Plasma neurofilament light is associated with white matter damage in Alzheimer's disease

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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, and synaptic damage in AD. However, few investigations have been carried out on the association between plasma NFL and white matter microstructure integrity. We have investigated the cross-sectional associations of plasma NFL, CSF total tau, phosphorylated tau, and Amyloid 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, 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 negatively correlates with FA and the positive correlation with RD, DA, and MD values in different regions. Our findings showed that plasma NFL is associated with white matter changes and AD-related features, including atrophy and hypometabolism. Plasma NFL promises to be an early biomarker of microstructural changes in MCI and MCI progression to AD.

Introduction

In Alzheimer's disease (AD), brain changes are 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 including volumetric changes and depositions of amyloid- β (A β) plaques and aggregated tau protein can be measured by magnetic resonance imaging (MRI), positron emission tomography (PET), and cerebrospinal fluid (CSF) assays (1). Given that the CSF collections need lumbar puncture, they are invasive and not suitable for common applications (2). There is a great lack of blood-based biomarkers with minimal invasiveness and low cost (3).

Neurofilament light (NFL) is a promising blood biomarker for monitoring Alzheimer's and axonal damage. Recent advancements allow us to use serum NFL as a biomarker for cognitive decline in AD and Parkinson's disease (4). NFL is part of the neural cytoskeleton and is a sensitive marker for neuroaxonal damage (5). Increased NFL levels correlate with future brain tissue loss, reduce metabolism, and cognitive decline (6). Higher plasma levels of NFL have a predictive value for cognitive decline in AD patients (3, 6, 7).

Diffusion Tensor Imaging (DTI) is understood to reflect neurodegeneration, white matter disruption, and synaptic damage in AD (8), while white matter changes could be a good target for early detection of dementia (9). However, little is known about the relation between plasma NFL and white matter microstructure integrity measured by DTI in Alzheimer's disease.

In this study, we have conducted a cross-sectional investigation on the associations of plasma NFL with white matter microstructural changes as detectable by the analysis of DTI in patients with mild cognitive impairment (MCI) from the Alzheimer's disease Neuroimaging Initiative (ADNI) cohort. Moreover, we assessed the relation between CSF biomarkers, including total tau, phosphorylated tau 181 (p tau 181), and A β with white matter changes. We hypothesize that plasma NFL correlates with white matter structural integrity and AD-related features, including hypometabolism, atrophy, and cognitive decline in patients with cognitive impairments. Also, we hypothesized that CSF biomarkers might correlate with white matter changes in our population. The MCI patients were enrolled in order to investigate the association in the early stage of dementia.

Materials And Methods

Data Acquisition

The data used in this study were extracted from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As a public-private partnership, the ADNI was launched in 2003, led by Principal Investigator Michael W. Weiner, MD. The initial goal of ADNI has been to combine 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 levels from the screening visit were available. We also downloaded the Diffusion Tensor Imaging (DTI) statistic results of all patients in the cohort at the screening visit. We enrolled 92 patients with MCI and a mean age of 73.04 years, including 51 men for which all the required data was available. Participants classified as MCI if their MMSE score was between 24 and 30, Clinical Dementia Rating was greater than 0.5, and 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 (10).

Plasma NFL measurements

Plasma NFL concentration assessment 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 are considered as carrier, as described by ADNI:

FDG-PET Processing

We extracted post-processed PET images that were normalized by SPM in the PET MNI template. Five MetaROI volumes, including right and left angular gyri, bilateral posterior cingulate gyrus, and left middle/inferior temporal gyrus, were used. The mean count from the MetaROI for each subject was extracted by SPM.

MRI processing

We also extracted the results of derived volumetric analysis of MRI images accessible as the volume of the whole brain, hippocampus, fusiform, mid temporal, entorhinal, and ventricles. The complete analysis and procedure are fully described in ADNI.

Cognitive assessments

The cognitive condition of participants was 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 regions of interest (ROI) analysis from the ADNI cohort. DTI scans underwent normalization using the MNI *nu_correct* tool (www.bic.mni.mcgill.ca/software/). Non-brain tissues were removed by the Brain Extraction Tool (BET) from FSL (11). The T1-weighted image was aligned to a version of the Colins27 brain template (12) using FSL's *flirt* (13). The Colin27 brain was zero-padded to have a cubic isotropic image size (220x220x220 1mm³) and then downsampled (110x110x110 2mm³) to be more similar to the DWI resolution. A single diffusion tensor (14) was modeled at each voxel in the brain, and scalar anisotropy and diffusivity maps were obtained from the resulting diffusion tensor eigenvalues (λ_1 , λ_2 , λ_3), then Fractional anisotropy (FA) and mean diffusivity (MD) were calculated. The FA image is registered from the JHU DTI atlas (15) for each participant using a previously described mutual information based elastic registration algorithm (16). We then applied the deformation to the stereotaxic JHU "Eve" WM atlas labels (http://cmrm.med.jhmi.edu/cmrm/atlas/human_data/file/AtlasExplanation2.htm) using nearest-neighbor interpolation to avoid intermixing of the labels. This placed the atlas ROIs in the same coordinate space as our DTI maps. Then the average FA and MD within the boundaries of each of the ROI masks for each subject were calculated. Tensor based spatial statistics (17) was also performed, and the mean FA in regions of interest along the skeleton was extracted. Tract-based spatial statistics (TBSS) was performed according to protocols outlined by the ENIGMA-DTI group http://enigma.loni.ucla.edu/wpcontent/uploads/2012/06/ENIGMA_TBSS_protocol.pdf

In short, all subjects were registered to the ENIGMA-DTI template in ICBM space and standard *tbss* steps were performed to project individual FA maps onto the skeletonized ENIGMA-DTI template. ROI extraction was also performed according to the following protocol to extract the mean FA in ROIs along with the skeleton: http://enigma.ionu.edu/wpcontent/uploads/2012/06/ENIGMA_ROI_protocol.pdf.

Statistical analysis

The analysis was performed using SPSS16. First, we used partial correlation to analyze the relation between the plasma level of NFL and average glucose uptake, volumetric variables, and MMSE score while controlling for age, sex, and APOE. Then, in order to analyze the correlation between plasma NFL and age or APOE genotype, we used a partial correlation model adjusted for sex, age, and APOE. Finally, we investigated the potential correlations of the DTI values including MD (Mean Diffusivity), RD (Radial Diffusivity), DA (Axial Diffusivity), and FA (Fractional Anisotropy) of each region according to the MNI atlas, with plasma NFL, CSF total tau, CSF p tau 181 and A β , separately using a partial correlation model controlled for the effect of age, sex and APOE ϵ 4 genotype. The bootstrap method was used to control type I error due to multiple comparisons. P values below 0.05 were considered as significant.

Results

Patient's characteristics

Our population consisted of 92 patients with MCI, 41 women and 51 men at the baseline visit of the ADNI cohort with a mean age of 73.04($\pm$ 6.41) years, and mean MMSE score of 27.88, while the mean volume of the participant's hippocampus was 7086.29 mm³. Other demographical details are described in Table 1.

Plasma NFL and demographic features

By investigating partial correlations controlled for age, sex, and APOE genotype between relevant baseline characteristics, we found that plasma NFL has a significant correlation with MMSE score (correlation coefficient: -0.254; p: 0.017), hippocampus (correlation coefficient: -0.280; p: 0.013), and entorhinal volume (correlation coefficient: -0.256; p: 0.023). Moreover, our findings 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). Also, plasma NFL correlates with patient's age (correlation coefficient: 0.521; p: <0.001) and APOE genotype (correlation coefficient: 0.225; p: 0.034).

Plasma NFL and microstructural changes

The voxel-wise partial correlation model in MCI patients revealed a strong correlation between plasma NFL levels and a widespread pattern change in white matter regions. We found a negative association between plasma NFL and FA values in the bilateral cingulum, left hippocampal cingulum, and right cerebral peduncle (as shown in Table 2). In addition, there is a positive correlation between plasma NFL

and MD values, which encompass bilateral anterior corona radiate, left anterior limb of the internal capsule, bilateral body of the corpus callosum, bilateral cingulum, left hippocampal cingulum, bilateral fornix, bilateral genu of the corpus callosum, right retrolenticular part of the internal capsule, right splenium of the corpus callosum, bilateral superior corona radiate, right superior fronto-occipital fasciculus, left superior longitudinal fasciculus, and right sagittal stratum (Table 2). The same results of partial correlation revealed an increase in DA value in the bilateral anterior corona radiate, bilateral corpus callosum, left hippocampal cingulum, right retrolenticular part of the internal capsule, left superior corona radiate, right superior fronto-occipital fasciculus, and right sagittal stratum (as shown in Table 2). Higher plasma NFL was associated with higher baseline RD values in wide regions including bilateral anterior corona radiate, left anterior limb of the internal capsule, bilateral body, and genu of the corpus callosum, bilateral cingulum, bilateral hippocampal cingulum, bilateral fornix, right inferior fronto-occipital fasciculus, right retrolenticular part of the internal capsule, bilateral superior corona radiate, right superior fronto-occipital fasciculus, left superior longitudinal fasciculus, right sagittal stratum, and left uncinate fasciculus (as shown in Table 2).

CSF biomarkers and microstructural changes

When CSF total tau was investigated in a correlation model with connectometry values, the lower baseline MD value in more widespread regions and higher FA value in some regions correlated with the CSF tau (as shown in Table 3). Our findings also indicate an overall negative association between AD and RD values with the CSF level of total tau protein (Table 3).

Significant associations were identified between higher CSF p tau 181 and lower MD, AD, and RD values in different wide brain pathways, and a positive correlation was observed in FA values in MCI patients (Table 4).

We cannot find any correlation between CSF A β level with RD values in these regions. In contrast, there is an association between A β level and some variables, including AD, FA, and MD in some regions as previously noted (Table 5).

Plasma NFL and CSF biomarkers

We only found a correlation between NFL in plasma with level CSF tau protein (correlation coefficient: 0.331; p: 0.002) and CSF phosphorylated tau protein (correlation coefficient: 0.282; p: 0.010). Meanwhile, there is no significant correlation between plasma NFL and A β in CSF.

Discussion

In a cross-sectional study performed on the ADNI cohort, we investigated the 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 regions (Table 2). First, we analyze the relation of

plasma NFL with other patient's characteristics, including MMSE score, hippocampus, fusiform, ventricles, entorhinal, mid temporal, and whole brain volume, average glucose uptake of angular, temporal, and posterior cingulate, age, and APOE ϵ 4 genotype. Finally, we assessed the correlation between CSF biomarkers and DTI value in each region.

Our findings revealed a significant correlation between plasma NFL with altered white matter microstructural changes in widespread brain regions. Plasma NFL has a negative correlation with FA and a positive correlation with RD, DA, and MD values in the bilateral cingulum, bilateral hippocampal cingulum, bilateral anterior corona radiate, left anterior limb of the internal capsule, right retrolenticular part of the internal capsule, bilateral superior corona radiate, right 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. who indicate that 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 (18). 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 (19). Crucially, these signature regions are involved in the white matter changes due to 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 (20). Also, the serum level of NFL correlates with lower FA and higher RD, DA, and MD in autosomal dominant Alzheimer's disease (21, 22). By investigating diffusion metrics, information about the white matter's different specifications can be obtained from DTI values.

On the other hand, the exact relationship between these four values and the physiopathology mechanism is complex (23). Several researchers have previously been attempting to clarify the relationship between CSF NFL and white matter damage in AD and MCI (24-27). In people without cognitive impairment, CSF NFL is associated with compromised white matter microstructure. However, Alzheimer's Dementia Neuroimaging Initiative (ADNI) cross-sectional data with a large sample size revealed significantly higher plasma NFL levels in patients with MCI compared to the cognitively unimpaired (28, 29). Generally, both CSF and plasma NFL track neurodegeneration both in the grey matter or the white matter (30).

Our findings also 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 that investigated the predictive role of plasma NFL in neurodegeneration and clinical progression of Alzheimer's disease (31, 32). At baseline, high plasma NFL was associated with worse general cognition (i.e., MMSE score) (33), which reflected damage to larger myelinated axonal processes of neurons (6). In addition, 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 , similar to the study by Mattsson et al.; however, they also found a correlation with A β (6).

Moreover, based on our results, plasma NFL is elevated in patients with the APOE ϵ 4 gene who have a higher risk for developing dementia (34, 35). These findings supported our initial hypothesis that higher plasma NFL levels are 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, 36). With this in mind, plasma NFL level can be utilized as a novel biomarker for neurodegeneration and be considered a candidate instrument for screening neurodegeneration effects in patients with AD (3, 37, 38).

As per our expectations 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 (25, 39, 40). 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 the lack of correlation between CSF tau and p tau with CSF A β levels (41). According to our results, A β is associated with white matter changes in fewer regions compared to p tau or tau in CSF and plasma NFL. CSF p-tau/A β ratio and p-tau levels are a predictor for MCI conversion to AD, but cortical amyloid or tau deposition using PET is the gold standard to detect high risk MCI patients (42).

Generally, plasma NFL track neurodegeneration both in the grey matter or the white matter (43). With these results in mind, our study provides a better understanding of the link between plasma NFL, CSF tau, p tau, and A β with white matter 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 screen changes in the nervous system for diagnosis and prognosis. Blood-based biomarkers are more accessible, noninvasive, and less costly than CSF and imaging markers. In recent studies, plasma NFL was shown as a reliable biomarker for the conversion of MCI to AD, and in our study it reflects white matter damage with neuroimaging measures. However, further efforts are necessary for a complete understanding and to define a standard cutoff for the blood measure of NFL.

Declarations

** Data used in this article's preparation were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI investigators contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at:

The declaration of interest: none

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Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

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Tables

TABLE1. Patient Characteristics

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)

TABLE 2. Significant Results of partial Correlation Analyses of DTI metrics and Plasma NFL Levels

Regions	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 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
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

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

TABLE 3. Significant Results of partial Correlation Analyses of DTI metrics and CSF Tau Levels

Regions	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

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

TABLE 4. Significant Results of partial Correlation Analyses of DTI metrics and CSF p Tau Levels

Regions	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*

*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.

TABLE 5. Significant Results Partial Correlation Analyses of DTI metrics and CSF A β Levels

Regions	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 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.