Plasma P-tau181 levels reflects white matter microstructural changes across Alzheimer's disease progression

Fardin Nabizadeh (fardinnabizade1378@gmail.com)
Neuroscience Research Group (NRG), Universal Scientific Education and Research Network (USERN), Tehran, Iran

Seyed Behnamedin Jameie
Neuroscience Research Center (NRC), Iran University of Medical Science, Tehran, Iran

Saghar Khani
Iran university of Medical science

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

Fatemeh Ranjbaran
Iran university of Medical science

Niloofar Deravi
Student Research committee, School of medicine, Shahid Beheshti University of Medical Science, Tehran, Iran

Mahsa Pourhamzeh (Poorhamze.m@iums.ac.ir)
Division of Neuroscience, Cellular and Molecular Research Center, Iran University of Medical Sciences, Tehran, Iran

Research Article

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

Posted Date: May 12th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-115316/v3

Abstract

Alzheimer's Disease (AD) is characterized by cognitive impairments and memory difficulties that hinder daily activities and lead to personal and behavioral problems. Plasma hyperphosphorylated tau protein at threonine 181 (p-tau181), a blood-based biomarker, has recently emerged as a new tool with sufficient sensitivity for distinguishing AD patients from healthy people. We herein investigated the association of plasma P-tau181 and white matter (WM) microstructural changes in AD. We examined data from a large prospective cohort of elderly individuals participating in the Alzheimer's Disease Neuroimaging Initiative (ADNI) which covers a wide clinical spectrum from normal cognition to AD dementia with measurements of plasma P-tau181 and imaging findings at baseline. A subset of 41 patients with AD, 119 patients with mild cognitive impairments (MCI), and 43 healthy controls (HC) were included in the study, all of whom had baseline blood P-tau181 levels and had also undergone Diffusion Tensor Imaging (DTI). The analysis revealed that the plasma level of P-tau181 have 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.

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 (1-3). 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 (4, 5).

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 (6). 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 (7). Radiological studies in people with AD mutations showed that WM damage occurs nearly 22 years before symptoms appear (8). Furthermore, neuroimaging studies indicate that WM networks are dysfunctional in preclinical Alzheimer's disease, even though neuronal loss or cortical atrophy are not evident (9).

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 (10, 11). 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 (12). Longitudinal studies have highlighted the limited specificity of Aβ pathology in predicting MCI progression toward AD-related cognitive impairment over time (13). In addition, Aβ plaques appear to have only subtle effects on cognition and brain health in humans (14). Recent clinical trials have failed to demonstrate the effectiveness of anti-Aβ immunotherapy in preventing neuronal loss (15, 16). P-tau, on the other hand, is closely linked to local neurodegeneration and cognitive decline (17, 18). Recently, Tau phosphorylated at threonine 181 (P-tau181) has been suggested as an available, quantified, and highly specific blood biomarker for AD (19). 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 (20). Plasma P-tau181 levels begin to rise 16 years before clinical symptoms appear in familial AD (21).

P-tau181 has recently emerged as a potential blood-based candidate for *in vivo* diagnosis of AD neuropathology (19, 22-24), 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. Participants were classified as AD patients if the participants' mini-mental state test (MMSE) score was 20 to 24, their clinical dementia rating (CDR) score was 0.5 to 1, and they met the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria (25). If they had an MMSE score of 24 to 30 and a CDR of more than 0.5, they were considered MCI.

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 tests N-terminal to mid-domain forms of P-tau181. The detailed procedure is described in adni.loni.usc.edu (19).

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 (26). 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 (27). Each T1-weighted anatomical image was linearly aligned to a version of the Colins27 brain template (28) using FSL's flirt (29) 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 1mm^3), which was then downsampled to 110x110x110 2mm^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 (30) as described in (31). 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 (32) to each subject (30). 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 aligned the atlas ROIs with our DTI maps in the same coordinate space. Within the boundaries of each of the ROI masks, we were able to measure the average FA and 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 (33) as well. The ENIGMA-DTI group outlined protocols for TBSS (http://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).

Cognitive assessments

The MMSE, which includes measures of orientation, attention, memory, language, and visual-spatial abilities, was used to assess the patients' cognitive status. 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 (http://adni.loni.usc.edu/methods/documents/), participants that have at least one ε4 allele are considered 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. Then, after adjusting for age, sex, and APOE, we used a partial correlation to check the association between plasma P-tau181 and other demographic variables across all participants and then within groups. The association between plasma P-tau181 and DTI values in each ROI was investigated using the same model.

The bootstrap 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. A 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 brain glucose uptake 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

When controlling for sex and APOE, there is a positive correlation between age and P-tau181 among all participants [correlation coefficient: 0.215, $P = 0.002$]. The partial correlation model showed that plasma P-tau181 has a strong correlation with education time [correlation coefficient: -0.166, $P = 0.019$], MMSE score [correlation coefficient: -0.216, $P = 0.002$], and brain glucose uptake in angular, temporal, and posterior cingulate [correlation coefficient: -0.231, $P = 0.001$], when adjusted for age, sex, and APOE genotype. Furthermore, we examined the correlation between P-tau181 and demographic characteristics within groups and there was only one correlation between P-tau181 and regional glucose uptake in brain of AD patients [correlation coefficient: -0.397, $P = 0.017$].

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

Initially, we used a partial correlation model to examine the association between P-tau181 level and DTI values in each ROI across all participants, adjusting for the effects of age, sex, 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, splenium of the right corpus callosum, left and right tapatum. Moreover, a higher level of P-tau181 correlates with overall higher MD and AxD in the splenium of the right and left corpus callosum, left and right tapatum, right posterior corona radiate, right sagittal stratum, right uncinate fasciculus, retrolenticular part of the right internal capsule, and left medial lemniscus (Table 2). Moreover, RD showed the same correlation in the left hippocampal cingulum, splenium of the right corpus callosum, left and right tapatum, right posterior corona radiate, right sagittal stratum, right uncinate fasciculus, retrolenticular part of the right internal capsule, and left medial lemniscus (Table 2).

The association between P-tau181 and connectometry values within each group revealed a significant correlation for MD, RD, and AxD in the left medial lemniscus, MD and AxD in the left inferior cerebellar peduncle, MD and RD in the right superior cerebellar peduncle among AD patients (Table 3). Only in the left medial lemniscus of the MCI group the P-tau181 correlates with MD and RD (Table 3). P-tau181 and AxD in the right superior cerebellar peduncle, as well as RD in the left uncinate fasciculus, were found to have a correlation in healthy controls (HC) (Table 3).

Neurofilament Light (NFL) is a scaffolding protein in the neural cytoskeleton that is thought to be a sensitive indicator of axonal damage (34). Increased NFL levels have been linked to potential brain tissue loss, decreased brain metabolism, and cognitive decline (35). So, we examined the association between P-tau181 and NFL plasma levels. The partial correlation model showed that P-tau181 has a strong correlation with plasma NFL levels [correlation coefficient: 0.323, $P = 0.000$] when adjusted for age, sex, and APOE genotype.

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 correlation 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 a partial correlation model controlled for age, APOE and sex 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, including the hippocampal cingulum, splenium of corpus callosum, tapatum, posterior corona radiate, sagittal stratum, uncinate fasciculus, retrolenticular part of the internal capsule, cerebellar peduncles, and Medial lemniscus.

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, a reliable biomarker with sufficient sensitivity and specificity is needed (16). CSF biomarkers can be identified several years before the onset of AD symptoms, with Aβ and Tau being the most significant ones (36). Many studies have emphasized the diagnostic role of total tau (T-tau) and P-tau in CSF and suggesting that they can predict dementia progression (37-40). On the other hand, some studies present contradictory results (41, 42). Regardless, in terms of specificity and sensitivity, P-tau is preferred in predicting AD over the other biomarkers (36). Blood-based biomarkers have been studied in recent years as a noninvasive and accessible marker for tracking people at risk of developing AD. Beside 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 (43). P-tau181 has been identified as a highly specific marker for AD development and tauopathy than T-tau in both CSF and blood (23, 24). Plasma P-tau181 act 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 (44). 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 (45). 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 (19). 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 (12, 46). Results of studies investigated WM damage in AD development were promising and revealed that changes in WM integrity in the temporal limbic and medial parietal is significantly related to NFTs pathology (47). 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. (48, 49).

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 (50, 51)(). 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 (52), as observed in the current study. In light of this, our findings mostly demonstrated WM neurodegeneration in relation to 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 was correlated with decreased FA and increased MD in the WM (53).

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 a significant WM damage in the internal capsule, corona radiates, uncinate fasciculus, cerebellar peduncles, medial lemniscus, and hippocampal cingulum (54). Our findings are in line with previous studies investigating WM microstructural changes related to AD (55, 56).

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 (57). 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 (58). 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 (59). 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 (60).

CSF Aβ and tau have previously been discovered to be a predictor of changes in the uncinate fasciculus (61), which is involved in language processing and damage to this area can result in language impairments (62). According to our findings, there is a significant correlation between plasma P-tau181 and WM integrity changes in uncinate fasciculus as part of 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 (63). Furthermore, our results indicated that level of plasma P-tau181 levels were 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 (63). Previously, several studies were reported significant association of CSF Aβ, tau, and P-tau biomarkers with WM damage in variety of brain regions, including the internal capsule, corona radiates, cerebellar peduncles and corpus callosum, which was close to our findings for plasma P-tau181 (64, 65).

In conclusion, our study provide 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 support 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.

Declarations

Acknowledgements

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer’s Association; Alzheimer’s Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & 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.

Conflict of interest

The authors have no conflicts of interest to disclose.

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

References

1. Mantzavinos V, Alexiou A. Biomarkers for Alzheimer's Disease Diagnosis. Curr Alzheimer Res. 2017;14(11):1149-54.
2. Oboudiyat C, Glazer H, Seifan A, Greer C, Isaacson RS. Alzheimer's disease. Semin Neurol. 2013;33(4):313-29.
3. Weller J, Budson A. Current understanding of Alzheimer's disease diagnosis and treatment. F1000Res. 2018;7:F1000 Faculty Rev-161.
4. Wu XL, Piña-Crespo J, Zhang YW, Chen XC, Xu HX. Tau-mediated Neurodegeneration and Potential Implications in Diagnosis and Treatment of Alzheimer's Disease. Chin Med J (Engl). 2017;130(24):2978-90.
5. Kandimalla R, Manczak M, Yin X, Wang R, Reddy PH. Hippocampal phosphorylated tau induced cognitive decline, dendritic spine loss and mitochondrial abnormalities in a mouse model of Alzheimer's disease. Hum Mol Genet. 2018;27(1):30-40.
6. Sadda SR, Borrelli E, Fan W, Ebraheem A, Marion KM, Harrington M, et al. A pilot study of fluorescence lifetime imaging ophthalmoscopy in preclinical Alzheimer’s disease. Eye. 2019;33(8):1271-9.
7. Nasrabady SE, Rizvi B, Goldman JE, Brickman AM. White matter changes in Alzheimer’s disease: a focus on myelin and oligodendrocytes. Acta Neuropathologica Communications. 2018;6(1):22.
8. Lee S, Viqar F, Zimmerman ME, Narkhede A, Tosto G, Benzinger TL, et al. White matter hyperintensities are a core feature of Alzheimer's disease: Evidence from the dominantly inherited Alzheimer network. Annals of neurology. 2016;79(6):929-39.
9. Erten-Lyons D, Woltjer R, Kaye J, Mattek N, Dodge HH, Green S, et al. Neuropathologic basis of white matter hyperintensity accumulation with advanced age. Neurology. 2013;81(11):977-83.
10. Huang H, Fan X, Weiner M, Martin-Cook K, Xiao G, Davis J, et al. Distinctive disruption patterns of white matter tracts in Alzheimer's disease with full diffusion tensor characterization. Neurobiology of aging. 2012;33(9):2029-45.
11. Bosch B, Arenaza-Urquijo EM, Rami L, Sala-Llonch R, Junqué C, Solé-Padullés C, et al. Multiple DTI index analysis in normal aging, amnestic MCI and AD. Relationship with neuropsychological performance. Neurobiology of aging. 2012;33(1):61-74.
12. Pini L, Pievani M, Bocchetta M, Altomare D, Bosco P, Cavedo E, et al. Brain atrophy in Alzheimer’s Disease and aging. Ageing Research Reviews. 2016;30:25-48.
13. Chiotis K, Saint-Aubert L, Boccardi M, Gietl A, Picco A, Varrone A, et al. Clinical validity of increased cortical uptake of amyloid ligands on PET as a biomarker for Alzheimer's disease in the context of a structured 5-phase development framework. Neurobiology of aging. 2017;52:214-27.
14. Gordon BA, McCullough A, Mishra S, Blazey TM, Su Y, Christensen J, et al. Cross-sectional and longitudinal atrophy is preferentially associated with tau rather than amyloid β positron emission tomography pathology. Alzheimer's & dementia (Amsterdam, Netherlands). 2018;10:245-52.

15. Rissman RA. Stress-induced tau phosphorylation: functional neuroplasticity or neuronal vulnerability? Journal of Alzheimer's disease : JAD. 2009;18(2):453-7.
16. Hampel H, Blennow K, Shaw LM, Hoessler YC, Zetterberg H, Trojanowski JQ. Total and phosphorylated tau protein as biological markers of Alzheimer's disease. Experimental gerontology. 2010;45(1):30-40.
17. Bejanin A, Schonhaut DR, La Joie R, Kramer JH, Baker SL, Sosa N, et al. Tau pathology and neurodegeneration contribute to cognitive impairment in Alzheimer's disease. Brain. 2017;140(12):3286-300.
18. Xia C, Makaretz SJ, Caso C, McGinnis S, Gomperts SN, Sepulcre J, et al. Association of In Vivo [18F]AV-1451 Tau PET Imaging Results With Cortical Atrophy and Symptoms in Typical and Atypical Alzheimer Disease. JAMA Neurol. 2017;74(4):427-36.
19. Karikari TK, Pascoal TA, Ashton NJ, Janelidze S, Benedet AL, Rodriguez JL, et al. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. Lancet Neurol. 2020;19(5):422-33.
20. Benussi A, Karikari TK, Ashton N, Gazzina S, Premi E, Benussi L, et al. Diagnostic and prognostic value of serum NfL and p-Tau(181) in frontotemporal lobar degeneration. Journal of neurology, neurosurgery, and psychiatry. 2020;91(9):960-7.
21. O'Connor A, Karikari TK, Poole T, Ashton NJ, Lantero Rodriguez J, Khatun A, et al. Plasma phospho-tau181 in presymptomatic and symptomatic familial Alzheimer's disease: a longitudinal cohort study. Molecular Psychiatry. 2020.
22. Olsson B, Lautner R, Andreasson U, Öhrfelt A, Portelius E, Bjerke M, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. Lancet Neurol. 2016;15(7):673-84.
23. Mielke MM, Hagen CE, Xu J, Chai X, Vemuri P, Lowe VJ, et al. Plasma phospho-tau181 increases with Alzheimer's disease clinical severity and is associated with tau- and amyloid-positron emission tomography. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2018;14(8):989-97.
24. Yang CC, Chiu MJ, Chen TF, Chang HL, Liu BH, Yang SY. Assay of Plasma Phosphorylated Tau Protein (Threonine 181) and Total Tau Protein in Early-Stage Alzheimer's Disease. Journal of Alzheimer's disease : JAD. 2018;61(4):1323-32.
25. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984;34(7):939-44.
26. Le Bihan D, Mangin JF, Poupon C, Clark CA, Pappata S, Molko N, et al. Diffusion tensor imaging: concepts and applications. Journal of magnetic resonance imaging : JMRI. 2001;13(4):534-46.
27. Smith SM. Fast robust automated brain extraction. Human brain mapping. 2002;17(3):143-55.
28. Holmes CJ, Hoge R, Collins L, Woods R, Toga AW, Evans AC. Enhancement of MR images using registration for signal averaging. J Comput Assist Tomogr. 1998;22(2):324-33.

29. Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage. 2002;17(2):825-41.
30. Leow AD, Yanovsky I, Chiang MC, Lee AD, Klunder AD, Lu A, et al. Statistical properties of Jacobian maps and the realization of unbiased large-deformation nonlinear image registration. IEEE Trans Med Imaging. 2007;26(6):822-32.
31. Jahanshad N, Lee AD, Barysheva M, McMahon KL, de Zubicaray GI, Martin NG, et al. Genetic influences on brain asymmetry: a DTI study of 374 twins and siblings. Neuroimage. 2010;52(2):455-69.
32. Mori S, Oishi K, Jiang H, Jiang L, Li X, Akhter K, et al. Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. Neuroimage. 2008;40(2):570-82.
33. Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage. 2006;31(4):1487-505.
34. Barry DM, Stevenson W, Bober BG, Wiese PJ, Dale JM, Barry GS, et al. Expansion of neurofilament medium C terminus increases axonal diameter independent of increases in conduction velocity or myelin thickness. Journal of Neuroscience. 2012;32(18):6209-19.
35. Mattsson N, Cullen NC, Andreasson U, Zetterberg H, Blennow K. Association between longitudinal plasma neurofilament light and neurodegeneration in patients with Alzheimer disease. JAMA neurology. 2019;76(7):791-9.
36. Tan CC, Yu JT, Tan L. Biomarkers for preclinical Alzheimer's disease. Journal of Alzheimer's disease : JAD. 2014;42(4):1051-69.
37. Lewczuk P, Lelental N, Lachmann I, Holzer M, Flach K, Brandner S, et al. Non-Phosphorylated Tau as a Potential Biomarker of Alzheimer's Disease: Analytical and Diagnostic Characterization. Journal of Alzheimer's disease : JAD. 2017;55(1):159-70.
38. Blennow K, Vanmechelen E, Hampel H. CSF total tau, Abeta42 and phosphorylated tau protein as biomarkers for Alzheimer's disease. Molecular neurobiology. 2001;24(1-3):87-97.
39. Schönknecht P, Pantel J, Hunt A, Volkmann M, Buerger K, Hampel H, et al. Levels of total tau and tau protein phosphorylated at threonine 181 in patients with incipient and manifest Alzheimer's disease. Neuroscience letters. 2003;339(2):172-4.
40. Lewczuk P, Esselmann H, Bibl M, Beck G, Maler JM, Otto M, et al. Tau protein phosphorylated at threonine 181 in CSF as a neurochemical biomarker in Alzheimer's disease: original data and review of the literature. Journal of molecular neuroscience : MN. 2004;23(1-2):115-22.
41. Rizzi L, Missiaggia L, Roriz-Cruz M. CSF Aβ(1-42), but not p-Tau(181), Predicted Progression from Amnestic MCI to Alzheimer's Disease Dementia. Neuromolecular medicine. 2018;20(4):491-7.
42. Haense C, Buerger K, Kalbe E, Drzezga A, Teipel SJ, Markiewicz P, et al. CSF total and phosphorylated tau protein, regional glucose metabolism and dementia severity in Alzheimer's disease. European journal of neurology. 2008;15(11):1155-62.

43. Shekhar S, Kumar R, Rai N, Kumar V, Singh K, Upadhyay AD, et al. Estimation of Tau and Phosphorylated Tau181 in Serum of Alzheimer's Disease and Mild Cognitive Impairment Patients. PloS one. 2016;11(7):e0159099-e.
44. Couchie D, Mavilia C, Georgieff IS, Liem R, Shelanski ML, Nunez J. Primary structure of high molecular weight tau present in the peripheral nervous system. Proceedings of the National Academy of Sciences. 1992;89(10):4378-81.
45. Janelidze S, Mattsson N, Palmqvist S, Smith R, Beach TG, Serrano GE, et al. Plasma P-tau181 in Alzheimer's disease: relationship to other biomarkers, differential diagnosis, neuropathology and longitudinal progression to Alzheimer's dementia. Nature medicine. 2020;26(3):379-86.
46. Mayo CD, Garcia-Barrera MA, Mazerolle EL, Ritchie LJ, Fisk JD, Gawryluk JR, et al. Relationship Between DTI Metrics and Cognitive Function in Alzheimer's Disease. Front Aging Neurosci. 2019;10:436-.
47. Kantarci K, Murray ME, Schwarz CG, Reid RI, Przybelski SA, Lesnick T, et al. White-matter integrity on DTI and the pathologic staging of Alzheimer's disease. Neurobiol Aging. 2017;56:172-9.
48. Alm KH, Bakker A. Relationships Between Diffusion Tensor Imaging and Cerebrospinal Fluid Metrics in Early Stages of the Alzheimer's Disease Continuum. Journal of Alzheimer's disease : JAD. 2019;70(4):965-81.
49. Amlien IK, Fjell AM. Diffusion tensor imaging of white matter degeneration in Alzheimer's disease and mild cognitive impairment. Neuroscience. 2014;276:206-15.
50. Alm KH, Bakker A. Relationships Between Diffusion Tensor Imaging and Cerebrospinal Fluid Metrics in Early Stages of the Alzheimer's Disease Continuum. Journal of Alzheimer's Disease. 2019;70(4):965-81.
51. Melah KE, Lu SY-F, Hoscheidt SM, Alexander AL, Adluru N, Destiche DJ, et al. Cerebrospinal fluid markers of Alzheimer's disease pathology and microglial activation are associated with altered white matter microstructure in asymptomatic adults at risk for Alzheimer's disease. Journal of Alzheimer's Disease. 2016;50(3):873-86.
52. Kantarci K. Fractional anisotropy of the fornix and hippocampal atrophy in Alzheimer's disease. Frontiers in aging neuroscience. 2014;6:316.
53. Li X, Li TQ, Andreasen N, Wiberg MK, Westman E, Wahlund LO. The association between biomarkers in cerebrospinal fluid and structural changes in the brain in patients with Alzheimer's disease. Journal of internal medicine. 2014;275(4):418-27.
54. Mayo CD, Mazerolle EL, Ritchie L, Fisk JD, Gawryluk JR. Longitudinal changes in microstructural white matter metrics in Alzheimer's disease. Neuroimage Clin. 2017;13:330-8.
55. Shim G, Choi KY, Kim D, Suh SI, Lee S, Jeong HG, et al. Predicting neurocognitive function with hippocampal volumes and DTI metrics in patients with Alzheimer's dementia and mild cognitive impairment. Brain and behavior. 2017;7(9):e00766.
56. Lombardi A, Amoroso N, Diacono D, Monaco A, Logroscino G, De Blasi R, et al. Association between Structural Connectivity and Generalized Cognitive Spectrum in Alzheimer's Disease. Brain sciences.

2020;10(11).
57. Gilligan TM, Sibilia F, Farrell D, Lyons D, Kennelly SP, Bokde ALW. No relationship between fornix and cingulum degradation and within-network decreases in functional connectivity in prodromal Alzheimer's disease. PloS one. 2019;14(10):e0222977.
58. Bubb EJ, Metzler-Baddeley C, Aggleton JP. The cingulum bundle: Anatomy, function, and dysfunction. Neuroscience & Biobehavioral Reviews. 2018;92:104-27.
59. Racine AM, Merluzzi AP, Adluru N, Norton D, Koscik RL, Clark LR, et al. Association of longitudinal white matter degeneration and cerebrospinal fluid biomarkers of neurodegeneration, inflammation and Alzheimer's disease in late-middle-aged adults. Brain imaging and behavior. 2019;13(1):41-52.
60. Nakata Y, Sato N, Nemoto K, Abe O, Shikakura S, Arima K, et al. Diffusion abnormality in the posterior cingulum and hippocampal volume: correlation with disease progression in Alzheimer's disease. Magnetic resonance imaging. 2009;27(3):347-54.
61. Drummond C, Coutinho G, Monteiro MC, Assuncao N, Teldeschi A, de Souza AS, et al. Narrative impairment, white matter damage and CSF biomarkers in the Alzheimer's disease spectrum. Aging. 2019;11(20):9188-208.
62. Friederici AD. The brain basis of language processing: from structure to function. Physiological reviews. 2011;91(4):1357-92.
63. da Rocha JLD, Bramati I, Coutinho G, Moll FT, Sitaram R. Fractional anisotropy changes in parahippocampal cingulum due to Alzheimer’s disease. Scientific reports. 2020;10(1):1-8.
64. Gold BT, Zhu Z, Brown CA, Andersen AH, LaDu MJ, Tai L, et al. White matter integrity is associated with cerebrospinal fluid markers of Alzheimer's disease in normal adults. Neurobiol Aging. 2014;35(10):2263-71.
65. Strain JF, Smith RX, Beaumont H, Roe CM, Gordon BA, Mishra S, et al. Loss of white matter integrity reflects tau accumulation in Alzheimer disease defined regions. Neurology. 2018;91(4):e313-e8.

Tables

Table 1. Demographic characteristics.

	HC (n = 43)	MCI n = 119	AD (n = 41)	*P* value
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
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.
Healthy Control (HC), Mild Cognitive Impairment (MCI), Alzheimer's disease (AD), Mini Mental State Examination (MMSE), fluorodeoxyglucose (*FDG*)-positron emission tomography (*PET*) .Results of ANOVA analysis between groups noted as *P* value and adjusted for age, sex, years of education.

Table 2. Results of partial correlation analyses of DTI metrics and CSF P-tau181 levels among all participants

	FA	MD	RD	AxD
Left hippocampal cingulum	-0.218**	0.164	0.182*	0.124
Splenium of right corpus callosum	-0.142*	0.171*	0.168*	0.163*
Splenium of left corpus callosum	-0.101	0.141*	0.133	0.152*
Left Tapatum	-0.167*	0.166*	0.169*	0.156*
Right Tapatum	-0.175*	0.189**	0.194**	0.174*
Left Medial lemniscus	0.048	-0.178*	-0.163*	-0.174*
Left Posterior corona radiata	0.069	0.123	0.102	0.139
Right Posterior corona radiata	0.074	0.188**	0.147*	0.223**
Right Sagittal stratum	-0.002	0.181*	0.164*	0.199**
Right Uncinate fasciculus	-0.134	0.199*	0.202**	0.188**
Retrolenticular part of right internal capsule	-0.030	0.192**	0.178*	0.189**

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

Each cell contains the partial correlation coefficient of DTI metrics value of the WM brain regions and plasma P-tau181 levels controlled for age, APOE, and sex (* $P < 0.05$, ** $P < 0.001$, *** $P < 0.001$)

Table 3. Significant Results of partial Correlation Analyses of DTI metrics and Plasma P-tau181 levels within groups

	FA	MD	RD	AxD
Alzheimer's patients				
Left Inferior cerebellar peduncle	0.233	-0.341*	-0.341	-0.335*
Left Medial lemniscus	-0.107	-0.420**	-0.351*	-0.469**
Right Superior cerebellar peduncle	0.258	-0.382*	-0.374*	-0.379
Mild Cognitive Impairments				
Left Medial lemniscus	0.138	-0.138*	-0.185*	-0.144
Healthy Controls				
Right Superior cerebellar peduncle	0.171	0.227	0.140	0.343*
Left Uncinate fasciculus	-0.289	0.319	0.333*	0.279

Abbreviations: P-tau181, hyperphosphorylated tau protein at threonine 181; FA, fractional anisotropy; MD, mean diffusivity; RD, Radial diffusivity; AxD, Axial diffusivity. Each cell contains the partial correlation coefficient of DTI metrics value of the WM brain regions and plasma P-tau181 levels controlled for age, APOE, and sex (* $P < 0.05$, ** $P < 0.001$, *** $P < 0.001$)