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ORIGINAL ARTICLE

Plasma phosphorylated-tau181 levels reflect white matter microstructural changes across Alzheimer's disease progression.

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Abstract

Alzheimer's Disease (AD) is characterized by cognitive impairments that hinder daily activities and lead to personal and behavioral problems. Plasma hyperphosphorylated tau protein at threonine 181 (p-tau181) has recently emerged as a new sensitive tool for the diagnosis of AD patients. We herein investigated the association of plasma P-tau181 and white matter (WM) microstructural changes in AD. We obtained data from a large prospective cohort of elderly individuals participating in the Alzheimer's Disease Neuroimaging Initiative (ADNI), which included baseline measurements of plasma P-tau181 and imaging findings. A subset of 41 patients with AD, 119 patients with mild cognitive impairments (MCI), and 43 healthy controls (HC) was included in the study, all of whom had baseline blood P-tau181 levels and had also undergone Diffusion Tensor Imaging. The analysis revealed that the plasma level of P-tau181 has a positive correlation with changes in Mean Diffusivity (MD), Radial Diffusivity (RD), and Axial Diffusivity (AxD), but a negative with Fractional Anisotropy (FA) parameters in WM regions of all participants. There is also a significant association between WM microstructural changes in different regions and P-tau181 plasma measurements within each MCI, HC, and AD group. In conclusion, our findings clarified that plasma P-tau181 levels are associated with changes in WM integrity in AD. P-tau181 could improve the accuracy of diagnostic procedures and support the application of blood-based biomarkers to diagnose WM neurodegeneration. Longitudinal clinical studies are also needed to demonstrate the efficacy of the P-tau181 biomarker and predict its role in structural changes.

Keywords Alzheimer's Disease · P-tau181 · white matter · biomarker, neurodegeneration

Introduction

Alzheimer's disease (AD) is a chronic and progressive neurodegenerative disease that causes cognitive decline and memory loss. AD is the most common cause of dementia, affecting millions of elderly people around the world (Mantzavinos and Alexiou 2017; Oboudiyat et al. 2013; Weller and Budson 2018). The hallmarks of AD are neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau (P-tau) protein and extracellular Amyloid-β (Aβ) plaques, which mostly accumulate in memory and cognitive-related regions such as the hippocampus (Kandimalla et al. 2018; Wu et al. 2017).

Since AD develops years or decades before a clinical diagnosis of dementia, patients with preclinical AD or mild cognitive impairment (MCI) may benefit from therapeutic interventions (Sadda et al. 2019). Despite the fact that AD is thought to be a grey matter-related disease, recent evidence suggests that white matter (WM) structural disruption and demyelination are pathophysiological features of the disease (Nasrabady et al. 2018). Radiological studies in people with AD mutations showed that WM damage occurs nearly 22 years before symptoms appear (Lee et al. 2016).

Data used in the 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 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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Furthermore, neuroimaging studies indicate that WM networks are dysfunctional in preclinical Alzheimer's disease, even though a neuronal loss or cortical atrophy is not evident (Erten-Lyons et al. 2013).

Diffusion tensor imaging (DTI) studies in AD patients using tract-based spatial statistics supports WM changes in the corpus callosum, cingulum, uncinate fasciculus, superior longitudinal fasciculus (SLF), and fornix (Bosch et al. 2012; Huang et al. 2012). As such, DTI changes were detected in the right cingulum and SLF of MCI patients with high CSF Tau levels compared to healthy controls, but not in MCI patients with non-increased CSF tau levels (Pini et al. 2016). Longitudinal studies have highlighted the limited specificity of Aβ pathology in predicting MCI progression toward AD-related cognitive impairment over time (Chiotis et al. 2017). In addition, Aβ plaques appear to have only subtle effects on cognition and brain health in humans (Gordon et al. 2018). Recent clinical trials have failed to demonstrate the effectiveness of anti-Aβ immunotherapy in preventing neuronal loss (Hampel et al. 2010; Rissman 2009). P-tau, on the other hand, is closely linked to local neurodegeneration and cognitive decline (Bejanin et al. 2017; Xia et al. 2017). Recently, Tau phosphorylated at threonine 181 (P-tau181) has been suggested as an available, quantified, and highly specific blood biomarker for AD (Karikari et al. 2020). P-tau181 levels in the blood appear to rise gradually as AD progresses, and are related to Aβ and NFTs levels in the brain. P-tau181 has been shown to be effective in distinguishing Alzheimer's disease from other neurodegenerative disorders in recent research (Benussi et al. 2020). Plasma P-tau181 levels begin to rise 16 years before clinical symptoms appear in familial AD (O'Connor et al. 2020).

P-tau181 has recently emerged as a potential blood-based candidate for in vivo diagnosis of AD neuropathology (Karikari et al. 2020; Mielke et al. 2018; Olsson et al. 2016; Yang et al. 2018), but its association with WM connections during AD development has yet to be investigated. The aim of this study is to shed light on the potential role of the P-tau181 biomarker in predicting WM abnormalities as AD progresses.

Materials and methods

Data acquisition

In an observational cross-sectional study, participants' information was acquired from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was established in 2003 as a public-private partnership led by Principal Investigator Michael W. Weiner, MD. The main purpose of ADNI is to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessments can be used to track the development of MCI and early AD.

Participants

We collected data from baseline visits for which demographic information, post-processed DTI, and plasma P-tau181 levels were available. For a better understanding, we also obtained data from a fluorodeoxyglucose (FDG)-PET study that indicates glucose absorption in the brain. Our cross-sectional study consisted of 41 AD patients,119 MCI patients, and 43 healthy control (HC) participants, all of whom had baseline plasma P-tau181 levels and post-processed DTI. We include the participants if their requisite data was available for the baseline visit. All MCI subjects were diagnosed as amnestic 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. The AD ADNI subjects were also diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD, and have MMSE scores between 20 and 26 (inclusive), and CDR of 0.5 or 1.

Plasma P-tau181 measurements

Plasma samples were analyzed at the University of Gothenburg, Sweden by using the Single-Molecule array (Simoa) technique by two monoclonal antibodies (Tau12 and AT270) which test N-terminal to mid-domain forms of P-tau181. The detailed procedure is described in adni.loni.usc.edu (Karikari et al. 2020).

Diffusion tensor imaging processing

DTI is an MRI technique that visualizes and quantifies WM tissue microstructure by detecting the translational motion of water molecules in the brain (Le Bihan et al. 2001). The DTI ROI analysis results were derived from ADNI. The Extraction Tool (BET) in FSL was used to correct, normalize, and remove extracerebral tissue from each participant's images (Smith 2002). Each T1-weighted anatomical image was linearly aligned to a version of the Colins27 brain template (Holmes et al. 1998) using FSL's flirt (Jenkinson et al. 2002) with 6 degrees of freedom to allow translations and rotations in 3D to bring data from different subjects into the same

3D coordinate space. The Colin27 brain was zero-padded to produce a cubic isotropic image size of 220x220x220 1 mm^3), which was then downsampled to 110x110x110 2 mm^3 to match the DWI resolution. To adjust echo-planar imaging (EPI) induced susceptibility artifacts, which can cause distortions at tissue-fluid interfaces, skull-stripped b0 images were linearly aligned to their respective T1-weighted structural scans using FSL's *flirt* with 9 degrees of freedom and then elastically registered to their aligned T1 scans using an inverse consistent registration algorithm with a mutual information cost function (Leow et al. 2007) as described in (Jahanshad et al. 2010). The resulting 3D deformation fields were then applied to the remaining 41 DWI volumes before mapping diffusion parameters. A corrected gradient table was calculated to account for the linear registration of the average b0 from the DWI images to the structural T1-weighted scan. A single diffusion tensor was modeled at each voxel in the brain from the eddy- and EPI-corrected DWI scans using FSL's *dtifit* command, and scalar anisotropy and diffusivity maps were obtained from the resulting diffusion tensor eigenvalues (λ1, λ2, λ3). The standard formula was used to figure out fractional anisotropy (FA). We used a previously mentioned shared information-based elastic registration algorithm to register the FA image from the JHU DTI atlas (Mori et al. 2008) to each subject (Leow et al. 2007). To prevent label intermixing, we used nearest neighbor interpolation to apply the deformation to the stereotaxic JHU "Eve" WM atlas labels (cmrm.med.jhmi.edu/cmrm/atlas/human_data/file/Atlas Explanation2.htm).

This aligned the atlas ROIs with our DTI maps in the same coordinate space. The ROIs were drawn semi-automatically. Within the boundaries of each of the ROI masks, we were able to measure the average FA and Mean Diffusivity (MD) for each subject. The left and right middle cerebellar peduncles, as well as the pontine crossing tract, were excluded from the 56 WM ROIs because they often fall out of the field of view entirely or partially (FOV). This is also occasionally true of the inferior and superior peduncles, as well as the left and right medial lemniscus. In order to calculate mean FA and MD, we only used non-zero voxels within the FOV. To get full overview measures of the areas, five more ROIs were evaluated in addition to the 52 JHU labels: the bilateral fornix, bilateral genu, bilateral body, and bilateral splenium of the corpus callosum, as well as the full corpus callosum. The mean FA in regions of interest along the skeleton was extracted using tensor-based spatial statistics (Smith et al. 2006) as well. The ENIGMA-DTI group outlined protocols for TBSS (enigma.loni.ucla.edu/wpcontent/uploads/2012/06/ENIGMA TBSS protocol.pdf). To summarize, all subjects were registered in ICBM space with the ENIGMA-DTI template, and standard TBSS steps were used to project individual FA maps onto the skeletonized ENIGMA-DTI template. To extract the mean FA in ROIs as well as the skeleton, the ROIs were extracted using the following protocol (http://enigma.loni.ucla.edu/wpcontent/uploads/2012/06/ENIGMA_ROI_protocol.pdf). In the end, four DTI parameters including FA, which shows directional dependence of the diffusion process, and MD, Radial Diffusivity (RD), and Axial Diffusivity (AxD), which reflects the amount of diffusion were represented.

Cognitive assessments

The MMSE, which includes measures of orientation, attention, memory, language, and visual-spatial abilities, was used to assess the patients' cognitive status. The Montreal Cognitive Assessment (MoCA) and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) were also applied for assessing the severity of the cognitive decline. From the ADNI Mini-Mental Examination, MMSE scores for each patient were collected.

ApoE genotyping and plasma NFL measurements

APOE genotyping and plasma NFL measurements were performed on collected blood samples, and the findings are available at ADNI. According to ADNI (adni.loni.usc.edu/methods/documents/), participants that have at least one ε4 allele are considered a carrier.

Statistical analyses

For statistical analysis, we used the SPSS16 software. The normality of variables was first tested using the Kolmogorov Smirnov and Shapiro-Wilk tests. The non-normal variables were then log-transformed to a normal distribution. We used a one-way ANOVA with Bonferroni correction for multiple comparisons to examine the differences between groups. We performed a simple linear regression model to assess the association of plasma P-tau181 with demographical and clinical variables which allow for defining covariates for all further analyses. Then, multivariable linear regression models were used for detecting the possible association of plasma P-tau181 as a dependent variable and DTI parameters in each ROI as independent variables, while controlling for the effect of confounders which are defined in the previous step of analyses. Benjamini Hochberg's correction method was used to address type I error due to multiple comparisons in the correlation models.

Results

Patient characteristics

The baseline cohort information of 203 participants was entered into this study. The mean age was 73, with 117 men

and 86 women in attendance. All of the participants were all educated and the average length of their education was 15.9 years. At least one APOE ε4 was found in 102 of the participants. The MMSE test had a mean score of 27.25. Table 1 provides detailed demographic information for each group. The plasma P-tau181 level differs significantly between the groups [F (2, 200) = 9.05, P = 0. .000] There is no significant difference in age [F (2, 200) = 0.425, P = 0.655] or mean education period [F (2, 200) = 2.50, P = 0.084] between the groups. The comparison of the APOE genotype status between the groups revealed a strong difference [F (2, 200) = 9.06, P = 0.000], and the average brain glucose uptake in angular, temporal, and posterior cingulate was significantly lower in the AD group [F (2, 200) = 43.9, P = 0.000].

Increased plasma P-tau181 level is correlated with demographic characteristics in MCI and AD patients

Simple regression demonstrated there was no association between age and level of plasma P-tau181 [P = 0.107]. The same model for other demographical and clinical variables revealed that subjects with lower education time [P = 0.005], brain glucose uptake in angular, temporal, and posterior cingulate [P = 0.000], MMSE score [P = 0.000], MoCA score [P = 0.000], higher ADAS-Cog score [P = 0.000] and more APOE ε4 allele [P = 0.000] had a higher level of plasma P-tau181. Based on these preliminary results, we added education time, brain glucose uptake in angular, temporal, and posterior cingulate, MMSE score, and APOE genotype as confounding factors in further regression models on the association between plasma P-tau181 and DTI parameters in each ROI.

Table 1 Demographic characteristics.

Age)years(	72.9 (± 6.2)	72.8 (± 6.8)	74.0 (± 8.6)	0.655
Sex (M/F)	22/21	71/48	24/17	0.625
Education (years)	16.4 (± 2.6)	16.0 (2.6)	15.2 (± 2.9)	0.084
MMSE	28.8 (± 1.4)	27.9 (± 1.9)	23.4 (± 1.8)	< 0.001
MoCA	25.6 (± 2.3)	23.5 (± 3.0)	17.9 (± 4.2)	< 0.001
ADAS-Cog 11	5.3 (± 2.7)	8.9 (± 4.9)	20.0 (± 7.4)	< 0.001
FDG-PET	1.30 (± 0.14)	1.29 (± 0.12)	1.06 (± 0.16)	< 0.001
APOE genotype				< 0.001
Without ε4	31	58	12	< 0.001
One ε4	12	49	23	< 0.032
Two ε4	0	12	6	< 0.048

Values are showed as mean(±SD) or raw numbers of patients

Results of ANOVA analysis between groups noted as p value and adjusted for age, sex, years of education

HC Healthy Control, *MCI* Mild Cognitive Impairment, *AD* Alzheimer's disease, *MMSE* Mini Mental State Examination, *MoCA* Montreal Cognitive Assessments, *ADAS-Cog* Alzheimer's Disease Assessment Scale-Cognitive Subscale, *FDG* fluorodeoxyglucose, *PET* Positron emission tomography

Increased plasma P-tau181 level is correlated with wide-spread microstructural changes of brain white matter in MCI and AD patients

Initially, we used separate univariate multiple linear regression models to examine the association between P-tau181 level and DTI values in each ROI across all participants, adjusting for the effects of education time, brain glucose uptake in angular, temporal, and posterior cingulate, MMSE score, and APOE genotype. There is a strong correlation between plasma P-tau181 levels and a pattern of changes in each FA, AxD, RD, and MD in the brain (Table 2). We found a negative correlation between P-tau181 and FA in the left hippocampal cingulum, left and right tapetum. Moreover, a higher level of P-tau181 correlates with overall higher MD, RD, and AxD in the right posterior corona radiate, and retrolenticular part of the right internal capsule (Table 2). Moreover, subjects with higher RD and MD in the right tapetum had a higher level of plasma P-tau181 (Table 2).

The association between P-tau181 and DTI values within each group revealed a significant correlation for AxD in the left medial lemniscus and right inferior fronto-occipital fasciculus, and FA in the left hippocampal cingulum, left fornix, and left medial lemniscus among AD patients (Table 3). In MCI subjects with higher MD, RD, AxD in the Right Posterior corona radiate had a higher level of plasma P-tau181. In addition, there was a positive association between MD and AxD in the retrolenticular part of the right internal capsule with plasma P-tau181

Table 2 Results of linear regression analyses of DTI metrics and CSF P-tau181 levels among all participants

	FA	MD	RD	AxD
Left hippocampal cingulum	**0.002***	0.099	0.051	0.325
Left Tapatum	**0.007***	0.012	0.010	0.021
Right Tapatum	**0.004***	**0.004**	**0.002**	0.009
Right Posterior corona radiata	0.772	**0.002**	**0.009**	**0.001**
Retrolenticular part of right internal capsule	0.269*	**0.004**	**0.006**	**0.004**

Each cell contains the p value of linear regression of DTI metrics value of the WM brain regions and plasma P-tau181 levels controlled for APOE, education, MMSE, FDG-PET and sex (statistical significant results in bold), *negative association

Abbreviations: *P-tau181* hyperphosphorylated tau protein at threonine 181, *FA* fractional anisotropy, *MD* mean diffusivity, *RD* Radial diffusivity, *AxD* Axial diffusivity

among these individuals. Also, FA and RD in the right tapetum were associated with plasma P-tau181 in the MCI group (Table 3). P-tau181 and AxD in the right superior cerebellar peduncle, right sagittal stratum, and right cerebellar peduncle as well as RD in the Right superior fronto-occipital fasciculus, and MD in right sagittal stratum were found to have a correlation in healthy controls (HC). Furthermore, we found that subjects with lower FA, higher MD, and RD in the right fornix have a higher level of plasma P-tau181. Also, the three DTI parameters in the left uncinate fasciculus including MD, RD, and AxD was significantly associated with P-tau181 in healthy individuals (Table 3).

Neurofilament Light (NFL) is a scaffolding protein in the neural cytoskeleton that is thought to be a sensitive indicator of axonal damage (Barry et al. 2012). Increased NFL levels have been linked to potential brain tissue loss, decreased brain metabolism, and cognitive decline (Mattsson et al. 2019). So, we examined the association between P-tau181 and NFL plasma levels. The multivariable linear regression model showed that higher P-tau181 is strongly associated with higher plasma NFL levels [$P = 0.000$] when adjusted for education time, brain glucose uptake in angular, temporal, and posterior cingulate, MMSE score, and APOE genotype.

The statistically significant correlation between increased plasma P-tau181 and brain white matter bundles analyzed with DTI parameters are demonstrated in Figs. 1, 2, and 3.

Discussion

The current cross-sectional analysis, which used the ADNI cohort, found that P-tau181 plasma levels were correlated with microstructural changes and NFL levels in the brains of AD and MCI patients. We investigated the association between plasma P-tau181 and participant demographic variables, including age, sex, education period, MMSE scores, APOE genotype, and brain regional glucose uptake between and within the groups. We used univariate multiple linear regression controlled for education time, brain glucose uptake in angular, temporal, and posterior cingulate, MMSE score, and APOE genotype to investigate the relation between plasma P-tau181 level and changes in WM microstructure. We provided evidence that baseline plasma P-tau181 levels are linked to extensive WM changes in all participants in the disease's pathological signature regions or unrelated areas, including the hippocampal cingulum, tapetum, fornix, posterior corona radiate, sagittal stratum, uncinate fasciculus, retrolenticular part of the internal capsule, cerebellar peduncles, fronto-occipital fasciculus, and Medial lemniscus. Based on previous studies, an increase in MD, RD, and AxD and a decrease in FA represent neurodegeneration and white matter loss (Stebbins 2010).

Due to the growing AD population and the associated social costs, as well as the fact that AD pathogenesis manifests several years before clinical signs occur,

Table 3 Significant Results of linear regression Analyses of DTI metrics and Plasma P-tau181 levels within groups

	FA	MD	RD	AxD
Alzheimer's patients				
Right Inferior fronto-occipital fasciculus	0.918*	0.121	0.227	**0.028**
Left hippocampal cingulum	**0.005***	0.416	0.265	0.824
Left fornix	**0.044***	0.209	0.140	0.511
Left Medial lemniscus	**0.021***	0.229	0.643	**0.014**
Mild Cognitive Impairments				
Right Posterior corona radiata	0.693*	**0.022**	**0.032**	**0.025**
Retrolenticular part of right internal capsule	0.590*	**0.034**	0.054	**0.028**
Right Tapetum	**0.015***	0.039	**0.027**	0.089
Healthy Controls				
Right cerebellar peduncle	0.943*	0.044	0.094	**0.016**
Right fornix	**0.020***	**0.014**	**0.012**	0.027
Right Sagittal stratum	0.057*	**0.027**	0.025	**0.044**
Right Superior fronto-occipital fasciculus	0.138*	0.030	**0.029**	0.037
Right Superior cerebellar peduncle	0.532*	0.095	0.255	**0.017**
Left Uncinate fasciculus	0.141*	**0.013**	**0.014**	**0.019**

Each cell contains the *p* value of linear regression of DTI metrics value of the WM brain regions and plasma P-tau181 levels controlled for APOE, education, MMSE, FDG-PET and sex (statistical significant results in bold), *negative association

Abbreviations: *P-tau181* hyperphosphorylated tau protein at threonine 181, *FA* fractional anisotropy, *MD* mean diffusivity, *RD* Radial diffusivity, *AxD* Axial diffusivity

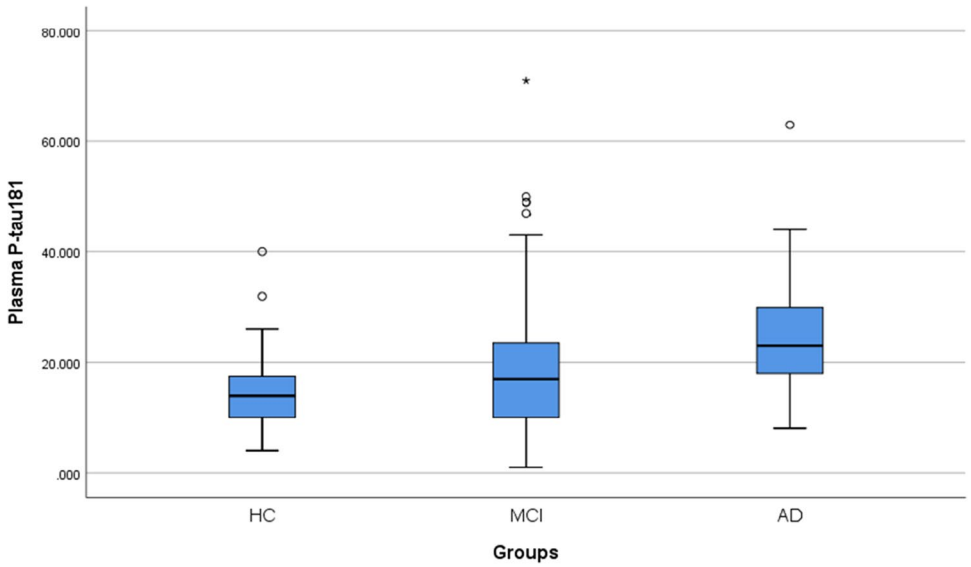

Fig. 1 Box plot: P-tau181 plasma level in Healthy Control (HC), mild cognitive impairment (MCI) and Alzheimer Disease (AD) groups.

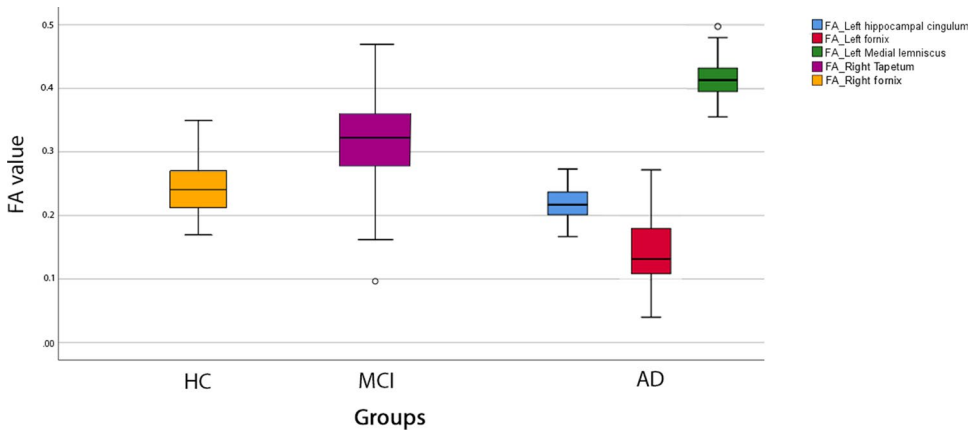

Fig. 2. Box plot: White matter bundles with statistical significant fractional anisotropy (FA) in HC, MCI and AD groups.

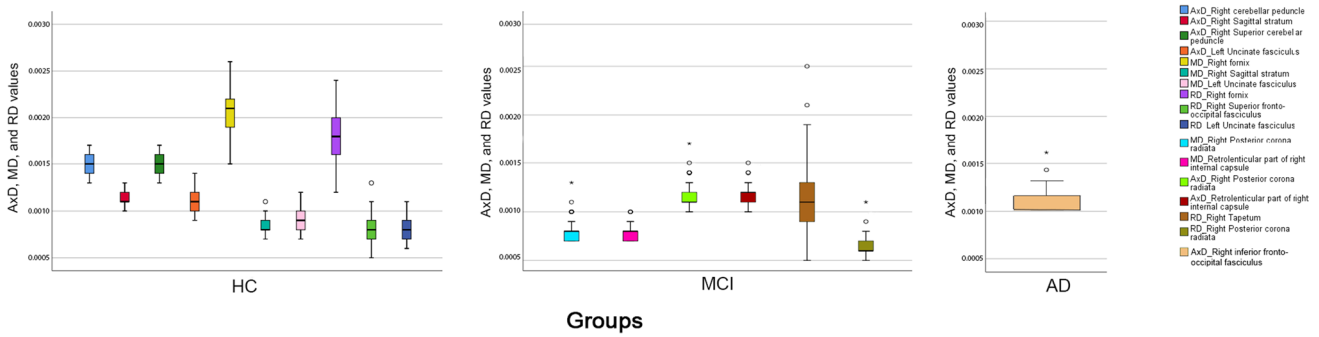

Fig. 3. Box plot: White matter bundles with statistical significant Mean Diffusivity (MD), Radial Diffusivity (RD), and Axial Diffusivity (AxD) in HC, MCI and AD groups.

a reliable biomarker with sufficient sensitivity and specificity is needed (Hampel et al. 2010). CSF biomarkers can be identified several years before the onset of AD symptoms, with Aβ and Tau being the most significant ones (Tan et al. 2014). Many studies have emphasized the diagnostic role of total tau (T-tau) and P-tau in CSF and suggest that they can predict dementia progression (Blennow et al. 2001; Lewczuk et al. 2004; Lewczuk

et al. 2017; Schönknecht et al. 2003). On the other hand, some studies present contradictory results (Haense et al. 2008; Rizzi et al. 2018). Regardless, in terms of specificity and sensitivity, P-tau is preferred in predicting AD over the other biomarkers (Tan et al. 2014). Blood-based biomarkers have been studied in recent years as a noninvasive and accessible marker for tracking people at risk of developing AD. Besides T-tau, plasma P-tau181 levels have a high diagnostic value, according to evidence, and their levels are far higher in AD patients than in MCI and healthy controls (Shekhar et al. 2016). P-tau181 has been identified as a highly specific marker for AD development and tauopathy than T-tau in both CSF and blood (Mielke et al. 2018; Yang et al. 2018). Plasma P-tau181 acts better than plasma T-tau for detecting pathological brain changes since it is more brain-specific, whereas T-tau can potentially be developed outside the CNS (Couchie et al. 1992). On the other hand, other studies have found much weaker correlations between plasma T-tau and CSF T-tau levels than those found in P-tau181 (Janelidze et al. 2020). According to the findings of the largest plasma P-tau181 analysis in the diagnosis of AD, which included the results of four independent cohorts, plasma P-tau181 level has a high performance in determining the clinical stage of AD patients with significant correlation with Aβ deposition in the brain, and also distinguishing AD from other neurodegenerative disorders (Karikari et al. 2020). In line with these findings, our results showed that plasma P-tau181 levels were significantly higher in AD and MCI patients than in healthy individuals. It was also linked to a lower MMSE score and lower brain glucose uptake in the angular, temporal, and posterior cingulate regions, implying poor cognitive function and hypometabolism.

DTI is a sensitive tool for detecting WM microstructural changes, such as demyelination and axonal damage. There is also evidence that WM disturbance found by DTI can be seen in preclinical stages of AD and is linked to changes in cognitive performance in several domains, including memory and executive function (Mayo et al. 2019; Pini et al. 2016). Results of studies that investigated WM damage in AD development were promising and revealed that changes in WM integrity in the temporal limbic and medial parietal are significantly related to NFTs pathology (Kantarci et al. 2017). Besides that, WM changes could be used to classify AD and MCI patients, as well as monitor CSF biomarkers in the early stages of the disease. (Alm and Bakker 2019; Amlien and Fjell 2014).

Although previous studies have reported a significant correlation between DTI metrics and CSF biomarkers including Aβ, T-tau, and P-tau, the association between blood-based biomarkers and WM damage is not clearly understood (Alm and Bakker 2019; Melah et al. 2016). Besides that, little attention has been paid to the relationship between plasma P-tau181 and WM changes. WM degeneration can be determined by a decrease in FA and an increase in MD variables (Kantarci 2014), as observed in the current study. In light of this, our findings mostly demonstrated WM neurodegeneration concerning the level of plasma P-tau181. Coupled with our results, X Li et al. indicated that pathological levels of CSF $A\beta_{1-42}$ and T-tau in AD patients with cognitive impairments were correlated with decreased FA and increased MD in the WM (Li et al. 2014).

In the onset of dementia and cognitive decline, changes may extend to a wide variety of regions. When comparing AD patients to healthy individuals without cognitive impairment, DTI results revealed significant WM damage in the internal capsule, corona radiates, uncinate fasciculus, cerebellar peduncles, medial lemniscus, fronto-occipital fasciculus, fornix, and hippocampal cingulum (Mayo et al. 2017). Our findings are in line with previous studies investigating WM microstructural changes related to AD (Lombardi et al. 2020; Shim et al. 2017).

Interestingly, plasma P-tau181 was found to be correlated with microstructural changes in the left hippocampal cingulum in our study, highlighting the role of the cingulum in the pathological progression of the disease (Gilligan et al. 2019). The cingulum bundle links the frontal, parietal, and medial temporal lobes, connecting the subcortical nucleus to the cingulate gyrus and extending into the hippocampal and parahippocampal regions. As a result, damage in the cingulum near the hippocampus leads to cognitive problems in a variety of domains, including language, memory, and executive function (Bubb et al. 2018). There is also evidence of a correlation between CSF P-tau and Aβ and a change in MD in the cingulum region, which could be detected using plasma P-tau 181 measurements as a reliable reflection of CSF levels (Racine et al. 2019). Furthermore, Nakata et al. presented convincing evidence of the posterior cingulum's involvement in cognitive functions, and neurodegeneration in this region appears to contribute to the development of AD (Nakata et al. 2009).

CSF Aβ and tau have previously been discovered to be a predictor of changes in the uncinate fasciculus (Drummond et al. 2019), which is involved in language processing, and damage to this area can result in language impairments (Friederici 2011). According to our findings, there is a significant correlation between plasma P-tau181 and WM integrity changes in uncinate fasciculus as part of the AD development process. Similarly, the parahippocampal WM, uncinate fasciculus, superior longitudinal fasciculus, cingulum, fornix, genu, and splenium of the corpus callosum all showed decreased FA in AD patients (da Rocha et al. 2020). Furthermore, our results indicated that the level of plasma P-tau181 levels was significantly correlated with DTI values in other regions including internal capsule, corona radiates, cerebellar peduncles, corpus

callosum, and medial lemniscus which have previously been linked to cognitive function in AD and MCI patients (da Rocha et al. 2020; Oishi and Lyketsos 2014). Previously, several studies were reported a significant association of CSF Aβ, tau, and P-tau biomarkers with WM damage in a variety of brain regions, including the internal capsule, corona radiates, fornix, cerebellar peduncles, and corpus callosum, which was close to our findings for plasma P-tau181 (Gold et al. 2014; Strain et al. 2018).

In conclusion, our study provides evidence regarding the association between plasma P-tau181 levels and neurodegeneration in brain WM regions of AD patients, demonstrating the biomarker's diagnostic potential and supporting the application of blood-based biomarkers as an early indicator for WM damages. Due to the increasing AD population and the resulting social costs and considering that AD pathogenesis appears several years before the emerging of the clinical signs, achieving a reliable biomarker with adequate sensitivity and specificity is necessary. Despite the fact that plasma P-tau181 outperforms CSF biomarkers and imaging techniques in terms of availability, low cost, and non-invasiveness, further research remains to be done to standardize biomarker measurement and establish pathological thresholds. Longitudinal studies are also needed to demonstrate the biomarker's efficacy in predicting structural changes.

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

Code availability Not applicable.

Authors' contributions FN and MP came up with the idea for the paper, FN, SK, and AR drafted it, and FN, MP, FR, and ND helped to write it. All of the authors reviewed the article.

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Declarations

Conflict of interest The authors have no conflicts of interest to disclose.

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