Assessment of White Matter Integrity in Mild Cognitive Impairment and Alzheimer's Disease

Els Fieremans[1], Jens H Jensen[1,2], Rachael L Deardorff[2], Amanda Allen[2], Jane Kwon[1], Ali Tabesh[2], Maria F Falangola[2], Steven H Ferris[1], and Joseph A Helpern[2]
[1]*Center for Biomedical Imaging, Radiology, New York University School of Medicine, New York, NY, United States,* [2]*Radiology and Radiological Science, Medical University of South Carolina, Charleston, SC, United States*

INTRODUCTION: Along with well-characterized cortical abnormalities, white matter (WM) microstructural changes such as axonal loss and demyelination have been demonstrated in postmortem studies of Alzheimer's Disease (AD)[1]. Diffusion MRI is a powerful tool to study WM integrity that is sensitive to microstructural loss preceding atrophy[2]. Diffusional kurtosis imaging (DKI) is a clinically feasible extension of diffusion tensor imaging (DTI) that quantifies non-Gaussian diffusion properties[3]. Recently, a simple WM model was introduced[4] that allows for a more detailed physical interpretation of the DKI metrics in terms of the characteristics of the WM microstructural integrity, such as the axonal water fraction, the intra-axonal diffusivity D_{axon}, and the extra-axonal axial and radial diffusivities, $D_{e,\parallel}$ and $D_{e,\perp}$[5]. As they are potentially more specific to the underlying disease processes, we report here our initial findings investigating changes in these WM parameters in subjects with mild cognitive impairment (MCI), AD patients, and age-matched healthy normal controls (NC).

METHODS: A group of forty-three subjects was recruited from the NYU AD Center consisting of patients diagnosed with probable AD (n=14; 7 male; mean age 78±3; global deterioration scale (GDS) 4.2±0.4; mini-mental state exam (MMSE) = 22±3; education level 15±3), subjects with MCI (n = 15; 6 male; mean age 79±9; GDS 3±0.3; MMSE = 27±7; education level 15±3) and NC (n = 14; 5 male; mean age 78±3; GDS 2±0; MMSE = 29±1; education level 16±3). MR experiments were conducted on a 3T Trio MR system (Siemens). DKI acquisition was performed with 3 b-values (0, 1000 and 2000 s/mm^2) along 30 diffusion encoding directions using single-shot twice-refocused-EPI. Other imaging parameters were: TR = 5900 ms, TE = 96 ms, averages = 2, FOV = 222×222 mm^2, matrix size = 82×82, parallel imaging factor of 2, slice thickness = 2.7 mm, 45 oblique axial slices.

DKI post-processing[6] provided parametric maps of the standard DTI metrics of mean diffusivity (MD), axial diffusivity $D_{\parallel}$, radial diffusivity $D_{\perp}$, and fractional anisotropy (FA), as well as the additional DKI metrics of mean kurtosis (MK), axial kurtosis $K_{\parallel}$, and radial kurtosis $K_{\perp}$. The DKI maps were then used to derive WM parametric maps[5] for the D_{axon}, $D_{e,\parallel}$, $D_{e,\perp}$, and AWF. The fractional anisotropy (FA) maps were non-linearly registered to the MNI FA-template[6], and all parametric maps were transformed into a standard space according to this registration using FSL[7]. By applying tract-based spatial statistics (TBSS), skeletonized voxel-wise analysis was performed to identify differences on the tract skeleton (based on FA > 0.3) for the DKI and WM metrics using FSL's "randomize" feature to determine areas of group differences, with correction for multiple comparisons, and age taken into account as a covariate. In addition, 40 regions of interest (ROI) were drawn based on the Johns Hopkins University WM label atlas[8] to test for group differences in each parameter.

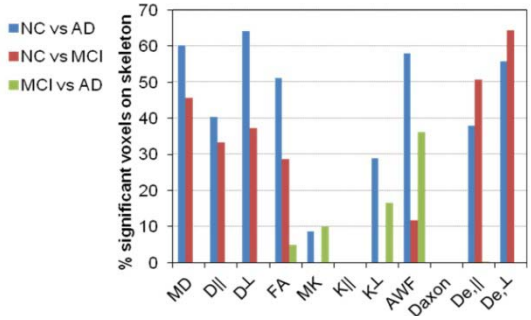

Fig. 1: Bar graph showing the sensitivity of each DKI- and WM metric using TBSS. The bars show the percentage of significantly different voxels on the skeleton for each metric and group comparison (NC vs MCI; MCI vs AD; NC vs AD).

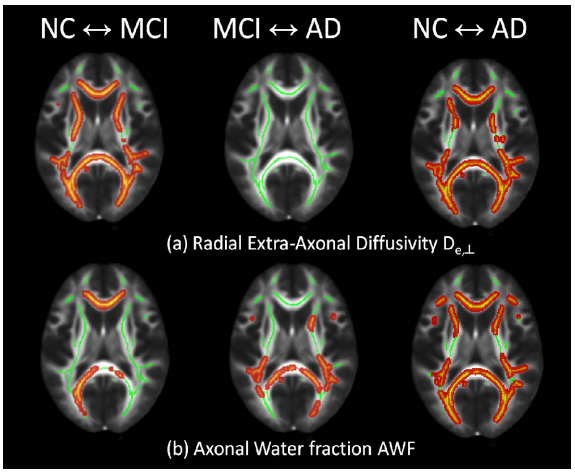

Fig. 2: TBSS results showing group differences between NC and MCI (left), MCI and AD (center) and NC and AD (right), for (a) radial $D_{e,\perp}$, and (b) AWF. Clusters of significant different voxels ($p < .05$) are shown in red-orange and overlaid on the FMRIB FA template, together with the mean skeleton (green). Clusters of increased $D_{e,\perp}$ were found for NC vs. MCI and NC vs. AD, while decreased AWF-clusters were found in all group comparisons.

RESULTS: As depicted in Fig. 1, all DTI metrics, as well as the AWF, $D_{e,\parallel}$ and $D_{e,\perp}$ show significant differences between NC and MCI, whereas the FA, MK, $K_{\perp}$ and AWF detect differences between MCI and AD. All metrics, except $K_{\parallel}$ and D_{axon}, are significantly different between NC and AD. Overall, the highest sensitivities are provided by $D_{e,\perp}$ (64%) in discriminating MCI from NC, and the AWF (36%) in discriminating AD from MCI. The ROI-analysis yielded similar results (not shown). Figure 2 shows the TBSS results of those WM metrics for the three group comparisons. Widespread lateral changes are observed in many WM tracts, particularly in the corpus callosum, forceps major, internal capsule, corona radiata, superior longitudinal and uncinate fasciculus. Figure 3 plots the $D_{e,\perp}$-values of the FA-skeleton in NC and MCI subjects vs. age, highlighting the ability of this parameter to separate these two groups (the regression lines assumed a single slope for both groups).

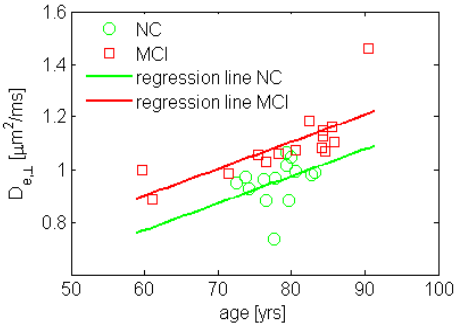

Fig. 3: The radial extra-axonal diffusivity $D_{e,\perp}$ vs. age. Average values over all skeleton voxels are shown for the NC (green circles) and MCI (red squares) subjects.

DISCUSSION: Our study indicates that the newly proposed measures of WM integrity, as derived from DKI, may be useful as early biomarkers for the AD pathology progression that provide complementary information relative to the standard DTI metrics. The observed increase in $D_{e,\perp}$ suggests pronounced demyelination during the conversion from NC to MCI, while the decrease in AWF from MCI to AD is consistent with axonal loss. Further study will focus on specific anatomic time courses of changes in axonal and myelin density and its relation with cerebral atrophy.

REFERENCES: **1** Brun A & Englund EA. *Ann. Neurol.* 19, 253 (1986); **2** Bozzali M et al. *Neurol.* 57, 1135 (2001); **3** Jensen JH et al. *MRM.* 53, 1432 (2005); **4** Fieremans E *et al. NMR Biomed.* 23 711 (2010); **5** Fieremans E et al. *Neuroimage* 58, 177 (2011); **6** Tabesh A et al. *MRM.* 65, 823 (2011); **7** Smith SM et al. *Neuroimage* 31, 1487 (2006); **8** Mori S *et al. MRI atlas of human white matter*. (Elsevier, 2005).

Grant funding: Alzheimer's Drug Discovery Foundation, Litwin Foundation for Alzheimer's Research, and NIH/NIA grant R01AG027852.