Characterizing white matter disruption in Alzheimer disease patients

X. Fan[1], K. Martin-Cook[2], M. F. Weiner[3], and H. Huang[1,4]

[1]Advanced Imaging Research Center, UT Southwestern Medical Center, Dallas, TX, United States, [2]Departmetn of Neurology, UT Southwestern Medical Center, Dallas, TX, United States, [3]Department of Psychiatry, UT Southwestern Medical Center, Dallas, TX, United States, [4]Department of Radiology, UT Southwestern Medical Center, Dallas, TX, United States

Introduction

Alzheimer disease (AD) is a highly progressive brain disease of older adults that affects as many as 5 million Americans. Although AD is generally considered to affect primarily gray matter, histological evidence has been found of white matter changes [1]. Diffusion tensor imaging (DTI) is highly sensitive to white matter structural change. DTI-derived fractional anisotropy (FA) and apparent diffusion coefficient (ADC) can be used to detect the subtle structural white matter abnormalities, as decreased FA and increased ADC are usually associated with disruption of white matter. Abnormalities of limbic system tracts, callosal tracts and projection tracts have all been reported in brains of patients with AD [e.g. 2-3]. Analysis on conventional MR images has confirmed a widespread cortical gray matter loss [e.g. 4-5]. This leads us to hypothesize that more cerebral white matter tracts are affected with AD progression. Unlike most DTI studies on AD which have focused on local white matter tracts by manually defining the regions of interest (ROI), examination of all major white matter tracts was performed. In this study, we employed a new automated protocol to quantify structural change of the white matter tracts. Voxel-based morphometry, specifically tract-based spatial statistics (TBSS) [6], was coupled with the digital white matter atlas [7] to create and test a novel index, Quantified Index of Cerebral white matter (QUIC), to characterize white matter integrity.

Methods

Data acquisition: Seven AD (age 69.5±6.6 years) and seven age-matched normal control subjects (age 68.3±5.9years) were recruited. A 3T Philips Achiva MR system was used. DTI data was acquired using a single-shot echo-planar imaging (EPI) sequence with SENSE parallel imaging scheme (SENSitivity Encoding, reduction factor =2.3). DWI parameters were: FOV=224/224/132-143mm, in plane imaging matrix = 112× 112, axial slices thickness = 2.2 mm, parallel to the anterior–posterior commissure line, 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, resulting total imaging time 13 minutes. ***Quantification of structural change of white matter tract:*** Tract-based spatial statistics (TBSS) was used to count and locate the voxels with statistically significantly lower FA or higher ADC in the template space. A white matter digital atlas was used to obtain the voxel count of a specific white matter tract and label the statistically significant voxels from TBSS analysis. The statistically significant voxels were then normalized with the total core voxel number of each tract. QUIC was calculated as follows, QUIC= voxel count of disrupted white matter/voxel count of a total tract.

Results

The voxels with statistically significantly lower FA (Fig. 1) or higher ADC (Fig. 2) were painted red. QUIC of all the tracts was then calculated and the ten largest QUIC values listed in Tables 1 and 2 were subjected to FA and ADC analysis. In Table 1, the statistically significantly decreased FA of AD patients at cingulum (CG) and corpus callosum (CC) matches previous findings [2, 3]. We found that sagittal stratum (SS), fornix (FX) and anterior corona radiata (ACR) also had decreased FA in large areas. From ADC analysis, we found that ADC values were significantly increased in corpus callosum (CC), posterior corona radiate (PCR) and anterior corona radiate (ACR) as illustrated in Fig. 2 and Table 2.

Discussion

An automated protocol to quantify structural changes of the white matter tract change was applied to all major white matter tracts. The quantification index, QUIC, successfully characterized the integrity of specific white matter tracts. While decreased FA of CG and CC was consistent with previous studies [2,3], Tables 1 and 2 showed that white matter tract disruption was not restricted to these tracts. Specifically association tract SS and projection tract ACR also have dramatic structural changes, which may be related to the disabilities of motion and language in advanced AD stage. To validate our results, data from more subjects will be added.

References: 1. Scheltens, P, et al (1995) Neurology 45: 883. 2. Zhang, Y et al (2007) Neurology 68: 13. 3. Stahl, R et al (2007) Radiology 243: 483. 4. Janke, AL, et al (2001) MRM 46: 661. 5. Thompson, PM, et al (2003) J. Neurosci. 23: 993. [6] Smith, SM et al (2006) NeroImage 31:1487. [7] Mori, S et al (2008) NeuroImage 40: 572.

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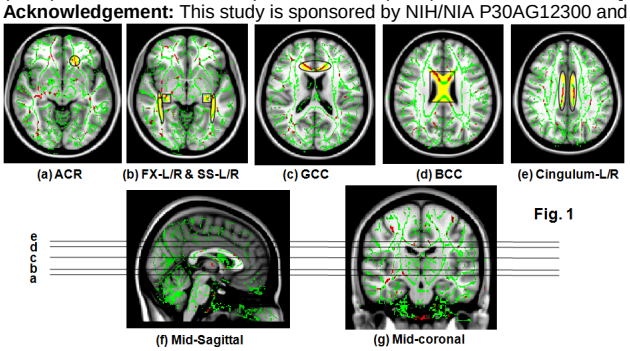

Fig. 1

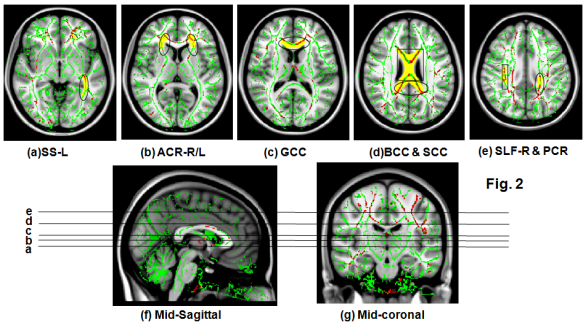

Fig. 2

Table 1: The white matter (WM) tracts with the top ten largest QUIC values from FA analysis

Tracts	WM voxel # of a tract	Disrupted WM voxel # of a tract	QUIC of FA
SS-L	332	162	0.49
CGC-R	345	145	0.42
CGC-L	134	49	0.37
CGH-L	205	74	0.36
FX/ST-R	330	101	0.31
FX/ST-L	198	59	0.30
GCC	1847	478	0.26
BCC	3000	666	0.22
SS-R	664	119	0.18
ACR-L	1152	204	0.18

Figure legend: Top row shows the white matter tracts with large QUIC values from FA (Fig.1) and ADC (Fig. 2) analysis. The positions of the axial slices are denoted by the lines in the mid-sagittal and coronal slice on the bottom row. Abbreviations: ACR/PCR: anterior/posterior coronal radiate; BCC/GCC/SCC: body/genu/spenium of corpus callosum; CG: cingulum; CGC/CGH: cingulum cingulate gyrus part / hippocampal part; CST: cortical spinal tract; FX: fornix; SLF: superior longitudinal fasciculus; SS: sagittal striatum.

Table 2: The white matter (WM) tracts with the top ten largest QUIC values from ADC analysis

Tracts	WM voxel # of a tract	Disrupted WM voxel # of a tract	QUIC of ADC
GCC	1847	919	0.50
BCC	3000	1304	0.43
SCC	2405	1001	0.42
PCR-L	797	277	0.35
ACR-L	1152	363	0.32
SLF-R	1392	418	0.30
ACR-R	1568	420	0.27
SS-L	332	88	0.27
FX	190	44	0.23
CST-R	655	145	0.22