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Association of Apolipoprotein E ε4 With Medial Temporal Tau Independent of Amyloid-β

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Supplemental content

IMPORTANCE Apolipoprotein E ε4 (*APOEε4*) is the single most important genetic risk factor for Alzheimer disease. While *APOEε4* is associated with increased amyloid-β burden, its association with cerebral tau pathology has been controversial.

OBJECTIVE To determine whether *APOEε4* is associated with medial temporal tau pathology independently of amyloid-β, sex, clinical status, and age.

DESIGN, SETTING, AND PARTICIPANTS This is a study of 2 cross-sectional cohorts of volunteers who were cognitively normal, had mild cognitive impairment (MCI), or had Alzheimer disease dementia: the Translational Biomarkers in Aging and Dementia (TRIAD) study (data collected between October 2017 and July 2019) and the Alzheimer's Disease Neuroimaging Initiative (ADNI) (collected between November 2015 and June 2019). The first cohort (TRIAD) comprised cognitively normal elderly participants (n = 124), participants with MCI (n = 50), and participants with Alzheimer disease (n = 50) who underwent tau positron emission tomography (PET) with fluorine 18–labeled MK6240 and amyloid-β PET with [^{18}F]AZD4694. The second sample (ADNI) was composed of cognitively normal elderly participants (n = 157), participants with MCI (n = 83), and participants with Alzheimer disease (n = 25) who underwent tau PET with [^{18}F]flortaucipir and amyloid-β PET with [^{18}F]florbetapir. Exclusion criteria were a history of other neurological disorders, stroke, or head trauma. There were 489 eligible participants, selected based on availability of amyloid-PET, tau-PET, magnetic resonance imaging, and genotyping for *APOEε4*. Forty-five young adults (<30 years) from the TRIAD cohort were not selected for this study.

MAIN OUTCOMES AND MEASURES A main association between *APOEε4* and tau-PET standardized uptake value ratio, correcting for age, sex, clinical status, and neocortical amyloid-PET standardized uptake value ratio.

RESULTS The mean (SD) age of the 489 participants was 70.5 (7.1) years; 171 were *APOEε4* carriers (34.9%), and 230 of 489 were men. In both cohorts, *APOEε4* was associated in increased tau-PET uptake in the entorhinal cortex and hippocampus independently of amyloid-β, sex, age, and clinical status after multiple comparisons correction (TRIAD: β = 0.33; 95% CI, 0.19-0.49; ADNI: β = 0.13; 95% CI, 0.08-0.19; *P* < .001).

CONCLUSIONS AND RELEVANCE Our results indicate that the elevated risk of developing dementia conferred by *APOEε4* genotype involves mechanisms associated with both amyloid-β and tau aggregation. These results contribute to an evolving framework in which *APOEε4* has deleterious consequences in Alzheimer disease beyond its link with amyloid-β and suggest *APOEε4* as a potential target for future disease-modifying therapeutic trials targeting tau pathology.

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Of genetic risk factors for sporadic Alzheimer disease,[1] the apolipoprotein E ε4 (*APOEε4*) allele is the most well established. The presence of 1 ε4 allele is linked with earlier development of Alzheimer disease,[2] and homozygosity for *APOEε4* is associated with onset of Alzheimer disease 10 years earlier compared with non-ε4 carriers.[3] The *APOEε4* allele is associated with increased production of amyloid-β[4] as well as with diminished clearance of cerebral amyloid-β compared with *ε3* and *ε2* alleles.[5,6] Consequently, individuals with the *APOEε4* genotype demonstrate increased cerebral amyloid-β deposition as measured by amyloid positron emission tomography (PET),[7] with amyloid-β positivity beginning earlier in life in *APOEε4* carriers than noncarriers.[8]

However, the *APOEε4* allele has been implicated in numerous other processes independent of amyloid-β in preclinical models of Alzheimer disease,[9,10] including neuroinflammation and neurodegeneration. In humans, the *APOEε4* allele is linked with medial temporal hypometabolism in cognitively normal elderly individuals[11] and individuals with Alzheimer disease[12] independently of amyloid-β burden, although the mechanisms underlying the process are not known. Because of the spatiotemporal association between tau aggregation and neurodegeneration,[13-15] aggregation of tau pathology presents a potential pathway for the specific patterns of neurodegeneration observed in *APOEε4* carriers.

The goal of this study is therefore to determine whether *APOEε4* is associated with cerebral tau pathology, independently of age, sex, clinical status, and amyloid-β deposition. Building on previous reports of specific patterns of neurodegeneration in *APOEε4* carriers,[11,12,16] we hypothesize that *APOEε4* is associated with tau pathology in medial temporal structures.

Key Points

Question Is the apolipoprotein E ε4 (*APOEε4*) genotype associated with tau pathology independently of amyloid-β?

Findings In this study of 2 cross-sectional cohorts (total n = 489), individuals who were *APOEε4* carriers had significantly higher entorhinal and hippocampal tau positron emission tomography signal than *APOEε4* noncarriers, controlling for cortical amyloid-β burden, age, sex, and clinical status.

Meaning Carriership of *APOEε4* is associated with tau pathology in medial temporal structures independently of amyloid-β, extending previous reports of greater medial temporal neurodegeneration and memory impairment in *APOEε4* carriers.

Methods

Participants

Translational Biomarkers in Aging and Dementia

The Translational Biomarkers in Aging and Dementia (TRIAD) cohort aims at describing biomarker trajectories and interactions as drivers of dementia. The TRIAD study was launched in 2017 as part of the McGill Centre for Studies in Aging. We assessed cognitively normal participants (n = 124), participants with mild cognitive impairment (MCI) (n = 50), and participants with Alzheimer disease dementia (n = 50) who underwent amyloid-β PET with fluorine 18-labeled [^{18}F]AZD4694, tau PET with [^{18}F]MK6240, structural magnetic resonance imaging, and genotyping for *APOEε4*. All participants had detailed clinical assessments including Mini-Mental State Examination, Clinical Dementia Rating (CDR), and cerebrovascular disease risk with the Hachinski Ischemic scale.[17] Cognitively normal control individuals had a CDR of 0, participants with MCI had a CDR of 0.5, and participants with Alzheimer disease had a CDR between 1 and 2, in addition to meeting standard diagnostic criteria.[18] Similar to other longitudinal cohort studies of aging and Alzheimer disease,[19] the TRIAD cohort is enriched for *APOEε4* carriers. Inclusion criteria for all participants are the ability to speak English or French, good general health (no diseases expected to interfere with study participation over time), absence of claustrophobia, and adequate visual and auditory capacities to follow neuropsychologic evaluation. This study's protocol was approved by McGill University's institutional review board, and informed written consent was obtained from each participants. There was no attempt to match cases between cohorts.

Alzheimer's Disease Neuroimaging Initiative

In this study, we assessed cognitively normal individuals (n = 157), individuals with amnestic mild cognitive impairment (n = 83), and individuals with Alzheimer disease (n = 25) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort who underwent amyloid-β PET with [^{18}F]florbetapir, tau PET with [^{18}F]flortaucipir, structural MRI, and genotyping for *APOEε4*. Cognitively normal control individuals had a CDR of 0, participants with MCI had a CDR of 0.5, and participants with Alzheimer disease had a CDR of 1 or greater in addition to meeting standard diagnostic criteria.[18] The Alzheimer's Disease Neuroimaging Initiative (ADNI) study was approved by the institutional review boards of all of the participating institutions. Informed written consent was obtained from all participants at each site. Full information regarding the ADNI inclusion and exclusion criteria can be accessed at http://adni.loni.usc.edu/.

Genetic Analyses

TRIAD

Determination of *APOE* genotypes for patients recruited at McGill was performed using the polymerase chain reaction amplification technique, followed by restriction enzyme digestion, standard gel resolution and visualization processes. Full details of this procedure can be found elsewhere.[20]

ADNI

Determination of *APOE* genotypes for ADNI patients took place at the University of Pennsylvania Alzheimer Disease Biomarker Laboratory. Complete details of genetic methods used in ADNI can be accessed at http://adni.loni.usc.edu/data-samples/clinical-data/.

Positron Emission Tomography Image Acquisition and Processing

TRIAD

All participants had a T1-weighted MRI that was used for coregistration. Full details of MRI acquisition and processing is described in the eMethods 1 in the Supplement. The PET scans were acquired with a Siemens High Resolution Research Tomograph. The [^{18}F]MK6240 images were acquired 90 to 110 minutes postinjection, and scans were reconstructed with the ordered subset expectation maximization algorithm on a 4-dimensional volume with 4 frames (4 × 300 seconds).[21] The [^{18}F]AZD4694 images were acquired 40 to 70 minutes following injection, and scans were reconstructed with the ordered subset expectation maximization algorithm on a 4-dimensional volume with 3 frames (3 × 600 seconds).[22] Immediately following each PET acquisition, a 6-minute transmission scan was conducted with a rotating cesium 137 point source for attenuation correction. Additionally, the images underwent correction for dead time, decay, and random and scattered coincidences. T1-weighted images were nonuniformity and field-distortion corrected and processed using an in-house pipeline. Then, PET images were automatically registered to the T1-weighted image space, and the T1-weighted images were linearly and nonlinearly registered to the ADNI template space. Subsequently, a PET nonlinear registration was performed using the linear and nonlinear transformations from the T1-weighted image to the ADNI space and the PET to T1-weighted image registration using advanced normalization tools. The PET images were spatially smoothed to achieve a final resolution of 8 mm full width at half maximum. The PET image partial volume correction was carried out using the PETPVC toolbox.[23] Briefly, the region-based voxelwise correction technique was used to perform partial volume correction using 10 tissue priors with a gaussian kernel with a full width at half maximum of 2.4 mm. The [^{18}F]MK6240 standardized uptake value ratio (SUVR) maps were generated using the inferior cerebellar gray matter as a reference region, and [^{18}F]AZD4694 SUVR maps were generated using the cerebellar gray matter as a reference region. A global [^{18}F]AZD4694 SUVR value was estimated for each participant by averaging the SUVR from the precuneus, prefrontal, orbitofrontal, parietal, temporal, anterior, and posterior cingulate cortices.[24]

ADNI

Full information regarding acquisition and preprocessing of PET data in ADNI is provided at http://adni.loni.usc.edu/data-samples/pet/. Preprocessed PET images downloaded from ADNI underwent spatial normalization to the ADNI standardized space using the transformations of PET native to MRI native space and MRI native to the ADNI space. Partial volume correction was carried out using the PETPVC toolbox[23] described previously in an effort to diminish off-target binding to the choroid plexus. [^{18}F]flortaucipir (also known as [^{18}F]T807 and/or [^{18}F]AV1451) SUVR maps were generated using the inferior cerebellar gray matter as a reference region,[25] and [^{18}F]florbetapir SUVR maps were generated using the cerebellar gray matter as a reference region. A global [^{18}F]florbetapir SUVR value was estimated for each participant by averaging the SUVR from the precuneus, prefrontal, orbitofrontal, parietal, temporal, anterior, and posterior cingulate cortices.[24]

Statistical Analyses

Two independent samples were investigated: (1) the TRIAD cohort assessed with [^{18}F]MK6240 and [^{18}F]AZD4694 and (2) an ADNI cohort assessed with [^{18}F]flortaucipir and [^{18}F]florbetapir. The primary outcome measure of the study was tau pathology as measured by voxelwise [^{18}F]MK6240 SUVR (TRIAD) and [^{18}F]flortaucipir SUVR (ADNI). In each cohort, we tested whether *APOEε4* is associated with tau pathology independently of amyloid-β, sex, or age using voxelwise multivariate linear regression models.

Baseline demographic and clinical data were assessed using *t* tests and χ^2 tests. Neuroimaging analyses were carried out using the VoxelStats toolbox (https://github.com/sulantha2006/VoxelStats), a MATLAB-based analytical framework that allows for the execution of multimodal voxelwise neuroimaging analyses.[26] All neuroimaging analyses described in subsequent paragraphs were repeated using partial volume–corrected data. Other statistical analyses were performed using the R Statistical Software Package, version 3.5.3 (the R Foundation). Given the large number of covariates in the statistical models, model diagnostics were carried out using the car package in R to determine the presence of multicollinearity. We computed the variance inflation factor, a measurement of how much variance in regression coefficients are inflated owing to multicollinearity in the statistical models.[27]

In the TRIAD cohort, the voxel-based model outlined here was built to test whether main effects between *APOEε4* carriership are associated with [^{18}F]MK6240 uptake independently of [^{18}F]AZD4694 uptake. To ensure that the results were not driven by an effect of clinical status (ie higher frequency of *APOEε4* carriers in the MCI and Alzheimer disease groups), we adjusted the model for clinical diagnosis. The model was also adjusted for age. Because *APOEε4* is associated with amyloid-PET uptake, amyloid-β was included as a covariate in every analysis. Sex was included as a covariate owing to sex differences in entorhinal tau aggregation[28] and stronger associations between *APOEε4* and tau in women.[29] Statistical parametric maps were corrected for multiple comparisons using random field theory,[30] with a cluster threshold of $P < .001$. The analysis was repeated using partial volume–corrected data. In every brain voxel, the model was of the form:

$$[^{18}\text{F}]\text{MK6240 SUVR} = \beta_o + \beta_1([^{18}\text{F}]\text{AZD4694 SUVR}) + \beta_2(\text{APOE}_{\varepsilon 4}) + \beta_3(\text{Clinical Status}) + \beta_4(\text{Age}) + \beta_5(\text{Sex}) + \varepsilon$$

Next, we tested the same hypothesis in the ADNI database, examining whether *APOEε4* carriership is associated with [^{18}F]flortaucipir uptake independently of [^{18}F]florbetapir uptake. This model was also adjusted for amyloid-β, sex, age, and clinical status. Statistical parametric maps were corrected for multiple comparisons using random field theory,[30] with a cluster threshold of $P < .001$. The analysis was repeated using partial volume–corrected data. In every brain voxel, the model was of the form:

$$[^{18}\text{F}]\text{Flortaucipir SUVR} = \beta_O + \beta_1([^{18}\text{F}]\text{Florbetapir SUVR}) + \beta_2(\text{APOE}_{\varepsilon 4}) + \beta_3(\text{Clinical Status}) + \beta_4(\text{Age}) + \beta_5(\text{Sex}) + \varepsilon$$

To better understand the association between *APOEε4* and medial temporal tau aggregation, we conducted subgroup

Table 1. Demographic and Key Characteristics of the Samples

Cohort	CU	MCI	P Value[a]	AD	P Value[a]
TRIAD cohort					
No.	124	50	NA	50	NA
Age, mean (SD), y	70.41 (6.5)	70.88 (7.7)	.007	66.69 (9.93)	.005
Male, No. (%)	53 (43)	25 (50)	.69	20 (40)	.61
Education, mean (SD), y	15.52 (3.86)	14.26 (3.79)	.06	14.2 (3.75)	.04
APOE ε4 carriers, No. (%), %	38 (31)	18 (36)	.49	26 (52)	.008
MMSE, mean (SD)	29.05 (1.25)	27.13 (2.39)	<.001	19.1 (7.31)	<.001
CDR SoB, mean (SD)	0.18 (0.45)	1.47 (1.23)	<.001	6.48 (4.08)	<.001
[^{18}F]AZD4694 SUVR, mean (SD)	1.48 (0.42)	1.86 (0.54)	<.001	2.42 (0.63)	<.001
ADNI cohort					
No.	157	83	NA	25	NA
Age, mean (SD), y	70.98 (5.91)	70.57 (7.09)	.63	74.11 (7.65)	.02
Male, No. (%)	71 (45)	49 (59)	.04	12 (48)	.66
Education, mean (SD), y	16.65 (2.5)	15.84 (2.85)	.02	16.26 (2.51)	.47
APOE ε4 carriers, No. (%)	49 (31)	27 (32.5)	.83	13 (52)	.04
MMSE, mean (SD)	28.97 (1.33)	28.05 (2.15)	<.001	19.67 (5.28)	<.001
CDR SoB, mean (SD)	0.009 (0.51)	1.46 (0.93)	<.001	7.18 (2.67)	<.001
[^{18}F]Florbetapir SUVR, mean (SD)	1.2 (0.22)	1.26 (0.29)	.07	1.47 (0.22)	<.001

Abbreviations: AD, Alzheimer disease dementia; ADNI, Alzheimer's Disease Neuroimaging Initiative; CDR SoB, Clinical Dementia Rating sum of boxes; CU, cognitively unimpaired; ^{18}F, fluorine 18 labeled; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; SUVR, standardized uptake value ratio; TRIAD, Translational Biomarkers in Aging and Dementia.

[a] *P* values reported are for comparisons with cognitively unimpaired participants. *P* values indicate values assessed with independent-samples *t* tests for each variable except sex and APOE *ε4* status, where contingency χ^2 tests were performed.

analyses, stratifying individuals according to the presence of cognitive impairment (ie, in cognitively unimpaired individuals and cognitively impaired individuals). The cognitively impaired groups consisted of the individuals with MCI and AD pooled together. These models were adjusted for amyloid-β, sex, and age. The analyses were repeated using partial volume–corrected data.

To derive an estimate of the association between *APOEε4* and medial temporal tau-PET SUVR across both cohorts, we used the Metafor package in R. We fit a meta-analytic fixed-effects model using β weights and standard errors for the estimates from each population, analyzed using the *rma* function. The same process was repeated for gene-dose and voxel-based morphometry analyses described subsequently.

The *P* value level of significance was .001, and all tests were 2-sided. Exploratory gene-dose analyses, *APOEε4*-voxel-based morphometry analyses, *APOEε4* × age interaction analyses, *APOEε4* × amyloid-PET interaction analyses, and *APOEε4* unadjusted for amyloid-PET analyses are described in eMethods 2 in the Supplement.

Results

Demographic and clinical information for both samples examined in this study is summarized in **Table 1**. Demographic comparisons between cohorts are reported in eTable 1 in the Supplement. Variance inflation factors (VIFs) for all variables were between 1 and 2, indicating that problematic levels of multicollinearity are not present in our analyses.[27]

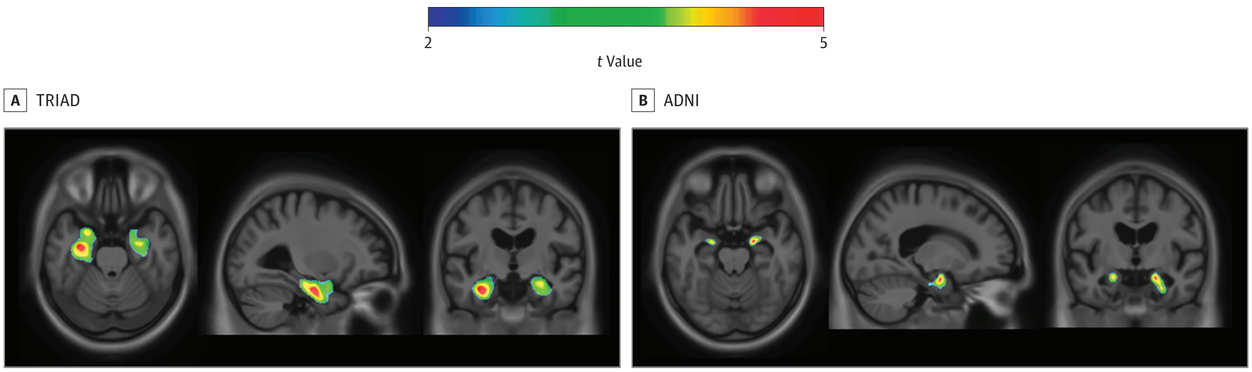
We tested the hypothesis that *APOEε4* is associated with greater [^{18}F]MK6240 uptake independently of global [^{18}F]AZD4694 uptake. Voxelwise analyses revealed that *APOEε4* carriership was associated with increased [^{18}F]MK6240 SUVR in the bilateral entorhinal cortex and hippocampus (random field theory corrected at $P < .001$; significant clusters: $P < .001$; $t = 4.42$; $\beta = 0.33$; 95% CI, 0.19-0.49) (**Figure 1**A). These results are independent of amyloid-β, clinical diagnosis, age, and sex. Results remained similar when using partial volume–corrected data (eFigure 1A in the Supplement; full model statistics of PVC data presented in **Table 2**). No statistically significant associations were observed beyond the medial temporal lobes.

We also tested the hypothesis that *APOEε4* is associated with greater [^{18}F]flortaucipir uptake independently of global [^{18}F]florbetapir uptake. Voxelwise analyses revealed that *APOEε4* carriership was associated with increased [^{18}F]flortaucipir SUVR in the bilateral entorhinal cortex (random field theory corrected at $P < .001$; significant clusters: $t = 4.527$; $\beta = 0.13$; 95% CI, 0.08-0.19) (Figure 1B). Results remained similar when using partial volume–corrected data (eFigure 1B in the Supplement; full model statistics of PVC data presented in Table 2). These results are independent of amyloid-β, clinical diagnosis, age, and sex. No statistically significant associations were observed beyond the medial temporal lobes.

Scatterplots of the association between neocortical amyloid-PET SUVR and medial temporal tau-PET SUVR stratified by *APOEε4* status are displayed in **Figure 2**. Density plots are also provided to visualize distribution of the data.

Full model statistics are presented in Table 2. While *t* values for the *APOEε4* medial temporal tau-PET SUVR associations were similar across studies, the regression β estimates for the TRIAD cohort were higher (TRIAD: $P < .001$; $t = 4.464$; $\beta = 0.33$; 95% CI, 0.19-0.49; ADNI: $P < .001$, $t = 4.52$; $\beta = 0.13$; 95% CI, 0.08-0.19). While the association between *APOEε4* and medial temporal tau-PET SUVR was significant in both co-

Figure 1. Association of Medial Temporal Tau Positron Emission Tomography With Apolipoprotein E ε4 (APOEε4) Independent of Amyloid-β



T-statistical parametric maps were corrected for multiple comparisons using a random field theory cluster threshold of *P* < .001, overlaid on the Alzheimer's Disease Neuroimaging Initiative reference template. Age, sex, clinical diagnosis, and amyloid-β standardized uptake value ratio were used as covariates the model. A, Voxelwise analyses revealed that *APOEε4* carriership was associated with increased fluorine 18–labeled [^{18}F] MK6240 in the bilateral entorhinal cortex and hippocampus. B, Voxelwise analyses revealed that *APOEε4* carriership was associated with increased [^{18}F]flortaucipir in the bilateral entorhinal cortex.

Table 2. Regression Coefficients of APOE4 on Medial Temporal Tau-PET

	Medial Temporal Tau-PET			Medial Temporal Tau-PET (PVC)		
Variable	β (95% CI)	*t* Value	*P* Value	β (95% CI)	*t* Value	*P* Value
TRIAD cohort[a]						
APOE4	0.33 (0.19 to 0.49)	4.42	<.001	0.26 (0.14 to 0.37)	4.25	<.001
Neocortical [^{18}F]AZD4694 SUVR	0.93 (0.81 to 1.05)	14.49	<.001	0.76 (0.65 to 0.87)	9.1	<.001
Male	−0.17 (−0.31 to −0.04)	−2.52	.01	−0.18 (−0.29 to 0.06)	−3.01	.003
Age	−0.008 (−0.02 to −0.0007)	−2.18	.02	−0.008 (−0.01 to 0.0004)	−2.12	.03
Clinical status						
MCI	0.2 (0.02 to 0.38)	2.28	.02	0.18 (0.03 to 0.34)	2.41	.01
AD	0.64 (0.44 to 0.85)	6.2	<.001	0.53 (0.36 to 0.71)	6.07	<.001
ADNI cohort[b]						
APOE4	0.13 (0.08 to 0.19)	4.53	<.001	0.12 (0.06 to 0.19)	3.95	<.001
Neocortical [^{18}F]florbetapir	0.23 (0.11 to 0.34)	4.1	<.001	0.26 (0.13 to 0.38)	4.05	<.001
Male	−0.02 (−0.004 to 0.004)	0.57	.57	−0.03 (0.02 to −0.09)	−1.11	.27
Age	−0.006 (−0.03 to 0.004)	0.28	.77	−0.001 (−0.006 to 0.003)	−0.73	.46
MCI	0.13 (0.07 to 0.19)	4.51	<.001	0.15 (0.09 to 0.22)	4.65	<.001
AD	0.49 (0.4 to 0.59)	10.27	<.001	0.45 (0.34 to 0.56)	8.29	<.001

Abbreviations: AD, Alzheimer disease dementia; ADNI, Alzheimer's Disease Neuroimaging Initiative; APOE4, apolipoprotein E ε4; ^{18}F, fluorine 18 labeled; MCI, mild cognitive impairment; PET, positron emission tomography; PVC, partial volume corrected data; SUVR, standardized uptake value ratio; TRIAD, Translational Biomarkers in Aging and Dementia.

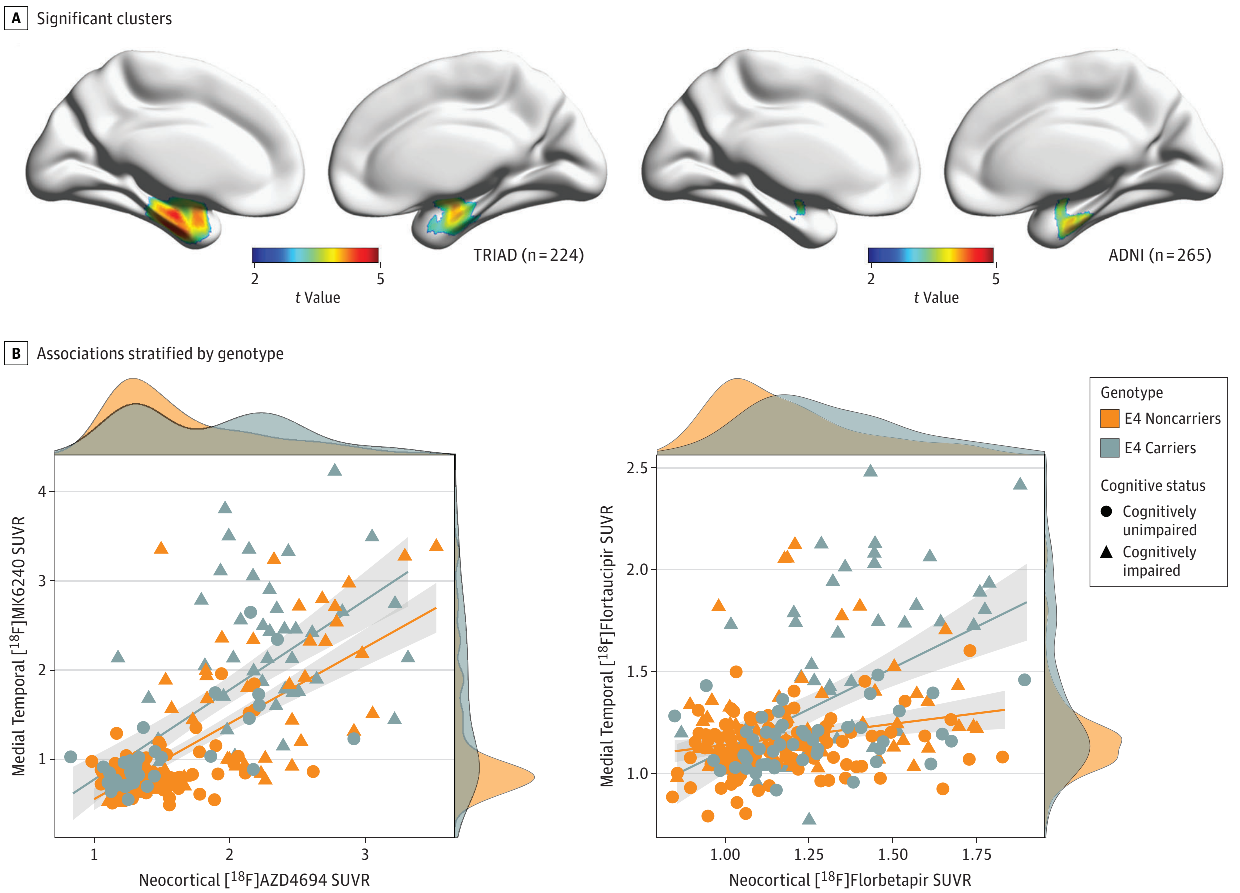
[a] Adjusted R^2: 0.61, F = 58.61 (non-PVC); adjusted R^2: 0.6, F = 56.39 (PVC).

[b] Adjusted R^2: 0.42, F = 0.33 (non-PVC), adjusted R^2: 0.35, F = 25.19 (PVC).

horts, β estimates for *APOEε4*-medial temporal tau-PET SUVR associations were smaller than those of amyloid-PET in TRIAD (*P* < .001, *t* = 14.49; β = 0.93; 95% CI, 0.81-1.05) or a clinical diagnosis of Alzheimer disease in ADNI (*P* < .001, *t* = 10.27; β = 0.49; 95% CI, 0.4-0.59).

To better understand the association between *APOEε4* and medial temporal tau aggregation, we conducted subgroup analyses by stratifying individuals according to cognitive impairment. When stratifying analyses by cognitive status in the TRIAD cohort, we observed that *APOEε4* was associated with medial temporal [^{18}F]MK6240 SUVR independently of [^{18}F]AZD4694 SUVR in cognitively normal elderly individuals (n = 124) and in cognitively impaired individuals (n = 100) (**Figure 3**). When conducting subgroup analyses in the ADNI cohort, we found that *APOEε4* was associated with [^{18}F]flortaucipir SUVR in the left entorhinal cortex in cognitively unimpaired elderly individuals (n = 157). The *APOEε4* carriership was also associated with [^{18}F]flortaucipir SUVR independently of [^{18}F]florbetapir SUVR in the bilateral entorhinal cortices in cognitively impaired individuals (n = 108). Full model statistics are presented in eTable 2 in the Supplement. Full model statistics for all exploratory analyses are reported in eTables 3-7 in the Supplement. Gene-dose associations are reported in eFigure 2 in the Supplement and associations unadjusted for amyloid-PET are reported in eFigure3 in the Supplement.

Figure 2. Associations Between Medial Temporal Tau Positron Emission Tomography (PET) and Neocortical Amyloid PET Stratified by Apolipoprotein E ε4 (APOEε4) Genotype



A, Clusters that remained significant after multiple comparisons correction with random field theory at $P < .001$ were used to extract tau-PET standardized uptake value ratio (SUVR) values in the TRIAD cohort (left) and ADNI cohort (right). B, Scatterplots displaying associations between medial temporal tau PET and neocortical amyloid PET stratified by *APOEε4* genotype in TRIAD (left) and ADNI (right). Density plots are provided along the x and y axes to visualize the distribution of the data for neocortical amyloid PET and medial temporal tau PET SUVR, respectively. In the TRIAD cohort, *APOEε4* carriership was associated with medial temporal fluorine 18–labeled [^{18}F] MK6240 SUVR ($t = 4.42$; $\beta = 0.33$; 95% CI, 0.19-0.49). In the ADNI cohort, *APOEε4* carriership was significantly associated with medial temporal [^{18}F]flortaucipir SUVR ($t = 4.527$; $\beta = 0.13$; 95% CI, 0.08-0.19).

Meta-analytic Estimates

When fitting a fixed-effect *rma* model to the coefficients and standard errors from the models in both cohorts, we found that the main association of *APOEε4* on medial temporal tau-PET SUVR was significant ($P < .001$, meta-analytic $\beta = 0.22$; 95% CI, 0.15-0.29).

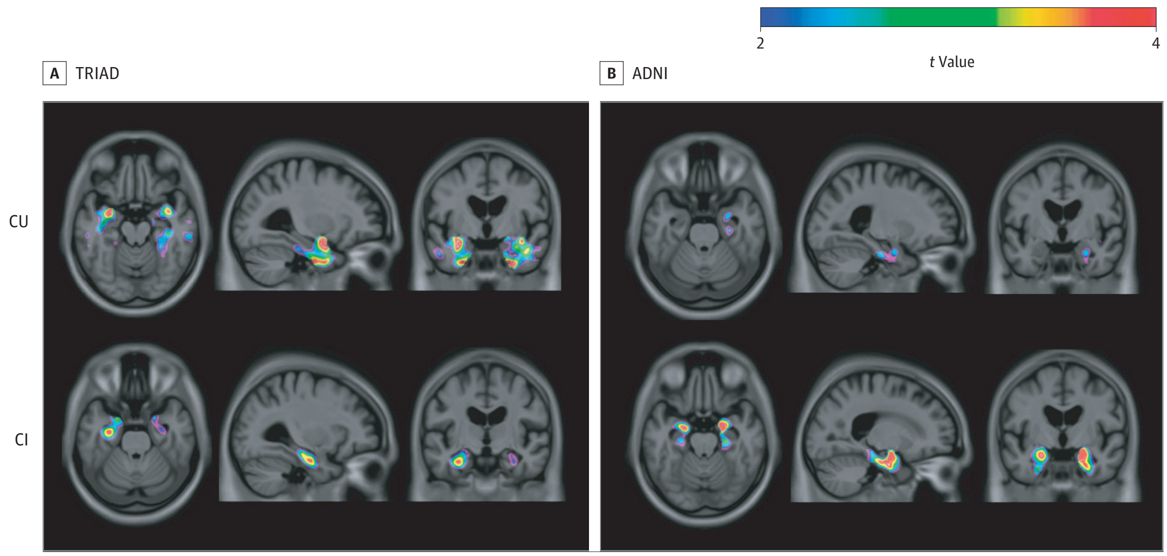
Discussion

This study provides evidence from 2 independent cohorts that *APOEε4* is associated with increased tau pathology in the entorhinal cortex and hippocampus independently of age, clinical status, sex, and amyloid-β. Our study is in agreement with a growing body of research demonstrating greater vulnerability of the medial temporal lobes to hypometabolism[11,12] and atrophy[31-33] in *APOEε4* carriers compared with noncarriers, independently of amyloid-β. Because of the topographical concordance between tau pathology and neurodegeneration,[13,14,34] our results suggest greater tau pathology may be responsible for the medial temporal neurodegeneration observed in *APOEε4* carriers.

Our findings of greater medial temporal tauopathy are consistent with specific neuropsychologic profiles of *APOEε4* carriers vs noncarriers. Patients with Alzheimer disease dementia who are *APOEε4* carriers perform worse on memory tasks than noncarriers at the same disease stage.[35,36] Correspondingly, memory tends to be relatively preserved in ε4-negative patients, while deficits in executive function and processing speed are more severe.[37,38] Patients with Alzheimer disease dementia who do not carry an ε4 allele are also more likely to present with nonamnestic phenotypes.[39] Taken together, these studies support a framework in which medial temporal structures are specifically vulnerable to the deleterious effects of *APOEε4*.

An outstanding question is why *APOEε4*'s association with tau pathology is restricted to the medial temporal lobe. While pyramidal neurons of the entorhinal cortex, subicu-

Figure 3. Association Between Medial Temporal Tau Positron Emission Tomography (PET) and Apolipoprotein E ε4 (APOEε4) Stratified by Cognitive Status



A, In cognitively unimpaired participants (n = 124), *APOEε4* carriership was associated with fluorine 18–labeled [^{18}F] MK6240 standardized uptake value ratio (SUVR) in the bilateral entorhinal cortex and hippocampus. In cognitively impaired participants (n = 100), *APOEε4* carriership was associated with increased [^{18}F]MK6240 in the bilateral hippocampus. B, In cognitively unimpaired patients (n = 157), *APOEε4* carriership was associated with [^{18}F]flortaucipir SUVR in the left entorhinal cortex. In cognitively impaired patients (n = 109), *APOEε4* carriership was associated with increased [^{18}F]flortaucipir in the bilateral entorhinal cortices and hippocampus. Age, sex, and amyloid-β SUVR were used as covariates in each model. Results remained similar when using partial volume–corrected PET data. CU indicates cognitively unimpaired; CI, cognitively impaired.

lum, and CA1 region of the hippocampus are vulnerable to early tau accumulation in Alzheimer disease,[40-42] limited data exist as to how *APOEε4* may preferentially (or selectively) affect tau aggregation in these structures.[10] Data from the Allen Brain Atlas suggest that messenger RNA expression of APOE is highest in the medial temporal lobes.[43] Apolipoprotein E immunoreactivity is observed in neurons bearing neurofibrillary tangles.[44] Furthermore, greater expression of neuronal *APOE* is associated with increased tau phosphorylation in transgenic animal models[45-47] and human stem cell models.[48] Truncated *APOEε4* fragments are also associated with greater tau hyperphosphorylation and neuronal cytoskeletal disruption.[49,50]

Our study builds on studies of tau-PET distribution across the Alzheimer disease spectrum[15] by identifying a unique regional contribution of *APOEε4* to tau pathology. Furthermore, neuropathologic[14] and tau-PET[51] studies that have identified medial temporal tauopathy in the absence of amyloid-β suggest that medial temporal tauopathy may be a consequence of aging. Correspondingly, later age at onset of Alzheimer disease dementia is linked to limbic-predominant or memory-predominant clinical presentations.[52] Even in cognitively normal individuals, increased tau pathology in the medial temporal lobe is associated with declines in subjective[53] and objective memory function as well as medial temporal gray matter volume.[54] Our study extends these findings by identifying *APOEε4* as a contributor to medial temporal tauopathy, independent of age and amyloid-β.

While the results of our study implicate *APOEε4* in the pathogenesis of both pathological hallmarks of Alzheimer disease,[55] *APOEε4* is not sufficient for a diagnosis of Alzheimer disease nor to cause dementia. Instead, our study supports a framework in which isocortical/medial temporal (Braak stage 1-2) tau pathology may be a consequence of specific vulnerability factors (such as aging[51,56] or genotype[9]), while amyloid-β facilitates the spread of tau pathology from the medial temporal lobe to neocortical regions,[57,58] associated with greater cognitive decline. In fact, significant tau pathology in neocortical regions is seldom observed independently of amyloid-β pathology,[59] although exceptions do exist.[60] Because accepted Alzheimer disease models suggest that amyloid-β accumulation occurs years before tau accumulation measured with cerebrospinal fluid,[61,62] longitudinal imaging studies are needed to clarify *APOEε4*'s association with medial temporal tau pathology across disease stages.

Strengths and Limitations

Some methodologic limitations should be considered when interpreting this study. The first is that this study is not designed to discover a biological mechanism underlying the association between *APOEε4* and tau independently of amyloid-β. It is important to mention that both TRIAD and ADNI cohorts are convenience samples of individuals motivated to participate in a study about Alzheimer disease and thus involve recruitment and sampling biases. Future work is needed to determine whether the effects of *APOEε4* on tau result in increased phosphorylation, conformational changes, or increased cortical spreading. Future studies should also investigate possible associations between *APOEε4* and amyloid-β in relation to tau pathology. Methodologic strengths of this study include large sample sizes as well as a replication in an independent cohort. In particular, replication of results obtained with first-generation and second-generation tau-PET ligands is an important methodological advance.

Conclusions

In summary, we found that *APOEε4* is associated with increased tau pathology in medial temporal structures independent of amyloid-β, sex, age, and clinical status. These results, in combination with preclinical data,[9,48] suggest that *APOEε4* may be an important therapeutic target for future disease-modifying clinical trials.

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