Assessment of White Matter Integrity in Mild Cognitive Impairment and Alzheimer’s Disease
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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 atrophy2. Diffusional kurtosis imaging (DKI) is a clinically feasible extension of diffusion tensor imaging (DTI) that quantifies non-Gaussian diffusion properties3. Recently, a simple WM model was introduced4 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 $D_{\text{axon}}$ and the extra-axonal axial and radial diffusivities, $D_{\text{ax}}$ and $D_{\text{rad}}$. As they are potentially more specific to the underlying disease processes, we report here our initial investigations investigating 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/mm²) 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 mm², matrix size = 82×82, parallel imaging factor of 2, slice thickness = 2.7 mm, 45 oblique axial slices.

DKI post-processing provided parametric maps of the standard DTI metrics of mean diffusivity (MD), axial diffusivity $D_a$, radial diffusivity $D_r$, and fractional anisotropy (FA), as well as the additional DKI metrics of mean kurtosis (MK), axial kurtosis $K_{\text{ax}}$ and radial kurtosis $K_{\text{rad}}$. The DKI maps were then used to derive WM parametric maps for the $D_{\text{axon}}$, $D_{\text{ax}}$, $D_{\text{rad}}$, and AWF. The fractional anisotropy (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. 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 to test for group differences in each parameter.

RESULTS: As depicted in Fig. 1, all DTI metrics, as well as the AWF, $D_{\text{ax}}$ and $D_{\text{rad}}$ show significant differences between NC and MCI, whereas the FA, MK, $K_{\text{ax}}$ and AWF detect differences between MCI and AD. All metrics, except $K_{\text{ax}}$ and $D_{\text{axon}}$, are significantly different between NC and AD. Overall, the highest sensitivities are provided by $D_{\text{ax}}$ (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 $D_{\text{ax}}$-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).

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 $D_{\text{ax}}$ 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.


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