White Matter Integrity Analyzed by Tract-Based Spatial Statistics in Elderly Subjects Without White Matter Lesions

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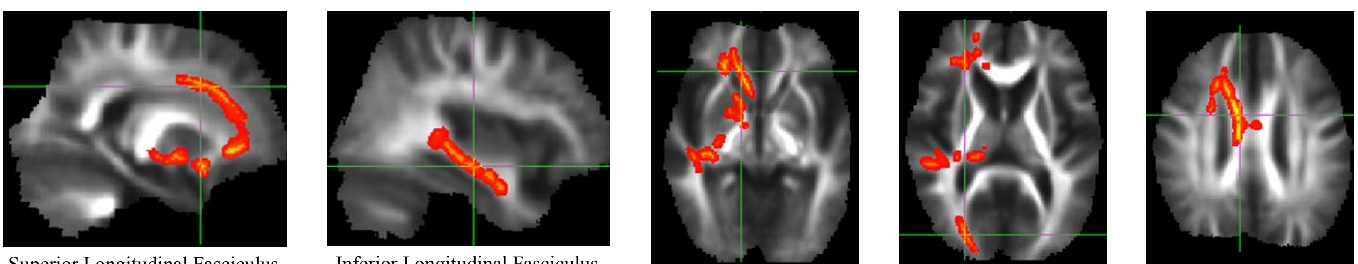
Purpose: Diffusion tensor imaging (DTI) can measure the directionality of diffusion of water *in vivo*. The neural tracts in the brain consist of spatially-organized axons encased in myelin sheaths that largely restrict water diffusion to along the axon, and fractional anisotropy (FA) is a sensitive parameter to measure the integrity of myelin. The other parameter, mean diffusivity (MD), measures the range of diffusion in all directions. The differences of FA and MD values between patients with Alzheimer's disease (AD), mild cognitive impairment (MCI), and normal age-matched elderly were commonly analyzed using ROI-based approaches. Voxel-based-morphology can be applied to compare the differences in the whole brain, but it is not suitable for analyzing the DTI data. Tract-based-spatial-statistics (TBSS) is a more robust method to compare the FA maps between different subject groups. One factor that is known to be associated with changes in white matter is the presence of white matter lesions. As DTI is extremely sensitive to microstructural changes, it is possible that such WM lesions may have an effect on FA and MD values. Most published studies analyzed subjects without excluding ones with white matter lesions. The purpose of this study was to compare the FA and MD between AD, MCI, and normal control (NC) subjects who have no obvious WM lesions.

Methods: A total of 60 subjects without 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. The subjects were scanned with a Siemens 3T MRI scanner. The DTI was acquired with a spin-echo single-shot EPI sequence with 64 encoding directions. The demographic characteristics were matched among the 3 groups. The AD subjects (n=19; 12 female, 7 male) had a mean age ± stdev of 75.3±5; the MCI subjects (n=18; 9 female, 9 male) had a mean age of 73.2±3.7; and the NC subjects (n=23; 16 female, 7 male) had a mean age of 73.6±5.9. All preprocessing and statistical analysis were performed with the FSL software package from Oxford's Analysis Group [1]. The scans were first eddy-current corrected and the brain extracted from the skull using an icosahedron triangular tessellation method. The FA maps from 60 brains were analyzed using TBSS. The software applies nonlinear spatial transformations to transform the FA map of each individual subject to a stereotactic space. A mean FA map is created and then thinned to create an FA skeleton, which represents the centers of all tracts common to the group. In the final step, spatially normalized FA maps from each subject were projected onto this skeleton, creating an FA skeleton for each subject. Once the skeletonized FA maps were obtained, group differences were investigated. The FA and MD values were compared in a voxel-wise fashion among all three groups. Statistical analysis was performed using a randomization permutation test based on general linear modeling.

Results: No significant differences were found in white matter tracts for any of the MD comparisons or when AD was compared with MCI and MCI was compared with NC. When AD subjects were compared to NC subjects, significant differences in FA value were detected in the neural tracts of the corpus callosum body, particularly in its radiations of the forceps major and forceps minor, which are categorically anterior and posterior cingulate fibers, respectively (Fig.1). There were also significant FA differences in the inferior and superior longitudinal fasciculus, which serve as connections between the occipital-parietal and temporal-frontal regions of the brain. In all these areas, the FA values of AD subjects were found to be less than those of NC subjects with a significance of $p<0.02$.



Superior Longitudinal Fasciculus *p<0.01* | Inferior Longitudinal Fasciculus *p<0.02* | Forceps Minor (Genu of CC) *p<0.01* | Forceps Major (Splenium of CC) *p<0.02* | Body of Corpus Callosum *p<0.01*

Figure 1. White matter tracts where FA values of AD are less than those of NC, projected onto the mean FA image of the study.

Conclusions: White matter lesions were commonly found in the elderly, and in this study we only identified 60 subjects without visible white matter lesions from a total of 243. We compared the group differences in FA maps of AD, MCI, and NC subjects. Our results between AD and NC were consistent with published reports. The FA decreases in the neural tract radiations of the corpus callosum, particularly in the posterior cingulate fibers; in the inferior longitudinal fasciculus, which serves as an occipital-temporal connection; and in the superior longitudinal fasciculus, which serves to connect the frontal, temporal, parietal, and occipital lobes. We did not find significant differences between AD and MCI, or between MCI and NC. In the same cohort we also performed ROI-based analysis. A small ROI was manually placed within the white matter of various brain regions and the MD and FA values were measured from the ROI. We did find that the FA in the parietal lobe WM showed significant differences between MCI and NC; and the FA in the parietal, temporal, and frontal lobe WM showed significant differences between AD and MCI. However, these findings were not shown in TBSS analysis. The results may suggest that although TBSS uses WM tract skeleton for spatial normalization, which is considered as an improvement than using the image template, the difference in small areas may be lost. The ROI based analysis uses native image, and may be more sensitive to detect them; however, it is time consuming and not suitable for analyzing differences in the whole brain. More research is needed to improve the group comparison analysis for DTI.

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