Diffusion Tensor Imaging Detects White Matter Changes in Preclinical Stages of Alzheimer Disease

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Purpose: Alzheimer disease (AD) is the most common cause of dementia, affecting 20-30 million people worldwide. AD has traditionally been considered as a disease of the gray matter. Recently, an increasing body of evidence demonstrate that white matter (WM) is disrupted in AD prior to the onset of cognitive changes[1]. Diffusion tensor imaging (DTI) measuring of WM microstructural integrity is a promising technique to detect WM changes associated with the progression of AD pathology. The purpose of this study was to investigate the WM microstructural changes in preclinical AD using DTI.

Method: Participants: One hundred and ninety two participants were selected from a larger population enrolled at Knight Alzheimer's Disease Research Center (Knight ADRC) of the Washington University School of Medicine (St Louis, MO, USA), in longitudinal studies of memory and aging.

Clinical assessments: A clinician determines the presence or absence of dementia and rates the severity in accordance with the Clinical Dementia Rating (CDR). CDR 0 indicates no cognitive impairment and CDR 0.5, 1, 2 and 3 indicate very mild, mild, moderate and severe dementia[2]. In our cohort, 182 participants were cognitively normal (CDR 0).

CSF Collection and Analysis: CSF (20-30 mL) was collected by lumbar puncture as previously described[3]. Samples were analyzed for total tau, tau phosphorylated at threonine-181 (ptau181), and Aβ1-42 by commercial enzyme-linked immunosorbent assay (Innotest; Innogenetics, Ghent, Belgium).

NIA-AA preclinical AD stages: Participants are divided into normal, preclinical but asymptomatic (stage1 and stage2 according to the definition of preclinical stages from NIA and Alzheimer's association[4]. CSF amyloid-β1–42 (Aβ1–42) was used as a marker of amyloid and CSF tau was used as a marker of neuronal injury. At baseline, participants were classified as normal if both episodic memory and CSF markers met our criteria for normal, in stage 1 if only Aβ1–42 was abnormal, in stage 2 if Aβ1–42 and either t-tau or p-tau181 were abnormal[5].

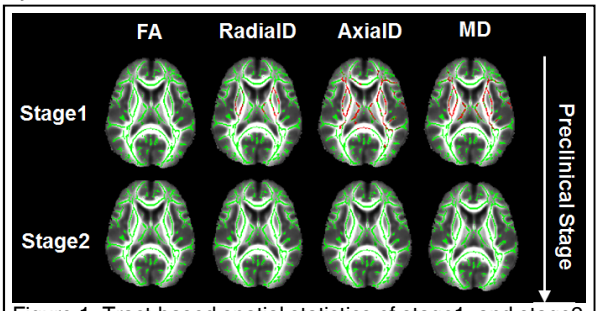

Figure 1. Tract-based spatial statistics of stage1, and stage2 in preclinical phase. DTI FA skeleton (green color) overlaid on the mean FA images of all participants. Red color shows skeletal voxels with significantly lower DTI indices, while significantly higher DTI indices shown as blue, p<0.05.

Imaging Acquisition and Processing: Diffusion MRI images were collected (2x2x2mm voxels, TR=9900ms, TE=102ms, flip angle=90deg, multi-bvalue scheme, 23 directions and *b*max = 1400s/mm^2). Data were collected in two 6 minute runs on 3T Trio scanner (Siemens, Erlangen, Germany). The diffusion tensor was calculated using log-linear regression algorithm and mean diffusivity (MD), fractional anisotropy (FA), radial diffusivity (RadialD) and axial diffusivity (AxialD) were computed for all datasets. The whole brain voxel-wise DTI-indices was analyzed using Tract Based Spatial Statistics (TBSS) (available in FSL).

Monte Carlo (MC) Simulation: Three geometry models were generated on a computer to represent normal white matter tracts (40% axon bundles, 5% cellularity and 55% extra-cellular space in Fig.2 Left), normal white matter with inflammatory cell infiltration in stage 1(40% axon bundles, 10% cellularity and 50% extra-cellular space in Fig.2 Middle), damaged white matter with both cell infiltration and edema in stage 2 (33% axon bundles, 7% cellularity and 60% extra-cellular space in Fig.2 right). Simulation temperature is 20˚C. The stochastic spin motion was simulated as the conventional Brownian motion with elastic reflection. Simulation protocol is same as our previous study[6]. The simulation for each geometry were repeated 5 times with added Rician noise (SNR=40). Student t-test is used to examine the group difference.

Table 1: MC protocol and simulated DTI indices (μm^2/ms), N=5, *: p<0.05

Preclinical Stage	DTI AxialD	DTI RadialD	Simulation Geometry
Normal	1.40±0.1	0.35±0.02	Normal axon fiber
Stage 1	1.20±0.1 *	0.30±0.02 *	Normal axon fiber + cell infiltration
Stage 2	1.39±0.1	0.34±0.02	Axon damage + cell infiltration + edema

Results: In preclinical stage 1, DTI RadialD, AxialD and MD significantly decreased compared to the normal group, in a wide spread WM regions including cerebral peduncle, anterior corona radiate, superior fronto-occipital fasciculus (Fig. 1, top row). Those results may suggest early inflammatory cell infiltration[7]. MC simulation confirmed that slightly increased amount of microglia cell activated after Blood-brain-barrier disruption is sufficient to cause DTI RadialD and AxialD decrease in stage1. In stage 2, DTI RadialD, AxialD and MD went back to normal level (Fig. 1, middle row), suggesting concurrent involvements of axonal injury, inflammatory cells infiltration and edema[7]. MC simulation also supported that the combination of axon damage, cell infiltration and edema could cause the pseudo-normalization of DTI indices in stage 2.

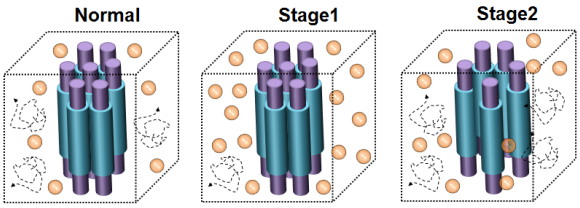

Figure 2. Monte-Carlo simulation was employed to evaluate the effect of microstructure change on DTI metrics at different stages of pre-clinical AD. Axons bundles are in purple color surround by myelin in blue color. Cellular populations are demonstrated as small balls in beige color and extra-cellular space is expressed as curves with arrows.

Discussion and Conclusion: A common DTI finding in AD dementia is increased RadialD and decreased FA, suggesting the degraded myelin and damaged axon integrity respectively[8]. In this preclinical stage1, we interestingly found, the DTI RadialD and AxialD both decrease, opposite to the finding in AD patients, which is consistent with other reports[1], but which we are now able to confirm in a definitive sample. In addition, DTI detected changes were pseudo-normalized in stage 2. These distinct DTI findings suggested that multiple pathological processes (including cell infiltration, edema, axonal damage, etc.) may co-occur and evolve heterogeneously in the preclinical stages. Advanced diffusion MRI methods capable to differentiate and quantify those pathological components will be greatly needed to improve the risk stratification for preclinical individuals, and to facilitate effective early treatment[7].

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