HHS Public Access

Author manuscript

Sci Transl Med. Author manuscript; available in PMC 2023 February 10.

Published in final edited form as:

Sci Transl Med. 2022 November 16; 14(671): eabl7646. doi:10.1126/scitranslmed.abl7646.

APOE ε4 genotype, amyloid-β, and sex interact to predict tau in regions of high APOE mRNA expression

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Abstract

The apolipoprotein E (*APOE*) ε4 allele is strongly linked with cerebral β-amyloidosis, but its relationship with tauopathy is less established. We investigated the relationship between *APOE* ε4 carrier status, regional amyloid-β (Aβ), MRI volumetrics, tau positron emission tomography (PET), *APOE* mRNA expression maps, and cerebrospinal fluid phosphorylated tau (CSF $ptau_{181}$).

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Author Contributions

Conception and design: AD, BAG, CDC, NSM. Resources and data curation: AD, LNK, SF, SJK, RLF, RCH, SES, AMF. Data analysis and interpretation: AD, BAG, CDC, NSM, AM, NJM, CC, DMH, AMF. Manuscript writing: AD, BAG. Manuscript revision: all authors. Manuscript approval: all authors. Study supervision: JCM, TLSB, BAG.

Declaration of Competing Interest

The following authors have no conflicts of interest regarding this study: AD, CDC, NSM, AM, LNK, SF, SJK, RLF, RCH, AMF, JCM, SES. SAS receives research support from The National Science Foundation. NJM is supported partly by the Alzheimer Association International Research Program. CC received grants from NIH and reports fees from GSK and Takeda. DMH is a Co-founder, C2N Diagnostics LLC serves on the Scientific advisory boards or consults for Genentech, Denali, C2N Diagnostics, Cajal Neurosciences, Takeda, Casma, and Eli Lilly. DMH is an inventor on a 1) a patent licensed by Washington University to C2N Diagnostics on the therapeutic use of anti-tau antibodies. This anti-tau antibody program has now been licensed to Abbvie; 2) a patent licensed by Washington University to Eli Lilly on a humanized anti-Aβ antibody. The lab of DMH receives research grants from the National Institutes of Health, Cure Alzheimer's Fund, Tau Consortium, the JPB Foundation, Good Ventures, C2N Diagnostics, NextCure, and Denali. TLSB has investigator initiated research funding from the NIH, the Alzheimer's Association, the Barnes-Jewish Hospital Foundation and Avid Radiopharmaceuticals (a wholly owned subsidiary of Eli Lilly) Dr. Benzinger participates as a site investigator in clinical trials sponsored by Avid Radiopharmaceuticals, Eli Lilly, Biogen, Eisai, Jaansen, and Roche. She serves as an unpaid consultant to Eisai and Siemens. She is on the Speaker's Bureau for Biogen.

350 participants underwent imaging and 270 had ptau$_{181}$. Models evaluated the main effect of *APOE* ε4 carrier status on regional neuroimaging values and then the interaction of ε4 status and global Aβ on regional tau PET and brain volumes as well as CSF ptau$_{181}$ values. A final model examined the additional interactive influence of sex. We found, for the same level of Aβ burden, *APOE* ε4 carriers showed greater tau PET signal relative to non-carriers in temporal regions, but no interaction was present for MRI volumes or CSF ptau$_{181}$. This potentiation of tau aggregation irrespective of sex occurred in brain regions with high *APOE* mRNA expression, suggesting local vulnerabilities to tauopathy. There were greater effects of *APOE* genotype in females, although the interactive sex effects did not strongly mirror mRNA expression.

One Sentence Summary:

APOE ε4 genotype is associated with greater tau PET levels for the same level of Aβ PET in regions of high APOE mRNA expression, but not for CSF tau.

Keywords

Alzheimer Disease; Tau PET; *APOE* ; Amyloid PET; Apoliporotein E; CSF; Genetic

1. Introduction

The apolipoprotein E (*APOE*) ε4 allele is the strongest genetic risk factor for late-onset Alzheimer disease (AD) (1). *APOE* has three alleles: ε3 is the most common, followed by ε4 and ε2. The ε2 allele is associated with a decreased risk of AD relative to ε3 whereas the presence of the ε4 allele increases the risk of AD dementia and is associated with an earlier age of symptom onset (2, 3). Moreover, the gene acts in a dose-dependent manner, with one ε4 allele increasing the risk of AD by ~3–4 fold and two ε4 alleles increasing the risk by ~12 fold (2, 4).

Given its prominent role in AD, it is critical to understand the underlying mechanism of the *APOE* ε4 allele and its effects on AD pathophysiology. The apoe protein has long been linked with amyloid-β (Aβ) plaques, one of the hallmarks of AD, with early research showing that apoe binds to Aβ peptides (5, 6) and that individuals carrying the *APOE* ε4 allele have greater Aβ plaque pathology compared to non-carriers in postmortem studies (7–10). Later *in vivo* work, utilizing positron emission tomography (PET) and cerebrospinal fluid (CSF) assays, mirror these postmortem observations. *APOE* ε4 carriers with the ε4 allele have consistently been shown to have elevated Aβ PET levels relative to non-carriers in a dose-dependent fashion (11) as well as lower CSF Aβ$_{1–42}$ levels (12–18) indicative of the presence of amyloid (19). Individuals with the *APOE* ε4 allele also begin accumulating pathology at an earlier age compared to non-carriers (14, 20).

Along with Aβ pathology, neurofibrillary tangles composed of hyperphosphorylated tau protein are a hallmark of AD. Previous work has shown that *APOE* ε4 carrier status is associated with tau pathology, but the underlying mechanisms of this relationship are still unclear. Specifically, individuals carrying the *APOE* ε4 allele have greater neurofibrillary tau pathology compared to non-carriers in postmortem studies when Aβ pathology is present

(10), but this association disappeared when Aβ pathology was not present (21, 22). Research utilizing CSF tau measures have reported both significant effects of the *APOE* ε4 allele (18, 23) even when controlling for CSF $A\beta_{1–42}$ levels (24), as well as weak or no effects (14, 17, 18, 20). Using animal models, it has also been observed that *APOE* ε4 carrier status exacerbates tau pathology and tau-mediated neurodegeneration independent of Aβ (25). This finding is consistent within several PET studies that show the *APOE* ε4 is associated with greater levels of tauopathy (26–33), although a minority of work has found the opposite effect (34). These prior analyses have provided important contributions to the literature but have limitations. The PET analyses do not typically examine if there is an interaction between genotype and Aβ (32), rarely includes both CSF and imaging measures of tau (32, 33), and when multiple modalities are included they may come from different cohorts (33). These caveats limit the ability to detect a APOE mediated potentiation of tauopathy as predicted by animal work.

Although genetic polymorphisms such as *APOE* genotype are often viewed holistically, the relative expression of genes including *APOE* varies in different brain regions (35, 36). The availability of gene expression data such as the Allen Human Brain Atlas (AHBA) now make it possible to relate AD pathology observed using neuroimaging to underlying topologies of genetic expression that they may reflect (35–40).

The goal of the current study is to evaluate whether *APOE* ε4 carrier status represents an additive or interaction effect with levels of Aβ in predicting tau PET. By comparing PET and CSF measures, we examined how *APOE* ε4 carrier status influences both soluble and insoluble forms of tau. Finally, we examined the relationship between *APOE* ε4 carrier status, regional Aβ and tau PET, and *APOE* mRNA expression patterns to relate *APOE* ε4 carrier status with the spatial distribution of *APOE* mRNA expression, Aβ, and tau in the human brain.

2. Results

2.1 Demographics

In the three hundred fifty individuals, age, sex, education, and racial makeup did not differ between *APOE* ε4 carrier and noncarrier groups. *APOE* ε4 carriers had a greater percentage of CDR > 0 participants, lower MMSE scores, higher CDR sum of boxes, as well as higher frequencies of tau and Aβ PET positivity compared to noncarriers (Table 1). For the individuals that had a CDR>0, 14 individuals had a clinical diagnosis of uncertain etiology and 31 had a primary AD diagnosis. The median absolute interval between the Aβ PET scan and the tau PET scan was 28 days (range 1–365), the median absolute lag with the lumbar puncture was 36 days (range 1–688), and the median absolute lag with the clinical visit was 121 days (range 0–562).

2.2 *APOE* ε4 carrier status, Aβ, tau PET, CSF $ptau_{181}$, and MRI relationships

APOE ε4 carriers had higher Aβ PET throughout the cerebral cortex and in the amygdala, hippocampus, and putamen. (Fig. 1A, Table S1). *APOE* ε4 carriers had higher tau PET primarily in temporal, hippocampus, and amygdala regions (Fig. 1B, Table S2). When

APOE ε4 carrier status and Aβ summary measure were included concurrently in models of regional tau PET, we found that the Aβ summary measure, but not *APOE* ε4 carrier status, significantly predicted tau PET levels (Fig. 1C, Fig. 1D, Table S3). This result suggests shared variance between these measures. Notably, there was significant interaction between *APOE* ε4 carrier status and the Aβ summary measure, with the ε4 carriers having elevated tau PET relative to non-carriers for the same level of Aβ pathology. This effect was predominately observed in the bilateral entorhinal, parahippocampal, and amygdala regions, as well as the right hemisphere temporal regions, (Fig. 1E, Fig. S1A, Table S4). When the three-way interaction was modeled, a number of regions demonstrated significant interaction between sex, genotype, and Aβ PET levels (Fig. 1F, Fig. 2A). The relationship was such that females had a larger interaction between genotype and continuous Aβ PET values. Full regional results from the tau PET models are in Table S2, S3, S4 and Fig S2.

APOE ε4 carrier status (model 1: β = 0.51, p = 8.11E-6) and Aβ summary measure (model 2: β = 0.60, p = 2.82E-28) separately predicted significant elevations in CSF $ptau_{181}$. As with tau PET, in the concurrent model, Aβ (model 3: β = 0.57, p = 2.12E-24) but not *APOE* ε4 carrier status (model 3: β = 0.16, p = 0.11) predicted CSF $ptau_{181}$ values. Unlike tau PET, there was no two-way interaction between Aβ PET levels and *APOE* ε4 carrier status on CSF $ptau_{181}$ (model 4: β = −0.04, p = 0.65, Fig. S1B) or three-way interaction between sex, Aβ PET levels, and *APOE* ε4 carrier status (model 5: β = 0.02, p = 0.91, Fig. 2B).

When examining regional volumes there were no significant main effects of *APOE* ε4 carrier status. Higher levels of the Aβ summary measure predicted lower volumes in the left and right hippocampal volumes (Fig. S1C) as well as the right amygdala volume (Table S5). This effect of global Aβ levels in these regions remained significant even in the joint model that included additive main effects of ε4 status (Table S6). There were no significant two-way or three-way interactions (Fig. 2C, Table S7).

2.3 *APOE* mRNA expression and *APOE* ε4 carrier status spatial relationship

To analyze the spatial association between *APOE* mRNA and effects of *APOE* ε4 carriers status, we associated all regional beta weights estimates, non-significant and significant, to *APOE* mRNA gene expression (Fig. 3I) from the following terms: *APOE* ε4 carrier status beta weights predicting regional Aβ PET (Fig. 3B), *APOE* ε4 carrier status beta weights predicting regional tau PET (Fig. 3D), the beta weights for the *APOE* ε4 carrier status and Aβ summary measure interaction estimated using regional tau PET (Fig. 3F), and the beta weights from the three way-interaction (Fig. 3G). Interestingly, the *APOE* ε4 carrier status beta weight for regional tau PET (r^2 = 0.53, p = 1.50e-04, Fig. 3C) and the interaction between Aβ summary measure and *APOE* ε4 carrier status beta weight for regional tau PET (r^2 = 0.31, p = 0.0022, Fig. 3E) were both significantly associated with the spatial *APOE* mRNA expression pattern. The spatial pattern of *APOE* mRNA gene expression has a reduced, albeit still significant, association with the spatial pattern of the main effect of *APOE* ε4 carrier status estimated on regional Aβ -PET (r^2 = 0.07, p = 0.016, Fig. 3A). There was no significant association between the spatial pattern of the three-way interaction between sex, genotype, and Aβ-PET (r^2 = 0, p = 0.28, Fig. 3G). Although there were minimal significant main effects of either Aβ or genotype on regional volumes, the relatively

pattern of these non-significant effects was strongly related to the spatial pattern of APOE mRNA expression (Fig. S4). This suggests a structured, albeit weak, effect on volumes.

3. Discussion

Given that tau is more strongly associated with cortical atrophy and cognitive decline compared to Aβ pathology (53–55), understanding the mechanism underpinning tau pathology could be key to the prevention of AD. Furthermore, possession of the *APOE* ε4 allele has been identified as posing the greatest genetic risk factor for developing late-onset AD. Therefore, it is imperative to investigate whether there is a relationship between *APOE* ε4 and tau deposition and to quantify what influence this relationship has above that of Aβ. While a strong association between the *APOE* ε4 allele and Aβ pathology is well-known (10, 12, 14), the ε4 allele relationship with tauopathy is less established with inconsistent findings from postmortem, CSF, or PET studies (10, 17, 18, 20, 26–33). The goals of this study were to examine the influence of *APOE* ε4 carrier status on PET and CSF measures of tau pathology, test if there was an interaction between Aβ pathology and *APOE* ε4 carrier status, and to compare how the spatial impact of this pathology relates to regional levels of *APOE* mRNA gene expression.

There exists an overwhelming body of literature describing the widespread effect of *APOE* ε4 on Aβ in postmortem (10), neuroimaging (56), biofluid (13, 16) studies. In contrast, the relationship between *APOE* ε4 and tau has been less consistent in the literature. Several postmortem studies have found the presence of the *APOE* ε4 allele increased tauopathy (10, 57) revealing greater pathology in diffuse cortical areas in AD patients compared to *APOE* ε4 noncarriers (57), while other studies did not find this relationship (58). Studies using CSF measures of tau pathology reported no association with *APOE* ε4 carrier status (13, 14, 17, 59), as well as significantly elevated levels of tau (23, 33, 60, 61). There are also mixed results on the relationship within PET studies where many have shown greater tau load on *APOE* ε4 carriers compared to noncarriers (27, 28, 30–32, 62), while others have not (34).

In the current study, we found a main effect where participants carrying the *APOE* ε4 allele had elevated levels of both CSF $ptau_{181}$ and tau PET relative to non-carriers. However, when a summary measure of Aβ PET was included as a covariate in the model, the main effect of *APOE* ε4 carrier status was greatly reduced, suggesting much of the influence that the *APOE* ε4 carrier status has on tau pathology is mediated through its regulation of Aβ. This suggests minimal additive influences of *APOE* and Aβ levels. When examining the interaction between *APOE* ε4 carrier status and Aβ, we found a significant effect for tau PET but not CSF $ptau_{181}$ levels, where the presence of an *APOE* ε4 allele potentiated the degree of tauopathy above the effects that can be ascribed to Aβ alone. This result is consistent with animal models where P301S tau transgenic mice expressing human *APOE* ε4 exhibited greater tau burden as well as neurodegeneration as compared to mice expressing *APOE* ε2 or *APOE* ε3 with the absence of APOE being protective (25).

In the current analyses the three-way interaction suggests a greater influence of the ε4 allele in women. This result is consistent with prior work suggesting APOE genotype has a differential AD risk by sex (63, 64) and may have a sex-dependent effect on in vivo

measures of tau pathology (62). Although the size of our population is robust (n=350) it is still modestly powered to estimate the three-way interaction between genotype, levels of Aβ, and sex. As a result, replication of this interaction between sex and genotype using additional cohorts in future studies is warranted. Although there was a modest effect of Aβ levels on medial temporal volumes, we found no evidence of potentiation by ε4 status. This is consistent with prior human work (20), but a difference from mouse models (25).

The discrepancy between CSF and PET is not entirely unexpected given the modest correlations seen between these modalities in literature (55, 65–67) suggesting they capture unique properties of the disease. The *APOE* ε4 carrier status may only exert its influence selectively in insoluble, aggregated, forms of tau. There is also emerging evidence that tau phosphorylated at different sites such as $ptau_{217}$ and $ptau_{231}$ changes quite early in the diseases (68–70), while tau PET is relatively late (71). Increased levels of $ptau_{181}$, $ptau_{205}$, $ptau_{217}$, $ptau_{231}$ may reflect a response to amyloidosis more than the aggregation of tau into neurofibrillary tangles per se. As a result the difference may not be due to the soluble and insoluble distinction, but instead an erroneous conceptualization in the field about how strongly ptau reflects tauopathy as defined neuropathological and with PET. Future analyses of other ptau phosphorylation sites, as well as other candidate markers such as microtubule binding region (MTBR)(72), may provide important insight into how *APOE* genotype influences biofluid measures beyond $ptau_{181}$.

The observed genotype effects on Aβ were prominent in medial parietal and frontal areas, although elevation was observed across the cortex. Elevated tau was most prominently observed in temporal, hippocampus, and amygdala regions. These spatial signatures (Fig. 1) are highly consistent with the stereotypical patterns of these pathologies found in the literature (48, 55). While *APOE* is often viewed holistically, its mRNA expression levels vary across the brain and spatially resemble structural and functional networks (35, 73). To understand our findings in relation to genetic expression in the cortex, we utilized the AHBA *APOE* mRNA genetic expression data translated to FreeSurfer regions (50). We found that higher regional *APOE* mRNA gene expression levels in the brain are more associated with the *APOE* ε4 influence on regional tau, rather than regional Aβ. This suggests that the local levels of *APOE* expression in the tissue may regulate each region's vulnerability to tauopathy.

The mechanism through which *APOE* influences tau pathology are unclear but there is building evidence that it has an immunomodulatory function (74, 75). ApoE plays a role in regulating microglial metabolism which is tied to microglial activation (76). Removal of astrocyte-derived apoE reduces tau-associated neurodegeneration (77), and overexpression of low-density lipoprotein receptor, an apoE metabolic receptor, alters markers of microglial suppression (76). The apoE protein may be an important therapeutic target, and lowering apoE ε4 levels with antisense oligonucleotides has been shown to reduce tauopathy and neurodegeneration in mouse models. (78). The *APOE* ε4 allele has also been shown to lead to blood-brain barrier dysfunction in the temporal lobe (79) which may also impact inflammation.

There are many strengths in this study. First, as there are discrepancies in literature on the *APOE* ε4 and tau relationship, we incorporated and compared both PET and CSF modalities. While there are suggestions that the effects of Aβ and *APOE* ε4 carrier status may be additive, we explicitly tested both additive and interactive effects. When performing these analyses Aβ was analyzed as a continuous variable rather than binarized into positive or negative. Such an approach avoids potential confounds such as genotype serving simply as a proxy of Aβ level or ε4 carriers on averaging simply having higher levels of Aβ. Our cohort contains over three hundred individuals, providing a robust sample for analysis. Finally, we integrated mRNA gene expression data from the AHBA to gain a more comprehensive understanding of the relationship. To our knowledge, this is the first study to compare the regional *APOE* mRNA gene expression patterns, tau PET, and Aβ PET effect to *APOE*.

There were also limitations. The current work focuses on the overall effect of the *APOE* ε4 allele without considering gene dosage as the analyses only had 18 ε4 homozygotes. The cohort is also primarily white, limiting the generalizability of APOE genotype effects to non-white cohorts. While the most comprehensive data of its kind, the AHBA mRNA dataset is derived from only a handful of individual brains that did not have AD. This means that it is only a rough approximation of mRNA expression and precludes the ability to examine whether mRNA expression varies as a function of demographic factors such as sex. There are also minimal samples available from the right hemisphere, resulting in the mRNA gene expression values being mirrored across hemispheres. This limits the ability to look at hemispheric specific effects. Additionally, AHBA data represents an aggregate expression in a bulk tissue sample. As *APOE* is primarily produced by astrocytes (80), the spatial association seen between *APOE* mRNA levels and tau pathology may be driven by the heterogeneity in cell distribution across the brain rather than the spatial distribution of *APOE* itself. The AHBA data has become an invaluable tool to the field. As comparing data from the AHBA to *in vivo* human imaging data is becoming common place (35–40), it would benefit the field if this data were expanded to provide opportunities to ask more in-depth questions. Given the strong animal work linking this gene to tau pathology (25, 74), we *a priori* looked at only *APOE* gene expression. Future research endeavors should expand analyses to consider additional genes or networks of gene expression. Finally, our cohort was comprised of individuals who were classified as either cognitively normal or who had mild dementia. Therefore, our results cannot directly assess how the influence of *APOE* may vary as dementia progressively worsens.

Conclusion

We found that presence of the *APOE* ε4 allele influences levels of Aβ PET, tau PET, and CSF $ptau_{181}$. We additionally found that an interaction of *APOE* ε4 and Aβ PET is associated with elevated regional tau PET but not CSF $ptau_{181}$ levels. The spatial pattern of the interaction effect on tau PET is mirrored by the levels of *APOE* mRNA gene expression in the cortex. Our results further elucidate the influence this prominent risk allele has on the pathogenesis of AD. Therefore, APOE ε4 carrier status needs to be considered for clinical trials targeting tau hyperphosphorylation or aggregation.

4. Materials and Methods

4.1 Participants

Participants were enrolled in the longitudinal studies of memory and aging at the Charles F. and Joanne Knight Alzheimer Disease Research Center (Knight ADRC) at Washington University in Saint Louis. Dementia severity was defined by the global Clinical Dementia Rating© (CDR©) (41), where CDR 0 indicates cognitive normality and CDR > 0 indicates cognitive impairment. For this study, three hundred and fifty participants were included who had a tau PET scan, an Aβ PET scan, a clinical assessment, and an *APOE* genotype assessment between years 2014 and 2018. *APOE* genotyping was performed as previously described (42). Participants who had one or more ε4 allele were assigned a positive APOE ε4 carrier status, while those with no ε4 allele were assigned a negative APOE carrier ε4 status. To fulfill the study criteria, each participant's Aβ PET and clinical assessments were required to have been completed within one year of their tau PET visit. Of the three hundred and fifty participants, two hundred and seventy of the participants had CSF $ptau_{181}$ within two years of Aβ PET. A summary table of demographic information for these individuals is provided in table 1. Data from the Knight ADRC can be freely requested (https://knightadrc.wustl.edu/professionals-clinicians/request-center-resources/).

4.2 Ethics Statement

All participants, or their caregivers, signed a standard informed consent document, and the Institutional Review Board at Washington University in St. Louis approved all procedures. ICMJE guidelines were followed in preparation of the manuscript.

4.3 Imaging Acquisition and Analysis

Structural T1-weighted scans were acquired on three Siemens MRI 3 Tesla scanners using a magnetization-prepared rapid gradient-echo sequence. The Siemens Biograph mMR (n = 346) and the MAGNETOM Vida (n = 3) T1 scans were acquired with a 1 × 1 × 1.2 mm resolution, 2300 ms repetition time, 2.95 ms echo time, 9 degree flip angle, 176 frames, and a 240 × 256 field of view in sagittal orientation. Structural T1 scans for the Siemens TIM Trio (n = 1) were acquired with a 1 × 1 × 1 mm resolution, 2400 ms repetition time, 3.16 echo time, 8 degree flip angle, 176 frames, and a 256 × 256 field of view in sagittal orientation. MRI images were processed through FreeSurfer v5.3-HCP (43) and were visually inspected. The FreeSurfer ROIs were subsequently utilized for PET processing. Tau PET imaging was performed on the Siemens Biograph PET CT using the ^{18}F-flortaucipir tracer and Aβ PET imaging was performed on the Siemens PET/MR using ^{18}F-florbetapir. All PET scans were processed through the PET Unified Pipeline (PUP, https://github.com/ysu001/PUP) using an 80-to-100-minute post-injection window for ^{18}F-flortaucipir and a 50-to-70-minute post-injection window for the ^{8}F-florbetapir tracer. The standardized uptake value ratio (SUVR) was calculated relative to the cerebellar cortex using the derived FreeSurfer ROIs (44, 45). Partial volume correction was performed using a geometric transfer matrix (44, 46). To calculate the Aβ summary measure, we averaged the left and right hemisphere partial volume corrected SUVRs from the lateral orbitofrontal, mesial orbitofrontal, rostral mesial frontal, superior frontal, superior temporal, mesial temporal, and precuneus regions as previously defined (45). Aβ positivity was defined using a cutoff of

1.22 for AV45 (Centiloid value 22.2(47)). As previously reported (48) tau PET positivity was defined as a value >1.22 from using an arithmetic mean of partial volume corrected SUVR values from the entorhinal cortex, amygdala, inferior temporal gyrus, and lateral occipital cortex.

4.4 CSF Assays

CSF (20 to 30 ml) was collected via lumbar puncture after overnight fasting as previously described (19). Samples were analyzed using the automated Lumipulse assay platform (LUMIPULSE G1200, Fujirebio, Malvern, PA) to determine levels of tau phosphorylated at threonine 181 ($ptau_{181}$).

4.5 *APOE* Gene Expression

To analyze the genetic spatial relationship, we obtained the AHBA *APOE* gene expression data (49). The *APOE* gene expression data was summarized from 58,692 measurements of gene expression from postmortem brains of six cognitively normal individuals and transformed onto the Desikan-Killiany cortical atlas built into FreeSurfer (50). In brief, mean averaged gene expression values were calculated for each gene from multiple probes and were spatially mapped from MNI152 space to FreeSurfer cortical regions. As there was limited data for the right hemisphere, gene expression data converted into FreeSurfer regions only included the 34 left hemisphere cortical regions. For the six individual brains, the median gene expression value for each cortical region was determined, and a summary brain map was created by calculating the median from the six median gene expression values for each region (50).

4.6 Statistical Analysis

All statistical tests were done in R version 4.0.3 (51). Demographics were compared between ε4 carriers and non-carriers using t-tests and Chi Squared tests as appropriate. To answer the main questions of interest first, we performed linear models to predict regional Aβ and regional tau PET levels, regional volume derived from MRI, and CSF $ptau_{181}$ from *APOE* ε4 carrier status (model 1).

Models 1 and 2 were run for each region independently with regional SUVRs or regional volumes or CSF $ptau_{181}$ as the dependent variable. *P*-values were corrected for multiple comparisons using the Benjamini-Hochberg procedure at a false discovery rate of 0.05. Subsequently, we ran additional linear models to examine the additive and interaction effects between the Aβ summary measure and *APOE* ε4 carrier status on regional tau PET, regional volumes, or CSF $ptau_{181}$ (models 3 and 4). The final model included a three-way interaction between sex, the Aβ summary measure, and *APOE* ε4 carrier status (model 5). For the regional tau PET interaction models, only the regions that were found to be statistically significant in model 1 predicting regional Aβ PET or regional tau PET respectively were analyzed in model 4 and 5. For all models age at tau PET visit and sex were included as covariates, and all continuous variables were scaled in all linear models to aid interpretation.

$$\text{Regional tau PET (or CSF ptau}_{181}\text{or regional volume or regional A}\beta\text{ PET)} = \beta_0 + \beta_1(\text{APOE } \varepsilon4 \text{ carrier status}) + \beta_2(\text{age}) + \beta_3(\text{sex}) + \epsilon \quad (1)$$

$$\text{Regional tau PET (or CSF ptau}_{181}\text{or regional volume)} = \beta_0 + \beta_1(\text{A}\beta \text{ summary measure}) + \beta_2(\text{age}) + \beta_3(\text{sex}) + \epsilon \quad (2)$$

$$\text{Regional tau PET (or CSF ptau1}_{181}\text{or regional volume)} = \beta_0 + \beta_1(\text{A}\beta \text{ summary measure}) + \beta_2(\text{APOE } \varepsilon4 \text{ carrier status}) + \beta_3(\text{age}) + \beta_4(\text{sex}) + \epsilon \quad (3)$$

$$\text{Regional tau PET (or CSF ptau}_{181}\text{or regional volume)} = \beta_0 + \beta_1(\text{A}\beta \text{ summary measure}) + \beta_2(\text{APOE } \varepsilon4 \text{ carrier status}) + \beta_3(\text{age}) + \beta_4(\text{sex}) + \beta_5(\text{A}\beta \text{ summary measure} \times \text{APOE } \varepsilon4 \text{ carrier status}) + \epsilon \quad (4)$$

$$\text{Regional tau PET (or CSF ptau}_{181}\text{or regional volume)} = \beta_0 + \beta_1(\text{A}\beta \text{ summary measure}) + \beta_2(\text{APOE } \varepsilon4 \text{ carrier status}) + \beta_3(\text{age}) + \beta_4(\text{sex}) + \beta_5(\text{A}\beta \text{ summary measure} \times \text{APOE } \varepsilon4 \text{ carrier status}) + \beta_6(\text{A}\beta \text{ summary measure} \times \text{sex}) + \beta_7(\text{APOE } \varepsilon4 \text{ carrier status} \times \text{sex}) + \beta_8(\text{A}\beta \text{ summary measure} \times \text{APOE } \varepsilon4 \text{ carrier status} \times \text{sex}) + \epsilon \quad (5)$$

To examine the relationship between spatial *APOE* mRNA expression, *APOE* ε4 carrier status, and Aβ summary measure, we performed a spatial rotational permutation as previously described (52). In brief, this method defines a set of null correlations by comparing the empirical correlation against two spatial maps by randomly rotating the spherical projections of one spatial map before projecting it back to the brain surface. The projection conserves spatial continuity of the empirical maps as well as hemispheric symmetry. Specifically, the *p*-value is derived by comparing the empirical Spearman's ρ to a null distribution of 10,000 correlations between one empirical map and the randomly rotated spherical projections using the total *APOE* mRNA expression values from the AHBA and the beta weights from the interaction term in model 4. The code used to perform spatial permutation testing can be downloaded here: https://github.com/frantisekvasa/rotate_parcellation. The *APOE* mRNA expression data was only available for the left hemisphere, so the gene expression data was mirrored for the left and right hemisphere for these analyses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We acknowledge the altruism of the participants and their families and contributions of the Knight ADRC research and support staff for their contributions to this work. Without the generous contribution and time the participants gave for these studies, this work would not be possible.

Funding

Support for these analyses was provided by NIH (P30AG066444, P01AG003991, P01AG026276, K01AG053474, RF1AG053303, RF1AG044546, UL1TR000448, P30NS098577, R01EB009352), Alzheimer's Association (AARG-17-532945), Alzheimer Association International Research Program (AARFD-20-681815), and The National Science Foundation (DGE-1745038). Computations were performed using the facilities of the Washington University Center for High Performance Computing, which were partially funded by NIH grants 1S10RR022984-01A1 and 1S10OD018091-01. We also acknowledge support from the Hope Center for Neurological Disorders, the Barnes-Jewish Hospital Foundation Willman Scholar Award, and Avid Radiopharmaceuticals (a wholly owned subsidiary of Eli Lilly) which provided technology transfer and provided precursor for AV-1451.

Abbreviations:

AD	Alzheimer disease
APOE	apolipoprotein E
Aβ	amyloid-β
PET	positron emission tomography
CSF	cerebrospinal fluid
AHBA	Allen Human Brain Atlas
Knight ADRC	Charles F. and Joanne Knight Alzheimer Disease Research Center
CDR	Clinical Dementia Rating
PUP	PET Unified Pipeline
SUVR	standardized uptake value ratio

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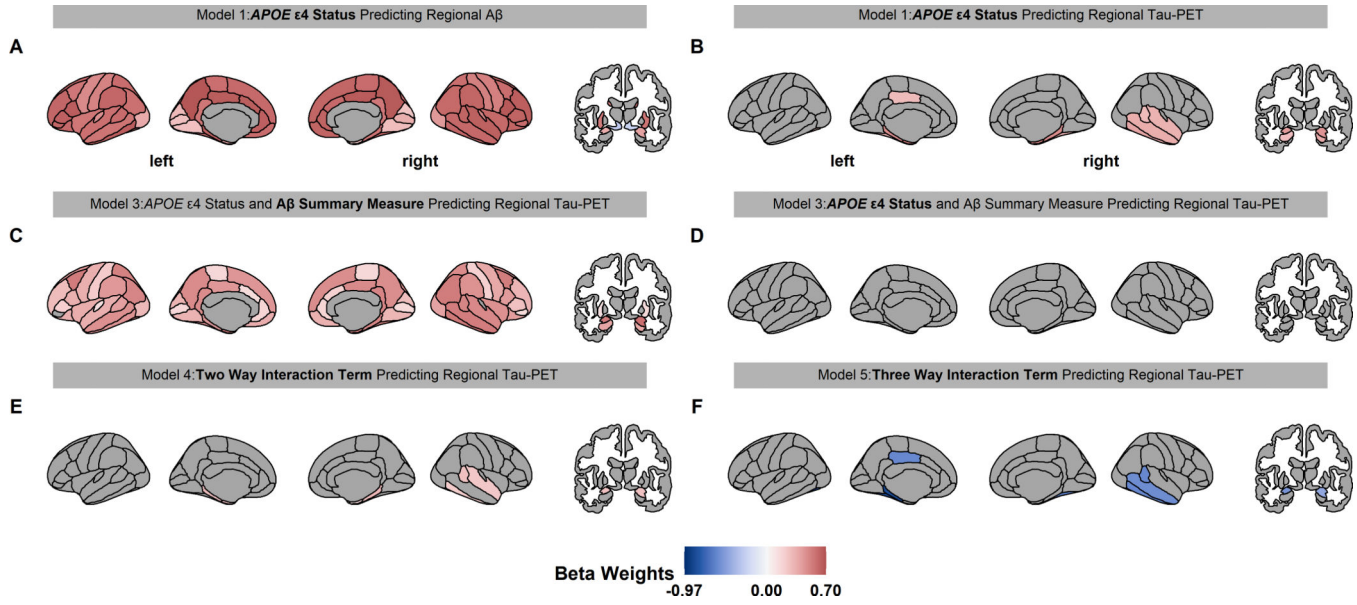

Fig 1.

Significant beta weights predicting regional Aβ and tau PET for linear models 1–5. The associated linear model is displayed above each brain with the beta weight term in bold text. Red and blue color indicate a positive and negative value, respectively. Only the regions that were statistically significant in figures 1A and B (conjunction) were analyzed in E and F. Aβ PET is increased throughout the brain in *APOE* ε4 carrier (A). *APOE* ε4 carriers have higher tau PET in the temporal, amygdala, and hippocampus regions (B). When *APOE* ε4 carrier status and Aβ PET were both in a model predicting regional tau PET, the Aβ summary measure was associated with tau PET throughout the brain (C), but *APOE* ε4 carrier status was not associated with tau PET (D). Importantly, the interaction between Aβ summary measure and *APOE* ε4 carrier status in predicting regional tau PET were significant in the entorhinal, temporal, and amygdala regions (E) and this potentiation varies by sex (F).

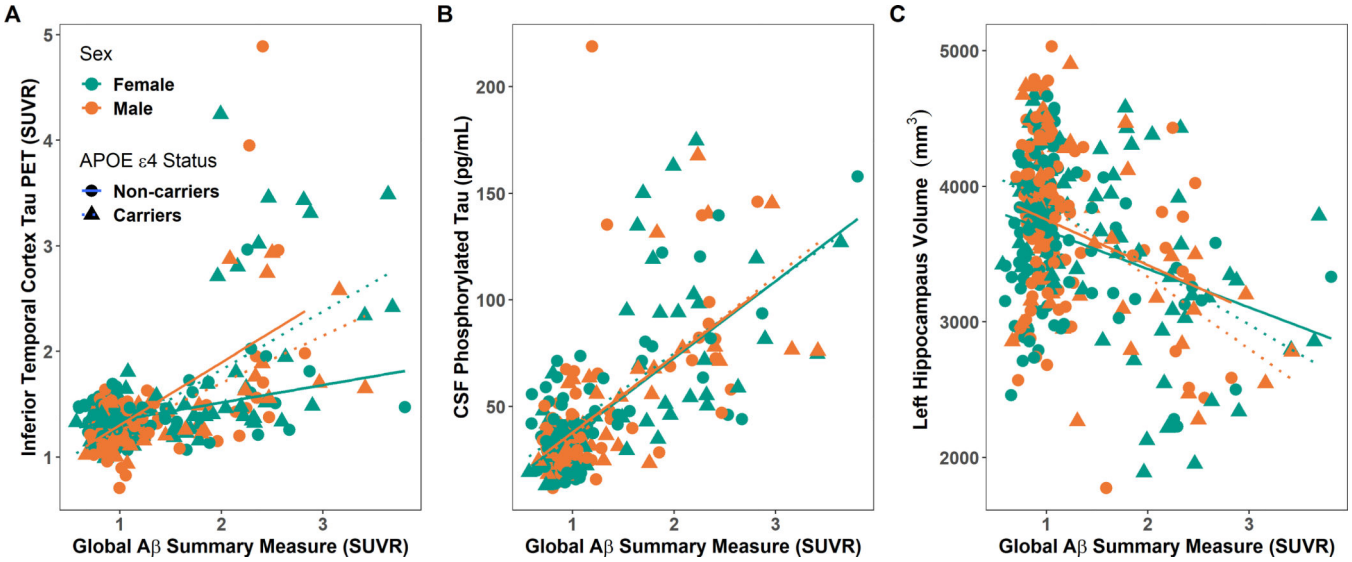

Fig 2.

Comparison between entorhinal tau PET SUVR (A), CSF $ptau_{181}$ (B) and regional volume (C) relationship relative to Aβ summary measure levels, *APOE* ε4 carrier status, and sex. The green color represents females and brown color represents males. and blue non-carriers. Triangles and dotted lines represent the fit for *APOE* ε4 carriers while circles and solid lines represent the fit for *APOE* ε4 non-carriers.

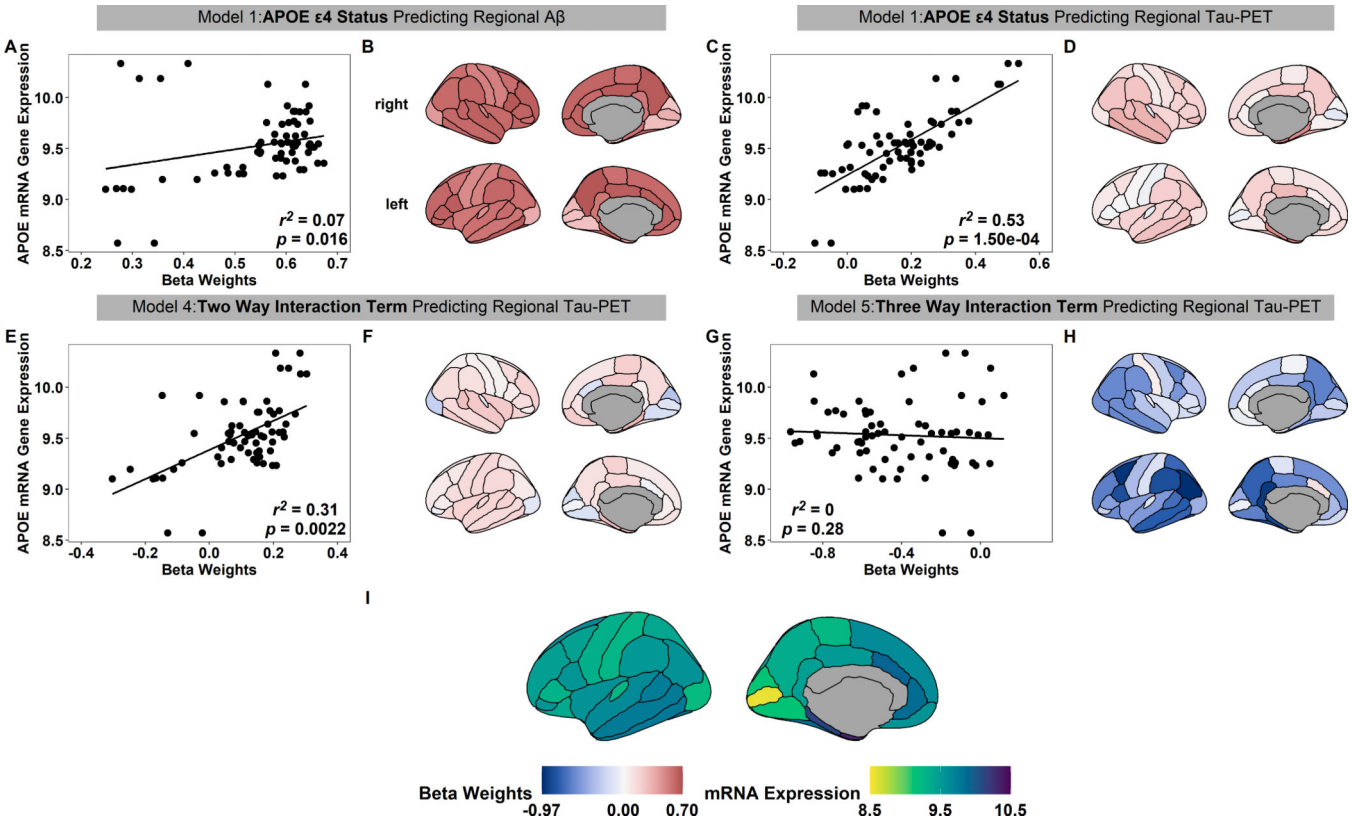

Fig 3.

The spatial relationship between *APOE* ε4 carrier status and *APOE* mRNA gene expression. The regional beta weights estimates from the *APOE* ε4 carrier status beta weights estimated on regional Aβ PET (B), *APOE* ε4 carrier status beta weights estimated on regional tau PET (D), the *APOE* ε4 carrier status and Aβ summary measure interaction estimated on regional tau PET (F), and the weights from the three-way interaction between sex, Aβ, and regional tau (H). The relationship between each beta weight and *APOE* mRNA gene expression (A,C,E,G). In the regression plots, black circles represent the beta weight of distinct brain regions, the black line indicates the linear regression fit, and the r^2 and *p*-values from spatial correlation tests are presented in the bottom right. *APOE* mRNA gene expression values for each region for reference (I).

Table 1.

Demographic summary for included participants.

Participant Demographics	*APOE* ε4 – (n=223)	*APOE* ε4 + (n=127)	*p-value*
Age, years	70.2 (7.9)	68.9 (8.3)	t = −1.43, p=0.15
Male, n (%)	103 (46.2)	52 (41.0)	χ^2=0.70, p=0.40
Education, years	16.3 (2.4)	16.3 (2.3)	t = −0.07, p=0.95
CDR > 0, n (%)	18 (8.1)	27 (21.2)	χ^2=11.42, p=0.0007
CDR = 0.5	14 (6.3)	22 (17.3)	
CDR > 0.5	4 (1.8)	5 (4.0)	
CDR Sum of Boxes	0.25 (1.04)	0.65 (1.52)	t = 2.96, p=0.003
MMSE	29.0 (1.7)	28.5 (2.5)	t = − 2.30, p=0.02
White, n (%)	200 (89.7)	110 (86.6)	χ^2 =0.48, p=0.49
Tau PET +, n (%)	85 (38.1)	64 (50.4)	χ^2 =6.34, p=0.01
Aβ PET +, n (%)	45 (20.2)	61 (48.0)	χ^2 =26.56, p<0.0001
Aβ Summary SUVR	1.12 (0.50)	1.49 (0.73)	t = 5.56, p<0.0001
Tau Summary SUVR	1.24 (0.31)	1.38 (0.41)	t = 3.47, p=0.0006

Mean (standard deviation) unless otherwise noted.

APOE = apolipoprotein E; CDR = Clinical Dementia Rating; Aβ = amyloid-beta.