의학박사 학위논문

여성 경도인지장애 및 알츠하이머병 환자군에서 확산텐서영상 지표들과 인지기능과의 관련성분석

Relationship between diffusion tensor imaging metrics and cognitive function in female patients with mild cognitive impairment and Alzheimer’s disease

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이 논문을 의학박사 학위 논문으로 제출함

2022 년 2 월

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감사의 글

부족한 제가 수련과 학업을 지속할 수 있도록 오랜 기간 이끌어 주시고 지켜봐 주신 스승님들 덕분에 이 논문의 결실을 맺을 수 있었습니다. 논문 작성에 힘을 북돋워 주시고 큰 도움을 주신 이중선 교수님, 아낌없는 조언과 관심으로 지켜봐 주신 김창윤, 김성윤, 주연호 교수님, 바쁘신 와중에도 심사해 주신 정범석 교수님께 깊이 감사 드립니다. 논문 작성에 도움을 주신 주성우 선생님, 오랜 수련과 학업 기간 함께 고생하며 울고 웃어준 동료 선생님들께도 감사의 마음을 전합니다.

마지막으로, 지금의 제가 있도록 변함없는 사랑과 지원을 주신 저의 부모님과, 항상 한결 같은 모습으로 곁에 있어주는 남편에게 감사와 사랑을 전하며 이 글을 마칩니다.

국문 요약

알츠하이머병은 단기기억장애를 보이는 대표적인 주요신경인지장애이며, 기억성 경도인지장애는 알츠하이머병의 전구 단계로 알려져 있다. 회백질의 위축과 변성이 알츠하이머병의 주요 병리로 알려져 있으나, 알츠하이머 병에서 백질의 이상이 회백질의 이상과는 독립적으로 발생하고, 회백질의 변성보다 선행할 가능성도 제기되고 있다. 본 연구에서는 대규모 공공 뇌영상 데이터를 이용하여 초기 알츠하이머병 환자군 및 경도인지장애 여성 환자군에서 대뇌 백질(심부 및 표재부 백질 포함)의 손상 및 변성여부를 확인하고, 손상된 부위와 인지기능저하와의 관련성을 확인하고자 하였다.

여성 알츠하이머병 환자군 20 명, 경도인지장애 환자군 86 명, 정상 대조군 193 명의 뇌영상을 알츠하이머 뇌영상 선도연구 데이터에서 다운받아 확산텐서영상 지표들을 군간 비교하였다. 군간 지표가 유의미하게 차이나는 백질 영역에서는 상관분석을 통해 확산텐서영상 지표들과 신경심리검사 점수들과의 연관성을 확인하였다.

연구 결과, 경도인지장애 환자군에서 정상 대조군에 비하여 frontal commissural tracts, uncinated fasciculus, superficial temporal tract 에서 백질의 변성이 진행되었고, 그 진행 정도를 나타내는 확산텐서영상 지표들과 인지기능저하의 정도가 연관성을 보였다. 알츠하이머병 환자군에서는 일부 경도인지장

애 환자군과 겹치는 영역도 있었으나 일관되지 않은 결과를 보였다.

향후 후속 연구를 통하여 알츠하이머병에서도 일관된 결과가 확인된다면, 본 연구에서 경도인지장애 환자군의 확산텐서영상에서 대뇌 백질 특정 영역의 이상이 유의미하게 발견되며 임상 지표들과 연관성을 보였다는 점에서, 확산텐서영상 지표들이 인지장애의 초기 단계를 식별하기 위한 단서가 될 가능성이 있다.

중심 단어: Alzheimer's disease, mild cognitive impairment, diffusion tensor imaging, white matter, cognitive function

Index

Tables

1. INTRODUCTION

1.1. Alzheimer's Disease and amnestic Mild Cognitive Impairment

Alzheimer's disease (AD) is a major neurocognitive disorder featuring cognitive impairments in short-term memory, executive and visuospatial functioning, and praxis[1]. Mild cognitive impairment (MCI) is a condition with objective cognitive decline while activities of daily living remains unimpaired [2]. Amnestic subtype of MCI (aMCI), a subtype of MCI, is identified as having progressive memory deterioration, either isolated memory deficit or associated with impairments in other cognitive domains such as language, visuospatial function, and frontal executive function. Individuals with aMCI are known to be at increased risk for progression to AD, or may be in the prodromal stage of AD [3].

1.2. White Matter Disruption in AD

Prior neuroimaging studies in AD has largely been focused on cortical atrophy, amyloid plaques and neurofibrillary tangles in the cerebral cortex and subcortical gray matter [4, 5]. But widespread damage to the crebral white matter (WM) has been also noted as the neurodegeneration progresses, evidenced by previous researches showing loss of oligodendrocytes, activation of microglial cells, demyelination, and reactive astrocytosis in the WM [6, 7]. These changes in WM may play an important role in the cognitive deteriorations of AD, and unraveling WM changes can provide insight into biopathological processes of AD. It could be of interest to uncover where the strongest microstructural changes occur in the cerebral WM in AD.

1.3. The Amyloid Cascade Hypothesis

The Amyloid Cascade Hypothesis postulates that degeneration of cerebral axons occurs prior to neuronal loss, and it is a result of Wallerian degeneration [8, 9]. In AD, the close correlation of taupathy with WM micostructural integrity and also with the cognitive symptoms suggests that changes in WM may occur independently or maybe precede gray matter changes. The Retrogenesis Model suggests that demyelination of WM in AD show a reverse temporal order to that observed in myelination[9, 10]. Above these hypotheses provide the idea that undermining early WM changes may be a clue for early detection of AD.

1.3. Diffusion Tensor Imaging

Although cerebral WM is affected in early disease process[11], the relationship between WM microstructure and cognitive symptoms in AD has been less discussed. Diffusion tensor imaging (DTI), a magnetic resonance imaging (MRI)-based imaging technique is capable of probing white matter tissue microstructure based on water molecule diffusion within the brain [12]. Parameters in DTI such as fractional anisotropy (FA), radial diffusivity (RD), axial diffusivity (AxD) and mean diffusivity (MD), can represent abnormalities in the WM tract fibers in AD.[13].

1.4. Superficial White Matter

Long-range of cortico-cortical connections include axons that pass from a given cortical location through the superficial white matter (SWM) to the deep WM, and then on to distant cortical/subcortical structures [14]. SWM is innervated below the infragranular layer of the cerebral cortex and this layer is known as the last myelinating fibers, sometimes in the fourth decade of life[15]. Therefore, SWM could represent some vulnerable tracts in the pathogenesis

of AD. To date, limited investigations of SWM in AD and its relationship with cognitive symptoms have been conducted, since its complex microstructure and significant inter-individual variability were challenging to study.

In this study, we aimed to investigate microstructural disruption of deep and superficial white matter tracts in MCI and early AD and to examine the relationships between white matter abnormalities and cognitive functions, using the Alzheimer's Disease Neuroimaging Initiative (ADNI), a publcly available neuroimaging datasets of patients with MCI and early AD.

2. MATERIALS AND METHODS

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). For up-to-date information, see www.adni-info.org.

2.1. Study Population and Data Collection

2.1.1. The Alzheimer's Disease Neuroimaging Initiative

We utilized publicly available neuroimaging datasets of the Alzheimer's Disease Neuroimaging Initiative (ADNI). ADNI is a multisite naturalistic longitudinal study of cognitively normal participants, participants with MCI, and participants with early stages of AD, established to facilitate standardized imaging techniques and development of biomarkers in AD[16]. Full eligibility criteria are described in the ADNI Procedures Manual(http://adni.loni.usc.edu/methods/documents/). Individuals from the ADNI database were included if 3 Teslar DTI data were available, and only female subjects were included to guarantee the biological homogeneity of the sample. All ADNI participants completed Institutional Review Board-approved written informed consent in each study site. Key eligibility criteria of ADNI are summarized in Table 1[17].

Table 1. Summary of ADNI Key Eligibility Criteria

All participants
Between 55 to 90 years of age (newly enrolled subjects)
A reliable study partner to provide an independent information
Speak English or Spanish
Stability of medications (permitted) for 4 weeks
Hachinski score ≤4
Geriatric Depression Scale < 6
Cognitively normal (CN)
Free of memory complaints
Normal memory function: scores on delayed recall of one paragraph from Wechsler Memory Scale Logical Memory II (LMS, ≥9 for ≥16 years, ≥5 for 8-15 years, ≥3 for 0-7 years of education)
The Mini-Mental State Examination (MMSE) scores between 24 to 30; The Clinical Dementia Rating (CDR) of 0
Absence of significant cognitive impairments or activities of daily living (ADL)
Significant memory concern (SMC)
Significant subjective memory complaints (Reported by subject, informant, or clinician)
MMSE scores between 24-30; CDR of 0
LMS II ≥9 for ≥16 years, ≥5 for 8-15 years, ≥3 for 0-7 years of education
Early MCI (EMCI)
Subjective memory complaints (Reported by subject, informant, or clinician)
LMS ≥16 years:9-11; 8-15 years: 5-9; 0-7 years: 3-6

MMSE scores between 24-30; CDR of 0.5 (memory box must be at least 0.5)
Absence of significant impairment in other cognitive domains, with preserved ADL
Absence of dementia
Late MCI (LMCI)
Subjective memory complaints (Reported by subject, informant, or clinician)
LMS (≥16 years:≤8; 8-15 years: ≤4; 0-7 years: ≤2)
MMSE scores between 24 to 30; CDR of 0.5
Absence of significant cognitive impairment in other domains, with preserved ADL
Absence of dementia
Mild AD (AD)
Subjective memory complaints (Reported by subject, informant, or clinician)
Objective memory impairment: LMS (≥16 years:≤8; 8-15 years: ≤4; 0-7 years: ≤2)
MMSE scores between 20-26; CDR of 0.5 or 1.0
Meets NINCDS/ADRDA criteria* for probable AD

* The criteria proposed by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [18]

2.2. Image Acquisition and Processing

2.2.1. Image Acquisition

The 3D T1-weighted magnetic resonance images were acquired with an magnetization-prepared rapid gradient-echo (MPRAGE) sequence with a spatial resolution of $1*1*1.2mm^3$. The ADNI1(2004-2009) MRI protocol focused on longitudinal structural imaging with 1.5T scanners using T1 and dual echo T2 weighted images. One-fourth of ADNI1 participants were also scanned using the same MRI protocol with 3T scanners. In ADNI GO/ADNI2 project

(2010-2016), 3T T1 weighted MRI scanning was performed with parameters similar to ADNI1. In ADNI3, al subjects were being scanned on 3T scanners (http://adni.loni.usc.edu/methods/documents/mri-protocols/).

In T1-weighted image, spatial resolution was improved slightly to 1 mm cubed in ADNI 3. In DTI, ADNI3 uses 2.0 mm isotropic voxels but ADNI1 and ADNI2 used 2.7 mm, with b = 0 and 1000 s/mm^2 weighted volumes. Full details of every MRI scanner protocols for T2*-weighted, MPRAGE T1-weighted, and diffusion images can be found at ADNI MRI protocols(http://adni.loni.usc.edu/methods/documents/mri-protocols/).

The parameters for brain image acquisition from all projects are presented in Table 2.

Table 2. Parameters for image acquisition

Sequence		**Protocol**
T1	ADNI1	Field of view (FOV), 192*240*256; voxel size, 1.2*1.2*1.2 mm^3; echo time (TE), min full echo; repetition time (TR), 2300 ms;
	ADNI2	Field of view (FOV), 208*240*256; voxel size, 1.2*1.2*1.2 mm^3; echo time (TE), min full echo; repetition time (TR), 2300 ms;
	ADNI3	Field of view (FOV), 208*240*256; voxel size, 1*1*1 mm^3; echo time (TE), min full echo; repetition time (TR), 2300 ms;
DTI	ADNI1	FOV, 240x 214x 144 mm; voxel size, 2.7*2.7*2.7 mm^3; TE, 54 ms; TR, 3000 ms; Single b = 1000s/mm^2 shell
	ADNI2	FOV, 232x232x160 mm; voxel size, 2.7*2.7*2.7 mm^3; TE, 56 ms; TR, 7200 ms; Single b = 1000s/mm^2 shell
	ADNI3 Basic	FOV, 232x232x160 mm; voxel size, 2*2*2 mm^3; TE, 56 ms; TR, 7200 ms; Single b = 1000s/mm^2 shell; b = 0 images interleaved throughout if possible in product sequence
	ADNI3 Advanced	FOV, 232x232x160 mm; voxel size, 2*2*2 mm^3; TE, 71 ms; TR, 3300 ms; Three shells: b = 500,1000,2000 s/mm^2 (112 total diffusion weighted directions).

2.2.2. Quality control and preprocessing

The quality control, preprocessing and whole-brain tractography and parcellation procedures were processed according to the methods in a study by Joo et al[19]. For the quality control of diffusion MRIs, the SlicerDiffusionQC (https://github.com/pnlbwh/SlicerDiffusionQC) software was used for detection and removal of bad gradient volumes. Each volume of diffusion was categorized to a good or bad gradient based on the interval to a median line from Kullback–Leibler divergence between successive diffusion volumes. Following automatic processing with software, study investigators carefully reviewed the classification results. The diffusion MRI data were preprocessed using the Psychiatry Neuroimaging Laboratory (PNL) pipeline(https://github.com/pnlbwh /pnlutil) after discarding bad gradient volumes. Axis alignment, centering, eddy current, and head motion correction were conducted.

2.2.3. Whole-brain Tractography and Parcellation

2.2.3.1. Psychiatry Neuroimaging Laboratory (PNL) pipeline software

Unscented Kalman filter (UKF)-based two tensor tractography was conducted with the PNL (https://github.com/pnlbwh/pnlpipe) standard pipeline. For the tractography, the parameters used by Rathi et al. were used[20]. Parcellation and segmentation of the T1-weighted images was conducted with FreeSurfer ver. 7.1(https://surfer.nmr.mgh.harvard.edu/). Registration of the T1 images to the baseline diffusion volume was performed with a non-linear registration method of the Advanced Normalization Tools [21]. In parcellation and segmentation of dMRI volumes, the same registration technique was used with modified FreeSurfer parcellated labels. For definition and extraction of individual WM tracts, White Matter Query Language was used[22]. A total of 83 WM tracts was identified in each participants. Diffusion metrics such

as FA, AxD, RD, and MD were estimated according to a previous methods[23].

2.2.3.2. Whitematteranalysis(WMA) clustering

Unscented Kalman filter (UKF)-based two-tensor tractography was performed with the default options [20] according to the standard pipeline (https://github.com/pnlbwh/pnlpipe). We parcellated the tractography data using the O'Donnell Research Group (ORG) white matter atlas and the whitematteranalysis (WMA) software (https://github.com/SlicerDMRI/whitematteranalysis) [24]. After the rigid-affine registration of the tractography data to the ORG atlas tractography data, a fiber clustering of the registered tractography data was performed as follows: 1) an initial 800-cluster white matter parcellation was created in accordance with the ORG atlas, 2) After the removal of false-positive clusters, the resulting fiber clusters were transformed into the input tractography space with information on the hemispheric location (left, right, or commissural), and 3) the fiber clusters were separated by their anatomical location. Then, the fiber clusters were appended to white matter tracts according to the anatomical definitions by the ORG atlas, resulting in 65 deep white matter tracts and 8 superficial white matter fibers. The mean FA and MD value of the white matter tract was calculated using the FiberTractMeasurements module in 3D Slicer (https://slicer.org).

2.3. Neuropsychiatric Tests

ADNI includes a variety of cognitive batteries, including the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Alzheimer's Disease Assessment Scale-Cognitive (ADAS-cog), Everyday Cognition (Ecog), Clinical Dementia Rating (CDR),

Functional Assessment Questionnaire (FAQ), Rey Auditory Verbal Learning Test (RAVLT), Weschler Memory Scale-Revised Logical Memory Test I and II (LMS), Trail Making Test: Parts A and B(TMT-A, B), Digit Span, Digit Symbol, Category Fluency, Boston Naming Test, Clock Drawing, Geriatric Deperssion Scale, and Neuropsychiatric Inventory Questionnaire, [17]. We utilized MMSE, MoCA, ADAS-Cog 11, ECog, CDR, RAVLT, and TMT-B from the ADNI database. All explanations of neuropsychiatric tests below were referenced from ADNI2 procedures manual(http://adni.loni.usc.edu/wp-content/uploads/2008/07/adni2-procedures-manual.pdf).

2.3.1. The Mini-Mental state Examination [25]:

The Mini-Mental state Examination (MMSE) is a fully structured screening tool extensively used in clinical settings and AD clinical trials. The MMSE evaluates orientation, memory, attention and calculation, language, and brief visuospatial functions. The total score ranges from a minimum of 0 to maximum of 30. The lower the MMSE score, the more severe the cognitive decline.

2.3.2. The Montreal Cognitive Assessment [26]***:***

The Montreal Cognitive Assessment test (MoCA) is a brief, which takes approximately ten minutes, cognitive screening instrument developed to detect the mild stage of cognitive dysfunction such as MCI. The MOCA has been proven to detect MCI in clinical settings with adequate sensitivity and specificity [27]. The MoCA has generally thought to have higher sensitivity than MMSE.

2.3.3. Alzheimer's Disease Assessment Scale-Cognitive [28]***:***

The Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-COG) is a structured

cognitive scale designed to evaluate the cognitive impairment in AD, which is widely used in AD drug research. ADAS-COG evaluates verbal memory (word recall and recognition, ability to remember test instructions), language (naming and comprehension), perceptual reasoning (following commands), orientations, ideational and constructional praxis (placing letter in envelope, copying geometric designs). The ADAS-Cog 11 includes 11 tasks composed of both subject- and observer-based assessments. Scores ADAS-Cog 11 range from minimum of 0 to maximum of 70, with higher score means poorer cognitive functioning.

2.3.4. Clinical Dementia Rating [29]***:***

The Clinical Dementia Rating (CDR) is a scale measured by structured interview that can be used as a measure of global functioning and activities of daily living in subjects with neurodegenerative diseases. It has five degrees of performance on six categories of cognitive function (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care). Total ratings obtained on each six categories are summarized to one global rating score, the CDR- Sum of Boxes (CDR-SOB). Reliability and validity of the CDR has been well established, with high inter-rater reliability in both clinical and research settings.

2.3.5. Everyday Cognition [30]***:***

The Everyday Cognition (ECog) has been designed to assess functional impairment of a subject with early stage of cognitive deterioration. The ECog is an informant (clinicians or guardians)-rated questionnaire consists of multiple subscales of functional status of the subject. Previous studies of ECog indicated that it correlates well with previously established measures of global cognition and functioning. ECog is a useful in differentiating CN, MCI and AD patients, and also in evaluating global functioning and activities of daily living in the elderly.

2.3.6. Rey Auditory Verbal Learning Test [31]*:*

The auditory verbal learning test is a widely used word list-learning task which assesses verbal learning and memory. In every 5 learning trials, 15 designated nouns are verbally presented by the administrator, and immediate free recall of the words is followed. The number of correct words on each trial is scored. Following about 30-minute delay with unrelated test, free recall of the 15 word list is carried out. On final word recognition test, the original 15 and distracter 15 words are presented. The number of correct and false positive answers are recorded. In this study, we utilized the parameter RAVLT_learning (RAVLT-L), which was obtained by subtracting the number of correctly recalled words of the first trial from that of the fifth trial.

2.3.7. Trail Making Test: Parts B [32]*:*

The Trail-Making Test (TMT) is a task of frontal executive function and processing speed. Part B of TMT (TMT-B) especially requires cognitive flexibility, shifting from number to letter sets under time limit. A total of 25 circles (13 circles numbered from 1 to 13 and 12 circles contain letters from A to L) are distributed on a standardized white paper. Then subject is requested to connect the circles with a line as quickly as possible, with alternating between numbers and letters in an ascending order. The total time (in seconds) required to complete part B is measured as scores (maximum 300 seconds), with higher scores mean poorer cognitive functioning. In this study we adopted TMT-B total score as a measure of frontal executive function and processing speed.

2.4. Statistical Analysis

All statistical analyses were performed using the R software (ver 4.0.2) [33]. P value of 0.05

was considered statistically significant.

An analysis of variance (ANOVA) was used for the comparisons of demographic and clinical characteristics between CN, MCI and AD patients. A total of 91 white matter tracts (83 deep white matter tracts and 8 superficial white matter fibers) were included in the group comparisons of DTI metrics. The false-discovery rate correction was used for adjusting multiple tests. Linear regression analysis was performed with covariates of age and age^2.

$$FA(predicted) = \beta_1\, age + \beta_2 age^2 + \epsilon$$

To reflect the effect of age on DTI metrics, we created a prediction model using the data of healthy controls and applied it to those of MCI and AD patients to achieve predicted FA, AxD, RD and MD value by each white matter tract.

$$FA(deviated) = \frac{\{FA(measured) - FA(predicted)\}}{FA(predicted)} * 100$$

Group differences in deviated FA, AxD, RD, and MD were evaluated with linear regression analysis. With regard to the association with cognitive functions, we only included the white matter tracts having significant group differences in DTI metrics. Pearson's partial correlation analysis was used to evaluate correlations between DTI values and scores of neuropsychiatric tests. To examine the effect of total cranial volume on correlations between DTI values and cognitive function, total intracranial volume was included as a covariate.

3. RESULTS

3.1. Demographics and Clinical Characteristics (Table 3)

Demographic and clinical characteristics of participants are provided in Table 3. Total 279 female participants(193 CN, 86 MCI, and 20 AD) were included in the study. There were no significant differences in age between groups (mean 70.85 ± SD 5.25 years old in CN, 70.70 ± 8.40 in MCI, 71,82 ± 8.83 in AD, F = 0.130, df = 45.757, P = 0.878). The AD group has lower years of education compared to the MCI group (mean 15.01 ± SD 2.63 years in MCI, 14.50 ± 2.14 in AD, F = 12.500, df = 51.455, p = 0.004). AD group has the highest CDR-SB (0.18 ± 0.71 in CN, 1.68 ± 2.04 in MCI, F = 43.474, df = 43.474, p < 0.001) and the lowest MMSE score (0.18 ± 0.71 in CN, 1.68 ± 2.04 in MCI, F = 45.030, df = 45.030, p < 0.001).

Table 3. Demographics and Clinical Characteristics of CN, MCI, and AD Participants

	CN (n=193) Mean (SD)	**MCI (n=86) Mean (SD)**	**AD (n=20) Mean (SD)**	**F**	**df**	**p (ANOVA)**
Age, mean (SD)	70.85 (5.25)	70.70 (8.40)	71.82 (8.83)	0.13	45.76	.878
Education, mean (SD)	16.34 (2.30)	15.01 (2.63)*	14.50 (2.14)*	12.50	51.46	.004
MMSE, mean (SD)	29.09 (1.21)†	26.73 (3.83)†	23.25 (1.80)†	111.06	45.03	<.001
CDR-SB, mean (SD)	0.18 (0.71)‡	1.68 (2.04)‡	4.78 (1.58)‡	100.82	43.47	<.001

AD, Alzheimer's disease; ANOVA, analysis of variance; CDR-SB, clinical dementia rating-sum of

boxes; CN, cognitively normal; MCI, mild cognitive impairment; MMSE, mini-mental state examination; SD, standard deviation;

3.2. Group Differences in DTI Metrics (Table 4, 5)

As group comparisons in DTI measures were our main interest, only tracts with significant group differences in DTI metrics were summarized in Table 4 and Table 5.

Compared to CN participants, MCI patients showed increased AxD in 6 deep white matter tracts - corpus callosum_1 (CC_1, ß = 3.009, corrected p = 0.028), CC_caudalmiddlefrontal (CC_CMF, ß = 2.600, corrected p = 0.043), CC_medialorbitofrontal (CC_MOF, ß = 2.114, corrected p = 0.028), CC_posterior cingulate (CC_PC, ß = 8.879, corrected p = 0.024), CC_rostralmiddlefrontal (RMF, ß = 2.444, corrected p =0.042), and CCommisural (ß = 1.854, corrected p = 0.024), and increased MD in 4 deep white matter tracts and 1 superficial white matter tract - CC_1(ß = 3.812, corrected p = 0.034), CC_MOF(ß = 2.791, corrected p = 0.037), CC_parsorbitalis (CC_PO, ß = 3.942, corrected p = 0.037), right uncinate fasciculus (UF, right, ß = 2.726, corrected p = 0.037), and left superficial temporal tract (Sup-T, left, ß = 2.679, corrected p = 0.006) (Table 4).

AD patients showed incrased AxD in 1 deep white matter tract - CC_MOF (ß = 4.517, corrected p = 0.013), and increased MD in 2 deep white matter tract - UF, left (ß = 4.964, corrected p = 0.041), CC_rostralanteriorcingulate (CC_RAC, ß = 21.119, corrected p = 0.023), and Sup_T, left (ß = 4.770, corrected p = 0.007), and increased RD in CC_RAC (ß = 24.504, corrected p = 0.023) tract, compared to CN group (Table 5).

Table 4. Group Comparisons of DTI metrics between CN and MCI participants for each tract*

	CN Mean (SD)	MCI Mean (SD)	ß†	Regression p value‡
AxD				
CC_1	$1.340 * 10^{-5}$ (6.074)	3.009 (8.679)	3.009	0.028
CC_CMF	$- 1.837 * 10^{-5}$ (6.611)	2.600 (7.185)	2.600	0.043
CC_MOF	$- 0.379 * 10^{-5}$ (4.737)	2.114 (5.254)	2.114	0.028
CC_PC	$- 10.870 * 10^{-5}$ (16.340)	8.879 (20.765)	8.879	0.024
CC_RMF	$0.950 * 10^{-5}$ (6.516)	2.444 (5.531)	2.444	0.042
CCommisural	$2.353 * 10^{-5}$ (3.987)	1.854 (3.607)	1.854	0.024
MD				
CC_I	$- 1.893 * 10^{-5}$ (7.522)	3.812 (10.698)	3.812	0.034
CC_MOF	$- 2.383 * 10^{-5}$ (6.810)	2.791 (7.109)	2.791	0.037
CC_PO	$0.1064 * 10^{-5}$ (9.017)	3.942 (5.672)	3.942	0.037
UF, right	$- 3.109 * 10^{-5}$ (6.322)	2.726 (7.309)	2.726	0.037
Sup-T, left	$1.089 * 10^{-5}$ (4.198)	2.679 (6.464)	2.679	0.006

AxD, axial diffusivity; CC, corpus callosum; CMF, caudalmiddlefrontal; CN, cognitively normal; DTI, diffusion tensor imaging; MCI, mild cognitive impairment; MD, mean diffusivity; MOF, medialorbitofrontal; PC, posteriorcingulate; PO, parsorbitalis, RMF, rostralmiddlefrontal; Sup-T, superficial-temporal; SD, standard deviation; UF, uncinate fasciculus

† ß represents the nonstandardized regression coefficient.

‡ false dicovery rate-corrected.

Table 5. Group Comparisons of DTI metrics between CN and AD participants for each tract*

	CN Mean (SD)	AD Mean (SD)	ß†	Regression p value‡
AxD				
CC_MOF	$-0.379 * 10^{-5}$ (4.737)	4.517 (5.154)	4.517	0.013
MD				
UF, left	$0.560 * 10^{-5}$ (6.494)	4.964 (5.980)	4.964	0.041
CC_RAC	$- 58.76 * 10^{-5}$ (17.480)	21.118 (34.070)	21.119	0.023
Sup-T, left	$1.089 * 10^{-5}$ (4.198)	4.770 (5.038)	4.770	0.007
RD				
CC_RAC	$-88.340 * 10^{-5}$ (19.510)	24.503 (36.886)	24.504	0.023

AD, Alzheimer's disease; AxD, axial diffusibvvity; CC, corpus callosum; CN, cognitively normal; DTI, diffusion tensor imaging; MCI, mild cognitive impairment; MD, mean diffusivity; MOF, medialorbitofrontal; RAC, rostralanteriorcingulate; RD, radial diffusivity; SD, standard deviation; Sup-T, superficial-temporal; UF, uncinate fasciculus.

† ß represents the nonstandardized regression coefficient.

‡ false dicovery rate-corrected.

3.3. Associations of DTI Metrics with Cognitive Functions (Table 6, 7, 8, and 9)

Correlations between DTI metrics and cognitive scores in CN, MCI, and AD participants are summarized in Table 6-9 (categorized according to main cognitive domains; Table 6, general cognitive function; Table 7, global functioning and ADL; Table 8, verbal and episodic memory; Table 9, processing speed and cognitive flexibility). Pearson's correlation coefficient was used to examine associations between DTI measures of white matter tracts and cognitive symptoms. Correlation coefficients were evaluated in CN, MCI, and AD group separately.

Among CN participants, 1) increased AxD were associated with worse MoCA scores(CC_CMF, CC_MOF, CC_RMF, and Ccommisural), worse ADAS-Cog 11 and CDR-SB scores (Ccommisural), and worse TMT-B performances(CC_CMF, CC_RMF, and Ccommisural). 2) increased MD were associated with worse worse MoCA and ADAS-COG 11 performances (CC_MOF), worse CDR-SB scores and ECog performnances (CC_MOF, UF, right, and sup-T, left), worse RAVLT-L performaces(CC_MOF), and worse TMT-B performances(CC_MOF, UF, right, Sup-T, left, and CC_RAC). 3) increased RD were associated with worse TMT-B performances(CC_RAC).

In MCI participants, 1) increased AxD were associated with worse MMSE scores(CC_1, CC_RMF, Ccom), worse MoCA scores(CC_1, CC_CMF, CC_RMF, and Ccom), worse ADAS-Cog 11 performances(CC_1, CC_RMF, and Ccom), worse CDR-SB scores(CC_1, CC_CMF, CC_RMF, and Ccom), worse ECog performances(CC_1, CC_CMF, CC_PC, CC_RMF, and Ccom), worse RAVLT-L performances(CC_1 and CC_PC), and worse TMT-B performances(CC_1, CC_PC, CC_RMF, and Ccom), 2) increased MD were associated with worse MMSE scores(CC_1, CC_MOF, UF, right, Sup-T, left, UF, left, and CC_RAC), worse MoCA score(CC_1, CC_MOF, UF, right, Sup-T, left, UF, left), worse ADAS-COG 11 performances(CC_1, UF, right, Sup-T, left, and UF, left), worse CDR-SB scores(CC_1, CC_MOF, UF, right, Sup-T, left, UF, left, and CC_RAC), worse ECog performances(CC_1,

CC_PO, Sup-T, left, UF, left, anc CC_RAC), worse RAVLT-L performances(CC_1, CC_MOF, UF, right, Sup-T, left, UF, left, and CC_RAC), and worse TMT-B performances(CC_1, CC_PO, UF, right, and Sup-T, left), and 3) increased RD were associated with worse MMSE scores, worse CDR-SB scores, worse ECog performances, and worse RAVLT-L performances(CC_RAC).

In AD group, increased MD and RD were associated with worse ADAS-Cog 11 performances(CC_RAC).

Table 6. Correlation coefficients between DTI metrics and neuropsychiatric test scores: General Cognitive Function

	MMSE			MoCA			ADAS 11		
	CN	MCI	AD	CN	MCI	AD	CN	MCI	AD
AxD									
CC_1	0.04	**-0.24**	0.27	-0.03	**-0.26**	0.15	-0.04	**0.22**	0.04
CC_CMF	0.02	-0.15	0.15	**-0.21**	**-0.23**	-0.32	0.15	0.07	-0.11
CC_MOF	-0.04	-0.17	0.23	**-0.15**	-0.02	0.02	0.10	0.17	-0.10
CC_PC	-0.10	-0.12	0.05	-0.01	-0.18	0.01	-0.06	0.13	0.39
CC_RMF	0.08	**-0.37**†	0.20	**-0.15**	**-0.44**†	-0.20	0.11	**0.32**†	0.19
CCom	-0.04	**-0.29**	0.28	**-0.15**	**-0.31**	0.05	**0.15**	**0.24**	0.06
MD									
CC_I	0.02	**-0.27**	0.16	-0.04	**-0.29**	0.24	-0.05	**0.30**	-0.05
CC_MOF	-0.10	**-0.25**	-0.07	**-0.26**†	**-0.22**	-0.11	**0.19**	0.21	0.09
CC_PO	-0.01	-0.14	-0.35	-0.06	-0.21	-0.25	-0.02	0.11	-0.04
UF, right	0.02	**-0.29**	0.13	-0.11	**-0.41**†	0.39	0.14	**0.36**†	0.52
Sup-T, left	-0.14	**-0.37**†	-0.04	-0.14	**-0.36**†	0.04	0.13	**0.27**	0.10
UF, left	-0.06	**-0.28**	-0.16	-0.02	**-0.30**	0.33	0.04	**0.23**	0.02
CC_RAC	0.11	**-0.30**	-0.05	-0.06	-0.15	0.09	0.02	0.11	**0.67**†
RD									
CC_RAC	0.10	**-0.30**	-0.07	-0.04	-0.12	0.07	0.01	0.11	**0.69**†

AD, Alzheimer's disease; ADAS 11, Alzheimer's Disease Assessment Scale-Cognitive 11 item; AxD, axial diffusivity; CC, corpus callosum; CN, cognitively normal; DTI, diffusion tensor imaging; MCI, mild cognitive impairment; MD, mean diffusivity; MMSE, mini-mental state examination; MoCA, Montreal Cognitive Assesment; MOF, medialorbitofrontal; PC, posteriorcingulate; PO, pars orbitalis; RAC, rostralanteriorcingulate; RD, radial diffusivity; RMF, rostralmiddlefrontal; Sup-T, superficial-temporal; UF, uncinate fasciculus.

Bold, $p < 0.05$

Bold†, $p < .007$ (Bonferroni corrected p)

Table 7. Correlation coefficients between DTI metrics and neuropsychiatric test scores: Global Functioning and ADL

	CDR-SB			ECog		
	CN	MCI	AD	CN	MCI	AD
AxD						
CC_1	0.03	**0.33**†	0.32	0.01	**0.33**†	-0.04
CC_CMF	0.12	**0.23**	0.35	0.10	**0.25**	0.29
CC_MOF	0.09	0.18	0.22	0.12	0.17	-0.03
CC_PC	0.06	0.20	-0.33	0.06	**0.26**	-0.07
CC_RMF	0.09	**0.44**†	-0.01	0.08	**0.35**†	-0.08
CCom	**0.15**	**0.34**†	-0.09	0.10	**0.33**†	0.02
MD						
CC_I	0.05	**0.40**†	0.18	-0.01	**0.30**	-0.18
CC_MOF	**0.21**	**0.32**†	0.29	**0.16**	0.20	-0.03
CC_PO	0.04	0.20	-0.20	-0.04	**0.23**	0.14
UF, right	**0.16**	**0.40**†	0.13	**0.19**	0.18	0.06
Sup-T, left	**0.21**†	**0.45**†	0.02	**0.18**	**0.33**†	-0.07
UF, left	0.10	**0.40**†	-0.23	0.13	**0.26**	0.14
CC_RAC	0.07	**0.40**†	0.28	0.09	**0.32**	0.26
RD						
CC_RAC	0.05	**0.37**†	0.48	0.09	**0.32**	0.31

AD, Alzheimer's disease; ADL, activities of daily living; AxD, axial diffusivity; CC, corpus callosum; CDR-SB, Clinical Dementia Rating-Sum of Boxes; CN, cognitively normal; DTI, diffusion tensor imaging; ECog, Everyday Cognition-total by study partner; MCI, mild cognitive impairment; MD, mean diffusivity; MOF, medialorbitofrontal; PC, posteriorcingulate; PO, pars orbitalis; RAC, rostralanteriorcingulate; RD, radial diffusivity; RMF, rostralmiddlefrontal; Sup-T, superficial-temporal; UF, uncinate fasciculus.

Bold, $p < 0.05$

Bold†, $p < .007$ (Bonferroni corrected p)

Table 8. Correlation coefficients between DTI metrics and neuropsychiatric test scores: Verbal and Episodic Memory

	RAVLT		
	CN	MCI	AD
AxD			
CC_1	0.06	**-0.24**	0.38
CC_CMF	-0.05	-0.12	0.18
CC_MOF	-0.03	-0.26	0.28
CC_PC	0.01	**-0.22**	-0.35
CC_RMF	-0.03	-0.20	0.17
CCom	0.05	-0.14	0.34
MD			
CC_I	-0.02	**-0.27**	0.21
CC_MOF	**-0.15**	**-0.24**	0.02
CC_PO	0.04	-0.18	-0.37
UF, right	-0.08	**-0.31**†	0.21
Sup-T, left	-0.07	**-0.31**†	-0.01
UF, left	-0.11	**-0.35**†	0.01
CC_RAC	-0.16	**-0.40**†	0.08
RD			
CC_RAC	-0.14	**-0.34**	0.08

AD, Alzheimer's disease; AxD, axial diffusivity; CC, corpus callosum; CN, cognitively normal; DTI, diffusion tensor imaging; MCI, mild cognitive impairment; MD, mean diffusivity; MOF, medialorbitofrontal; PC, posteriorcingulate; PO, pars orbitalis; RAC, rostralanteriorcingulate; RAVLT, Rey Auditory Verbal Learning Test; RD, radial diffusivity; RMF, rostralmiddlefrontal; Sup-T, superficial-temporal; UF, uncinate fasciculus.

Bold, $p < 0.05$

Bold†, $p < .007$ (Bonferroni corrected p)

Table 9. Correlation coefficients between DTI metrics and neuropsychiatric test scores : Processing Speecd and Cognitive Flexibility

	TMT		
	CN	MCI	AD
AxD			
CC_1	0.02	**0.24**	0.12
CC_CMF	**0.19**	0.17	0.18
CC_MOF	0.14	0.12	0.03
CC_PC	0.10	**0.27**	0.20
CC_RMF	**0.18**	**0.33**†	-0.18
CCom	**0.15**	**0.30**†	0.02
MD			
CC_I	0.06	**0.25**	0.81
CC_MOF	**0.27**†	0.19	0.02
CC_PO	0.06	**0.39**†	-0.07
UF, right	**0.19**	**0.23**	0.31
Sup-T, left	**0.16**	**0.29**	0.11
UF, left	0.10	0.13	-0.27
CC_RAC	**0.20**	0.04	-0.03
RD			
CC_RAC	**0.20**	0.03	-0.01

AD, Alzheimer's disease; AxD, axial diffusivity; CC, corpus callosum; CN, cognitively normal; DTI, diffusion tensor imaging; MCI, mild cognitive impairment; MD, mean diffusivity; MOF, medialorbitofrontal; PC, posteriorcingulate; PO, pars orbitalis; RAC, rostralanteriorcingulate; RD, radial diffusivity; RMF, rostralmiddlefrontal; Sup-T, superficial-temporal; TMT, Trails Making Test B score; UF, uncinate fasciculus.

Bold, p <0.05

Bold†, p <.007 (Bonferroni corrected p)

4. DISCUSSION

This study aimed to examine degenerative changes of the cerebral whte matter tract including superficial white matter tract and their relationships with cognitive functioning in cognitively normal participants and patients with MCI and AD. One of our finding is that participants with MCI showed WM alterations compared to CN, largely within frontal/anterior callosal commissural regions, and these degenerative changes were associated with cognitive functioning especially in patients with MCI.

The corpus callosum (CC) is the largest cerebral WM tract which connects the two cerebral hemispheres, consisting of over 190 million axons [34]. Atrophy of CC may lead to functional disability because of reduced interhemispheric integration. The shape and size of the CC has been previously showed to change in early AD, as annual rates of atrophy was significantly larger in AD patients (−7.7%) than in controls (−0.9%) [35]. The regional frontal callosal WM degeneration in our study is partially in line with previous findings that reduction of volume was predominant in subregions C1 and C5 in CC [35]. The previous explanation for regional callosal atrophy in AD is that shrinkage of CC reflect neuronal degeneration of axons in cortical layer III lost as AD process[36]. Teipel et al. showed that CC atrophy occurs independently of WM degeneration in AD and therefore it may reflect specific AD pathology [37]. Alhough the role of frontal callosal fibers in AD remains unclear yet, our findings demonstrated WM degenerations in frontal CC fibers and significant associations between DTI metrics cognitive functioning, suggesting the microstructural abnormalities in WM could be a manifestation of the AD progression. Further study would be needed to unravel the function of the frontal callosal fibers in MCI and AD.

In the current study, we found a increased MD of fibers of the uncinate fasciculus both in MCI and AD patients and its associations with cognitive scores. The uncinate fasciculus (UF)

is a long-range association fibers connecting the anterior temporal lobes with the anterior prefrontal cortex [38], and it contains the cholinergic fibers from the basal nucleus of Meynert that innervate these cortical regions [39]. Empirical evidence indicates a role of UF for episodic memory, language, social emotional processing, and prefrontal inhibition of the medial temporal lobe structures, and previous DTI literatures provide relatively strong evidence for the role of the UF in episodic memory [40]. Previous findings of the UF in AD remains inconclusive. Some reserchers showed a correlation between DTI metrics in the UF and cognitive symptoms evaluated by MMSE or ADAS-cog in AD patients[41] in line with our investigation, while others concluded there is strong evidence for involvement of UF degeneration in the frontotemporal dementia but not in AD [40].

WM degeneration of the left superficial temporal tract was evident both in MCI and AD participants, and was significantly corrleated with most of cognitive scores in our study. Superficial WM disruptions in temporal lobe in MCI and AD have recently been replicated in DTI studies [42-45]. Based on Braak & Braak staging system, the evolution of neurofibrillary tangles and related neurodegeneration in AD initially develops in the temporal lobe and then spreads to the adjacent neocortex in later stages of AD, [46, 47]. Our results is consistent with patterns of neurofibrillary tangle spreads in early stages of AD, including MCI.

In contrast to MCI, our findings in AD were inconsistent. Participants with AD showed WM alterations in CC_1, UF, sup-T, and CC_RAC but correlations with cognitive functions were not significant, except CC_RAC and ADAS-cog scores. Modest sample size in AD might contribute to our results. It may raise the hypothesis that the degenerative changes of WM associated with AD influence differently from MCI, or vulnerability of cognitive functions to WM change in AD differ from MCI, but previous literatures showed the neuropathological features of amnestic MCI appear to be intermediate between those of normal controls and very

early Alzheimer's dementia [48, 49]. Future study with larger sample size is thought to be needed to explain these results.

The findings of our study should be considered in the following limitations. First, our study sample was only of moderate size, especially in AD group (N = 20). Second, some demographic characteristics (years of education) of the participants were different between MCI and AD groups. Third, according to prior findings that sex difference may exist in WM degeneration in MCI patients [50], our study participants were limited to famale gender. Fourth, our findings were mainly limited to MCI group, and inconsistent results in AD group also making it difficult to generalize. Fifth, effects of GM degeneration on WM changes were not considered. As microstructural changes of WM can be potentially attributed to a linked GM pathology.

Despite these caveats, we found an association between increased diffusivity measures and cognitive functions in female MCI patients. Our study permits new insights into the effects of WM degenerations of frontal commisural fibers, UF, and superficial temporal tracts. Further research is needed to replicate these findings with larger samples including male gender to advance our understandings.

5. Conclusion

DTI could be a biomarkers for identifying the early stages of cognitive dysfunctions in MCI. Given that the DTI parameters changes in some regions of deep and superficial WM, it can play an important role in the diagnosis of MCI. To support this idea, we also showed that there is major WM abnormality in MCI patients and it is associated with cognitive scores measuring general cognitive function and verbal memory in MCI patients. The microstructural changes of frontal commissural tracts, uncinate fasciculus, and left superficial temporal tract are related to the clinical symptoms in MCI.

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ABASTRACT

Alzheimer's disease (AD) is a major neurocognitive disorder presented with short-term memory impairment, and amnestic mild cognitive impairment (aMCI) is known to be a precursor condition of AD. Although atrophy and degeneration of the gray matter are known as major pathologies of AD, white matter abnormalities in AD may occur independently of gray matter abnormalities, and possibily precede gray matter degeneration.

In this study we aimed to investigate the relationship between white matter microstructural integrity and the degree of cognitive deteriorations in female patients with aMCI and AD, using the Alzheimer’s Disease Neuroimaging Initiative (ADNI) data.

Diffusion tensor images of 20 patients with AD, 86 patients with aMCI, and 193 cognitively normal participants were downloaded from the ADNI database. Parameters of diffusion tensor imaging were compared between groups. Amnestic MCI patients showed significantly disrupted hite matter integrity in the frontal commissural tracts, uncinated fasciculus, and superficial temporal tract group compared to the normal control group. These degenerative changes were also associated with cognitive functioning especially in patients with MCI. In AD group, the results were inconsistent.

Diffusion tensor imaging indicators may have the potential to be clues to identify early stages of cognitive impairment. Follow-up researchs of relationship between white matter disruption and cognitive impairment in AD would be needed.

Keywords: Alzheimer’s disease, mild cognitive impairment, diffusion tensor imaging, white matter, cognitive function