Comparison of White Matter Integrity between Alzheimer's Disease Patients with and without White Matter Lesions Analyzed by Tract-Based Spatial Statistics

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Purpose: Diffusion tensor imaging (DTI) can measure the directionality of water diffusion in vivo. The neural tracts in the brain have a high degree of spatial organization, which causes water to diffuse more rapidly in the direction aligned with the internal fibrous structures. In such voxels, fractional anisotropy (FA) is a measure of the degree of anisotropy, whereas mean diffusivity (MD) is the measure of the total diffusion, and both are sensitive for detecting microstructural changes in white matter. Tract-based-spatial-statistics (TBSS) is a robust method for comparing diffusivity maps between different groups of subjects. One factor that is known to be associated with changes in white matter is the presence of white matter lesions (WML), which represent microvascular ischemic changes that are often indicative of tissue dysfunction. As DTI is sensitive to microstructural changes, it is possible that the presence of WML may change the integrity of the white matter tracts and alter the FA and MD values. Most published studies have analyzed subjects without excluding those with white matter lesions. The purpose of this study was to compare the FA and MD maps between a group of AD subjects with WML and a group of AD subjects without WML.

Methods: Eighteen AD subjects (N=18, 10 female, 8 male, mean age ± stdev 75±5.1) containing no obvious white matter lesions, dementia-inducing structural abnormalities, or concurrent conditions that might interfere with cognitive function were selected from a total of 243 subjects by two neuroradiologists. These were matched with 18 AD subjects (12 female 6 male, mean age±stdev 74.8±9.3) containing significant WM lesions as detected on T2-weighted FLAIR images. All preprocessing and statistical analyses were performed with the FSL software package from Oxford's Analysis Group [1]. TBSS analysis was performed on the FA and MD maps of the 36 total subjects, and the skeletonized maps were compared in a voxel-wise fashion between the two AD groups using a permutation test with threshold-free cluster enhancement. All tests were considered significant at $p<0.01$.

Results: Significant differences were found in FA values in the body of corpus callosum in the left hemisphere. There were also significant FA differences found in the putamen, and in the general region of the anterior corona radiata corresponding to the anterior thalamic radiation and inferior fronto-occipital fasciculus (figure 1). In all these areas, the FA values of the AD group containing white matter lesions were markedly lower than those of the group containing no lesions with a significance of $p<0.01$ or better. In terms of MD values, however, comparisons between the two groups revealed no significant differences at the significance threshold.

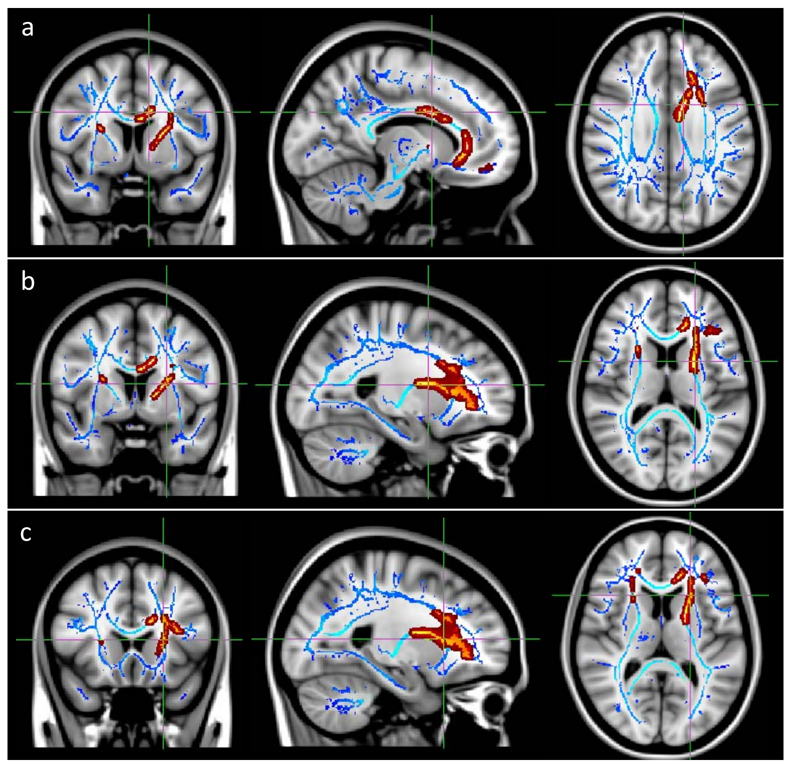

Figure 1. White matter tracts where FA values of AD subjects containing white matter lesions (WML) are lower than those of AD subjects containing no WML. The respective coronal, sagittal, and axial views on an averaged T1-weighted brain from 152 subjects provided by the Montreal Neurological Institute are depicted here. The significant areas projected onto the group mean FA skeleton correspond to the (a) corpus callosum *p<0.01*, (b) putamen *p<0.01*, and (c) anterior corona radiata *p<0.01.*

Discussion: Our comparison of FA and MD maps between one AD group containing no white matter lesions and one age-matched AD group containing white matter lesions revealed significant differences in FA maps. The white matter tracts showing significant differences are located in the limbic system and parietal lobes. The anterior cingulate gyrus and the inferior fronto-occipital fasciculus of the anterior corona radiata, which has been implicated to be involved with higher-order aspects of motor behavior and the spatial aspects of attention, were identified in these group-wise comparisons. These two groups share the same clinical AD diagnoses with matched demographic characteristics; therefore, the findings suggest that the presence of WML may affect DTI measurements, particularly in terms of FA values, possibly through the alteration of local environmental microstructure. Interestingly, there were no significant differences in the MD maps, suggesting that the presence of WML alters the packing of fiber bundles rather than cellular matrix integrity. As other studies have also associated WML with altered diffusivity measurements, this finding suggests that interpretation of DTI study results should consider taking into account the presence of WML.

Reference: [1] S.M. Smith, et.al. NeuroImage, 23(S1):208-219, 2004.