# Evaluation of the Impact of White Matter Lesion on the Fractional Anisotropy Maps in Alzheimer's Disease Patients and Normal Healthy Controls

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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. 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 taking into account of the presence white matter lesions. As white matter lesions are commonly seen in the elderly, it is difficult to find a clean group of subjects without white matter lesion. We have enrolled a relatively large cohort of Alzheimer's Disease (AD) patients into our research program, and have identified a group of AD and normal control (NC) subjects without white matter lesion to evaluate their differences in FA and MD values using ROI-based analysis [1]. In the present work, we have further identified a group of AD subjects with severe presentation of white matter lesions and compared the FA maps between AD subjects with and without WML, and a group of NC subjects without WML. The purpose is to evaluate the effects of WML on the integrity of white matter tract in AD and NC subjects.

**Methods:** Sixteen AD subjects (N=16) containing no obvious white matter lesions, dementia-inducing structural abnormalities, or concurrent conditions that might interfere with cognitive function were selected from our longitudinal cohort. The presence of WML was evaluated by two neuroradiologists on FLAIR images, by using the Age-Related White Matter Changes (ARWMC) rating scale of the European Task Force [2]. Five brain regions (frontal, parieto-occipital, temporal, the infratentorial area and the basal ganglia) were rated with four-point rating: 0-no lesion, 1-focal lesion, 2-beginning confluence of lesions, 3-diffuse involvement of the entire region, with or without involvement of U fibers. Subjects with visibly significant WM lesions rating scores 2 and 3 in any part of the regions were excluded. These AD subjects were matched with another group of AD subjects (N=17) containing significant WM lesions with score of 2 in multiple region or score of 3 in any region. Eleven NC subjects without WML (N=11) and five NC subjects with WML (N=5) were selected through the same procedure. Because there was only 5 NC subjects with severe WML, the number of subjects was too small to form a group, and they were excluded in the statistical comparison. The calculation of FA maps and the motion correction, linear and non-linear registrations were performed with the FSL software package from Oxford's Analysis Group [3]. Statistical analysis was performed using SPM on the co-registered mean FA maps of the 49 total subjects, and the outcome from t-test were compared in a voxel-wise fashion between each of AD with and without WML and NC without WML groups with p=0.0001 and cluster size of 30 voxels. This threshold was set based on the results that showed significant voxel-wise differences without much noise. Also, individual tractography was performed in several AD and NC subjects for visual comparison.

**Results:** First of all, all AD subjects with and without WML were combined and compared to the NC subjects without WML (**Fig.1a**). Significant differences in FA values were found in regions corresponding to the neural tracts of the corpus callosum body in the left cerebral cortex. 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. Then, the AD subjects with and without WML were separately compared to the NC group. It can be seen that the AD subject with severe WML show smaller differences compared to NC (**Fig.1b**), while the AD subjects without WML show a more extensive difference compared to the NC (**Fig.1c**). Lastly, comparisons between the AD groups with WML and without WML revealed no significant differences, even at the significance threshold of p=0.001 (**Fig.1d**). In the group of AD subjects with WML, since the location of WML were highly variable, that might have contributed to a higher degree of heterogeneity in the integrity of white matter tracts. Therefore, instead of using group comparison, individual tractography may provide more detailed information about the impact of WML. **Figure 2** shows 2 case examples, one from AD and another from NC both without WML. It can be seen that the fiber tracts originated from the corpus callosum is denser and extends longer into cortical areas in the NC compared to the AD subject.

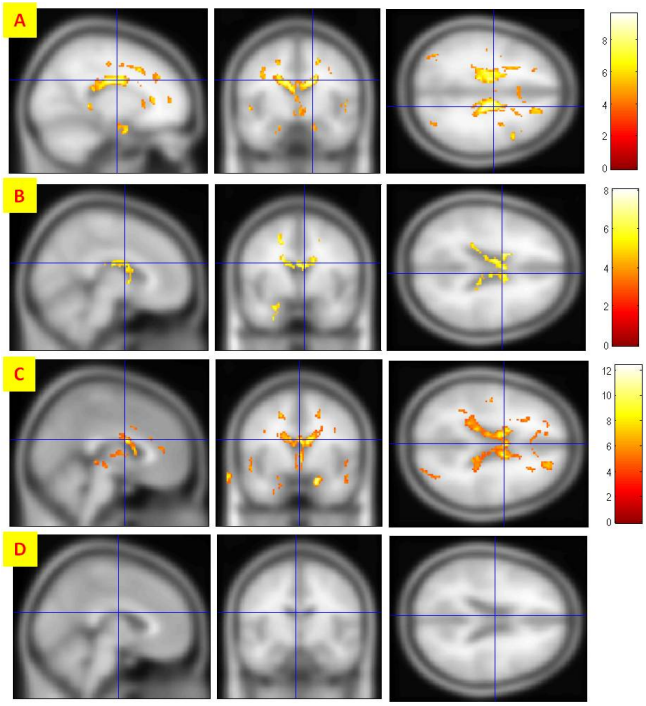


**Figure 1. Negative Z-maps resulting from t-test for each statistical analysis comparing; (A) 33 ADs with and without WML and 11 NCs without WML; (B) 17 ADs with WML and 11 NCs without WML; (C) 16 ADs without WML and 11 NCs without WML; (D) 17 ADs with WML and 16 ADs without WML. There is no significant difference even at p = 0.001.**

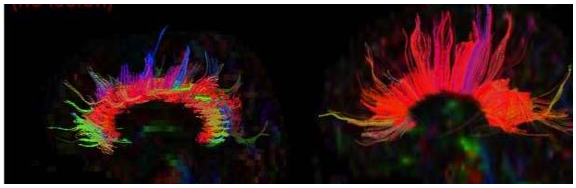

**Figure 2. Corpus Callosum White matter tracts for AD (left) and NC (right).**

**Discussion:** In the combined analysis between AD and NC, the areas showing significant differences in white matter tracts are located in the limbic 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. The findings are consistent with literature reports. We further investigated the impact of white matter lesion on the integrity of white matter tracts, by comparing the FA values between AD subjects with and without WML. We found that the difference between AD with WML and NC is smaller than the difference between AD without WML and NC. This result suggests that the AD group containing white matter lesions have more heterogeneity white matter abnormality, thus less likely to show significant differences in the areas that are known to be involved in AD compared to NC. Comparing between AD groups with and without WML, there was no significant difference. These two groups share the same clinical AD diagnoses with matched demographic characteristics; therefore, the findings suggest that the presence of WML did not significantly affect DTI measurements. Another possibility is also related to the high heterogeneity in group with WML, and less likely to show significant differences.

**References:** [1] Liao et al. Alzheimer Disease & Associated Disorders 2010, 24:317-324. [2] Wahlund et al. Stroke 2001;32:1318–1322. [3] S.M. Smith, et.al. NeuroImage, 23(S1):208-219, 2004.