Free water elimination DTI in preclinical Alzheimer's: evidence for early axonal degeneration

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Target Audience: Clinicians and researchers who study aging and Alzheimer's disease.

Purpose: Alzheimer's disease is a devastating neurodegenerative condition that involves significant accumulation of beta-amyloid plaques, phosphorylation of tau protein leading to development of neurofibrillary tangles, and loss of neuronal connectivity. This latter pathology is evidenced by significant alterations to myelinated axons in Alzheimer's disease. Given its high sensitivity to barriers in white matter, diffusion imaging has proven to be a useful technique for measuring some of the earliest changes that occur in the disease. However, traditional models of diffusion are known to be susceptible to partial volume effects. In this work we utilized the free water elimination (FWE) DTI model which corrects for partial volume effects with CSF, and may also be sensitive to changes in the extracellular space. The model is described by $S_i = S_0[(1-f)\exp(-b_i g_i^T D g_i) + f exp(-bD_{iso})]$ (1), where S_i and S_0 are the signal from the i-th diffusion and non-diffusion weighted measurements, respectively, f is the free water fraction, D_{iso} is the diffusivity of free water ($3x10^{-3}$ mm^2/s), $\boldsymbol{D}$ is the tissue diffusion tensor, b_i and g_i are the diffusion-weighting amplitude (in s/mm^2) and unit gradient encoding vector, respectively. In order to test the utility of this model, we scanned participants from the Wisconsin Registry for Alzheimer's Prevention, a cohort enriched for risk factors for Alzheimer's. All participants underwent lumbar puncture, allowing us to test the extent to which participants who show early signs of pathology as indicated by cerebrospinal fluid measures, show altered white matter as indicated by the FWE DTI model.

Methods: A cohort of 71 cognitively healthy adults (20 males and 51 females, age: 61.3 ± 6.2 yrs) underwent both lumbar puncture and diffusion imaging at 3T using an 8-channel receive-only head coil. In order to fit the FWE model without spatial constraints, multiple nonzero b-values were acquired (2): (number of images x b-value s/mm^2): 7 x 0, 6 x 300, 21 x 1200, and 24 x 2700 s/mm^2. Other pertinent parameters are: TR = 6500 ms, TE = 102 ms, slice orientation: sagittal, slice thickness = 3 mm, and in-plane resolution = 2.5 mm x 2.5 mm. CSF biomarkers of interest were total Tau, phosphorylated Tau (pTau181), neurofilament light chain protein (NFL), monocyte chemoattractant protein-1, soluble amyloid precursor protein alpha and beta, Chitinase-3-like protein, and β-amyloid-42.

The FWE DTI model was fit in each subject's native space. A subject specific template was then created using DTI-TK as a means to leverage the full tensor information for optimal normalization. Regions of interest (ROI) were drawn in the template space and subsequently warped back to the native spaces to use as seed point for deterministic tractography. The reconstructed tracts were the fornix, cingulum bundles, and the corpus callosum, which was further subdivided into five separate regions. These tracts were used to define ROIs that were subject specific and tract specific. The mean value of fractional anisotropy, mean diffusivity, and *f*-value were extracted for each ROI for statistical analysis. Analysis was carried out by fitting a generalized linear model in SPSS, treating the diffusion metrics as dependent variables and the CSF biomarkers as predictors, along with age and sex as covariates. In this way the effect of each biomarker was analyzed separately on each of the seven tracts and three metrics. As a means of controlling for multiple comparisons, a false discovery rate threshold of $p \leq 0$ .05 was utilized.

In addition to the tractography analysis, a voxel based analysis (VBA) was performed across a whole brain white matter. This analysis utilized nonparametric permutation testing using the randomize function in FSL (3). Prior to the VBA, all metric maps were smoothed with a 4mm full width half max Gaussian smoothing kernel. As with the tractography analysis, the effect of age and sex was controlled and we tested the main effect of each biomarker on the three diffusion metrics of interest. For each permutation test, 25,000 permutations were carried out. Multiple comparisons were accounted for through the use of a family wise error threshold of $p \leq 0$ .05. Minimum cluster size was 20 contiguous voxels.

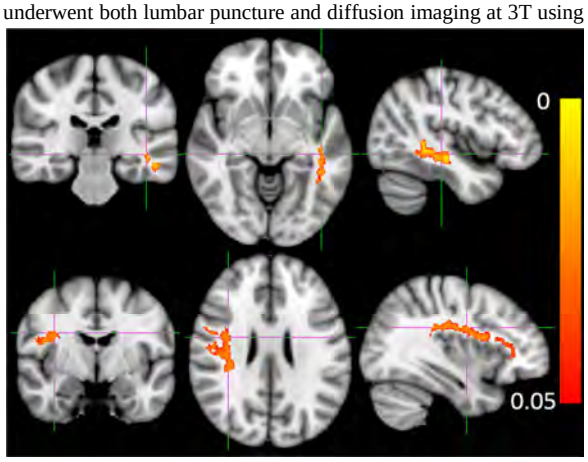

Fig 1: Single cluster examples of significant clusters where increased *f*-value correlates with an increase of pTau181 (top) or NFL (bottom) in CSF samples, respectively. There were l4 separate clusters covering more than 9082 mm^3 for which *f*-value was correlated with pTau. For NFL there were 18 clusters totaling 13456 mm^3.

Results: Tractography analysis yielded relationships in nine tracts with an uncorrected p-value less than 0.05. However, no results survived multiple comparison correction. The VBA yielded several clusters which maintained significance after family- wise error correction. The only diffusion metric which showed a correlation with any of the biomarkers was the *f*-value. Of note, there was a robust positive correlation between pTau181 and *f*-value in left temporal lobe white matter. Interestingly, NFL, a marker of axonal degeneration was positively correlated with *f*-value throughout the brain including a large swathe of short association fibers in the right inferior frontal white matter (see Fig. 1). All correlations were positive (e.g. see plot in Fig. 2). While widespread effects were found in the VBA, none of the cluster overlapped significantly with tracts studied with tractography.

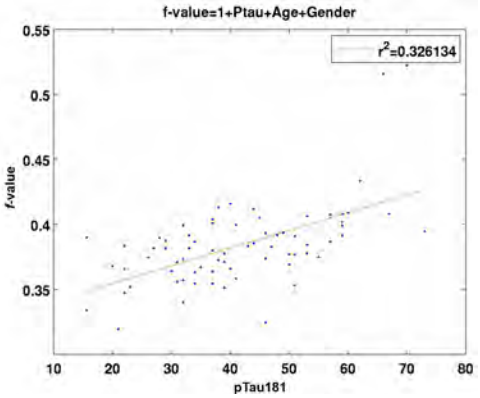

Fig 2: Scatter plot of *f*-value vs. pTau181 from the temporal lobe cluster in Fig. 1.

Discussion and Conclusions: This is the first study demonstrating an association between CSF markers pTau181 and NFL, and white matter microstructure using the FWE model in an asymptomatic population at increased risk for AD. Affected regions included temporal lobe and inferior frontal white matter. The temporal lobe has been previously linked with AD-associated neurodegeneration (4). Given that tau and NFL are components of the axonal cytoskeleton our results suggest that *f*-value may be sensitive to early axonal degeneration. Given the need for sensitive markers of pathology, our results suggest that diffusion imaging with FWE may hold promise for early disease detection, in addition to providing a novel outcome measure for prevention and treatment trials.

Reference: 1. Pierpaoli C, Jones DK. ISMRM Vol. c. ; 2004. p. 1215. 2. Hoy AR, et al. Neuroimage. 2014;103:323–333. 3. Winkler AM, et al. Neuroimage 2014;92:381–97. 4. Bendlin BB, et al. PLoS One 2012;7:e37720.