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ORIGINAL ARTICLE

Plasma neurofilament light levels correlate with white matter damage prior to Alzheimer's disease: results from ADNI

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Abstract

Background The blood biomarker neurofilament light (NFL) is one of the most widely used for monitoring Alzheimer's disease (AD). According to recent research, a higher NFL plasma level has a substantial predictive value for cognitive deterioration in AD patients. Diffusion tensor imaging (DTI) is an MRI-based approach for detecting neurodegeneration, white matter (WM) disruption, and synaptic damage. There have been few studies on the relationship between plasma NFL and WM microstructure integrity.

Aims The goal of the current study is to assess the associations between plasma levels of NFL, CSF total tau, phosphorylated tau181 (P-tau181), and amyloid-β (Aβ) with WM microstructural alterations.

Methods We herein have investigated the cross-sectional association between plasma levels of NFL and WM microstructural alterations as evaluated by DTI in 92 patients with mild cognitive impairment (MCI) provided by Alzheimer's Disease Neuroimaging Initiative (ADNI) participants. We analyzed the potential association between plasma NFL levels and radial diffusivity (RD), axial diffusivity (AxD), mean diffusivity (MD), and fractional anisotropy (FA) in each region of the Montreal Neurological Institute and Hospital (MNI) atlas, using simple linear regression models stratified by age, sex, and APOE ε4 genotype.

Results Our findings demonstrated a significant association between plasma NFL levels and disrupted WM microstructure across the brain. In distinct areas, plasma NFL has a negative association with FA in the fornix, fronto-occipital fasciculus, corpus callosum, uncinate fasciculus, internal capsule, and corona radiata and a positive association with RD, AxD, and MD values in sagittal stratum, corpus callosum, fronto-occipital fasciculus, corona radiata, internal capsule, thalamic radiation, hippocampal cingulum, fornix, and cingulum. Lower FA and higher RD, AxD, and MD values are related to demyelination and degeneration in WM.

Conclusion Our findings revealed that the level of NFL in the blood is linked to WM alterations in MCI patients. Plasma NFL has the potential to be a biomarker for microstructural alterations. However, further longitudinal studies are necessary to validate the predictive role of plasma NFL in cognitive decline.

Keywords Neurofilament light chain · Diffusion tensor imaging · Alzheimer's disease · Mild cognitive impairment · Biomarker · White matter

Introduction

Alzheimer's disease (AD) is one of the most prevalent neurodegenerative diseases, affecting millions of individuals worldwide and causing a negative impact on the health care system [1]. Structural changes occur in the brain mainly with aging before AD manifestation. These pathological events include structural changes, depositions of amyloid-β (Aβ) plaques, and hyperphosphorylated tau (P-tau) protein aggregation. Severe cognitive declines are detected using

Data used to prepare 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 the 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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diagnostic methods such as magnetic resonance imaging (MRI), cerebrospinal fluid (CSF), and positron emission tomography (PET) assays [1]. Since the CSF collection via lumbar puncture (LP) is invasive and unsuitable for common application [2], there is an unmet demand for cost-effective, blood-based biomarkers with minimal invasiveness [3].

Biomarkers are essential in disease diagnosis as well as monitoring progression and response to disease-modifying therapies. Accordingly, neurofilament light (NFL) is one of the neural cytoskeleton's scaffolding proteins and is considered a sensitive marker of axonal damage [4]. Recent advancements support the role of serum NFL as a biomarker for cognitive decline in both AD and Parkinson's diseases [5]. Increased NFL levels have been linked to future brain tissue loss, decreased brain metabolism, and cognitive impairment [6]. Furthermore, previous investigations indicated that increased NFL plasma levels might predict cognitive deterioration in individuals with MCI and AD patients [3, 6–8].

Diffusion tensor imaging (DTI) allows in vivo non-invasive measurement of neurodegeneration, white matter (WM) disruption, and synaptic damage in patients with AD [9]. Emerging research points to WM changes as a marker for pathological significance, which could be a promising target for early dementia diagnosis [10]. Early accumulation of CSF and plasma P-tau has been reported in the corpus callosum of Alzheimer's brain, which is also associated with WM decline [11, 12].

There is not enough evidence of whether plasma NFL is associated with WM microstructure in people with MCI, and owing to the potential predictive role of NFL for AD [13], in the current research, we carried out a cross-sectional assessment to clarify the association between plasma NFL levels with DTI-detected microstructural changes of WM in the MCI patients. As recent studies have shown plasma NFL as a biomarker of AD [3, 6, 14], we aimed to examine the association of WM changes and NFL in the early stages before reaching AD.

Materials and methods

Data acquisition

The Alzheimer's Disease Neuroimaging Initiative (ADNI) database provided the data for this investigation (adni.loni.usc.edu). The ADNI was founded in 2003 as a public–private partnership directed by Principal Investigator Michael W. Weiner, MD. The initial purpose of ADNI is to assess the progression of MCI and early AD by combining all serial PET, MRI, biological markers, clinical and neuropsychological measures. www.adni-info.org has the most up-to-date information.

Participants

We provided all required data from the baseline visits of participants at ADNI-2 and ADNI-GO cohort for whom the plasma NFL levels, CSF markers, and DTI statistic results were available. We included 92 MCI patients (41 women and 51 men) with a mean age of 73.04 years. All MCI subjects were diagnosed as MCI based on the following criteria: this diagnostic classification required Mini-Mental State Examination (MMSE) scores between 24 and 30, a memory complaint, objective memory loss measured by education-adjusted scores on the Wechsler Memory Scale Logical Memory II, a Clinical Dementia Rating (CDR) of 0.5, absence of significant impairment in other cognitive domains, essentially preserved activities of daily living and absence of dementia [15]. All the extracted data were from the baseline visit.

Plasma NFL measurement

Plasma concentration of NFL was assessed at the Clinical Neurochemistry Laboratory, University of Gothenburg, Sweden. Plasma NFL level was analyzed by the Single-Molecule array (Simoa) technique, which uses purified bovine NFL and monoclonal antibodies as a calibrator for assay. All samples were collected at baseline visit and 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 and assessment of CSF Aβ1-42, tau, and P-tau181

The APOE genotyping of MCI patients was performed on collected blood samples. The participants with at least one ε4 allele are considered carriers, as described by ADNI (http://adni.loni.usc.edu/methods/documents/).

Luminex platform acquired CSF samples, and levels of CSF biomarkers such as A1-42, total tau, and P-tau181 were determined using the Luminex platform micro-bead-based multiplex immunoassay. Tau phosphorylated at threonine 181 (p-tau181) has been verified as a biomarker for AD and is now being used in studies. ADNI (http://adni.loni.usc.edu/methods/documents/) contains more information on CSF specimen collection and analytic measurement.

Cognitive assessments

The Mini-Mental State Exam (MMSE), a typical cognitive function test, was used to examine the individuals' cognitive

status. Orientation, attention, memory, language, and visual-spatial skills are all assessed by MMSE. The ADNI database was used to obtain MMSE values for each patient.

DTI processing and image analysis

We downloaded the results of the DTI regions of interest (ROI) analysis from the ADNI cohort. DTI scans underwent normalization using the Montreal Neurological Institute and Hospital (MNI) *nu_correct* tool (www.bic.mni.mcgill.ca/software/). non-brain tissues were removed by the Brain Extraction Tool (BET) from FSL [16]. The T1-weighted image was aligned to a version of the Colins27 brain template [17] using FSL's *flirt* [18]. The Colins27 brain was zero-padded to have a cubic isotropic image size ($220 \times 220 \times 220$ 1 mm^3) and then down-sampled ($110 \times 110 \times 110$ 2 mm^3) to be more similar to the Diffusion-weighted imaging (DWI) resolution. A single diffusion tensor was modeled at each voxel in the brain [19]. Scalar anisotropy and diffusivity maps were obtained from the resulting diffusion tensor eigenvalues (λ1, λ2, λ3). Then Fractional anisotropy (FA), which shows directional dependence of the diffusion process and mean diffusivity (MD), Radial diffusivity (RD), and Axial diffusivity (AxD), which reflects the amount of diffusion were calculated. Lower FA and higher RD, AxD, MD are related to demyelination and degeneration in WM. We used a previously mentioned shared information-based elastic registration algorithm to allocate the FA image from the Johns Hopkins University (JHU) DTI atlas [20] to each subject [21]. To prevent label intermixing, we used nearest-neighbor interpolation to apply the deformation to the stereotaxic JHU "Eve" WM atlas labels (http://cmrm.med.jhmi.edu/cmrm/atlas/human_data/file/Atlas Explanation2.htm). This placed the atlas ROIs in the same coordinate space as our DTI maps. Then, the average FA and MD were calculated within the boundaries of each ROI mask of each subject. Tensor-based spatial statistics [22] were also performed, and the mean FA in the ROIs was extracted along with the skeleton. Tract-based spatial statistics (TBSS), an automated, observer-independent approach for assessing FA in the major white matter tracts on a voxel-wise basis across groups of subjects was performed according to the protocols outlined by the ENIGMA-DTI group (http://enigma.loni.ucla.edu/wpcontent/uploads/2012/06/ENIGMA_TBSS_protocol.pdf). Briefly, all subjects were registered to the ENIGMA-DTI template in International Consortium for Brain Mapping (ICBM) space, a stereotaxic probabilistic white matter atlas, and standard TBSS steps were performed to project individual FA maps onto the skeletonized ENIGMA-DTI template. ROI extraction was also performed to extract the mean FA in ROIs along with the skeleton based on http://enigma.loni.ucla.edu/wpcontent/uploads/2012/06/ENIGMA_ROI_protocol.pdf.

Statistical analysis

The SPSS software (Statistical Package for the Social Sciences, version 16, USA) was used to analyze the data. All analyses were performed while stratifying for APOE ε4 genotype, age (median age:73.2), and sex. First, we conducted several simple linear regression models for assessing the association of plasma NFL and clinical and demographical variables as well as the level of CSF biomarkers (total tau, P-tau181, and Aβ1-42). Next, we measured the association of plasma NFL level and DTI values (including MD, RD, AxD, and FA) in brain regions using simple linear regression models. Multiple comparisons caused type I error; hence the Benjamini–Hochberg method was utilized to address it. Results at P value ≤ 0.05 are considered as significant.

Results

Patient's characteristics

The mean age of the studied population was 73.04 ± 6.41 years, while the mean MMSE score was 27.88. The details of demographical characteristics are described in Table 1. By investigating associations between relevant baseline characteristics and level of plasma NFL stratified by APOE ε4 allele, age, and sex, we found that there was a significant association between plasma NFL and age independent of APOE ε4 carrier (APOE ε4 non-carrier: $\beta = 0.58$, P value < 0.001; versus APOE ε4 carrier: $\beta = 0.52$, P value < 0.001), and also sex (Men: $\beta = 0.54$, P value < 0.001; versus Women: $\beta = 0.45$, P value $= 0.003$) (Table 2). Moreover, education was only associated with plasma NFL in patients with Ages lower than 73.2 years ($\beta = -0.39$, P value $= 0.007$). The results also showed that MMSE score and plasma NFL are significantly associated in APOE ε4 carriers ($\beta = -0.38$, P value $= 0.008$), men ($\beta = -0.36$, P value $= 0.009$), and subjects with Ages higher

Table 1 Demographic characteristics of participants

Sex (M/W)	51/41
Age (mean, SD), years	73.04 (±6.41)
Education (mean, SD), years	16.07 (±2.64)
MMSE score (mean, SD)	27.88 (±1.81)
Plasma NFL level (mean, SD), pg/mL	1160.00 (±322.67)
CSF total tau (mean, SD), pg/mL	278.79 (±107.40)
CSF P-tau 181 (mean, SD), pg/mL	26.59 (±12.73)
CSF Aβ (mean, SD), pg/mL	39.85 (±19.47)
APOE ε4 (±)	47/45
Total Number	92

MMSE Mini-Mental State Exam; *P-tau181* phosphorylated tau181; *Aβ* amyloid-β; *NFL* neurofilament light

Table 2 Linear regression of plasma NFL and demographical and clinical variables stratified by APOE ε4 allele, age, and sex

Characteristics	APOE ε4 non carriers (n = 45)		APOE ε4 carriers (*n* = 47)		Age < 73.2 (*n* = 46)		Age > 73.2 (*n* = 46)		Women (*n* = 41)		Men (*n* = 51)	
	β	*P* value	*β*	*P* value	*β*	*P* value	*β*	*P* value	*β*	*P* value	*β*	*P* value
Age	**0.583**	**< 0.001**	**0.517**	**< 0.001**	0.265	0.078	0.342	0.02	**0.455**	**0.003**	**0.544**	**< 0.001**
Sex	0.005	0.973	− 0.165	0.268	− 0.073	0.63	− 0.093	0.537	_	_	_	_
Education	− 0.18	0.237	-0.21	0.156	0.157	0.298	**− 0.395**	**0.007**	− 0.3	0.057	− 0.491	0.626
MMSE score	− 0.258	0.088	**− 0.38**	**0.008**	− 0.258	0.083	**− 0.299**	**0.043**	− 0.362	0.02	**− 0.361**	**0.009**
APOE ε4	_	_	_	_	0.149	0.324	0.165	0.273	0.17	0.289	0.037	0.796
CSF total tau	**0.463**	**0.002**	**0.296**	**0.048**	**0.327**	**0.034**	**0.441**	**0.003**	**0.403**	**0.012**	0.268	0.066
CSF P-tau181	**0.41**	**0.008**	0.274	0.068	**0.339**	**0.028**	**0.409**	**0.006**	**0.33**	**0.043**	**0.315**	**0.029**
CSF Aβ	**− 0.579**	**0.08**	0.131	0.629	-0.111	0.719	0.428	0.144	0.144	0.654	-0.027	0.926

β value is the coefficient of NFL association and demographical and clinical variables. *P* value as defined using the linear regression model to detect significant associations in MCI subjects. Significant results are bolded

MMSE Mini-Mental State Exam; *P-tau181* phosphorylated tau181; *Aβ* amyloid-β; *NFL* neurofilament light

than 73.2 years ($\beta = -0.29$, *P* value = 0.043). Assessing the association between plasma NFL and CSF total tau and P-tau181 led to significant results except in men and APOE ε4 carriers, respectively. Association of CSF Aβ and NFL were not significant in any of the stratified models (Table 2).

Plasma NFL and DTI in APOE ε4 stratified analyses

The voxel-wise linear regression models in MCI patients revealed that there were WM region-specific associations between NFL in APOE ε4 carriers and non-carriers. As shown in Table 3, we found a negative correlation between plasma NFL concentration and FA values in the internal capsule, fronto-occipital fasciculus, fornix, and corpus callosum in APOE ε4 carriers and corona radiata in non-carriers (Table 3).

The same results of regression models revealed a positive association between plasma NFL and AxD values in regions of corona radiate, and sagittal stratum in APOE ε4 carriers and hippocampal cingulum, internal capsule, and uncinate fasciculus in non-carriers (Table 3). Furthermore, increased plasma NFL level was associated with higher baseline RD values in broad WM regions, including corona radiate, internal capsule, corpus callosum, fronto-occipital fasciculus, and fornix in APOE ε4 carriers and cingulum, hippocampal cingulum, and uncinate fasciculus in non-carriers (Table 3). The results for MD value were approximately similar while patients with APOE ε4 had a significant association between increased level of plasma NFL and increased MD in corona radiate, internal capsule, corpus callosum, and fornix. Also increased MD value in the cingulum, hippocampal cingulum, and uncinate fasciculus associated with increased plasma NFL was detected in APOE ε4 non-carriers (Table 3).

Plasma NFL and DTI in age-stratified analyses

As shown in Table 4, plasma levels of NFL were investigated in regression models with diffusion values in patients with an age of higher and lower than 73.2. We observed that patients with ages lower than 73.2 years had more significant associations compared to patients higher than 73.2 years old.

There were strong positive associations between plasma NFL and MD, RD, and AxD values in the internal capsule, corpus callosum, sagittal stratum, fronto-occipital fasciculus, corona radiate, and fornix (Table 4). Our findings showed the negative associations between NFL and these measures in corpus callosum, fornix, fronto-occipital fasciculus, and uncinate fasciculus.

Plasma NFL and DTI in sex-stratified analyses

In both women and men, there were significant positive associations between plasma NFL and AxD in the corpus callosum, sagittal stratum, fronto-occipital fasciculus, and corona radiate, and thalamic radiation and internal capsule only in men. Both women and men with a higher level of plasma NFL had lower FA in the fornix and fronto-occipital fasciculus. Moreover, our findings revealed associations between NFL level and MD and RD measures in the corpus callosum, sagittal stratum, hippocampal cingulum, fornix, fronto-occipital fasciculus, internal capsule, and corona radiate (Table 5).

Discussion

There are limited reports on the association of NFL and WM structures across age, sex, and APOE4 carrier in individuals with mild cognitive impairment. Our results showed

Table 3 Significant results of linear regression analyses of DTI values and Plasma NFL Levels stratified by APOE ε4 allele

Regions	DTI value	APOE ε4 carriers ($n=47$)		APOE ε4 non carriers ($n=45$)	
		β	P value	β	P value
Left anterior corona radiata	AxD	**0.611**	**0.001 >**	0.246	0.103
Right anterior corona radiata		**0.588**	**0.001 >**	0.265	0.079
Left superior corona radiata		**0.517**	**0.001 >**	0.303	0.043
Right sagittal stratum		**0.588**	**0.001 >**	0.292	0.052
Genu of left corpus callosum		**0.568**	**0.001 >**	0.336	0.024
Splenium of right corpus callosum		**0.534**	**0.001 >**	0.366	0.014
Right hippocampal cingulum		0.298	0.042	**0.451**	**0.002**
Posterior limb of left internal capsule		0.253	0.086	**0.394**	**0.007**
Right uncinate fasciculus		0.9	0.548	**0.424**	**0.004**
Retrolenticular part of right internal capsule		0.484	0.001	**0.379**	**0.01**
Anterior limb of left internal capsule	FA	**-0.509**	**0.001 >**	− 0.003	0.985
Anterior limb of right internal capsule		**− 0.501**	**0.001 >**	0.053	0.731
Right inferior fronto-occipital fasciculus		**− 0.496**	**0.001 >**	− 0.044	0.774
Right fornix		**− 0.514**	**0.001 >**	− 0.217	0.152
Genu of left corpus callosum		**− 0.484**	**0.001**	− 0.08	0.6
Left posterior corona radiata		− 0.081	0.59	**− 0.351**	**0.018**
Left anterior corona radiata	MD	**0.626**	**0.001 >**	0.263	0.081
Right anterior corona radiata		**0.605**	**0.001 >**	0.263	0.081
Anterior limb of left internal capsule		**0.58**	**0.001 >**	0.233	0.123
Genu of left corpus callosum		**0.596**	**0.001 >**	0.255	0.091
Right fornix		**0.558**	**0.001 >**	0.192	0.206
Left cingulum		0.386	0.007	**0.399**	**0.007**
Right cingulum		0.398	0.006	**0.417**	**0.004**
Left hippocampal cingulum		0.431	0.003	**0.38**	**0.01**
Right hippocampal cingulum		**0.372**	**0.01**	**0.453**	**0.002**
Right uncinate fasciculus		0.124	0.408	**0.452**	**0.002**
Anterior limb of left internal capsule	RD	**0.617**	**0.001 >**	0.187	0.22
Left anterior corona radiata		**0.605**	**0.001 >**	0.26	0.084
Right Superior fronto-occipital fasciculus		**0.592**	**0.001 >**	0.353	0.017
Genu of left corpus callosum		**0.586**	**0.001 >**	0.206	0.175
Right fornix		**0.568**	**0.001 >**	0.189	0.213
Retrolenticular part of right internal capsule		**0.57**	**0.001 >**	0.373	0.012
Left cingulum		0.405	0.005	**0.398**	**0.007**
Right cingulum		0.422	0.003	**0.463**	**0.001**
Right uncinate fasciculus		0.138	0.357	**0.445**	**0.002**
Right hippocampal cingulum		0.392	0.006	**0.438**	**0.003**

β value is the coefficient of NFL association and DTI values. Significant results are bolded after correction with Benjamini–Hochberg method. P value as defined using the linear regression model to detect significant associations in MCI subjects

RD radial diffusivity, *AxD* axial diffusivity, *MD* mean diffusivity, *FA* fractional anisotropy

significant associations between plasma NFL and CSF total tau and P-tau181 were independent of being APOE ε4 carrier and age. CSF total tau and CSF P-tau181 were significantly associated with plasma NFL in both men and women. The marginal significant association of CSF total tau and plasma NFL in men can be due to the small sample size (P value = 0.066).

Our analyses showed a significant association between plasma NFL levels and abnormal WM microstructural in various brain areas. The results suggest the associations of NFL with WM might be more region-specific in APOE4 carrier versus non-carrier as well as in men versus women. In this analysis, we included individuals with baseline MCI and the significant association of NFL with MWI in MCI

Table 4 Significant results of linear regression analyses of DTI values and Plasma NFL Levels stratified by age

Regions	DTI value	Age < 73.2 (n = 46)		Age > 73.2 (n = 46)	
		β	P value	β	P value
Retrolenticular part of right internal capsule	AxD	**0.473**	**0.001**	0.301	0.042
Splenium of right corpus callosum		**0.465**	**0.001**	0.336	0.022
Right sagittal stratum		**0.444**	**0.002**	0.316	0.032
Left sagittal stratum		**0.478**	**0.001**	0.135	0.371
Right superior fronto-occipital fasciculus		**0.453**	**0.002**	**0.472**	**0.001**
Left superior fronto-occipital fasciculus		**0.442**	**0.002**	**0.376**	**0.01**
Right Fornix		**0.24**	**0.107**	**0.448**	**0.002**
Splenium of right corpus callosum	FA	**− 0.334**	**0.023**	− 0.003	0.985
Right fornix		− 0.23	0.124	**− 0.417**	**0.004**
Right inferior fronto-occipital fasciculus		− 0.169	0.263	**− 0.362**	**0.013**
Left uncinate fasciculus		− 0.15	0.318	**− 0.355**	**0.015**
Left inferior fronto-occipital fasciculus	MD	**0.514**	**0.001 >**	0.22	0.142
Splenium of right corpus callosum		**0.455**	**0.001**	0.32	0.03
Retrolenticular part of right internal capsule		**0.469**	**0.001**	0.373	0.011
Left sagittal stratum		**0.486**	**0.001**	0.167	0.267
Right posterior corona radiata		**0.477**	**0.001**	0.144	0.339
Left uncinate fasciculus		**0.449**	**0.002**	0.243	0.104
Right superior corona radiata		**0.446**	**0.002**	0.283	0.056
Right superior fronto-occipital fasciculus		**0.442**	**0.002**	**0.471**	**0.001**
Right fornix		0.248	0.096	**0.467**	**0.001**
Left inferior fronto-occipital fasciculus	RD	**0.51**	**0.001 >**	0.201	0.181
Left sagittal stratum		**0.464**	**0.001**	0.179	0.234
Right posterior corona radiata		**0.49**	**0.001**	0.091	0.548
Right superior corona radiata		**0.448**	**0.002**	0.289	0.052
Left superior corona radiata		**0.431**	**0.003**	0.286	0.054
Left uncinate fasciculus		**0.537**	**0.002**	0.255	0.087
Right superior fronto-occipital fasciculus		**0.433**	**0.003**	**0.468**	**0.001**
Right fornix		0.246	0.099	**0.468**	**0.001**
Retrolenticular part of right internal capsule		0.411	0.005	**0.396**	**0.006**

β value is the coefficient of NFL association and DTI values. Significant results are bolded after correction with Benjamini–Hochberg method. P value as defined using the linear regression model to detect significant associations in MCI subjects

RD radial diffusivity, *AxD* axial diffusivity, *MD* mean diffusivity, *FA* fractional anisotropy

patients might suggest the use of this non-invasive plasma biomarker to detect MCI before progress to AD, which also tracks well with.

CSF levels of P-tau and P-tau181. Based on our findings, APOE ε4 carriers and non-carriers, women and men, and patients with an age of higher and lower than 73.2 had an association between plasma NFL and WM microstructural changes in different regions. There were WM region-specific associations between NFL and AxD in APOE4 carrier versus non-carriers, suggesting a possible discrepancy in WM structural change in APOE4 carriers versus non-carriers. Further studies are required to shed light on this finding. As previous studies demonstrated the WM microstructural difference associated with APOE ε4 [23]. APOE ε4 carriers had lower FA values in the genu and splenium of the corpus callosum compared to non-carriers in cognitively healthy individuals which emphasize on effect of APOE ε4 on WM microstructural changes in normal aging [24].

Non-invasive biomarkers with screening ability of change in cognition state and degenerative nervous system are required. As a non-invasive, and cost-effective, and accessible blood-based biomarker, NFL which tracks well with CSF markers can be of use to screen patients for further imaging studies [25]. Moreover, cognitive tests might not be sensitive enough to screen cognitive impairment. Therefore, identifying non-invasive plasma biomarkers like NFL that can track well with microstructural changes and neurodegeneration in both grey and white matters can be of use in clinical settings and research [26, 27].

Table 5 Significant results of linear regression analyses of DTI values and Plasma NFL Levels stratified by sex

Regions	DTI value	Women ($n=41$)		Men ($n=51$)	
		β	P value	β	P value
Right sagittal stratum	AxD	**0.572**	**0.001 >**	**0.434**	**0.001**
Genu of left corpus callosum		**0.484**	**0.001**	**0.47**	**0.001**
Right superior fronto-occipital fasciculus		**0.469**	**0.002**	**0.575**	**0.001 >**
Left superior fronto-occipital fasciculus		0.475	0.016	**0.583**	**0.001 >**
Right anterior corona radiata		0.384	0.013	**0.566**	**0.001 >**
Left anterior corona radiata		**0.462**	**0.002**	**0.476**	**0.001 >**
Anterior limb of left internal capsule		0.27	0.088	**0.542**	**0.001 >**
Retrolenticular part of right internal capsule		0.398	0.01	**0.536**	**0.001 >**
Left posterior thalamic radiation		0.279	0.078	**0.504**	**0.001 >**
Right fornix	FA	**− 0.475**	**0.002**	− 0.401	0.004
Right superior fronto-occipital fasciculus		− 0.227	0.153	**− 0.491**	**0.001 >**
Left superior fronto-occipital fasciculus		− 0.234	0.142	**− 0.509**	**0.001 >**
Right sagittal stratum	MD	**0.567**	**0.001 >**	**0.436**	**0.001**
Genu of left corpus callosum		**0.469**	**0.002**	**0.471**	**0.001 >**
Left hippocampal cingulum		**0.476**	**0.002**	0.374	0.007
Right fornix		**0.449**	**0.003**	**0.485**	**0.001 >**
Retrolenticular part of right internal capsule		0.42	0.006	**0.606**	**0.001 >**
Right superior fronto-occipital fasciculus		0.456	0.003	**0.593**	**0.001 >**
Left superior fronto-occipital fasciculus		0.373	0.016	**0.588**	**0.001 >**
Right anterior corona radiata		0.371	0.017	**0.588**	**0.001 >**
Right superior corona radiata		0.309	0.049	**0.556**	**0.001 >**
Anterior limb of left internal capsule		0.337	0.031	**0.549**	**0.001 >**
Right sagittal stratum	RD	**0.545**	**0.001 >**	**0.418**	**0.002**
Left hippocampal cingulum		**0.502**	**0.001**	0.365	0.008
Right fornix		**0.462**	**0.002**	**0.484**	**0.001 >**
Right superior fronto-occipital fasciculus		0.447	0.003	**0.598**	**0.001 >**
Left superior fronto-occipital fasciculus		0.371	0.017	**0.588**	**0.001 >**
Retrolenticular part of right internal capsule		0.407	0.008	**0.607**	**0.001 >**
Right superior corona radiata		0.293	0.063	**0.577**	**0.001 >**
Left superior corona radiata		0.348	0.026	**0.531**	**0.001 >**
Right anterior corona radiata		0.355	0.023	**0.57**	**0.001 >**

β value is the coefficient of NFL association and DTI values. Significant results are bolded after correction with Benjamini–Hochberg method. P value as defined using the linear regression model to detect significant associations in MCI subjects

RD radial diffusivity, *AxD* axial diffusivity, *MD* mean diffusivity, *FA* fractional anisotropy

Our findings revealed a significant correlation between the plasma NFL with altered WM microstructural changes in widespread brain regions. Plasma NFL has a negative correlation with FA and a positive correlation with RD, AxD, and MD values in the cingulum, hippocampal cingulum, corona radiate, internal capsule, fronto-occipital fasciculus, fronto-occipital fasciculus, sagittal stratum, corpus callosum, thalamic radiation, and fornix. Similarly, with these findings, Spotorno et al. indicated that higher plasma NFL level 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 [28]. WM differences between MCI patients and healthy controls are primarily observed in the corpus callosum along with limbic pathways, including the fornix, cingulum, and uncinate fasciculus [29]. Crucially, these signature regions are involved in the WM changes due to AD. Indeed, alterations in the WM integrity in these regions are associated with disease progression from the early stages to the late stages of AD [30]. Also, an investigation on the patients with autosomal dominant AD (patients with a mutation in Aβ production genes), showed that the serum level of NFL correlates with lower FA and higher RD, AxD, and MD which is in line with our study [31, 32].

By investigating diffusion metrics, information about the WM's different specifications can be obtained from

DTI values. However, the exact relationship between these four values of FA, RD, AxD, MD, and the physiopathology mechanisms of AD has not been completely understood. Commonly, lower FA, and higher RD, AxD, and MD in relation to demyelination and degeneration in WM have been reported [33]. Several studies have reported the association between CSF levels of NFL and WM damage in both MCI and AD [34–37]. In people without cognitive impairment, the CSF level of NFL is associated with compromised WM microstructure. However, ADNI cross-sectional data with a large sample size revealed significantly higher plasma NFL levels in the patients with MCI than cognitively healthy individuals [38, 39].

Furthermore, we observed that plasma levels of NFL have a strong correlation with MMSE scores in APOE ε4 carriers, men, and patients with age higher than 73.2. Our outcomes demonstrated that the plasma level of the NFL might be an accurate biomarker for reflecting the cognitive status of patients in preclinical stages of AD. Moreover, plasma NFL was associated with more WM regions in APOE ε4 carriers with almost similar regional patterns of associations seen in the younger age. Moreover, the associations of NFL and WM regions in non-carrier APOE4 were similar to the regions with significant NFL associations in older age. These results suggest that NFL might detect region-specific changes of WM specific to APOE4 carrier state and age [40, 41]. Further investigations are necessary to replicate these results. The plasma levels of NFL are associated with age and APOE ε4 carrier state, two important risk factors of cognitive decline and can be used as a screening tool to detect cognitive decline in the early stage [3, 13, 42]. We showed that NFL is associated with WM regions in both men and women with MCI. Some studies recently have shown a cognitive decline in men [43, 44]. This is while most epidemiological studies have reported a more cognitive decline in women than men. Our results suggest that choosing biomarkers, and sex-stratified analytical approaches can shed further light on cognitive decline in men [45].

Similar to Mattson et al. our results revealed higher plasma levels of NFL are significantly associated with total tau and P-tau181 in CSF [6]. We did not find any significant association between NFL and Aβ. Similarly, a study has shown that 80% of individuals with Aβ aggregation have no cognitive problems [42] suggesting tracking NFL levels with tauopathy at the early stage of cognitive decline [46–48].

Conclusion

Our study provides a better understanding of the link between plasma NFL and WM changes in MCI patients. Our findings support applying the NFL's blood-based measures as a non-invasive and costless biomarker for monitoring people with a high risk of AD in the early stages. In recent studies, plasma NFL was shown as a reliable biomarker for converting MCI to AD, and our research reflects WM damage with neuroimaging measures. However, further longitudinal studies are necessary to validate the predictive role of plasma NFL in cognitive decline.

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Author contributions FN & MP: Designed the study, analyzed the data, and wrote the paper; FN, MB, MRR, SBK & FR: collected data, analyzed and interpreted the data, and wrote the draft version of the manuscript. The manuscript was revised and approved by all authors.

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Availability of data and material The datasets analyzed during the current study are available upon request with no restriction.

Declarations

Conflict of interest The authors declare no conflict of interest regarding the publication of this paper.

Ethical approval Since the data in this paper were obtained from the ADNI database (adni.loni.usc.edu), it does not include any research involving human or animal subjects.

Statement of human and animal rights All human and animal studies have been approved by the appropriate ethics committee and have

therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent For this type of study, formal consent is not required.

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