

# CHARACTERIZING WHITE MATTER CONNECTIVITY IN ALZHEIMER'S DISEASE AND MILD COGNITIVE IMPAIRMENT: AUTOMATED FIBER QUANTIFICATION

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## ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative disease characterized by progressive dementia. Diffusion tensor imaging (DTI) has been used widely to delineate the white matter integrity/degeneration in AD. Automated fiber quantification (AFQ) method is a fully automated method, which can identify the major white matter fiber tracts and then evaluate the white matter properties. The main purpose of this study is to assess the white matter integrity and abnormalities in a cohort of amnesic Mild Cognitive Impairment (aMCI) and AD patients as well as normal controls (NCs). We tested the utility of diffusion tensor imaging measures along white matter tracts as features to classify the AD from NCs using support vector machine. The results showed that we have detected credible and robust potential early biomarker that may be useful for clinical application in AD.

**Key Words**— Alzheimer's disease; diffusion-weighted MRI; tract-specific analysis; white matter; support vector machine

## 1. INTRODUCTION

Alzheimer's disease (AD), one of the most common causes of dementia in the elderly patients, is a chronic neurodegenerative disorder. Amnesic mild cognitive impairment (aMCI) is a transitional state between normal old subjects and the dementia patients, presenting with prominent memory impairment and high risk for progressing to AD [1, 2].

Diffusion-weighted imaging (DWI) [3] is a non-invasive form of magnetic resonance imaging (MRI) technique based on measuring water diffusion in brain tissue at a voxel level in multiple directions. There were many different fantastic

analytical methods have been developed based on the diffusion tensor model (diffusion tensor imaging, DTI), including standard region of interest (ROI) analysis [4], voxel-based analysis, tract-based spatial statistics (TBSS) [5], TRActs Constrained by UnderLying Anatomy (TRACULA) [6], automated fiber quantification (AFQ) [7], and 3D tract-specific analysis [8], etc. Among these methods, AFQ is a fully automated method which can reliably identify 20 major white matter fiber tracts and allow further analysis of diffusion properties. Briefly, AFQ method has benefits in terms of: (1) overcoming the limitations related to manual interaction, thus is fully automatic and can be applied to large datasets; (2) measuring point-wise diffusion profiles along the tract of interest and can detect subtle changes in the white matter integrity [7, 9]. Hence, AFQ is widely used across clinical and basic science, such as in studying brain development and aging [10], schizophrenia [11], and major depressive disorder [12].

In the present study, we firstly identified 20 major white matter tracts of each subject using the AFQ method, and then the fiber points of each tract was resampled to 100 equidistant points, and finally the diffusion measurements, fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AxD) of each subject were extracted along the fiber tracts [7, 9]. After that, statistical analyses were then performed on these diffusion metrics (100 segments of each tract) to identify the specific locations of altered white matter properties in aMCI or AD in comparison to normal controls (NCs). We hypothesized that brain white matter measures presenting severe damage in AD patients would be evident in aMCI patients, but to a lesser degree; and that abnormal microstructural white matter integrity measures would be correlated with the minimal state examination (MMSE), which measured the severity of cognitive impairment. Lastly, we evaluated

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whether these microstructural white matter integrity measures could be indexed as features to classify the NC, aMCI and AD.

## 2. MATERIALS

The present study included 120 subjects (39 NCs, 34 aMCI, and 47 AD). The detailed diagnostic criteria can be found elsewhere [13-15]. Demographic, psychological and statistics related information can be found in Table I.

MRI examinations were performed at the Department of Radiology of the Chinese PLA General Hospital using a 3.0T MR (Skyra, Siemens, Germany) with a 20-channel head coil. During the examinations, the subjects were given comfortable foam padding to minimize head motion and ear plugs to reduce the scanner noise. Sagittal T1-weighted structural images were acquired for each subject using a magnetization-prepared rapid gradient (MPRAG) echo sequence with the following parameters: repetition time (TR) = 2530 ms, echo time (TE) = 3.43 ms, inversion time (TI) = 1100 ms, field of view (FOV) = 256 mm × 256 mm, acquisition matrix = 256 × 256, flip angle (FA) = 7°, and slice thickness = 1 mm with 192 continuous slices. The diffusion weighted images were acquired using EPI sequence and all acquisitions were aligned on the anterior commissure-posterior commissure plan. The diffusion gradients were applied in 64 non-collinear directions ( $b = 1000 \text{ s/mm}^2$ ) and one image was acquired with no diffusion weighting ( $b=0$ ,  $b_0$  image). The other parameters: TR = 7000 ms, TE = 91 ms, matrix = 128 × 128, FOV = 256 mm × 256 mm, FA = 90°, slice thickness = 3 mm with 45 axial slices (no gap).

TABLE I. Demographics of participants

	NC	aMCI	AD	P
Number of subjects	39	34	47	
Age(year)	68.5 ± 7.1	69.5 ± 8.8	69.7 ± 9.3	0.796
Gender(M/F)	18/21	13/21	20/27	0.792
MMSE	28.5 ± 1.4	26.6 ± 2.5 <sup>a</sup>	16.1 ± 7.3 <sup>a,b</sup>	<0.001

Note: Chi-squared tests were used for gender comparisons between groups; one-way ANOVA and *post hoc* two sample two-sided t-tests were used for age and MMSE comparisons. <sup>a</sup>Significant compared to NC. <sup>b</sup>Significant compared to aMCI.

## 3. METHODS

### 3.1. Automatic Tracts Identification

The preprocessing and global deterministic tractography was performed according to standard pipelines. For the routine DTI processing, correction of eddy currents and head motion, skull-stripped, and tensor model fitting were all performed using an open-source VISTASOFT package version 1.0 (<https://github.com/vistalab/vistasoft>). After that, several microstructural white matter integrity measures (FA, MD, RD, and AxD) were computed. Then, we identified 20 major fiber tracts of the whole brain using AFQ standard

pipeline (version 1.2) (<https://github.com/yeatmanlab/AFQ>) [7, 9]. First, whole-brain deterministic fiber tractography was estimated. The tracking starts within a white matter mask defined as voxels with  $FA > 0.3$ , then the path integration procedure traces the fiber in both directions along principal diffusion axes, and is terminated when the  $FA < 0.2$  or the minimum angle between the last path segment and next step is greater than 30°. After that, the fiber tract segmentation was performed using the waypoint region of interest procedure. Finally, fiber refinement was accomplished by comparing each candidate fiber to fiber tract probability maps. These fibers are the bilateral anterior thalamic radiation, corticospinal tract (CST), cingulum cingulate, cingulum hippocampus, inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), uncinate fasciculus, arcuate fasciculus, and forceps major and forceps minor of the corpus callosum [9]. After tract identification, each fiber in a tract was resampled to have 100 equidistant points, and then the mean values of the microstructural white matter integrity measures were extracted.

### 3.2. Statistical Analysis

Comparison of the tract profile that extracted along the entire white matter tract point by point can be used to evaluate the local alterations that associated with AD. For each identified pathway, one-way analysis of variance (ANOVA) of each point-wise diffusion measures (FA, MD, RD and AxD) was performed after regressing out age and gender effects ( $P < 0.05$ , FDR corrected). In order to verify the significant differences between each pair of groups, we performed a *post hoc* analysis by using two-sample two-sided t-test after controlling for age and gender as covariates ( $P < 0.05$ , FDR corrected).

### 3.3. Correlation Analysis

To investigate the relationship between diffusion metrics and the cognitive ability in the patients groups, we explored the Pearson's correlations between the MMSE scores and the diffusion properties that averaged over the entire length of the white matter tract at each of the major tracts in the aMCI and AD groups ( $P < 0.05$ ). Furthermore, we also picked up the points that were significantly different along the whole tract among the NC, aMCI and AD groups, and then their mean values and the correlation with the MMSE was analyzed using the same method.

### 3.4. Classification Analysis

To evaluate the multivariate performance of point-wise diffusion metrics, we used the non-linear support vector machine (SVM) classifier which was implemented in LIBSVM (<https://www.csie.ntu.edu.tw/~cjlin/libsvm/>) with a

radial basis function (RBF) kernel, and it was employed to solve binary classification problems (NC versus aMCI, NC versus AD and aMCI versus AD). We removed two fibers that did not track completely. As a result, four kinds of point-wise diffusion indicators (FA, MD, RD and AxD) were extracted, which were 7200 features (18 fibers  $\times$  100 points  $\times$  4 types) for each subject. The performance of the classifier was evaluated via leave-one-out cross-validation (LOOCV) method to consider performance generalization. The classification results were evaluated by accuracy (ACC), sensitivity (SEN) and specificity (SPE) based on the LOOCV. The diagnostic capabilities of the features were evaluated using area under the receiver operating characteristic curve (AUC) [16, 17].

## 4. RESULTS

### 4.1. Pointwise Differences in Tract Profile

Compared with the NC and aMCI subjects, AD patients had lower FA and higher MD, RD and AxD values within portions of the left and right cingulum cingulate, callosum forceps minor, left and right inferior fronto-occipital fasciculus (IFOF), right uncinate and right arcuate fasciculus (Fig 1). We also found similar alteration patterns in other white matter measures (MD, RD and AxD). Here we only provided the FA map due to space limit.

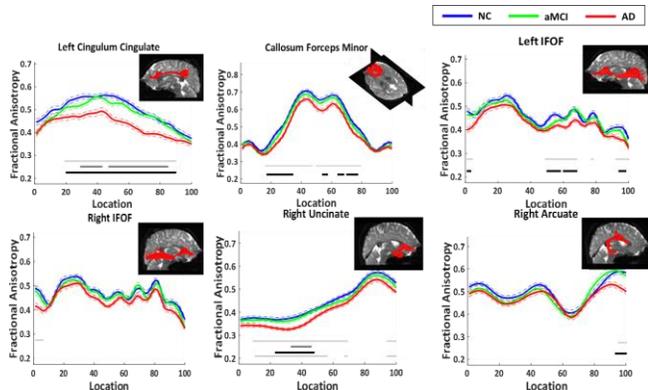


Figure 1. The line plots of FA values of 6 identified fiber tracts from NC and patient groups (blue for NC, green for aMCI, and red for AD). Each plot shows the mean $\pm$ -standard error for each group. The light grey bars under the FA indicate the regions of significant difference between NC and AD; the dark grey bars indicate the regions of significant difference between aMCI and AD; the black bars indicate the regions of significant difference between NC, aMCI and AD; The x-axis represents the location from the beginning to the termination ROI.

### 4.2. Correlation Analysis

To investigate the relationship between diffusion metrics and cognitive ability, partial correlation analysis between MMSE

and the average FA (MD, RD and AxD) value of each fiber tract was performed in aMCI and AD groups ( $P < 0.05$ ). As Figure 2 showed, there exist significant positive correlations between MMSE and the average FA of the following tracts: the left cingulum cingulate ( $r = 0.46$ ;  $P < 0.001$ ), the right cingulum cingulate ( $r = 0.42$ ;  $P < 0.001$ ). Negative correlations were also found between MMSE and the average MD of the following fiber tracts: the left IFOF ( $r = -0.28$ ;  $P = 0.011$ ), the right IFOF ( $r = -0.23$ ;  $P = 0.038$ ), callosum forceps minor ( $r = -0.33$ ;  $P = 0.003$ ) (Due to the space limit, we only present the FA and MD results for demonstration in Fig. 2).

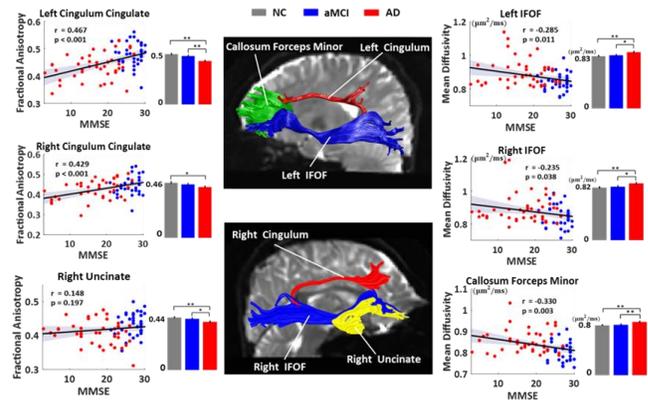


Figure 2. Scatterplots show the correlation between the average FA/MD of 6 main WM tracts and MMSE score in AD/aMCI \*  $P < 0.01$ , \*\* $P < 0.001$ .

### 4.3. Classification Results

As showed in Figure 3, the LOOCV result showed that the accuracy was 83.72% (SPE = 76.92%, SEN = 89.36%, AUC = 0.87) when we evaluated the performance of distinguishing AD from NCs. This rate would be reduced by approximately 5-10% for all metrics to classify AD from aMCI or aMCI from NC (Fig. 3).

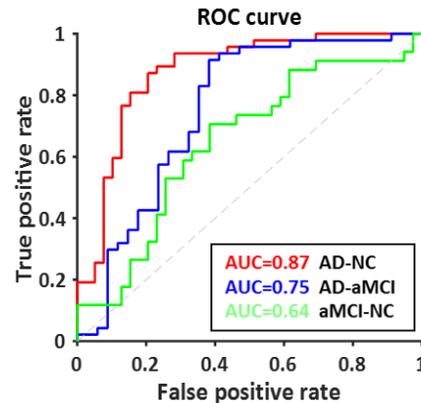


Figure 3. The ROC curve of cross-validation.

## 5. SHORT DISCUSSION

In this study, we investigated the integrity of white matter structures in AD (aMCI) patients using the AFQ method. The correlation analysis and the classification analysis suggested that the diffusion measures could be a potential biomarker for clinical application in AD.

The integrity of the cingulum fibers which connect the medial temporal lobe and the posterior cingulate cortex were reported to be compromised in the early stage of AD [18, 19]. For callosum forceps minor, which is the anterior part of the corpus callosum, connects the homologous regions of the anterior frontal lobes between two hemispheres [20, 21]. The IFOF, connects the occipital lobe and frontal lobe [22]; and were reported to be associated with emotion, object recognition, cognitive function, and visual processing [23, 24] and these daily function abilities were significantly decreased and also along with diffusion abnormalities in AD [25]. And it should be noted that the present study showed that the most severe alteration in AD is the middle and posterior parts of this fiber, which might possibly explain that the information transfer between visual cortex and frontal and temporal cortex are impaired in AD, even in the early stage of MCI [26]. It is generally known that the uncinate fasciculus connects the orbitofrontal cortex and anterior part of the temporal lobe, and plays an important role in memory and cognition [27]. And the abnormalities of the uncinate fasciculus in AD have also been confirmed by previous related studies [22, 28]. Furthermore, most of these alterations in white matter properties were significantly correlated with the cognitive abilities measured by MMSE in AD and aMCI groups. And thus again, the present study provided additional evidence for a structural basis to theories of large-scale network disconnection in AD [29-32].

These results also indicated that the diffusion measures can be used as an early predictor of future cognitive decline and progress of AD, which was confirmed by the further exploration by classification. And we admitted that better classification could potentially be achieved via parameter tuning, good feature selection steps, or other methods like deep-learning, etc. However, this might lead to the risk of over-fitting or the problem of reduced generalizability to data from an independent new scanner [17].

In summary, using the AFQ method, we identified many tracts with abnormal microstructural white matter properties in AD/aMCI. The exploratory results of AD/NC classification indicated these diffusion measures could be a potential biomarker of AD for clinical applications.

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