RESEARCH ARTICLE

Association of *APOE*-ε4, Osteoarthritis, β-Amyloid, and Tau Accumulation in Primary Motor and Somatosensory Regions in Alzheimer Disease

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Abstract

Background and Objectives

One of the most prevalent chronic diseases, osteoarthritis (OA), may work in conjunction with *APOE*-ε4 to accelerate Alzheimer disease (AD) alterations, particularly in the primary motor (precentral) and somatosensory (postcentral) cortices. To understand the reasoning behind this, we investigated how OA and *APOE*-ε4 influence the accumulation of β-amyloid (Aβ) and tau accumulation in primary motor and somatosensory regions in Aβ-positive (Aβ+) older individuals.

Methods

We selected Aβ+ Alzheimer Disease Neuroimaging Initiative participants, defined by baseline ^{18}F-florbetapir (FBP) Aβ PET standardized uptake value ratio (SUVR) of AD summary cortical regions, who had longitudinal Aβ PET, the records of OA medical history, and *APOE*-ε4 genotyping. We examined how OA and *APOE*-ε4 relate to baseline and longitudinal Aβ accumulation and tau deposition measured at follow-up in precentral and postcentral cortical areas and how they modulate Aβ-associated future higher tau levels, adjusting for age, sex, and diagnosis and using multiple comparison corrections.

Results

A total of 374 individuals (mean age 75 years, 49.2% female, 62.8% *APOE*-ε4 carriers) who underwent longitudinal FBP PET with a median follow-up of 3.3 years (interquartile range [IQR] 3.4, range 1.6–9.4) were analyzed, and 96 people had ^{18}F-flortaucipir (FTP) tau PET measured at a median of 5.4 (IQR 1.9, range 4.0–9.3) years postbaseline FBP PET. Neither OA nor *APOE*-ε4 was related to baseline FBP SUVR in precentral and postcentral regions. At follow-up, OA rather than *APOE*-ε4 was associated with faster Aβ accumulation in postcentral region (β = 0.005, 95% CI 0.001–0.008) over time. In addition, OA but not the *APOE*-ε4 allele was strongly linked to higher follow-up FTP tau levels in precentral (β = 0.098, 95% CI 0.034–0.162) and postcentral (β = 0.105, 95% CI 0.040–0.169) cortices. OA and *APOE*-ε4 were also interactively associated with higher follow-up FTP tau deposition in precentral (β = 0.128, 95% CI 0.030–0.226) and postcentral (β = 0.124, 95% CI 0.027–0.223) regions.

Discussion

This study suggests that OA was associated with faster Aβ accumulation and higher Aβ-dependent future tau deposition in primary motor and somatosensory regions, providing novel insights into how OA increases the risk of AD.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Data used in preparation of this article were obtained from the Alzheimer Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of the 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 in Appendix 2 at links.lww.com/WNL/C803.

Glossary

Aβ = β-amyloid; **AD** = Alzheimer disease; **ADNI** = Alzheimer Disease Neuroimaging Initiative; **CI** = cognitively impaired; **CU** = cognitively unimpaired; **GLM** = generalized linear model; **IQR** = interquartile range; **MCI** = mild cognitive impairment; **OA** = osteoarthritis; **FBP** = ^{18}F-florbetapir; **FTP** = ^{18}F-flortaucipir; **ROI** = region of interest; **SPM** = statistical parametric mapping; **SUVR** = standardized uptake value ratio.

Osteoarthritis (OA) is one of the most common chronic health conditions, leading to clinical manifestations including pain, stiffness, swelling, and limitations in joint function.[1] All over the world, approximately 240 million individuals experience symptomatic OA, including 10% of men and 18% of women aged 60 years and older.[2] Besides, more than 11% of those aged 65 years and older experience dementia, mainly caused by Alzheimer disease (AD), accounting for 60%–80% of patients with dementia.[3] PET imaging has been commonly used to measure the aggregation of extracellular β-amyloid (Aβ) plaques and intracellular neurofibrillary tau tangles,[4,5] the key hallmarks of AD.[6] According to the National Institute on Aging and Alzheimer's Association research framework,[7] Aβ positive (Aβ+) individuals defined by PET imaging are in the AD continuum, who are more likely to undergo cognitive decline than Aβ biomarker normal individuals.[8] Of importance, OA may increase the AD risk in older individuals, according to previous reports.[9,10] Both animal[11] and human tissue[12] studies have suggested that OA may accelerate Aβ pathology. Furthermore, 2 human cohort studies found that OA was related to a higher incidence of dementia[13] or faster hippocampal atrophy[14] in older individuals.

The precentral gyrus, also known as the primary motor cortex, is responsible for executing motor movements, while the postcentral gyrus, referred to as the primary somatosensory cortex, processes the sensations from the body.[15] One previous autopsy study[16] found similar significant senile plaques in primary motor and somatosensory cortices to that found in other cortical areas in patients with AD. By contrast, the number of neurofibrillary tangles in these 2 regions was marginally lower than those in the entorhinal, frontal, and parietal associative areas. Our group recently observed significant tau deposition measured by PET imaging in precentral and postcentral regions but not in medial temporal areas of individuals who were Aβ PET positive but CSF $A\beta_{42}/A\beta_{40}$ negative,[17] suggesting that tau tangles aggregation in primary motor and somatosensory cortices may also occur in the early stage of AD. Another study[18] reported that the somatosensory responses measured by magnetoencephalography were affected early in AD progression and may affect their behavioral and functional performances. Moreover, several studies[19-21] found significant gray matter atrophy in precentral and postcentral regions in patients with OA compared with that in healthy controls. In addition, it has been reported that patients with knee OA had a significant disrupted representation of the knee in both primary motor[22] and primary sensory[23] cortices. Together, these studies[16-23] suggest that primary motor and somatosensory cortices are significantly involved in OA and AD disorders.

Furthermore, 2 animal studies[24,25] revealed that inflammatory OA mice model with an expression of the human *APOE*-ε4 gene, the most important genetic risk factor of sporadic AD,[26] developed a more severe OA compared with mice with the human *APOE*-ε3 gene. It has also been demonstrated that the *APOE*-ε4 allele could promote inflammatory changes in microglia and astrocytes.[27] Together, it raises the possibility that OA and *APOE*-ε4 alleles may interact to affect the abnormal changes of AD pathophysiology in primary motor and somatosensory regions. However, the rationale behind this is still not fully understood.

In this study, we analyzed Aβ+ older individuals from the Alzheimer Disease Neuroimaging Initiative (ADNI) who had longitudinal ^{18}F-florbetapir (FBP) Aβ PET scans, *APOE*-ε4 genotype, and OA medical history records. Parted of them had follow-up ^{18}F-flortaucipir (FTP) tau PET scan measured at a median of 5.4 years postbaseline Aβ PET scan. We investigated how OA and *APOE*-ε4 independently and interactively affect the aggregation of cortical Aβ plaques and tau tangles in precentral and postcentral cortical regions in the AD continuum.[7] The ultimate goal is to provide imaging evidence to underlie the mechanism behind OA-related high risk of AD and help better health management of older individuals, especially individuals with both OA and AD disorders.

Methods

Participants

Data used in this study were obtained from the ADNI database (ida.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD as we previously described.[28] For up-to-date information, see adni-info.org. We identified cognitively unimpaired (CU) individuals and cognitively impaired (CI) individuals (MCI and dementia due to AD) with longitudinal Aβ PET, the records of OA medical history, and *APOE*-ε4 genotyping and who were Aβ+ at baseline. The OA (key words "Osteoarth" or "arthritis") history was determined as with or without OA disorder according to the participants' self-reported medical history (RECMHIST.csv and INITHEALTH.csv files downloaded from the ADNI website on December 30, 2021). Individuals with and without OA disease histories were defined as OA+ and

OA–, respectively, and carrying and noncarrying 1 *APOE*-ε4 allele were defined as *APOE*-ε4+ and *APOE*-ε4–, respectively.

Standard Protocol Approvals, Registrations, and Patient Consents

The ADNI study was approved by institutional review boards of all participating centers, and written informed consent was obtained from all participants or their authorized representatives.

Aβ PET Imaging

The details of FBP Aβ PET image acquisition are provided on the ADNI website (adni-info.org). In brief, from 50 to 70 minutes after injection, FBP PET data were collected in 4 × 5-minute frames. The T1-weighted structural MRI and completely preprocessed FBP PET images were downloaded from the LONI website (ida.loni.usc.edu). FBP scans were coregistered to their corresponding structural MRI scans.[4] The Desikan-Killiany atlas[29] was referred to define 34 regions of interest (ROIs) in FreeSurfer (version 7.1.0), and these ROIs were used to extract cortical tracer retention of FBP. The mean FBP uptake in the whole cerebellum was calculated as the reference, and the regional FBP uptake was normalized to generate FBP standardized uptake value ratios (SUVRs). Aβ+ was defined as FBP SUVR in AD summary cortical regions (composed of frontal, cingulate, parietal, and lateral temporal cortical regions) ≥1.11 as previously described.[5] Because 1 big composite (made up of brainstem, whole cerebellum, and eroded white matter) reference has shown less variance in longitudinal changes of FBP SUVRs,[30]s we used the big composite reference to calculate the SUVRs in precentral and postcentral regions for the following analyses.

Tau PET Imaging

The information on FTP tau PET image acquisition was also provided on the ADNI website (adni-info.org). From 75 to 105 minutes after injection, 6 × 5-minute frames of FTP PET data were collected. The fully preprocessed FTP PET scans were coregistered to their corresponding T1-weighted MRI scans. FTP uptakes in 34 cortical ROIs were also extracted in individual structural MRI space as previously described.[29] A mean inferior cerebellar gray matter FTP uptake was referred to calculate regional FTP SUVR.[31] The intensity-normalized and spatially normalized FTP PET images at the voxel-wise level in the Montreal Neurological Institute space and finally smoothed using a Gaussian kernel of 8 mm in statistical parametric mapping (SPM) 12 (Welcome Department of Imaging Neuroscience, London, United Kingdom) were used for the voxel-wise analyses as previously described.[17]

Statistical Analysis

Unless otherwise stated, statistical analyses were conducted using R (version 4.0.4; The R Foundation for Statistical Computing, Vienna, Austria). The Shapiro-Wilk test and a visual examination of the data histograms were used to determine whether the distributions were normal. The differences in continuous and categorical characteristics at baseline between OA+ and OA– were compared using 2-tailed Mann-Whitney *U* and Fisher exact tests, respectively. Data were presented as median (interquartile range, IQR) or n (%) unless otherwise noted. A false discovery rate of <0.05 using the Benjamini-Hochberg approach was used for multiple comparison corrections.

To determine the associations of OA disease and *APOE*-ε4 allele with cortical Aβ plaques in AD, we first investigated how OA and *APOE*-ε4 relate to baseline FBP SUVRs in precentral and postcentral cortical regions using generalized linear models (GLMs) as follows:

Model 1: Baseline FBP SUVR – OA × *APOE*-ε4 + age + sex + diagnosis

Model 1 investigated the main effect of OA and *APOE*4 status and their interaction on baseline FBP SUVR, controlling for age, sex, and diagnosis.

We subsequently investigated how OA and *APOE*-ε4 relate to longitudinal changes of FBP SUVR in precentral and postcentral cortical regions using linear mixed-effects models (lme4 package) as follows:

Model 2: FBP SUVR – Time × OA × *APOE*-ε4 + age + sex + diagnosis + (1 + Time|Subject)

Model 2 investigated how OA status and *APOE*4 status and their interaction are associated with longitudinal changes of FBP SUVR over time, including the same covariates above.

Furthermore, we studied how OA and *APOE*-ε4 relate to follow-up FTP SUVRs in precentral and postcentral cortices measured at a median of 5.4 years postbaseline Aβ PET scan and how they modulate the association between baseline FBP SUVR and follow-up FTP SUVRs using GLMs as follows:

Model 3: Follow-up FTP SUVR – OA × *APOE*-ε4 + baseline FBP SUVR+ age + sex + diagnosis

Model 3 investigated how OA status and *APOE*4 status and their interaction are related to the follow-up FTP SUVR levels, including baseline FBP SUVR, age, sex, and diagnosis.

Model 4: Follow-up FTP SUVR – baseline FBP SUVR × OA × *APOE*-ε4 + age + sex + diagnosis

Model 4 investigated how baseline FBP SUVRs, OA status, and *APOE*4 and their interaction are related to the follow-up FTP SUVR levels, including the same covariates above.

Notably, to rectify the data's non-normal distribution, we used a "log" link function from the Gaussian family in GLMs for the FTP SUVR.

We also compared the voxel-wise FTP SUVR PET images between the OA+ group and the OA– (ref) group using a 2-sample *t* test in SPM12, controlling for age, sex, and

Table 1 Demographics of Aβ-Positive Participants Included in This Study

	OA−	OA+
n (%)	255 (68.2)	119 (31.8)
Age, y, median (IQR, range)	75 (10, 55–92)	76 (9, 61–93)
***APOE*-ε4, n (%)**	162 (63.5)	73 (61.3)
CI, n (%)	182 (71.4)	78 (65.6)
Female, n (%)	126 (49.4)	58 (48.7)
Education, y, median (IQR, range)	16 (4, 8–20)	16 (4, 6–20)
Follow-up visits, median (IQR, range)	2 (1, 2–6)	2.5 (1, 2–5)
Duration of follow-up, y, median (IQR, range)	3.1 (3.2, 1.6–9.4)	3.9 (3.4, 1.7–9.1)
Baseline FBP SUVR of precentral region, median (IQR, range)	0.87 (0.13, 0.67–1.26)	0.86 (0.13, 0.70–1.11)
Baseline FBP SUVR of postcentral region, median (IQR, range)	0.83 (0.15, 0.61–1.18)	0.84 (0.15, 0.65–1.07)
Participants with tau PET measured at a median of 5.4 y postbaseline (n = 96)		
n (%)	65 (68.0)	31 (32.0)
Age, y, median (IQR, range)	74 (10, 55–87)	75 (6, 63–84)
***APOE*-ε4, n (%)**	37 (56.9)	16 (51.6)
CI, n (%)	37 (56.9)	21 (67.7)
Female, n (%)	34 (52.3)	11 (35.5)
Education, y, median (IQR, range)	16 (4.0, 12–20)	16 (4.50, 12–20)
Time interval from baseline Aβ PET, y, median (IQR, range)	5.3 (1.9, 4.0–9.3)	5.5 (1.6, 4.0–7.7)
Baseline FBP SUVR of precentral region, median (IQR, range)	0.83 (0.12, 0.67–1.06)	0.86 (0.11, 0.75–1.11)
Baseline FBP SUVR of postcentral region, median (IQR, range)	0.80 (0.12, 0.61–1.00)	0.83 (0.12, 0.69–1.07)

Abbreviations: Aβ = β-amyloid; CU = cognitively unimpaired; CI = cognitively impaired; FBP = ^{18}F-florbetapir; IQR = interquartile range; OA = osteoarthritis; SUVR = standardized uptake value ratio.

diagnosis. The voxel-wise comparisons between the OA+ and OA− groups were presented using an uncorrected voxel threshold of $p < 0.001$. We performed these analyses separately in *APOE*-ε4 carriers, *APOE*-ε4 noncarriers, and the whole cohort.

Data Availability

The ADNI database (adni.loni.usc.edu) provided all the data used in this study. Any qualified investigator may request the derived data from the corresponding author upon the terms of a data use agreement.

Results

Demographic Characteristics

The demographic characteristics of participants at baseline are summarized in Table 1. We analyzed 374 Aβ+ individuals (114 CU, 212 MCI, and 48 dementia due to AD) with longitudinal Aβ PET (median duration 3.3 [IQR 3.4, range 1.6–9.4] years), records of OA medical history, and *APOE*-ε4 genotyping. Of them, 260 (69.5%) were CI, 235 (62.8%) were *APOE*-ε4 carriers, 184 (49.2%) were female individuals, and 119 (31.8%) were OA+. Of them, 97 individuals (38 CU, 58 MCI, and 1 with dementia due to AD) had follow-up FTP PET scans measured at a median of 5.4 years postbaseline FBP PET. Notably, 1 MCI individual whose follow-up FTP SUVRs in precentral and postcentral regions were 5.8 and 6.7 standard deviations above the sample's mean value were excluded from the following analysis. No significant differences were found in age, education, baseline FBP SUVR in precentral and postcentral regions, and percentages of female individuals, *APOE*-ε4 carriers, and CI between OA+ and OA− groups.

Association of OA and *APOE*-ε4 Allele With Aβ Accumulation in Primary Motor and Somatosensory Cortices

At baseline, female individuals and impaired cognition were related to higher baseline FBP SUVRs of precentral and postcentral cortices. By contrast, neither OA nor *APOE*-ε4 allele was associated with baseline FBP SUVRs of precentral and postcentral cortices (Table 2). Longitudinally, OA+ individuals showed significantly faster rates of Aβ accumulation in precentral and postcentral regions than OA− individuals.

Notably, the rapid rates of Aβ accumulation in the precentral region disappeared after multiple comparison corrections. By contrast, *APOE*-ε4 did not have an independent influence or interactive effect with OA in longitudinal Aβ accumulation in precentral and postcentral cortices (Table 2). The other factors did not significantly correlate with longitudinal Aβ accumulation either.

Association of OA and *APOE*-ε4 Allele With Follow-up Tau Deposition in Primary Motor and Somatosensory Cortices

In 96 participants with follow-up FTP tau PET measured at a median of 5.4 years postbaseline Aβ PET, OA disorder was associated with a higher follow-up FTP SUVR in precentral and postcentral cortices (Table 2). In addition, the association between OA disorder and follow-up FTP SUVR was much more robust in *APOE*-ε4 carriers than in *APOE*-ε4 noncarriers. Younger ages and female individuals were related to higher tau deposition in precentral and postcentral regions. However, the *APOE*-ε4 allele did not show an independent effect in follow-up tau aggregation of these regions.

The voxel-wise analysis supported the predefined ROI analysis. Specifically, OA status was associated with higher FTP tau deposition in the precentral and postcentral cortices in 53 *APOE*-ε4 carriers (Figure 1, A–C). However, the significance did not survive after correction with a family-wise error corrected $p < 0.05$ at the cluster level. In addition, no significant difference was found in FTP tau between OA+ and OA− groups in 43 *APOE*-ε4 noncarriers (Figure 1, D–F) and the whole cohort (data not shown).

Association of OA and *APOE*-ε4 Allele With Aβ-Related Tau Accumulation in Primary Motor and Somatosensory Cortices

Table 3 summarizes and Figure 2 shows that higher baseline Aβ PET and OA disorder were independently and interactively related to significant or marginal higher follow-up tau deposition in precentral and postcentral cortices. Younger ages and female individuals were also associated with greater tau deposition. Notably, these associations became marginal or disappeared after multiple comparison corrections. By contrast, *APOE*-ε4 had no independent influence or interactive effect with OA or baseline Aβ PET in follow-up tau accumulation in precentral and postcentral cortices (Table 3).

Discussion

In this study, we investigated how OA disorder and *APOE*-ε4 allele relate to longitudinal changes of Aβ plaques in precentral and postcentral cortices over a median of 3.3 years and corresponding follow-up tau tangles measured at a median of 5.4 years postbaseline Aβ PET. This showed that OA disorder but not the *APOE*-ε4 allele was associated with faster longitudinal Aβ accumulation and follow-up tau deposition in precentral and postcentral cortices. The OA disorder showed a significant positive association with the follow-up tau deposition in precentral and postcentral cortices independently and interactively with the *APOE*-ε4 allele. In addition, we found that OA disease but not the *APOE*-ε4 allele was related to higher Aβ-associated tau levels in the precentral cortex. These results offer novel insights into why OA disorders, a common chronic disease in older individuals, increase the risk of AD.

The previous animal study[11] observed increased numbers of Aβ plaques and higher expression of neuroinflammatory factors in the brain in OA-induced amyloid precursor protein/presenilin 1 (APP/PS1) mice compared with those in the age-matched and sex-matched APP/PS1 mice, but less was known about how OA affects cortical Aβ accumulation in the human brain. Our analyses with a large longitudinal Aβ PET dataset revealed that OA disease could accelerate the rates of Aβ accumulation in primary motor and somatosensory cortices related to general bodily movement and sensation. One animal study found that early peripheral joint injury may trigger central spinal microglia activation, which increases the release of proinflammatory cytokine.[32] The proinflammatory cytokine might facilitate the production of Aβ and promote the seeding of Aβ plaques.[33] Together, it is likely that the peripheral inflammation induced by OA might trigger a proinflammatory response in the central neuron system and subsequently accelerate Aβ plaques accumulation in AD.

Consistent with previous study,[34,35] we also found *APOE*-ε4 allele is not related to faster Aβ accumulation in Aβ+ individuals. However, we observed OA-associated faster Aβ accumulation in primary motor and somatosensory cortices in Aβ+ individuals. Although Aβ accumulation in precentral and postcentral regions are usually involved in the late stage of AD,[36] OA disease may accelerate Aβ aggregation in precentral and postcentral cortices in early or intermediate stages of AD (73% of individuals in this study were non-demented). Consequently, OA-related faster Aβ accumulation in precentral and postcentral regions should be paid more attention to in the future.

No PET study has investigated the association between OA and tau aggregation in AD. This study found that OA disorder was positively related to elevated follow-up tau tangles in precentral and postcentral cortical regions measured approximately 5 years later. The OA disorder also interacted with the *APOE*-ε4 allele in predicting higher follow-up tau deposition. The voxel-wise findings were in line with the region-wise analysis. Notably, our laboratory[4,8,37] and other groups[38-41] have demonstrated that Aβ deposition can drive cortical tau aggregation in AD. Intriguingly, we further found that OA disorder was significantly associated with higher Aβ-related follow-up tau aggregation in the precentral and postcentral regions. However, the *APOE*-ε4 allele did not show an independent or interactive effect in Aβ-related follow-up tau aggregation in either precentral or postcentral areas. Altogether, these findings suggest that OA disease may be associated with faster Aβ accumulation over time and higher future tau aggregation in primary motor and somatosensory cortices in the AD continuum,[7] and the more prominent tau

Table 2 Association of OA and *APOE*-ε4 With Aβ Deposition in Primary Motor and Somatosensory Cortices

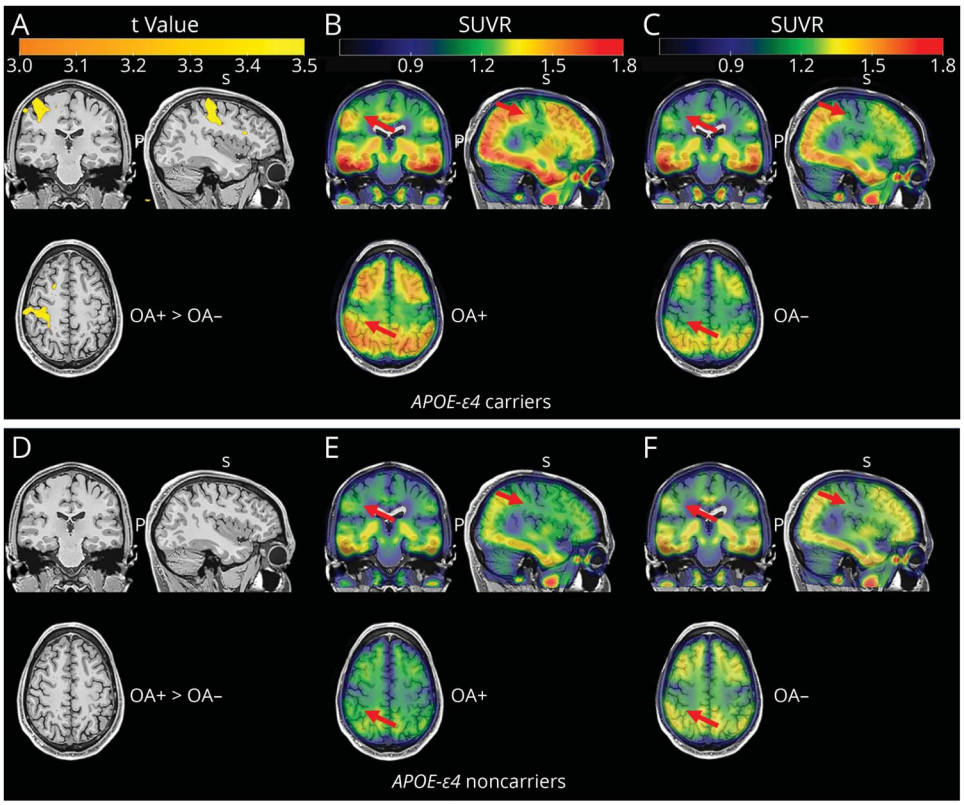
	Precentral			Postcentral		
	β (95% CI)	*p* Value	p_{adj}	β (95% CI)	*p* Value	p_{adj}
Model 1 (Outcome: baseline FBP SUVR)						
Age	0.001 (−0.0003 to 0.002)	0.127	0.222	0.001 (−0.001 to 0.002)	0.327	0.458
Sex (male)	−0.022 (−0.042 to −0.003)	0.024	0.056	−0.032 (−0.052 to −0.011)	0.002	0.005
Diagnosis (CI)	0.051 (0.030 to 0.073)	<0.001	<0.001	0.053 (0.030 to 0.075)	<0.001	<0.001
OA (OA+)	−0.002 (−0.024 to 0.003)	0.904	0.904	0.005 (−0.032 to 0.022)	0.709	0.709
***APOE*-ε4 (*APOE*4+)**	0.006 (−0.018 to 0.030)	0.625	0.874	0.013 (−0.012 to 0.039)	0.302	0.458
OA × *APOE*-ε4	−0.007 (−0.048 to 0.035)	0.758	0.884	−0.0145 (0.058 to 0.029)	0.517	0.604
Model 2 (Outcome: longitudinal FBP SUVR)						
Time	0.011 (0.008 to 0.014)	<0.001	<0.001	0.008 (0.006 to 0.010)	<0.001	<0.001
Age	0.001 (−0.0002 to 0.003)	0.106	0.195	0.001 (−0.001 to 0.002)	0.330	0.453
Sex (male)	−0.022 (−0.041 to −0.003)	0.022	0.061	−0.032 (−0.051 to −0.012)	0.002	0.005
Diagnosis (CI)	0.051 (0.030 to 0.071)	<0.001	<0.001	0.049 (0.027 to 0.071)	<0.001	<0.001
OA (OA+)	0 (−0.025 to 0.026)	0.995	0.995	−0.004 (−0.031 to 0.023)	0.766	0.843
***APOE*-ε4 (*APOE*4+)**	0.005 (−0.019 to 0.029)	0.693	0.847	0.014 (−0.011 to 0.039)	0.277	0.435
OA × *APOE*-ε4	−0.005 (−0.046 to 0.036)	0.810	0.891	−0.014 (−0.057 to 0.030)	0.543	0.664
Time × OA (OA+)	0.004 (0.0001 to 0.007)	0.046	0.102	0.005 (0.001 to 0.008)	0.015	0.033
Time × *APOE*-ε4 (*APOE*4+)	−0.001 (−0.004 to 0.002)	0.513	0.706	−0.0003 (−0.004 to 0.003)	0.855	0.855
Time × OA × *APOE*-ε4	0.003 (−0.002 to 0.009)	0.232	0.364	0.004 (−0.002 to 0.009)	0.180	0.330
Model 3 (Outcome: follow-up FTP SUVR)						
Aβ	0.777 (0.525 to 1.027)	<0.001	<0.001	0.658 (0.405 to 0.909)	<0.001	<0.001
Age	−0.005 (−0.009 to 0.001)	0.015	0.127	−0.005 (−0.009 to −0.0002)	0.006	0.014
Sex (male)	−0.068 (−0.119 to −0.018)	0.008	0.021	−0.070 (−0.121 to −0.019)	0.007	0.014
Diagnosis (CI)	0.043 (0.012 to 0.099)	0.123	0.141	0.026 (−0.029 to 0.082)	0.354	0.354
OA (OA+)	0.098 (0.034 to 0.162)	0.003	0.011	0.105 (0.040 to 0.169)	0.001	0.011
***APOE*-ε4 (*APOE*4+)**	−0.042 (−0.101 to 0.017)	0.163	0.163	−0.038 (−0.098 to 0.021)	0.205	0.273
OA × *APOE*-ε4	0.128 (0.030 to 0.226)	0.011	0.021	0.124 (0.027 to 0.223)	0.013	0.021

Abbreviations: Aβ = β-amyloid; *APOE*4+ = individuals with *APOE*-ε4 allele; β_{std} = standardized β value; CI = cognitively impaired; FBP = ^{18}F-florbetapir; FTP = ^{18}F-flortaucipir; OA = osteoarthritis; OA+ = individual with osteoarthritis; p_{adj} = adjusted *p* value, which was obtained by using the Benjamini-Hochberg method multiple comparison corrections; SUVR = standardized uptake value ratio.

deposition in the precentral region may be explained by the more substantial Aβ-dependent tau accumulation in OA+ individuals.

One functional MRI study[22] found that patients with knee OA showed a significant anterior shift in the knee representation and swap of the relative position of the knee and ankle representations in the motor cortex, providing further evidence for the link between OA and motor cortex. In addition, Stanton et al.[23] reported that tactile acuity at the knee was decreased in painful knee OA, implying a disrupted representation of the knee in the primary sensory cortex. Furthermore, a few brain stimulation studies[42-44] demonstrated the critical function of the primary motor cortex in reducing pain for older individuals with OA diseases. These studies suggest that primary motor and somatosensory cortices are significantly involved in OA disease. Our findings provide novel PET imaging evidence that OA may be associated with more aggregation of Aβ plaques and tau tangles in primary motor and somatosensory cortices in Aβ+ older individuals. Together with previous findings that an elevated tau level was closely linked to neurodegeneration,[4,45,46] the higher tau aggregation in primary motor and somatosensory cortices may lead to more

Figure 1 Voxel-wise Comparisons of Follow-up Tau PET Between OA+ and OA− Groups in Aβ+ Older Individuals



(A) Comparison of FTP tau PET between OA+ and OA−, and the mean tau PET images of (B) OA+ group and (C) OA− group in *APOE*-ε4 carriers. (D) Comparison of FTP tau PET between OA+ group and OA− group, and the mean tau PET images of (E) OA+ group and (F) OA− group in *APOE*-ε4 noncarriers. Brain maps were created at $p < 0.001$ at the voxel level without cluster correction and overlayed in an MRI template in MNI space. Red arrows indicate cortical regions of interest. Aβ = β-amyloid; MNI = Montreal Neurological Institute and Hospital; OA+ = participants with osteoarthritis; OA− = participants without osteoarthritis; SUVR = standardized uptake value ratio.

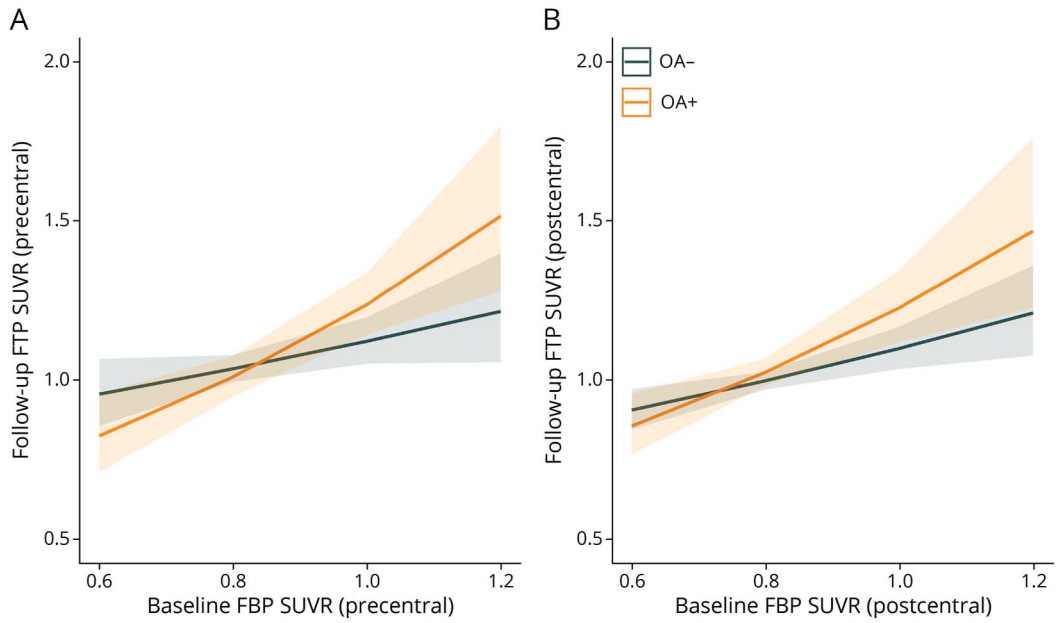
neurodegeneration in these regions and result in more motor and sensory dysfunction, including olfaction, hearing, and even walking speed.[47,48] Considering the high prevalence of OA disease in older individuals, more attention and better clinical management are extremely important for individuals in the AD continuum with an OA disease history.

Table 3 Association of OA, *APOE*-ε4, and Baseline Aβ PET With the Future Tau Levels in Primary Motor and Somatosensory Cortices

	Precentral			Postcentral		
	β (95% CI)	***p* Value**	**p_{adj}**	**β (95% CI)**	***p* Value**	**p_{adj}**
Aβ	0.504 (0.007 to 1.006)	0.047	0.103	0.579 (0.149 to 1.012)	0.008	0.063
OA (OA+)	0.688 (0.091 to 1.282)	0.021	0.103	0.449 (−0.073 to 0.970)	0.084	0.185
***APOE*-ε4 (*APOE*4+)**	−0.087 (−0.649 to 0.468)	0.761	0.837	−0.221 (−0.670 to 0.253)	0.362	0.546
Age	−0.004 (−0.008 to −0.0002)	0.039	0.103	−0.005 (−0.008 to −0.001)	0.013	0.063
Sex (male)	−0.056 (−0.106 to −0.006)	0.029	0.103	−0.060 (−0.110 to −0.011)	0.017	0.063
Diagnosis (CI)	0.035 (−0.018 to 0.089)	0.195	0.357	0.022 (−0.031 to 0.074)	0.425	0.546
Aβ × OA (OA+)	0.871 (0.205 to 1.534)	0.009	0.099	0.649 (−0.040 to 1.256)	0.032	0.088
Aβ × *APOE*-ε4 (*APOE*4+)	0.055 (−0.585 to 0.702)	0.868	0.868	0.215 (−0.360 to 0.796)	0.464	0.546
OA × *APOE*-ε4	−0.438 (−1.426 to 0.540)	0.379	0.521	−0.316 (−1.274 to 0.646)	0.516	0.546
Aβ × OA × *APOE*-ε4	0.621 (−0.493 to 1.753)	0.274	0.431	0.519 (−0.646 to 1.684)	0.379	0.546

Abbreviations: Aβ = β-amyloid; *APOE*-ε4+ = individuals with *APOE*-ε4 allele; CI = cognitively impaired; OA = osteoarthritis; OA+ = individual with osteoarthritis; p_{adj} = adjusted *p* value, which was obtained by using the Benjamini-Hochberg method multiple comparison corrections.

Figure 2 Associations Between Baseline FBP SUVR and Follow-up FTP SUVR in Precentral and Postcentral Cortical Regions



The comparisons of Aβ-related higher tau levels between OA+ and OA− groups in (A) precentral and (B) postcentral regions. Aβ = β-amyloid; FBP = ^{18}F-florbetapir; FTP = ^{18}F-flortaucipir; OA+ = participants with osteoarthritis; OA− = participants without osteoarthritis; SUVR = standard uptake value ratio.

The major strength of this study is that we analyzed a series of Aβ PET and tau PET image data, which revealed the relationship between OA, *APOE*-ε4, and AD key pathologies in Aβ+ older individuals. This is important for understanding how OA increases the risk of AD. However, this study has a few limitations. First, the OA medical history was defined by referring to self-reported medical history in the ADNI cohort. Thus, future studies with more precise assessments of OA disease in other datasets would be beneficial. Second, the OA disorder most commonly affects joints in the patient's hands, knees, hips, and spine, although it can damage any joint, while this study cannot explain the association between any subtypes of OA and AD. Third, the sample size of participants with follow-up tau PET was relatively small, which may need to be validated in other cohorts with large sample sizes and more longitudinal tau PET data. Moreover, we did not adjust for body mass index and physical activity as the covariates because we investigated the association between OA and AD, but they may be associated with faster Aβ accumulation according to the previous literature.[49,50]

Overall, this longitudinal Aβ PET and follow-up tau PET imaging study suggest that OA diseases may accelerate faster Aβ accumulation and induce higher Aβ-related tau deposition in primary motor and somatosensory cortices in Aβ+ older individuals. The association between OA and AD pathologies, such as faster Aβ plaque accumulation and more significant Aβ-dependent tau deposition in precentral and postcentral cortices, highlights the importance of considering the influence of other common chronic health conditions (e.g., OA) for better health management of AD patients in future.

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Disclosure

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Tengfei Guo, PhD	Institute of Biomedical Engineering, Shenzhen Bay Laboratory; Institute of Biomedical Engineering, Peking University Shenzhen Graduate School, China	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data; and additional contributions: obtaining funding and study supervision

Appendix 2 Coinvestigators

ADNI coinvestigators are listed at links.lww.com/WNL/C803.

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