White matter disruption and its relationship with cognitive function and cortical atrophy in Alzheimer's disease

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Introduction

Gray matter loss is widely accepted as a biological marker of Alzheimer's disease (AD) progression. The purpose of this study is to find an effective white matter biomarker which may indicate disease severity and progression. Fractional anisotropy (FA) of diffusion tensor magnetic resonance imaging (DT-MRI) is highly sensitive to the structural changes of white matter tracts. In this study, DTI and T1 weighted images were acquired from 38 subjects (20 AD, 18 controls). To identify tracts that could be potential white matter biomarkers, we surveyed all white matter tracts by labeling of the ICBM-DTI-81 digital atlas [1] and correlated FA values of individual white matter tracts with cognitive testing score and cortical atrophy map respectively. The correlation analysis showed that the relationship of white matter tracts with cognitive function is heterogeneous and fornix is the most sensitive tract to cognitive testing scores. Correlation between FA and the cortical atrophy map revealed that disruption of limbic tracts including both the fornix and the cingulum is well correlated with gray matter loss throughout the cortex while other disrupted white matter tracts are correlated with cortical loss in more localized areas. The correlation plots of FA vs cognitive testing scores and the correlation maps of FA vs cortical atrophy may also provide valuable information for the diagnosis of AD.

Methods

Subjects and data acquisition: A total of 38 subjects (20 AD and 18 age-matched normal subjects) were recruited for this study from longitudinally followed cohorts of ADNI (Alzheimer's Disease Neuroimaging Initiative). A 3T Philips Achieva MR system was used. DTI data was acquired using a single-shot echo-planar imaging (EPI) sequence with SENSE parallel imaging scheme (reduction factor =2.3). DWI parameters were: FOV=224/224/143mm, in plane imaging matrix = 112× 112, axial slices thickness = 2.2 mm, 30 independent diffusion-weighted directions with b-value = 1000 sec/mm^2, TE=97ms, TR=7.6s. To increase signal noise ratio (SNR), two repetitions was performed. Co-registered three-dimensional magnetization-prepared rapid acquisition gradient echo (3D-MPRAGE) images were also obtained with the same FOV as that in diffusion tensor imaging. ***Correlation of FA to cognitive function:*** FA maps of 38 subjects were nonlinearly registered to the white matter digital atlas space, the ICBM-DTI-81 space. Labeling of all 50 major white matter tracts was then transferred to FA data (Details in another ISMRM abstract). These 50 major tracts were surveyed with no *a priori* information at the tract level. Total score for the CERAD Neuropsychological Battery [2] from the clinical assessment was used as the measure of cognitive function. Regression analysis was conducted with CERAD Battery score as one factor and FA values of individual white matter tracts as dependent variable. The slopes of the correlation lines were compared to rank the sensitivity of structural changes of disrupted white matter tracts to cognitive function. ***Correlation of FA to cortical atrophy:*** Z-score of RAVENS parameter [3], which reflects the regional tissue volumes in a normalized space, was calculated to characterize the cortical atrophy at each cortical voxel. FA values of each white matter tract were correlated with the cortical atrophy at all cortical voxels. Overall sensitivity of a specific white matter tract to the cortical atrophy was calculated and ranked by summing up the correlation coefficients over the cortical voxels where significant correlation occurs

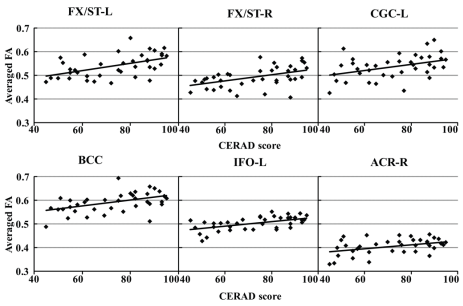
Results

Correlation between FA changes and cognitive scores: Among the 50 tracts evaluated, 6 tracts (FX/ST-L/R, CGC-L, BCC, IFO-L and ACR-R) had significantly positive correlation with CERAD scores (FDR-corrected p<0.05). Abnormality of these tracts has been reported previously [4-5]. These tracts are listed in Table 1 in the order of linear regression slope. The slopes of the regression lines indicate how sensitively the FA values of a tract change with the CERAD scores. The linear relationship between FA and CERAD score of these tracts is illustrated in Fig. 1. The slope values ranging from 0.828 to 1.548 are various for different tracts. By ordering the tracts with the regression slope, we found that FX/ST in both hemispheres is most sensitive to the changes of cognitive function. ***Correlation between FA changes of individual tracts with cortical atrophy:*** Positive correlation between FA reduction and cortical gray matter atrophy was found for all disrupted white matter tracts. Due to the limited space, among 6 tracts shown in Table 1 and Fig. 1, only significantly correlated cortical areas (FDR-corrected p<0.05) of limbic tracts are displayed in Fig. 2 where color encodes the correlation strength R. From Fig. 2, the correlation is generally stronger in the left cortex than in the right cortex for all disrupted tracts. Our correlation analysis shows that the correlation pattern is heterogeneous for different categories of white matter tracts. Limbic tracts including FX and CG had the most widely and strongest correlation with atrophied cortical areas. Other tracts, i.e. BCC, IFO-L and ACR-R, had overall less significant and weaker correlation with atrophied cortical area. They all showed strong correlation with temporal lobe atrophy.

Conclusion and discussion

In this study, we sought a white matter biomarker sensitive to the cognitive status and cortical atrophy of AD patients by surveying all white matter tracts. We found that a variable relationship to cognitive function and cortical atrophy among all tracts. Correlating the FA change of disrupted tracts with cortical atrophy revealed that FA reduction of limbic tracts had significantly positive correlation with the most widely distributed cortical regions. Both analyses indicate that fornix is most sensitive tract to AD progression. The crura of the fornix are located in the temporal lobe where abnormality in structure and function are most common in AD. We are presently examining fornix structural change in a longitudinal study of subjects with mild cognitive impairment.

Tracts	Linear regression slope	Pearson's *R* value	*p*-value
FX/ST-L	1.548	0.609	0.003
FX/ST-R	1.309	0.593	0.007
CGC-L	1.298	0.409	0.023
BCC	1.283	0.474	0.005
IFO-L	0.944	0.642	0.001
ACR-R	0.828	0.592	0.025



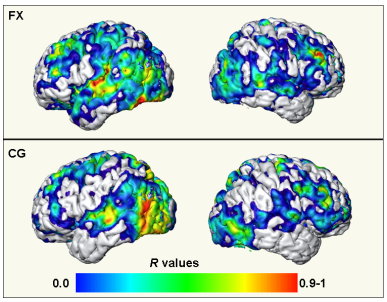


Table 1(left): Analysis results for correlation between FA and CERAD total scores, ordered with linear regression slope.
Fig. 1 (middle): The linear regression plots of six tracts whose FA values correlate significantly with CERAD scores. The horizontal and vertical axes are the CERAD score and FA value of each tract, respectively. The diamonds represent the data points of CERAD score and FA value for all 38 subjects, and the straight lines demonstrate the regression lines that fit the diamonds.
Fig. 2 (right): Coefficient maps for correlation between FA of limbic tracts and cortical atrophy at all cortical voxels. The color indicates the strength of correlation.

References: [1]. Mori, S et al (2008) NeuroImage 40: 572; [2]. Chandler, MJ et al (2005) Neurology 65: 102. [3] Davatzikos, C et al (2001) Neuroimage 14: 1361. [4]. Zhang, Y et al (2007) Neurology 68: 13. [5]. Stahl, R et al (2007) Radiology 243: 483. **Acknowledgement:** This study is sponsored by NIH/NIA P30AG12300 and NIH RR02584.