White matter degeneration in early- and late-myelinating tracts through the course of Alzheimer's disease

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INTRODUCTION: We recently introduced a white matter (WM) model[1] that relates DKI metrics directly to WM microstructure. In applying these WM tract integrity (WMTI) metrics to Alzheimer's disease (AD), we found that increased diffusivity in the extra-axonal space (suggesting myelin breakdown) characterizes the transition from normal aging to amnestic mild cognitive impairment (aMCI), a precursor to AD, while decreased axonal water fraction (a marker of axonal density loss) occurs from aMCI to AD (under review). Apart from showing high diagnostic accuracy, these metrics were strongly correlated with processing speed, providing functional relevance to these parameters. *Purpose:* This study applies these WMTI metrics to the study of AD within the framework of retrogenesis[2]; late-myelinating (LM) tracts are more susceptible to aging and disease, and are therefore expected to decline more so than early-myelinating (EM) tracts, which remain comparatively stable in the course of AD. Prior DTI studies suggest this trend occurs in AD and normal aging[3]. Here, we predicted a group x tract interaction, where LM tracts were expected to degenerate in the course of AD vis-à-vis stable EM tracts. We also expected that metrics reflecting myelin integrity in LM tracts would correlate with verbal fluency, a cognitive function mediated by association fibers known to be affected in AD. *Target Audience:* AD researchers interested in imaging biomarkers.

METHODS: Subjects from the NYU AD Center were demographically similar normal controls (NC; n=15; age 77.54±4.01, MMSE=29.33±0.72), aMCI subjects (n=12; age 79.05±7.23, MMSE= 27.75±1.71), and AD subjects (n=14; age 78.30±9.55, MMSE=21.64±5.80). Subjects performed the verbal fluency task (i.e. Animals) as part of their clinical evaluation, and the raw scores were used in this analysis. MRI data were acquired using a 3T Trio MR system (Siemens). DKI acquisition was performed with 3 b-values (0, 1000, 2000 s/mm^2) along 30 diffusion encoding directions using single-shot twice-refocused-EPI. Other imaging parameters were: TR=5900ms, TE=96ms, averages=2, FOV=222×222mm^2, matrix size=82×82, parallel imaging factor of 2, slice thickness=2.7mm, 45 oblique axial slices. DKI post-processing provided parametric maps of the diffusion metrics. DKI maps were used to derive WMTI parametric maps for the D_{axon}, AWF, $D_{e,\parallel}$, and $D_{e,\perp}$[1]. The FA maps were non-linearly registered to the MNI FA-template, and all parametric maps were transformed into a standard space according to this registration using FSL. ROI's were drawn based on the JHU WM label atlas, and the means of the tract metrics from both hemispheres were calculated. Consistent with the tracts and the procedures in prior studies[2], the means of the metrics in the posterior limb of the internal capsule and the cerebral peduncles represent the EM tracts, while the means of the WMTI metrics in the sagittal stratum and the superior longitudinal fasciculus represent the LM tracts (Figure 1). Mixed models and partial correlations (age=covariate) were run.

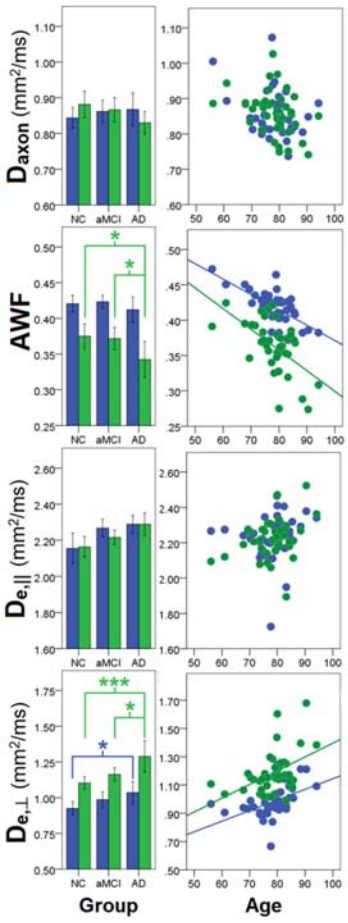

Figure 2. WMTI metrics of **EM (blue)** & **LM (green)** tracts, by group and age.

RESULTS: The results are summarized in Figure 2. There was an interaction effect for AWF $F(2, 37)=3.89$, $p<0.05$, $\eta^2=0.17$; AWF in EM tracts did not differ across the groups, but AWF in LM 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 LM tracts was significantly lower than in EM 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 EM tracts was higher in AD than NC, but $D_{e,\perp}$ in LM 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. There was an interaction effect for D_{axon} $F(2, 37)=3.79$, $p<0.05$, $\eta^2=0.17$, but no main effects. The model was not significant for $D_{e,\parallel}$. Lower AWF and higher $D_{e,\perp}$ were associated with increasing age. There was a moderate partial correlation between $D_{e,\perp}$ in LM tracts and verbal fluency $r(38)=-0.47$, $p<0.01$ (Bonferroni-corrected); no other sig. correlations were observed.

DISCUSSION: Our results show that (1) axonal density (i.e. AWF) declines in LM tracts in the course of AD, but remains stable in EM tracts, (2) myelin breakdown (i.e. $D_{e,\perp}$) in LM tracts worsens in the course of AD, as well as in EM tracts but not until later stages of disease, (3) AWF and $D_{e,\perp}$ were most associated with age, and (4) increased $D_{e,\perp}$ in LM tracts was correlated with fewer words produced on a verbal fluency test. *Conclusion:* These results using WMTI metrics parallel findings in DTI-based studies, but specify the WM microstructural changes that occur in the course of AD, as well as demonstrate their functional relevance. Our results highlight the importance of WM changes in addition to gray matter pathology in the study of AD. Future work with larger samples should verify these findings using a longitudinal design.

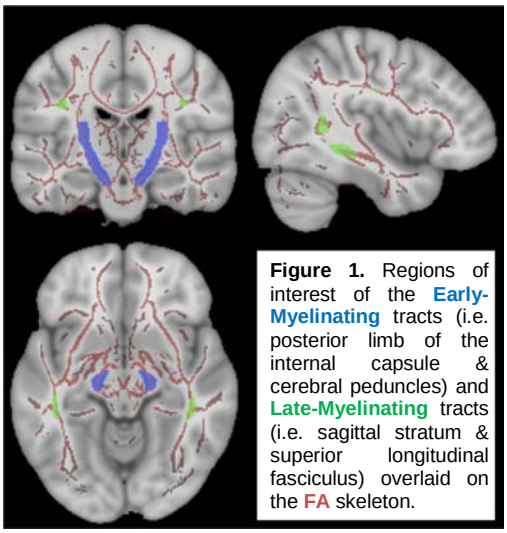

Figure 1. Regions of interest of the **Early-Myelinating** tracts (i.e. posterior limb of the internal capsule & cerebral peduncles) and **Late-Myelinating** tracts (i.e. sagittal stratum & superior longitudinal fasciculus) overlaid on the **FA** skeleton.

REFERENCES: [1]Fieremans E et al. White matter characterization with diffusional kurtosis imaging. *NeuroImage.* 2011;58:177-188. [2]Bartzokis G. Age-related myelin breakdown: A developmental model of cognitive decline and Alzheimer's disease. *Neurobiol Aging.* 2004;25:5-18. [3]Brickman AM et al. Testing the white matter retrogenesis hypothesis of cognitive aging. *Neurobiol Aging*. 2012;33:1699-1715.