White Matter Lesion Effect on Tract-Based Spatial Statistics for Alzheimer's Patients and Healthy Controls

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Purpose:

Diffusion tensor imaging can measure the directionality of water diffusion in vivo, and as 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 internal fibrous structures, both fractional anisotropy (FA) – the measure of the degree of anisotropic diffusion – and mean diffusivity (MD) – the measure of total diffusion – are sensitive for detecting microstructural changes in white matter. 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 have an effect on FA and MD values. Most published studies have analyzed subjects without excluding those with white matter lesions. Using tract-based-spatial-statistics, a robust method for comparing diffusivity maps between different groups of subjects, we compared the FA values in a pair-wise fashion among four groups of subjects: Alzheimer's (AD) subjects with WML, AD subjects without WML, normal control (NC) subjects with WML, and NC subjects without WML.

Methods:

A total of 60 subjects were studied in this investigation. 17 AD subjects and 11 NC subjects 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 16 AD subjects and 16 NC subjects containing significant WM lesions as detected on T2-weighted FLAIR images. Diffusion tensor imaging (DTI) was performed on a Siemens 3T MRI scanner by using a spin-echo single-shot EPI sequence and 64 encoding directions. The subsequent processing and statistical analysis of the acquired DTI images were performed with the FSL software package from Oxford's Analysis Group [1]. TBSS analysis was performed on the FA maps of the 60 total subjects, and the skeletonized maps were compared in a voxel-wise fashion between the four groups using a permutation test with threshold-free cluster enhancement. All tests were considered significant at $p<0.05$ after being fully corrected for multiple comparisons across space.

Results:

The following six paired analyses were used to assess voxel-wise FA differences among the four groups: AD subjects with WML vs AD subjects without WML, AD subjects with WML vs NC subjects without WML, AD subjects with WML vs NC subjects with WML, AD subjects without WML vs NC subjects without WML, AD subjects without WML vs NC subjects with WML, and finally NC subjects with WML vs NC subjects without WML. In these six paired analyses, only AD subjects without WML were found to have significantly decreased FA when compared to NC subjects with WML and NC subjects without WML. These significant decreases in FA corresponded to white matter tracts including the inferior longitudinal fasciculus, the inferior fronto-occipital fasciculus, and the anterior cingulate gyrus (**Figure 1**). All other paired analyses revealed no significant differences at the significance threshold.

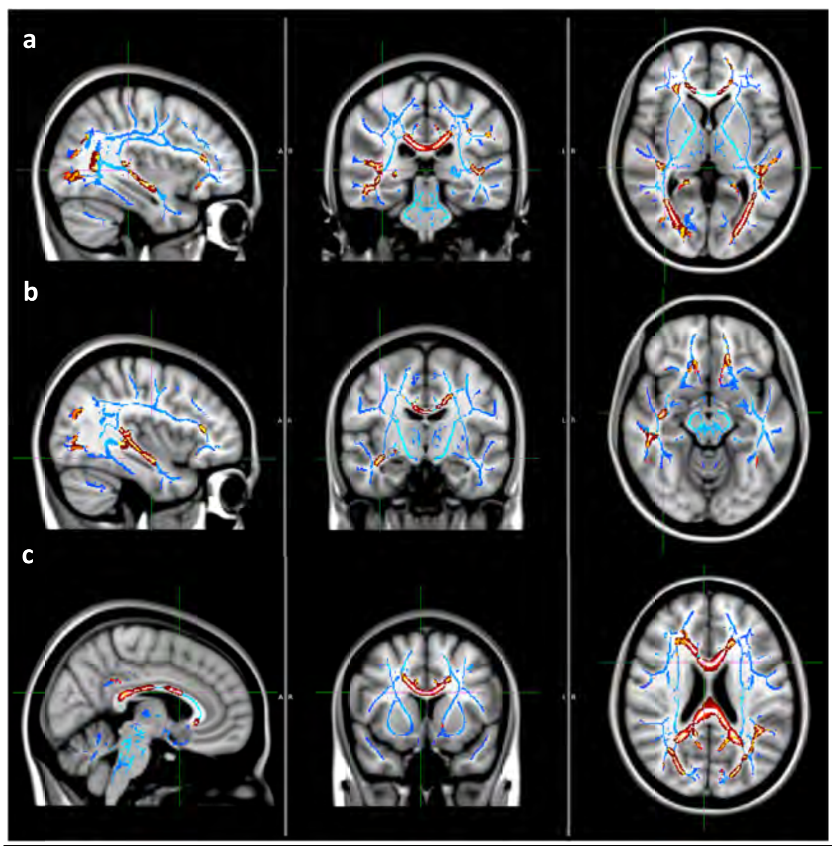

Figure 1. White matter tracts where FA values of AD subjects with no WML are lower than those of NC subjects with no WML. The respective coronal, sagittal, and axial views on an averaged T1-weighted brain from 152 subjects provided by the Montreal Neurological Institute are depicted here. The significant areas projected onto the group mean FA skeleton correspond to the (a) inferior longitudinal fasciculus, (b) inferior front-occipital fasciculus, and (c) anterior cingulate gyrus.

Conclusions:

Our comparison of FA maps between these four groups revealed significant differences in FA maps corresponding to white matter tracts associated with motor and memory function that have been strongly supported by literature to be involved with cognitive function. The inferior fronto-occipital fasciculus has been reported to be involved with high-order elements of motor behavior and attention, and the inferior longitudinal fasciculus has been implicated to be involved with cognitive impairment. Interestingly, none of the AD subjects with WML had significant differences in FA when compared to either group of normal controls, which may be reflective of the small sample size of this study. A limitation of this study is that individuals within the WML groups have a heterogeneous distribution of WML across the brain that may not be consistent from subject to subject. Further investigation into the effect of WML burden on TBSS analysis would be to further subcategorize the WML groups based on the anatomical location of white matter lesions.

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