Plasma neurofilament light and cerebrospinal fluid biomarkers are associated with white matter damage in Alzheimer's disease

Fardin Nabizadeh (✉ fardinnabizade1378@gmail.com)

Neuroscience Research Group (NRG), Universal Scientific Education and Research Network (USERN),
Tehran, Iran

Mohammad Balabandian

Iran University of Medical Science

Mohammad Reza Rostami

Iran University of Medical Science

Samuel Berchi Kankam

School of Medicine, Tehran University of Medical Science, Tehran, Iran

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Abstract

The most replicated blood biomarker for monitoring Alzheimer's disease is neurofilament light (NFL). Recent evidence revealed that the plasma level of the NFL has a strong predictive value in cognitive decline and is elevated in AD patients. The Diffusion Tensor Imaging (DTI) is understood to reflect white matter disruption, neurodegeneration largely, and synaptic damage in AD. However, there is no investigation of the association between plasma NFL and white matter microstructure integrity. we have investigated the cross-sectional associations of plasma NFL, CSF tau, p tau, and A β with white matter microstructural changes as measured by DTI in 92 mild cognitive impairment (MCI) participants. We investigated potential correlations of the DTI values of each region of the MNI atlas, with plasma NFL, CSF total tau, CSF p tau, and as well as CSF A β , separately using a partial correlation model controlled for the effect of age, sex and APOE ϵ 4 genotype. Our findings revealed a significant correlation between plasma and CSF biomarkers with altered white matter microstructural changes in widespread brain regions. Plasma NFL has a negative correlation with FA and positive correlation with RD, AD, and MD values in different regions. Plasma NFL promises to be an early biomarker of microstructural changes in MCI and for MCI progression to AD.

Introduction

In Alzheimer's diseases (AD), brain changes present years before clinical signs become apparent, and biomarkers have an important role in defining disease pathological signs, progression, and monitoring disease-modifying therapies. Pathological events in the brain include volumetric changes and depositions of amyloid- β plaques and aggregated tau protein, can be measured by magnetic resonance imaging (MRI), positron emission tomography (PET), cerebrospinal fluid (CSF) assays (1). Given that CSF collection needs lumbar puncture and imaging biomarkers are costly, therefore, they are not suitable for common application (2). Blood-based biomarkers with minimal invasiveness and low cost largely lack to track the neurodegenerative process of AD via the identification of the underlying pathological process (3).

Neurofilament light (NFL) is the most promising blood biomarker for monitoring Alzheimer. Recent advancements allow us to use serum NFL as a biomarker for AD in high risk adults (4). NFL is a part of the neural cytoskeleton and is a sensitive marker for neuroaxonal damage (5). Increased levels of NFL correlate with future brain tissue loss, reduce metabolism, and cognitive decline (6). Recent evidence revealed that the plasma level of the NFL has a strong predictive value in cognitive decline and is elevated in AD patients (3, 6, 7).

The Diffusion Tensor Imaging (DTI) is understood to reflect neurodegeneration and white matter disruption, neurodegeneration largely, and synaptic damage in AD (8) and also is a good marker for the early detection of AD and for monitoring disease progression (9). However, there is no investigation of the

relation between plasma NFL and white matter microstructure integrity measured by DTI in Alzheimer's disease.

In this study, we have investigated the associations of plasma NFL, CSF tau, p tau, and A β with white matter microstructural changes as measured by DTI, cross-sectionally in mild cognitive impairment (MCI) patients obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Our initial hypothesis is that plasma NFL and CSF biomarkers' levels might correlate with greater white matter damage in signature AD regions and reflect the underlying pathophysiological processes.

Materials And Methods

Data Acquisition

The data used in this paper extracted from Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI is a public-private partnership, led by Principal Investigator Michael W. Weiner, MD was launched in 2003. The initial goal of ADNI has been combining all serial positron emission tomography (PET), magnetic resonance imaging (MRI), other biological markers, and clinical and neuropsychological measurements to assess the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). We obtained all required data from baseline visits of participants from the ADNI-2 and ADNI-GO for whom the plasma NFL, and CSF tau, p tau, A β levels from screening visit were available. We also downloaded the Diffusion Tensor Imaging (DTI) statistic results of all patients in the cohort at screening visit. We entered 92 patients with MCI. If the MMSE of participants is between 24 and 30, Clinical Dementia Rating greater than 0.5 are classified as MCI if, they had cognition and performance decline, according to the Stroke-Alzheimer's Disease and Related Disorders Association and National Institute of Neurological and Communicative Disorders and (10).

Plasma NFL measurements

Plasma NFL concentration assessing was performed at the Clinical Neurochemistry Laboratory, University of Gothenburg, Sweden. Plasma NFL was analyzed by the Single-Molecule array (Simoa) technique. This technique uses a combination of purified bovine NFL and monoclonal antibodies as a calibrator for assay. All samples were measured in duplicate, except for one (due to technical reasons). Analytical sensitivity was <1.0 pg/mL, and no sample contained plasma NFL levels below the detection limit.

ApoE Genotyping, CSF A β , t-tau, and p-tau Assessments

The APOE genotyping was performed on collected blood samples and results are available at ADNI. The participants with at least one ϵ 4 allele considered as carrier.

CSF collected samples were obtained by lumbar puncture as described by ADNI:

<http://adni.loni.usc.edu/methods/documents/>. levels of CSF biomarkers, including A β , t-tau, and p-tau, were assessed using the micro-bead-based multiplex immunoassay on Luminex platform. For more details regarding CSF specimen collection and analyte measurement, please refer to ADNI.

MRI and PET Analysis and Processing

We extracted post-processed PET images that were standardized in a voxel. Results were available as an average for right and left angular gyri, bilateral posterior cingulate gyrus, and left middle/inferior temporal gyrus. We also extracted the and volumetric data of the whole brain, hippocampus, fusiform, mid temporal, entorhinal, and ventricles.

Post Processed 18F-AV-45 PET images were downloaded as an average amyloid burden of frontal, anterior cingulate, precuneus, and parietal cortex relative to the cerebellum.

Processing method described in :(<http://adni.loni.usc.edu/methods>).

Cognitive assessments

Cognitive condition of participants assessed by the Mini-Mental State Exam (MMSE), which is a commonly used test of cognitive function among the elderly; it includes tests of orientation, attention, memory, language, and visual-spatial skills. MMSE scores were extracted for each patient from the ADNI Mini-Mental Examination.

DTI Imaging Processing

We downloaded the results of the DTI ROI analysis from ADNI cohort that were performed by Thompson Imaging Genetics Center at the Laboratory of Neuro Imaging UCLA School of Medicine and available in (<http://adni.loni.usc.edu/methods>). Details of analysis process described in ADNI.

Statistical analysis

The analysis was performed using SPSS16. First, we used a partial correlation to analyzing the relation between all demographic features, including age, sex, APOE ϵ 4 genotype, average amyloid burden,

average glucose uptake, and MMSE score with CSF biomarkers or plasma NFL while controlling for age, sex, and APOE. Then for analyzing the correlation between age and other demographic features or biomarkers level, we used a partial correlation model adjusted for sex and APOE. Next, we investigated whether CSF biomarkers and plasma NFL cooperate by implementing partial correlation adjusted for age, sex, and APOE. In the last, We investigated potential correlations of the each DTI values of regions according the MNI atlas, with plasma NFL, CSF total tau, CSF p tau, and as well as CSF A β , separately using a partial correlation model controlled for the effect of age, sex and APOE ϵ 4 genotype.

Results

Our population consisted of 92 subjects with MCI, 41 women and 51 men at the baseline visit of ADNI cohort with a mean age of 73.04 years, minimum 56 and maximum 87.8, Mean ADAS 11 score of the study group was 9.08, and mean MMSE score was 27.88, while mean volume of participant's hippocampus was 7086.29 mm³ (Tab1).

Investigating partial correlations controlled for Age, sex, and APOE genotype between relevant baseline characteristics, we found that plasma NfL has a significant correlation with patient's age (correlation coefficient: 0.521; p : 0.000), MMSE score (correlation coefficient: -0.254; p : 0.017), APOE genotype (correlation coefficient: 0.225; p : 0.034), hippocampus (correlation coefficient: -0.280; p : 0.013), entorhinal (correlation coefficient: -0.256; p: 0.023) and ventricles volume (correlation coefficient: 0.268; p : 0.015). Analysis showed Association between patient's age with MMSE score (correlation coefficient: -0.282; p : 0.007), hippocampus (correlation coefficient: -0.428; p : 0.000) and ventricles volume (correlation coefficient: 0.432; p : 0.000), and Average Amyloid burden of frontal, anterior cingulate, precuneus, and parietal cortex relative to the cerebellum (correlation coefficient: 0.356; p : 0.001). Also there is correlation between NfL in plasma with level CSF Tau protein (correlation coefficient: 0.331; p : 0.002) and CSF hyperphosphorylated tau protein (correlation coefficient: 0.282; p : 0.010). Moreover, our finding indicate there is also a significant correlation between plasma NFL and average FDG-PET of angular, temporal, and posterior cingulate (correlation coefficient: -0.250; p : 0.020).

The voxel-wise partial correlation model in MCI patients revealed a strong correlation between plasma NFL levels and a widespread pattern change in different white matter pathways. We found a negative association between plasma NFL and FA values in bilateral cingulum, left hippocampal cingulum, right Cerebral peduncle, left External capsule, bilateral fornix, left Genu of corpus callosum, right Inferior fronto-occipital fasciculus, left Superior fronto-occipital fasciculus, right tapatum, and left Uncinate fasciculus (Tab2). Also, there is a positive correlation between plasma NFL and MD values, which encompass bilateral Anterior corona radiate, left Anterior limb of internal capsule, bilateral Body of corpus callosum, bilateral Cingulum, left hippocampal cingulum, bilateral fornix, bilateral Genu of corpus callosum, right Posterior thalamic radiation, right Retrolenticular part of internal capsule, right Splenium of corpus callosum, bilateral Superior corona radiate, bilateral Superior fronto-occipital fasciculus, left Superior

longitudinal fasciculus, bilateral Sagittal stratum, bilateral tapatum, and left Uncinate fasciculus (Tab2). Same results of partial correlation revealed an increase in AD value in bilateral Anterior corona radiate, left Anterior limb of internal capsule, bilateral corpus callosum, left hippocampal cingulum, right fornix, right Posterior thalamic radiation, right Retrolenticular part of internal capsule, bilateral Superior corona radiate, bilateral Superior fronto-occipital fasciculus, and right Sagittal stratum (Tab2). Higher plasma NFL was associated with higher baseline RD value in wide regions including bilateral Anterior corona radiate, left Anterior limb of internal capsule, bilateral corpus callosum, bilateral Cingulum, bilateral hippocampal cingulum, bilateral fornix, right Inferior fronto-occipital fasciculus, right Posterior thalamic radiation, right Retrolenticular part of internal capsule, bilateral Superior corona radiate, bilateral Superior fronto-occipital fasciculus, left Superior longitudinal fasciculus, bilateral Sagittal stratum, bilateral tapatum, and left Uncinate fasciculus (Tab2).

When CSF tau was investigated in a correlation model with connectometry values, lower baseline MD value in more widespread regions, and higher FA value in some regions correlates with CSF tau (Tab3). Our finding also indicates an overall negative association between AD and RD values with the CSF level of tau protein (Tab3). Increasing in the average amyloid burden and lower ventricles volume is correlated with tau (correlation coefficient: 0.355; p : 0.020) (correlation coefficient: -0.306; p : 0.007) and p tau (correlation coefficient: 0.366; p : 0.001) (correlation coefficient: -0.266; p : 0.020) in CSF respectively.

Significant associations were identified between Higher CSF p tau and lower MD, AD, and RD values in wide different brain pathways, and positive correlation observed in FA values in MCI patients (Tab4).

We cannot find any correlation between CSF A β level with RD values in regions, By contrast, there is an association between A β level and some variables including AD, FA, and MD in some regions, hippocampus volume, MMSE scores, and in average Amyloid burden in regions previously noted (Tab5).

In the last, we Investigated the association between baseline patients characteristics, CSF biomarkers, and APOE 4 genotype. We implemented a partial correlation controlled for sex and age for this purpose. our findings revealed that APOE 4 genotype has strong correlation with Amyloid burden in PET imaging (correlation coefficient: 0.425; p : 0.000), tau (correlation coefficient: 0.342; p : 0.001) and p tau in CSF (correlation coefficient: 0.361; p : 0.001).

Discussion

In a cross-sectional study performed on the ADNI cohort, we investigated predictive role of plasma levels of NFL for regional white matter changes in patients with MCI. Results of voxel-wise partial correlation analysis in our patients revealed a significant correlation between plasma NFL levels and a widespread pattern change in different white matter pathways (Tab2). First, we analyze the relation of plasma NFL and age to other patient's characteristics, including MMSE score, hippocampus, fusiform, ventricles, Entorhinal, mid temporal, and whole brain volume, average amyloid deposition in frontal, anterior cingulate, precuneus, and parietal cortex, average glucose uptake of angular, temporal, and posterior cingulate, CSF level of A β , total tau, p tau, and APOE ϵ 4 genotype. In the next, we implemented a voxel-

wise analysis to assess the correlation of plasma and CSF biomarkers with each DTI value in ROI regions by using partial correlation controlled for effect of age, sex, and APOE ϵ 4 genotype.

Our findings revealed a significant correlation between plasma and CSF biomarkers with altered white matter microstructural changes in widespread brain regions. Plasma NFL has a negative correlation with FA and positive correlation with RD, AD, and MD values in bilateral Cingulum, bilateral hippocampal cingulum, bilateral Anterior corona radiate, Left Anterior limb of internal capsule, Right Posterior thalamic radiation, Right Retrolenticular part of internal capsule, bilateral Superior corona radiate, bilateral Superior fronto-occipital fasciculus, Right Inferior fronto-occipital fasciculus, Left Superior longitudinal fasciculus, Right Sagittal stratum, Bilateral full corpus callosum, and Bilateral fornix. Our findings are in line with Spotorno et al. indicates higher plasma NFL is associated with lower FA value in superior longitudinal fasciculus, the fronto-occipital fasciculus, the anterior thalamic radiation, and the dorsal cingulum bundle in frontotemporal dementia (12). White matter differences between patients with MCI and healthy controls are mostly observed in the corpus callosum, along with limbic pathways, including the fornix, cingulum, and uncinate fasciculus (13). Crucially, these signature regions are involved in the pathological course of Alzheimer's disease, and alterations in white matter integrity in these regions are known to be associated with disease progression from the early stages of AD (14). Also, serum level of NFL correlates with lower FA and Higher RD, AD, and MD in autosomal dominant Alzheimer's disease (15, 16). By investigating diffusion metrics, information about the different specifications of the White matter can be obtained from DTI values. On the other hand the exact relationship between this four values and the physiopathology mechanism is complex (17). Several researchers have previously been working to clarify the relationship between CSF NFL and white matter damage in AD and MCI (18-21). Also, our findings showed that plasma level of NFL has a strong correlation with patient's age, MMSE score, hippocampus, entorhinal, and ventricles volume, and these results are in line with recent research investigated the predictive role of plasma NFL in neurodegeneration and clinical progression of Alzheimer disease (22, 23). At baseline, high plasma NFL was associated with worse general cognition (i.e. MMSE score) (24), which reflected damage to larger myelinated axonal processes of neurons (6). As well as we found that higher plasma NFL has a significant correlation with higher levels of tau and p tau in CSF, but there is no correlation with CSF A β , similarly with Mattsson et al., but also they found a relation with A β (6).

Moreover, based on our results, plasma NFL is elevated in patients with APOE ϵ 4 gene who have a higher risk for developing dementia (25). These findings supported our initial hypothesis that higher plasma NfL levels associated with baseline AD specific changes and altered white matter connections. Coupled with recent evidence, we found a notable correlation between plasma NfL and hypometabolism in angular, temporal, and posterior cingulate (3, 26). With this in mind, plasma NFL level can be utilized as a novel biomarker for neurodegeneration and be considered as candidate instrument to screen neurodegeneration effects in patients with AD (3, 27, 28).

As our expect, and in line with previous studies, our findings revealed a significant correlation between CSF levels of tau, p tau, and A β with DTI values in wide regions affected in the earliest stages of AD (19, 29, 30). Meanwhile, our results showed CSF biomarkers correlated with a higher FA value in some regions. Arguably, the correlations between plasma NfL and CSF biomarkers are often not statistically significant within diagnostic groups and may present confounding errors in diagnosis (6). Another important finding in contrast to Buckley et al. is lack of correlation between CSF tau and p tau with CSF A β levels, whereas there is a strong correlation between average amyloid deposition in frontal, anterior cingulate, precuneus, and parietal cortex relative to the cerebellum with this two biomarkers (31). According to our results, A β is associated with white matter changes in fewer regions comparing to p tau or tau in CSF and plasma NFL. CSF p-tau/A β ratio and p-tau levels are predictor for MCI conversion to AD, but cortical amyloid or tau deposition by using PET is the gold standard to detect high risk MCI patients (32).

The apolipoprotein E (*APOE*) is a most important genetic risk factor for developing AD (33); likewise, recent studies revealed there is a strong correlation between CSF biomarkers and APOE genotype (34, 35); similarly, we found CSF p tau, tau, and amyloid burden are significantly associated with APOE ϵ 4 genotype after implementing a partial correlation adjusted for age and sex.

Generally, plasma NFL track neurodegeneration both in the grey matter or the white matter (36). With these results in mind, our study provides a better understanding of the link between plasma NFL and connectometry changes in Alzheimer's progression. Our findings support the application of the NFL's blood-based measures as a noninvasive and costless biomarker for monitoring people with a high risk of AD in the early stages.

Conclusion

Biomarkers provide the ability to screening changes in the nervous system for diagnosis and prognosis. Blood-based biomarkers are more accessible, noninvasive, and less costly than CSF and imaging markers. Plasma NFL in recent studies showed as a reliable biomarker for conversion of MCI to AD, and in our study reflect white matter damage with neuroimaging measures. However, more efforts are needed for complete understanding and define a standard cutoff for blood measure of NFL.

Declarations

******Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing

of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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Competing interests

The authors declare no competing interests.

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Tables

Table1. Patient Characteristic

	MCI (N=92)
Sex(M/F)	51/41
Age(mean, SD), years	73.04($\pm$ 6.41)
Education(mean, SD) ,years	16.07($\pm$ 2.64)
MMSE score (mean, SD)	27.88($\pm$ 1.81)
Hippocampus volume (mean, SD), mm ³	7086.29($\pm$ 980.74)
Entorhinal volume (mean, SD), mm ³	3700.28($\pm$ 737.38)
Fusiform volume (mean, SD), mm ³	18776.93($\pm$ 2390.82)
Midtemporal volume (mean, SD), mm ³	20914.77($\pm$ 2346.20)
Ventricles volume (mean, SD), mm ³	37346.21($\pm$ 21504.29)
Whole brain volume (mean, SD), mm ³	1067638.30($\pm$ 99241.80)
APOE ϵ 4 +/-	47/45
Total Number	92

Mini-Mental State Exam(MMSE)

TABLE2. Significant Results of partial Correlation Analyses of DTI metrics and Plasma NFL Levels

White matter tract	Fractional anisotropy	Mean diffusivity	Radial diffusivity	Axial diffusivity
	<i>Correlation Coefficient</i>	<i>Correlation Coefficient</i>	<i>Correlation Coefficient</i>	<i>Correlation Coefficient</i>
Left Cingulum	-0.258*	0.245*	0.278*	0.115
Right Cingulum	-0.270*	0.252*	0.293**	0.094
Left hippocampal cingulum	-0.267*	0.276*	0.290**	0.237
Right hippocampal cingulum	-0.230*	0.215	0.236*	0.154
Left Anterior corona radiata	-0.072	0.312*	0.277*	0.349**
Right Anterior corona radiata	-0.064	0.296*	0.267*	0.326*
Left Anterior limb of internal capsule	-0.218	0.278*	0.289*	0.224*
Right Posterior thalamic radiation	-0.205	0.217	0.219*	0.202
Right Retrolenticular part of internal capsule	-0.213	0.337	0.354**	0.258*
Left Superior corona radiata	-0.123	0.289*	0.303*	0.252*
Right Superior corona radiata	-0.167	0.267*	0.290*	0.220*
Left Superior fronto-occipital fasciculus	-0.221*	0.317*	0.313*	0.320*
Right Superior fronto-occipital fasciculus	-0.213	0.381**	0.376**	0.386**
Right Inferior fronto-occipital fasciculus	-0.249*	0.174	0.247*	0.030
Left Superior longitudinal fasciculus	-0.154	0.221*	0.232*	0.155
Right Sagittal stratum	-0.183	0.309*	0.317*	0.271*
Bilateral full corpus callosum	-0.207	0.260*	0.252*	0.261*
Bilateral fornix	-0.303*	0.270*	0.284*	0.222*

*p < 0.05

**p<0.001

***p<0.001

Pearson’s correlation coefficient of DTI metrics value of the brain regions and plasma NFL levels controlled for age, APOE, and sex.

TABLE3. Significant Results of partial Correlation Analyses of DTI metrics and CSF Tau Levels

White matter tract	Fractional anisotropy	Mean diffusivity	Radial diffusivity	Axial diffusivity
	<i>Correlation Coefficient</i>	<i>Correlation Coefficient</i>	<i>Correlation Coefficient</i>	<i>Correlation Coefficient</i>
Left Anterior corona radiata	0.249*	-0.286*	-0.301**	-0.230*
Right Anterior corona radiata	0.287*	-0.311**	-0.328**	-0.247*
Left Cerebral peduncle	-0.118	-0.127	-0.039	-0.260*
Right Cerebral peduncle	0.050	-0.209	-0.176	-0.245*
Left Corticospinal tract	-0.006	-0.223	-0.209	-0.244*
Left Posterior corona radiata	-0.132	-0.304**	-0.236*	-0.361**
Right Posterior corona radiata	-0.089	-0.188	-0.131	-0.247*
Left Posterior thalamic radiation	0.233*	-0.294**	-0.294**	-0.279*
Left Posterior limb of internal capsule	-0.184	-0.205	-0.035	-0.374**
Right Posterior limb of internal capsule	-0.249*	-0.335**	-0.256*	-0.389**
Left Retrolenticular part of internal capsule	0.035	-0.278*	-0.254*	-0.275*
Left Superior corona radiata	-0.204	-0.351**	-0.286*	-0.409***
Right Superior corona radiata	-0.179	-0.319**	-0.273*	-0.366**
Left Superior fronto-occipital fasciculus	0.205	-0.337**	-0.335**	-0.339**
Right Superior fronto-occipital fasciculus	0.208	-0.326**	-0.327**	-0.321**
left Sagittal stratum	0.170	-0.402***	-0.387***	-0.396***
Right Sagittal stratum	0.303**	-0.304**	-0.327**	-0.241*
Bilateral full corpus callosum	0.293**	-0.323**	-0.327**	-0.292**
Left tapatum	0.267*	-0.338**	-0.329**	-0.351**
Right tapatum	0.207	-0.292**	-0.281*	-0.307**
Bilateral fornix	0.212	-0.241*	-0.239*	-0.232*

*p < 0.05

**p<0.01

***p<0.001

Pearson’s correlation coefficient of DTI metrics value of the brain regions and plasma NFL levels controlled for age, APOE, and sex.

TABLE4. Significant Results of partial Correlation Analyses of DTI metrics and CSF p Tau Levels

White matter tract	Fractional anisotropy	Mean diffusivity	Radial diffusivity	Axial diffusivity
	<i>Correlation Coefficient</i>	<i>Correlation Coefficient</i>	<i>Correlation Coefficient</i>	<i>Correlation Coefficient</i>
Left Anterior corona radiata	0.209	-0.253*	-0.265*	-0.204
Right Anterior corona radiata	0.249*	-0.280*	-0.294**	-0.223
Left Cerebral peduncle	-0.111	-0.117	-0.033	-0.235*
Right Cerebral peduncle	0.069	-0.209	-0.176	-0.247*
Left Corticospinal tract	0.042	-0.222	-0.214	-0.232*
Left Posterior corona radiata	-0.058	-0.286*	-0.238*	-0.320**
Left Posterior thalamic radiation	0.202	-0.232*	-0.238*	-0.211
Left Posterior limb of internal capsule	-0.162	-0.192	-0.038	-0.343**
Right Posterior limb of internal capsule	-0.220	-0.170	-0.022	-0.337**
Left Retrolenticular part of internal capsule	0.051	-0.299**	-0.234*	-0.341**
Right Retrolenticular part of internal capsule	0.122	-0.258*	-0.241*	-0.247*
Left Superior corona radiata	-0.157	-0.335**	-0.282*	-0.378**
Right Superior corona radiata	-0.149	-0.298**	-0.259*	-0.335**
Left Superior fronto-occipital fasciculus	0.168	-0.308**	-0.305**	-0.311**
Right Superior fronto-occipital fasciculus	0.160	-0.304**	-0.303**	-0.303**
left Sagittal stratum	0.193	-0.335**	-0.351**	-0.334**
Right Sagittal stratum	0.303**	-0.294**	-0.321**	-0.225*
Bilateral full corpus callosum	0.275*	-0.294**	-0.301**	-0.257*
Left tapatum	0.229*	-0.280*	-0.276*	-0.286**
Right tapatum	0.209	-0.260*	-0.256*	-0.261*
Right fornix	0.204	-0.254*	-0.249*	-0.250*
Right Uncinate fasciculus	-0.041	0.238*	0.221	0.256*

*p < 0.05

**p<0.01

***p<0.001

Partial correlation coefficient of DTI metrics value of the brain regions and plasma NFL levels controlled for age, APOE, and sex.

TABLE5. Significant Results partial Correlation Analyses of DTI metrics and CSF A β Levels

White matter tract	Fractional anisotropy	Mean diffusivity	Radial diffusivity	Axial diffusivity
	<i>Correlation Coefficient</i>	<i>Correlation Coefficient</i>	<i>Correlation Coefficient</i>	<i>Correlation Coefficient</i>
Right hippocampal cingulum	-0.270	-0.466*	-0.318	-0.664***
Left Cerebral peduncle	-0.332	-0.080	0.088	-0.425*
Right Superior corona radiata	-0.444*	-0.041	0.038	-0.145
Right Retrolenticular part of internal capsule	-0.426*	-0.044	0.120	-0.309
Right Sagittal stratum	-0.463*	-0.078	0.050	-0.294

*p < 0.05

**p<0.01

***p<0.001

partial correlation coefficient of DTI metrics value of the brain regions and plasma NFL levels controlled for age, APOE, and sex.