	Late-myelinating**	1.10 ± 0.08	1.16 ± 0.07	1.29 ± 0.19	0.64	0.01	<0.01
	SLF**	1.06 ± 0.07	1.09 ± 0.04	1.18 ± 0.17	0.92	0.02	<0.01
	ILF**	1.15 ± 0.10	1.24 ± 0.13	1.40 ± 0.23	0.54	0.03	<0.01

Note: Asterisks indicate significant omnibus ANCOVA results for each regional metric, where $^*p < 0.05$, $^{**}p < 0.01$. WMTI = white matter tract integrity, AWF = axonal water fraction, D_{axon} = intra-axonal diffusivity, extra-axonal axial ($D_{e,\parallel}$) and radial ($D_{e,\perp}$) diffusivities.

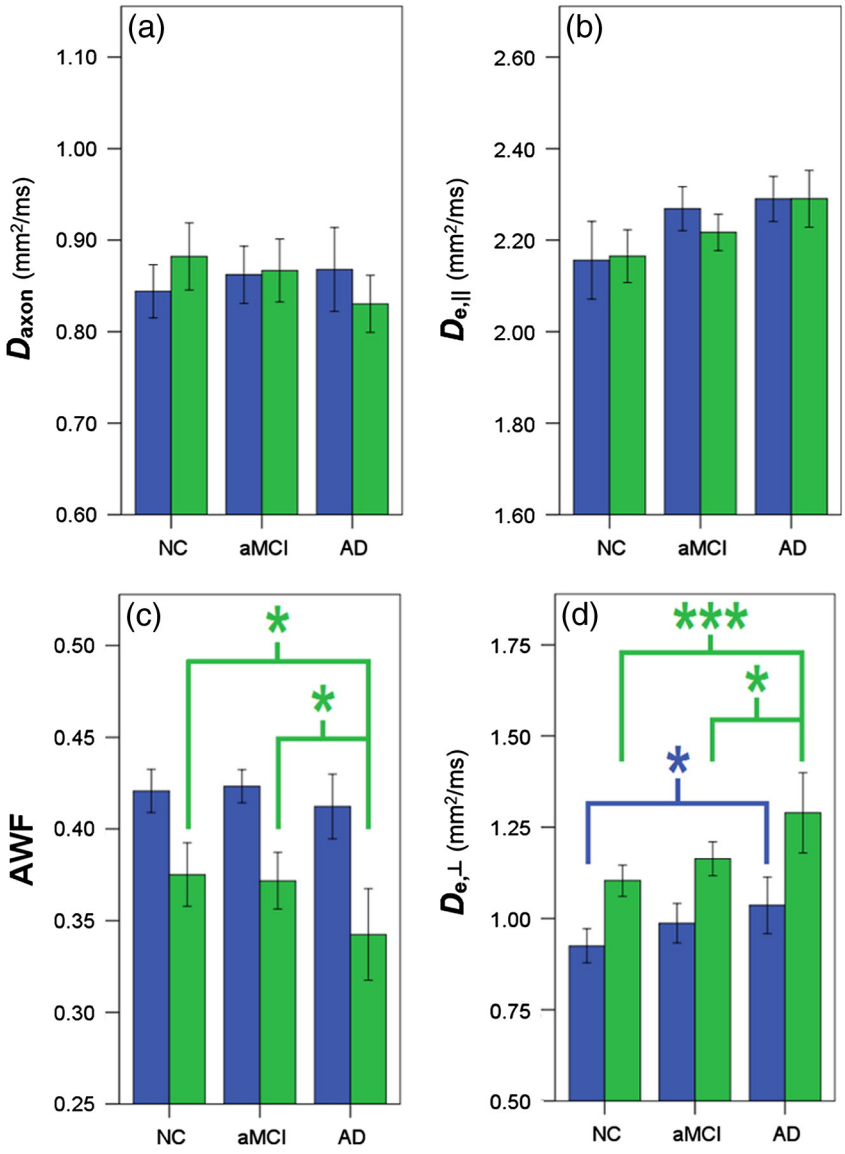

Fig. 2. Mixed model results. Bar graphs depicting the mixed models for (a) D_{axon}, (b) $D_{e,\parallel}$, (c) AWF, and (d) $D_{e,\perp}$. Graphs (c) and (d) depict interaction effects. That is, AWF decreases and $D_{e,\perp}$ increases in late-myelinating tracts (green bars) through the course of AD, in contrast to early-myelinating tracts (blue bars) that remain stable until later in the disease when $D_{e,\perp}$, too, increases. Whiskers = 95% confidence intervals. NC = normal controls, aMCI = amnestic mild cognitive impairment, AD = Alzheimer's disease. $^{*}p < 0.05$, $^{***}p < 0.001$. (For interpretation of the references to colors in this figure legend, the reader is referred to the web version of this article.)

with $D_{e,\parallel}$ than with AWF [Hotelling's $t(37) = -3.72$, $p < 0.001$]. The correlations between semantic verbal fluency and both metrics of extra-axonal diffusivity (i.e. $D_{e,\perp}$ and $D_{e,\parallel}$) were not significantly different [Hotelling's $t(37) = -1.60$, *ns*], indicating that semantic verbal fluency is preferentially associated with extra-axonal diffusivity rather than AWF.

Table 3
Spearman's correlations between age-residualized WMTI metrics in late-myelinating tracts and the semantic verbal fluency *z*-score (n = 40).

	Semantic verbal fluency (*z*-score)	
	r	*p*-value
AWF in late-myelinating tracts	0.42	0.007
D_{axon} in late-myelinating tracts	0.15	0.366
$D_{e,\parallel}$ in late-myelinating tracts	−0.44	0.004
$D_{e,\perp}$ in late-myelinating tracts	−0.61	<0.001

Note: WMTI = white matter tract integrity, AWF = axonal water fraction, D_{axon} = intra-axonal diffusivity, extra-axonal axial ($D_{e,\parallel}$) and radial ($D_{e,\perp}$) diffusivities.

4. Discussion

This study sought to apply recently proposed WMTI metrics as derived from DKI in subject groups that simulate the progression of AD, to further elucidate the specific changes in WM. Our results show that both AWF decreases and $D_{e,\perp}$ increases in late-myelinating tracts through the course of AD, in contrast to the early-myelinating tracts, wherein these metrics were stable until later in the disease. In the late-myelinating tracts, AWF and $D_{e,\perp}$ values were significantly lower and higher, respectively, than their corresponding values in early-myelinating tracts, which is consistent with WM ontogeny. In addition, increased $D_{e,\perp}$ and $D_{e,\parallel}$ in late-myelinating tracts were associated with decreased semantic verbal fluency, a cognitive function that declines in AD and is mediated by these tracts. These findings have the following

implications regarding the regional progression of WM changes in AD, and identify potential biomarkers of a neurobiological substrate of cognitive dysfunction.

4.1. Changes in WMTI metrics reflect preferential vulnerability of late-myelinating tracts in AD

The preferential vulnerability of late-myelinating areas to aging and AD is a proposed mechanism by which cognition declines. This trend has been referred to as "retrogenesis," or a "return to childhood" insofar as the disease is characterized by a decline in cognitive and functional abilities that inversely mirrors the acquisition of these skills in development (Reisberg et al., 1999). Post-mortem studies indicate that pathological markers of neurodegenerative diseases first develop in areas that are last to myelinate prior to affecting early-myelinating areas (Braak and Braak, 1996), and that a loss of myelin integrity accounts for cognitive decline (Peters et al., 1996; Wallin et al., 1989). Mechanistically, this occurs because when myelin breaks down with aging, the homeostatic remyelination process is characterized by the formation of thinner and shorter intermodal lengths of myelin, resulting in a reduced rate of conduction along affected myelinated nerve fibers (Fancy et al., 2011; Peters, 2009). In vivo detection methods of this known biological process are key to the development of potential targets that could ameliorate the burden of cognitive impairment in neurodegenerative diseases of aging. In accord with other studies (Bartzokis et al., 2012; Brickman et al., 2012a; Stricker et al., 2009), our study contributes to this literature by providing in vivo corroboration of known myelopathology.

Specifically, these findings support the potential use of novel WMTI metrics to clarify the particular tissue properties of WM that undergo changes through the course of AD. The results of our mixed models suggest that axonal density, what AWF is modeled to estimate, preferentially decreases in late-myelinating tracts, particularly at the later stages of AD (Fig. 2c). Similarly, myelin breakdown (as estimated by increased $D_{e,\perp}$) in late-myelinating tracts also occurs through the course of AD, especially in the later stages when such decline likewise occurs in early-myelinating tracts (Fig. 2d). Neither changes in the intra-axonal environment (D_{axon}; indicating axonal injury), nor in axial extra-axonal diffusivity ($D_{e,\parallel}$; suggesting alterations in extra-axonal diffusivity due to gliosis, loss of oligodendrocytes, inflammation and the like), demonstrated the hypothesized pattern.

These dissociations corroborate and extend known processes in AD. First, AWF as a metric of axonal density loss may be a marker of the widespread neuronal degeneration resulting from intra-cellular neurofibrillary changes in late-myelinating areas (Braak and Braak, 1996), whereas the integrity of axonal projections is relatively unaffected unlike in acute ischemia (Hui et al., 2012). While cerebrovascular disease is known to exacerbate or even precipitate AD (Kalaria et al., 2012), further work could disentangle the extent to which WMTI metrics can reflect its acute or chronic effects on AD. Second, the specificity of our findings implicating myelin breakdown relates to previous findings from other groups. It is possible that along with neurofibrillary changes, dysregulation in the homeostatic functions of myelin is a crucial mechanism by which cognitive and functional declines arise in AD (Bartzokis, 2004). Indeed, while the mixed model for $D_{e,\parallel}$ was not significant (Fig. 2b), the data trends are consistent with glial activation in both late- and early-myelinating tracts through the disease course. Myelin breakdown may especially be observed in late-myelinating tracts that, given WM ontogeny, are particularly vulnerable to AD, but may also be observed later in the disease in early-myelinating tracts. For both processes of axonal density loss and myelin breakdown, the results of this study suggest that these declines are most apparent in the dementia stage, indicating that these particular WM regions may be involved in later stages of disease. However, our previously published voxelwise analyses did implicate other widespread regions, mostly late-myelinating than early-myelinating, as significantly differentiating normal controls from aMCI (Fieremans et al., 2013).

4.2. Extra-axonal diffusivity in late-myelinating tracts and semantic verbal fluency

These previously described findings relating to degeneration in axonal density and myelin integrity in late-myelinating tracts presuppose that these changes may influence the declines in higher-order cognition that characterize the course of AD. To add to this, we identified that myelin integrity in particular (as indicated by WMTI metrics of extra-axonal diffusivity) was more specifically correlated with semantic verbal fluency, a cognitive function that is also known to decline in AD and is believed to be facilitated by the late-myelinating longitudinal fasciculi of interest in this study (Brickman et al., 2006; Chen et al., 2009; Henry et al., 2004). Thus, not only are these WMTI metrics potentially sensitive to specific regional differences in degeneration as the disease progresses, but these metrics also are functionally relevant and can serve as potential markers of the neuroanatomical substrate of cognitive decline, which are in much need (Salthouse, 2011).

4.3. WMTI metrics may specifically reflect the particular vulnerability of late-myelinating tracts in AD compared to conventional diffusion metrics

The DKI acquisition implemented in this study also provides the conventional diffusion metrics via DKE post-processing. Thus, while not the focus of the current study, follow-up mixed models were conducted using the conventional diffusion metrics instead to examine the extent to which these metrics also reflect the hypothesized effects. As can be seen in Supplementary Table 2, mixed models were significant for the mean diffusivity, radial diffusivity, and axial kurtosis. Of note, mean and radial diffusivities demonstrated group differences in *both* early- and late-myelinating tracts, whereas the current findings specifically supported the hypothesized interaction effect (i.e. preferential decline in late-myelinating tracts). Although these data appear supportive of the WMTI metrics, it must be emphasized that these are suggestive trends at best due to the multiple tests conducted with the modest sample size in this preliminary study. Future replications and extensions of this work can hopefully be adequately powered to conduct more robust statistical tests of these comparative effects.

4.4. Clinical implications and future directions

Although most typified by medial temporal atrophy and memory decline, AD is increasingly regarded as a disease that affects widespread brain tissue, as evidenced by the growing number of neuroimaging studies that implicate various other regions, tracts, and networks (Risacher and Saykin, 2013), and the neuropsychological literature that has long documented declines in non-memory domains (e.g. semantic verbal fluency) as also pathognomonic of the disease (Albert et al., 2001; Salmon et al., 2002). Accordingly, this study provides a demonstration of how WMTI metrics, as obtained from DKI, can indicate the microstructural integrity of key tracts associated with cognition that also undergo degeneration in the course of AD. Similar to the ease with which neuropsychological testing is implemented and yields meaningful indices, it is the intention of many developers of neuroimaging biomarkers to provide functionally meaningful quantitative metrics that can be derived from clinically-feasible imaging sequences with relatively straightforward post-processing. Given the promising findings in this preliminary study, future work incorporating complementary imaging modalities may help clarify other contributors to WM changes and cognition in AD.

These results can inform potential interventions by enabling the consideration of alternative prevention or treatment strategies that target mediators of axonal density or myelin integrity in late-myelinating regions. Considering the preferential vulnerability of these areas as

shown in this study, it is possible that therapies focused on WM constituents or on the processes that perturb its homeostatic functions may provide alternative or complementary strategies for addressing this widespread brain disease that affects more than one region and involves varied pathologies (e.g. Bartzokis, 2012; Hider et al., 2011). The field is in need of effective therapeutics that can perhaps benefit other diseases in which cognitive decline, as influenced by loss of WM integrity, is a similar problem. Subsequent research must employ experimental designs or more robust statistical analyses that directly test the association between metrics of WM integrity and cognitive function to bolster this argument.

4.5. Limitations

Despite the large effect sizes found here that provide in vivo corroboration of known neuropathological processes, this study has limitations. First, since the patient groups studied here represent a cross-sectional simulation of the temporal course of AD, corroboration of these findings using a longitudinal design is necessary to fully elucidate the primacy or saliency of regional differences through the course of disease (O'Dwyer et al., 2011a; Sexton et al., 2011), although our prior findings imply that myelin breakdown may precede axonal density loss (Fieremans et al., 2013). Future clinical research must also endeavor to more thoroughly characterize the presence and potential contribution of vascular risk factors in the event that these may be meaningful effect modifiers.

Second, other WM pathologies identified via non-diffusion imaging techniques were not incorporated here. For instance, T2-weighted imaging identifies WM hyperintensities that represent a variety of pathologies that may increase the likelihood of dementia onset (Brickman et al., 2012b; van Straaten et al., 2008). However, in our data set, the prevalence of WM hyperintensities was not statistically significantly different between the groups (cf. Fieremans et al., 2013), suggesting that the effects introduced by these hyperintensities that are not already detected by DKI would not systematically alter our results. The relative contribution of these in vivo imaging techniques to quantifying WM integrity, be it through quantifying WM hyperintensities or diffusion properties, is unknown and beyond the scope of this paper, but is currently under active investigation (Maillard et al., 2013). Multi-modal neuroimaging studies incorporating WMTI metrics would be ideal, provided that this future work is sufficiently powered to incorporate various other metrics.

Third, there are many other tracts identified in recent in vivo imaging studies as either late- or early-myelinating that could have been considered here (Kochunov et al., 2012; Lebel et al., 2012). However, given the modest sample size and the preliminary nature of this study, focusing the analyses on regions that have been identified in previous studies was considered both conceptually and practically justified. Our decision to combine the left and right regions in the analyses for the sake of consistency with prior imaging studies that hypothesized similar effects (Brickman et al., 2012a; Stricker et al., 2009) could also bear further scrutiny in future studies, although follow-up analyses of these data reveal no significant differences between each WMTI metric of the corresponding left and right regions (data not shown). Similarly, future work can explore whether certain tracts that contributed to the composites used here were primarily driving the results. For instance, in the aforementioned studies, FA in the ILF showed greater age-related (Brickman et al., 2012a) and AD-related (Stricker et al., 2009) effects. We found contrasting results in that FA in the SLF appeared to distinguish the groups more so than the ILF (Supplementary Table 2), and that the tract-specific group differences did not systematically favor ILF effects across the WMTI metrics (Table 2). Regardless, replication of these findings with larger samples is necessary before any definitive conclusions can be made. Lastly, subsequent work could also further investigate the functional relevance of these metrics by employing psychometrically robust measures of cognition beyond those employed here.

4.6. Conclusions

We applied recent innovations in modeling of WM microstructure using DKI-derived parameters to demonstrate the extent to which WMTI metrics can clarify the vulnerability of late-myelinating tracts in AD. Our results indicate that the primary changes in WM appear to be related to the loss of axonal density and myelin breakdown, particularly in late-myelinating tracts, through the course of the disease. Albeit preliminary, the large effects found in this study suggest that these metrics can potentially serve as robust in vivo biomarkers of disease progression that warrant further investigation.

Conflict of interest

The authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2013.11.001.

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