The role of ApoE4 in the connectivity-mediated spreading of tau pathology at lower amyloid levels

Anna Steward MSc,[1] Davina Biel PhD,[1] Anna Dewenter PhD,[1] Sebastian Roemer MD,[1,2] Fabian Wagner MD,[1] Amir Dehsarvi PhD,[1] Saima Rathore PhD,[3] Diana Otero Svaldi PhD,[3] Ixavier Higgins PhD,[3] Matthias Brendel MD,[4,5] Martin Dichgans MD,[1,5] Sergey Shcherbinin PhD,[3] Michael Ewers PhD,[1,6] Nicolai Franzmeier PhD [1,5,7]

1) Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Munich, Germany
2) Department of Neurology, University Hospital, LMU Munich, Munich, Germany
3) Eli Lilly and Company, Indianapolis, IN, USA
4) Department of Nuclear Medicine, University Hospital, LMU Munich, Munich, Germany
5) Munich Cluster for Systems Neurology (SyNergy), Munich, Germany
6) German Center for Neurodegenerative Diseases (DZNE), Munich, Germany
7) Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy, University of Gothenburg, Sweden

Revision date: 09.05.2023
Manuscript Word count: 3725

Corresponding Author:
Dr. Nicolai Franzmeier
Nicolai.Franzmeier@med.uni-muenchen.de
Tel: +49 89 4400 46162

KEY POINTS

Question: Do apolipoprotein E ε4 (ApoE4) carriers show accelerated amyloid-related tau spreading?

Findings: In this study of two longitudinal tau-PET samples (total n = 367), ApoE4 carriers showed an acceleration of amyloid-mediated tau spreading at a lower amyloid threshold compared to ApoE4 non-carriers, controlling for age and sex.

Meaning: ApoE4 carriage is associated with earlier amyloid-induced tau spreading indicating that the timing of therapeutic windows in anti-amyloid therapies may need special consideration in ApoE4 carriers compared to non-carriers to successfully attenuate tau spreading.

ABSTRACT

Importance: For the efficacy of Alzheimer's disease (AD) therapies to effectively attenuate clinical progression, it may be critical to intervene before the onset of amyloid-associated tau spreading, which drives neurodegeneration and cognitive decline. Yet, timepoints at which amyloid-associated tau spreading accelerates may depend on subject-specific risk factors, such as Apolipoprotein E ε4 (ApoE4), which is linked to faster disease progression; however, the impact of ApoE4 on amyloid-related tau spreading is unclear.

Objective: To assess if ApoE4-carriers show accelerated amyloid-related tau spreading and propose amyloid-PET thresholds at which tau spreading accelerates in ApoE4-carriers vs. non-carriers.

Design: This cohort study combined ApoE genotyping, amyloid-PET and longitudinal tau-PET from two independent samples: ADNI (n=237; collected from 2015-04 to 2022-08) and AVID A05 (n=130; collected from 2013-12 to 2017-07) with a mean tau-PET follow-up time of ADNI/A05=1.9/1.4 years.

Setting: ADNI is an observational multi-centre Alzheimer's disease neuroimaging initiative and AVID A05, an observational clinical trial.

Participants: Subjects classified as cognitively normal (ADNI/A05 n=152/77) or mildly cognitively impaired (n=107/53) were selected based on ApoE genotyping, amyloid- and longitudinal tau-PET data availability. Subjects with ApoE ε2/ε4 genotype and/or classified as demented were excluded. Resting-state fMRI connectivity templates were based on 42 healthy ADNI subjects.

Main Outcome(s) and Measure(s): A mediation of amyloid-PET on the relationship between ApoE4-status and subsequent tau-PET increase through Braak-stage regions. An interaction between ApoE4-status and amyloid-PET on annual tau-PET increase through Braak-stage regions and connectivity-based spreading stages (tau epicentre connectivity ranked regions).

Results: The mean age(SD) of the 237/130 ADNI/A05 subjects was 73.9±7.35/70.2±9.7 years, of which 107/45(45.1%/34.6%) were ApoE4 carriers. Across both samples, we found that higher amyloid-PET mediated ApoE4-related tau-PET increases globally (ADNI/A05 B=0.14/0.25, p=0.006/<0.001) and in earlier Braak regions. Further, we found a significant ApoE4-status by amyloid-PET interaction on annual tau-PET increases consistently through early Braak- and connectivity-based stages where amyloid-related tau accumulation was accelerated in ApoE4-carriers vs. non-carriers at lower centiloid thresholds, corrected for age and sex.

Conclusions and Relevance: Amyloid-related tau accumulation accelerates in ApoE4 carriers at lower amyloid levels, suggesting that ApoE4 facilitates earlier amyloid-driven tau spreading across connected brain regions. Possible therapeutic implications might be further investigated to determine when best to prevent tau spreading and thus cognitive decline depending on ApoE4 status.

INTRODUCTION

In Alzheimer's disease (AD), amyloid-beta (Aβ) is thought to initiate the spreading of neurofibrillary tau pathology[1] from temporal-lobe epicentres to connected cortical regions,[2-6] driving neurodegeneration and cognitive decline.[7-10] Accordingly, Aβ-targeting therapies should ideally be applied at low tau levels to efficiently attenuate the AD cascade and slow tau-related neurodegeneration[11] and clinical progression.[12,13] Therefore, it is crucial to determine Aβ thresholds at which tau spreading is triggered, to potentially inform treatment decisions.[12]

Tau spreading from the medial temporal lobe to the cortex is, however, modulated by patient-specific factors including sex,[14,15] vascular comorbidities,[16] brain network architecture[17] and genetic predispositions. Therefore Aβ thresholds marking tau spreading may vary inter-individually.[18-20] Carriage of the Apolipoprotein E ε4 (ApoE4) allele,[21] the strongest risk factor for sporadic AD, has been linked to abnormal Aβ-independent tau biomarker levels[20,22,23] and cortical tau spreading patterns which closely align with cerebral APOE mRNA expression.[24] Yet, ApoE4 carriage is neither linked to higher risk of developing primary tauopathies nor to spreading of age-related medial temporal lobe tau to the cortex in the absence of Aβ,[25,26] therefore tau spreading in ApoE4 carriers is seemingly linked to Aβ. However, it is unclear whether ApoE4-carriage lowers the Aβ threshold for tau spreading, ensuing earlier symptom onset and faster clinical progression.[20,27] Given that clinical AD progression is thought to be largely driven by tau rather than Aβ,[10,12] anti-Aβ interventions may require earlier intervention within disease progression in ApoE4 carriers to effectively intercept tau spreading and consequent cognitive deterioration.[28] Addressing this is critical since 40-60% of sporadic AD patients carry at least one ApoE4 allele[29] and will likely seek anti-amyloid treatment in the future.

The major goal of this study was to investigate whether ApoE4-carriage is associated with earlier and faster Aβ-related tau spreading throughout the cortex. We assessed ApoE4 status, baseline ^{18}F-Florbetaben/Florbetapir amyloid-positron emission tomography (PET) and longitudinal ^{18}F-Flortaucipir tau-PET in non-demented subjects across the spectrum of aging and AD, including

patients at earliest stages of amyloidosis, a potentially promising target group for anti-Aβ treatments owing to less progressed pathology than that typically found in demented subjects in which tau accumulation is more likely driven by local replication rather than Aβ-related trans-neuronal spread.[30-32] Samples were taken from the Alzheimer's disease neuroimaging initiative (ADNI; n=237) and AVID A05 (n=130) to independently validate findings. To capture AD-related tau aggregation and spread via tau-PET, we used Braak-stage-specific readouts, temporal-lobe tau meta regions of interest (ROIs)[33], as well as individualized connectivity-based tau stages (Q1-Q4) which specifically capture the gradual spread of tau across connected brain regions.[3,34] Using these data, we first assessed whether faster tau accumulation in ApoE4 carriers was mediated by higher Aβ and secondly, whether tau accumulation accelerated at lower Aβ levels in ApoE4 carriers vs. non-carriers. Based on this analysis, we determined PET-based Aβ cut-points at which tau accumulation rates diverged between ApoE4 carriers vs. non-carriers. Thirdly, we ran simulated trials to determine whether therapeutic effects on tau accumulation can be detected at lower Aβ levels in ApoE4 carriers vs. non-carriers.

METHODS

ADNI Participants

We included 237 non-demented ADNI subjects with at least two ^{18}F-Flortaucipir tau-PET scans and baseline ^{18}F-Florbetapir/Florbetaben (n=175/62) amyloid-PET within 6 months of the baseline tau-PET. Centiloids (CL) were estimated from global ^{18}F-Florbetapir and ^{18}F-Florbetaben SUVRs according to ADNI guidelines (https://adni.loni.usc.edu/wp-content/uploads/2010/09/ADNI_GeneralProceduresManual.pdf). ADNI investigators diagnosed subjects as cognitively normal (CN; Mini Mental State Examination [MMSE]≥24, Clinical Dementia Rating [CDR]=0, non-depressed), mildly cognitively impaired (MCI; MMSE≥24, CDR=0.5, objective memory-impairment on education-adjusted Wechsler Memory Scale II, preserved activities of daily living). Subjects with the ApoE ε2/ε4 genotype were excluded to avoid confounding effects of the potentially protective ε2 allele[35]. ADNI investigators obtained ethical approval; all participants provided written informed consent. Supplementary analyses included an additional 34 subjects diagnosed with dementia (MMSE = 20–26, CDR ≥ 0.5, NINCDS/ADRDA criteria for probable AD) fulfilling the same PET data availability criteria (^{18}F-Florbetapir/Florbetaben: n=21/13).

A05 Participants

130 non-demented subjects were selected from the AVID-1451-A05 phase 2/3 trial (NCT02016560; inclusion criteria: https://clinicaltrials.gov/ProvidedDocs/60/NCT02016560/Prot_000.pdf), with at least two ^{18}F-Flortaucipir tau-PET and a ^{18}F-Florbetapir amyloid-PET scan within 30 days of the initial tau-PET scan. All tau-PET follow-up scans were taken at fixed intervals (9 and 18 months). CL values were estimated from global ^{18}F-Florbetapir SUVRs according to AVID guidelines.[36] Participants were classified as CN (MMSE≥29, no history of cognitive impairment) or MCI (24≥MMSE<29, showing MCI according to NIA-AA working group's diagnostic guidelines).[37] Subjects with the ApoE ε2/ε4 genotype were excluded. The study was approved by the clinical investigator's local Institutional Review Board; all participants provided written informed consent. Supplementary analyses included an additional 35 subjects diagnosed with dementia (10 < MMSE <

24, showing possible or probable AD based on NIA-AA working group's diagnostic guidelines) fulfilling the same PET data availability criteria.

Connectivity Assessment

Functional connectivity of 42 Aβ negative CN ADNI subjects from the same ADNI sample, was assessed using the 200 ROI Schaefer atlas[38] as Fisher-z transformed Pearson-moment correlations between ROI pairs. Subject-specific connectivity matrices were averaged to determine a connectivity template, negative values and autocorrelations were set to 0, following our pre-established approach.[39] All neuroimaging acquisition and processing is described in the supplementary. Subject-specific tau spreading ROIs were generated by grouping 95% of regions into quartiles according to their template-based connectivity to 5% of brain regions with highest baseline tau-PET i.e. the subject-specific tau epicentre (Q1=strongest connectivity to the epicentre; Q4=weakest connectivity to the epicentre).[3,17,30]

Statistical Analysis

Group demographics were compared using ANOVAs for continuous and chi-squared ($\chi 2$) tests for categorical variables. ROI-specific annual tau-PET change rates were estimated using linear mixed models with longitudinal tau-PET SUVR values as the dependent variable and time from baseline as the independent variable, including random slope and intercept.[3,17,30] To confirm previous evidence that ApoE4 carriers have elevated Aβ and faster tau accumulation, we assessed differences in baseline CL and global tau-PET change rates between ApoE4 carriers and non-carriers using ANCOVAs controlling for age and sex.[20]

To test our main hypothesis that ApoE4 carriers show accelerated Aβ-related tau accumulation and spread, we first investigated whether faster ApoE4-related tau accumulation is mediated by higher Aβ. Therefore, bootstrapped mediation models with 1000 iterations conducted in R (https://cran.r-project.org/web/packages/mediation/mediation.pdf) were fitted for both samples (ADNI/A05) separately with ApoE4 status as the independent variable, CL as the mediator and the annual rate of global tau-PET change as the dependent variable (i.e. the average tau-PET change across all 200

cortical Schaefer ROIs). These models were additionally stratified by Braak-stage to determine whether ApoE4 effects on tau accumulation were most present in early tau susceptible regions. All mediation models were controlled for age and sex.

To further assess whether ApoE4 induces an acceleration of tau spreading at lower Aβ levels, we tested the CL by ApoE4 interaction on annual tau-PET SUVR change rates through Braak and connectivity stage ROIs (Q1-Q4). In line with evidence for non-linear progression of tau according to amyloid[40], quadratic interaction models fit the data better than linear interactions (according to Akaike information criterion and ANOVAs) therefore we report quadratic regression models controlled for age and sex (see supplementary eTable 2). CL thresholds in which ApoE4 carrier and non-carrier tau accumulation trajectories diverged were defined in all regression models according to a non-parametric resampling technique which involved identifying where 95% confidence intervals (CI) of the regression lines diverged or re-converged on the y-axis averaged across 1000 bootstrapped regressions to ensure thresholds were robust and not influenced by specific observations. To explore whether ApoE4 induces an acceleration of tau spreading at lower Aβ levels across an extended Aβ spectrum, linear models with CI thresholds were repeated with additional subjects diagnosed with dementia. All analyses were carried out in ADNI and A05.

Lastly, we tested in the larger ADNI sample with good coverage of early-stage and preclinical AD patients, if the sensitivity for detecting potential treatment effects on tau accumulation was higher among ApoE4 carriers at lower Aβ-levels. To this end, simulated interventions with attenuated tau-PET change rates of 30% (i.e. simulated effect of interest) were carried out for global tau-PET increase or tau-PET change rates in the temporal meta[33] or Q1 ROI.[3,30] Simulated interventions were performed using two approaches, by defining a 70 CL wide window with an upper and lower boundary which was shifted from -20 to 140 CLs using a sliding-window approach vs. defining a lower CL boundary for defining the sample of interest, which was systematically increased from -20 to 70 in steps of 10. The required sample sizes were estimated using the R-package "pwr" (settings: two-sample t-test, comparing actual vs. attenuated cognitive changes; two-tailed, alpha=0.05, power=0.8; see https://cran.r-project.org/web/packages/pwr/pwr.pdf). Statistical analyses were

computed using R statistical software version 4.0.2 http://www.R-project.org; [41] Our primary hypothesis-driven analyses were not controlled multiple comparisons due to our independent validation approach across two samples, yet, FDR-corrected p-values are also reported in tables.[42] A STROBE reporting summary can be found in the supplementary.

Data availability

ADNI data are publicly available (adni.loni.usc.edu) upon registration and compliance with the data use agreement. A05 data are available from Eli Lilly upon conclusion of a data sharing agreement. The analysis R-code is available upon request from the authors.

RESULTS

Sample Characteristics

237 ADNI subjects, including 107 ApoE4-carriers, were included. ANOVAs and $\chi 2$ revealed no significant differences between sex, clinical status (CN/MCI), years of education, but ApoE4 carriers had significantly lower MMSE scores, were significantly younger with a higher proportion meeting amyloid-PET positivity thresholds[43,44] and had shorter tau-PET follow up. Of the 130 A05 subjects, including 45 ApoE4-carriers, were included. Sample characteristics were congruent with ADNI except for clinical status: there were significantly less CN ApoE4-carriers than CN non-carriers or MCI ApoE4-carriers. Results are summarized in Supplementary eTable 1. As expected, ApoE4-carriers had significantly higher CL (ADNI $F(1,232)=45.123$, $p<0.001$; A05 $F(1,125)=20.73$, $p<0.001$ and also a faster annual rate of global tau-PET SUVR accumulation (ADNI $F(1,232)=15.470$, $p<0.001$; A05 $F(1,125)=11.383$, $p<0.001$, controlling for age and sex. The demographic and clinical characteristics of additional dementia subjects added to supplementary analyses are displayed in Supplementary eTable 5. Tau-PET uptake and accumulation rates stratified by diagnostic group and ApoE4-status are shown in Figure 1 (for further stratification by Aβ-status see supplementary eFigure 1).

Faster tau accumulation in ApoE4 carriers is mediated by higher Aβ

We firstly assessed whether higher ApoE4-conferred Aβ burden mediates faster tau accumulation. Supporting this, bootstrapped mediation analyses revealed that the association between ApoE4-status and faster annual rate of tau-PET SUVR accumulation was mediated by higher CL (ADNI: average causal mediation effect [ACME]: $B=0.14$, $p=0.006$; A05: ACME: $B=0.25$, $p<0.001$, Figure 2A). When repeating the mediation analysis stratified by Braak-ROIs, we found no mediation of amyloid on ApoE4-risk on tau accumulation in Braak I, but a mediation in Braak III, followed by a weakening effect in subsequent Braak ROIs, in both samples (Fig.2D&E&Table1). This suggests that ApoE4-carriage does not accelerate the initial emergence of tau pathology in the earliest tau-vulnerable region, Braak I, but may propel amyloid-related tau accumulation particularly in cortical regions.[1,12]

For exploratory purposes, we also found no main effect of ApoE4 on tau accumulation in Braak I (ADNI: F=2.95, p=0.087; A05: F=2.31, p=0.131) suggesting the initial dynamics of tau are not driven by Aβ or ApoE. Sensitivity analyses also controlling for clinical diagnosis are shown in supplementary eTable 3.

ApoE4 carriage lowers the threshold for amyloid-related tau spreading

Second, we tested whether ApoE4 not only accelerates tau accumulation via increased amyloid (i.e. mediation effect), but whether ApoE4 and amyloid have synergistic effects on accelerating tau accumulation as suggested by previous cross-sectional studies.[45,46] Supporting this, we found significant CL by ApoE4-status interactions on annual tau accumulation rates for Braak ROIs III-V in ADNI (all $p<0.01$, Fig.3A-C) and for Braak III and V in A05 ($p<0.05$, Fig.3E&G). On average, tau trajectories diverged at ~15CL for ADNI and at ~12CL for A05, as determined by non-parametric resampling. This result pattern was consistent for connectivity-based tau stages, which better capture individualized tau spread. Here, significant ($p<0.05$) ApoE4 times CL interactions were found for Q1-Q2 in ADNI (Fig.3I&J) and A05 (Fig.3M&N), where ApoE4-related tau accumulation accelerated at ~13CL for ADNI and ~12CL for A05. The strength of the interaction effect became weaker across Q1-Q4, suggesting that ApoE4-carriage is specifically associated with accelerated tau spreading from patient-specific epicentres to closely connected regions (Table 2). Sensitivity analyses also controlling for clinical diagnosis are shown in supplementary eTable 4. Exploratory analyses also including subjects with dementia (n=271/165 ADNI/A05) yielded consistent results (supplementary eFigure 3, eTable 6). Together, these results suggest that ApoE4-carriage facilitates tau spreading at lower amyloid thresholds. Linear regression models revealed further, that higher annual rate of tau-SUVR accumulation was predictive of faster MMSE decline in ADNI ($\beta=-0.32$, $p<0.001$) and A05 ($\beta=-0.28$, $p=0.002$; Supplementary eTable 7). This suggests that earlier ApoE4-related tau accumulation in the presence of Aβ may translate into faster cognitive decline.

ApoE4 is associated with higher sensitivity to detect treatment-related tau attenuation at lower amyloid levels

Lastly, we assessed whether the sensitivity to detect therapeutic effects on tau accumulation at lower Aβ levels is higher in ApoE4 carriers. We computed required sample sizes to detect simulated intervention effects with 30% attenuation of tau-PET change as an endpoint through Global, Temporal-Meta and Q1 ROIs in ADNI. When employing a sliding window approach spanning 70CL, we found that detecting tau attenuation as a treatment effect requires overall lower sample sizes in ApoE4 carriers compared to ApoE4 non-carriers (Supplementary eFigure 2A/C/E). For global and Q1 tau-PET readouts, the sensitivity to detect treatment effects diverged particularly at ~10CL, consistent with the previous analysis in which we show ApoE4-related tau accumulation acceleration at this CL threshold (Figure 3). Congruent results were obtained when employing a lower CL boundary approach (Supplementary eFigure 2B/D/F), indicating that ApoE4 carrier inclusion in trials using tau-PET as a surrogate endpoint can reduce sample sizes required to detect treatment effects, especially at lower Aβ levels. This exploratory analysis could not be reliably repeated in A05 owing to skewed sample sizes across the CL spectrum leading to biased power estimations.

DISCUSSION

We demonstrate that ApoE4-carriage i) is associated with enhanced Aβ pathology that mediates faster tau accumulation across early Braak-stage regions, and ii) that cortical tau spreading accelerates in ApoE4-carriers at lower Aβ levels. This suggests a potential indirect and direct effect of ApoE4 on tau: first by driving Aβ accumulation which triggers tau accumulation and second, by lowering the Aβ-threshold at which tau spreading accelerates from local epicentres across connected regions. We found that Aβ-related tau trajectories diverge around 12-15CL between ApoE4 carriers and non-carriers, at which neuritic plaque pathology is already observed post-mortem[47] but below the typical 26CL cut-off for amyloid-PET positivity.[48] This indicates that tau spreading may be triggered earlier in ApoE4 carriers and therefore may be beneficial to explore disease-modifying anti-Aβ treatments at lower Aβ levels. Supporting this, our simulated trials show that tau accumulation attenuation can be detected at lower Aβ levels in ApoE4 carriers, therefore encouraging earlier disease modifying intervention in carriers of the strongest risk factor for developing sporadic AD.

Our first major finding that Aβ mediates faster tau-PET increase in ApoE4 carriers vs. non-carriers provides evidence that accelerated tau progression in ApoE4 carriers is partly driven by stronger Aβ deposition. Mediating effects of Aβ on the association between ApoE4 and accelerated tau accumulation were specifically found for cortical Braak-stage regions but not for the entorhinal cortex (i.e. Braak I), where age-related tau-PET increase is also found in the absence of Aβ.[49] This is in line with past research demonstrating that tau accumulation in the entorhinal cortex is not mediated by Aβ in ApoE4 carriers[50], suggesting that ApoE4 is specifically linked to Aβ-related cortical tau accumulation, but not to the initial entorhinal emergence of tau. This result pattern also provides an explanation for why ApoE4 carriers without Aβ pathology exhibit tau in the medial temporal lobe but seldom beyond this region and do not develop pure tauopathies.[25,26]

Our second main finding revealed that ApoE4 doesn't only drive accelerated tau accumulation through higher Aβ levels, but also has possible synergistic effects with Aβ on tau spreading, congruent with cross-sectional evidence of higher tau-PET at given level of Aβ in ApoE4 carriers.[46]

Specifically, we demonstrated that the rate of Aβ-related tau accumulation is moderated by ApoE4 across regions vulnerable to early-stage tau aggregation and spread i.e. regions strongly connected to tau epicentres (i.e. Q1-Q2).[3,17,30] These results are congruent with a bi-phasic AD pathophysiological framework which proposes an Aβ-dependent then a later Aβ-independent tau accumulation phase[31], supported by mouse-model evidence demonstrating that Aβ-targeting antibodies reduce early but not later tau changes.[51] ApoE4-related tau trajectories diverged at relatively low levels of around 12-15CL consistently across both samples, suggesting that ApoE4 influences tau accumulation before patients are Aβ-PET positive using commonly applied thresholds.[47,48] This finding highlights the need for earlier CL-gauged therapeutic windows for ApoE4 carriers to effectively intervene Aβ-related tau spreading.[28]

A key question is how Aβ facilitates tau spreading despite their spatial incongruity and how ApoE4 modulates this process. Recent network-connectivity research suggests that the onset of trans-neuronal tau spreading is subject to remote connectivity changes induced by the emergence of Aβ in regions connected to the entorhinal cortex[52] (where tau typically emerges first). This process may be accelerated in Apoe4 carriers who, according to electrophysiological[53] and fMRI[54] evidence, exhibit hyperconnectivity in primary Aβ-harbouring regions compared to non-carriers. Remote Aβ-induced hyperconnectivity to tau epicentres may facilitate its spread to the rest of the cortex in ApoE4 carriers. It is unclear why ApoE4 carriers exhibit increased neuronal hyperconnectivity, but recent neuroinflammation research reveals that ApoE4-related Aβ plaques are structurally less compact[55] and trigger a greater inflammatory response[56] which may amplify it's pathological effects. Further, recent work in transgenic mouse models has found that ApoE4 is associated with earlier Aβ seeding and a stronger Aβ-induced astrogliosis[57] and recent work in humans has shown that markers of astrocyte abnormality (i.e. GFAP) are linked to a stronger association between Aβ and tau biomarkers.[58] Therefore, ApoE4 may be related to an earlier Aβ-induced astrogliosis, triggering an earlier onset tau spreading, however, this remains to be specifically tested.

Lastly, our exploratory analysis in which we employed simulated interventions across several Aβ-defined therapeutic windows and boundaries illustrated that, compared to non-carriers, fewer ApoE4 carriers are required to detect intervention-related tau attenuation at lower Aβ levels. This analysis translates this study's major findings into an interventional context by conveying how the rate and timing of Aβ-related tau accumulation and chosen readout region impacts clinical trial design and consequently, meeting surrogate endpoints. Q1 exhibited the largest inter-group differences possibly reflecting its sensitivity to capturing individualized tau-PET accumulation[3]. Importantly, this analysis is calculated according to observed tau accumulation rates and not specific to anti-Aβ intervention thus does not consider when anti-Aβ treatment can no longer attenuate tau accumulation, which we predict would occur in line with the centiloid thresholds established in the previous analysis.[3]

Us amongst others argue that the current rigid approach of dichotomising subjects according to pre-established Aβ-PET thresholds without considering subject-specific risk factors begs reconsideration.[33] There are reports of Aβ-PET negative individuals with AD-like tau pathology[59,60] who may exemplify subjects who enter the AD spectrum while formally defined as Aβ-negative owing to accelerated tau spreading at lower Aβ levels. This concept may clarify why empirical research has identified increased MTL tau in Aβ-negative ApoE4 carriers compared to non-carriers[25,61] by proposing this increased tau to be Aβ-related, but at sub-threshold levels. A novel aspect of the present study is including MCI Aβ-negative subjects which inevitably includes non-AD spectrum subjects; however, this is statistically and conceptually necessary to detect the subthreshold Aβ-related tau spreading in AD spectrum individuals.

A strength of the present study is the independent validation in the A05 sample, which conveyed overall congruent results. Nevertheless, CN ApoE4 carriers are underrepresented in A05, leading to slightly more advanced tau levels (see Figure 1), which may explain why mediation and interaction effects tend to be skewed slightly towards later Braak stages. Furthermore, the use of individualised

connectivity-based tau spreading stages can more sensitively capture spatial heterogeneity in tau accumulation therefore better gauging the extent of tau spreading compared to Braak-stage specific readouts.[62] Nevertheless, several caveats should be considered when interpreting our results. Firstly, unspecific Flortaucipir off-target is commonplace[63] particularly in the hippocampus and basal ganglia hence their exclusion from our analysis. However, we cannot confirm that confound was not introduced from off-target binding elsewhere. Excluded regions such as the hippocampus may be particularly informative about early stage tau-spreading[64,65] which unfortunately we can't explore until larger data with second-generation tau-PET tracers become available to us. Secondly, tau accumulation modelling across connected regions relies on the accurate mapping of tau-PET to rsfMRI-assessed functional connectivity which, owing to distant multi-synaptic connections,[66,67] cannot be structurally confirmed owing to current methodological shortcomings.[68] Thirdly, this project's focus is purely pathophysiological and has exclusively drawn conclusions from a surrogate endpoint, i.e. Tau accumulation, but as future clinical progression is strongly linked to tau severity we believe our findings are likely to translate into clinical outcomes. Accordingly, we demonstrate that longitudinal MMSE scores, converted to annual MMSE change rates, align with tau-PET increases and predict tau-PET changes (Supplemental eTable 4). It should be mentioned that ADNI and A05 have slightly different clinical diagnostic criteria for MCI and CN, however we believe this did not lead to incongruous clinical classifications between the two cohorts owing to the rigorous expert clinical judgement in both protocols. Moreover, we emphasise the exploratory nature of the sample size estimation analysis which was not replicated in A05 due to insufficient data throughout the CL spectrum and overly dispersed tau-PET SUVR change rates influencing power predictions. Additionally, this project has reported p-values uncorrected for multiple comparisons to reduce type II error, which we believe to be statistically appropriate given the hypothesis-driven and cross-validation approach.[42,69] Finally, this study would generally benefit from longer tau-PET follow-up times, which is particularly relevant at early and potentially slower tau spreading stages and the inclusion of more diverse cohorts since ApoE4 may have different effects across ethnicities.[70]

In conclusion, we demonstrate independently validated evidence that ApoE4 is related to accelerated and earlier Aβ-related tau spreading which may drive faster clinical AD progression in ApoE4 carriers. Our findings have implications for trial design by illustrating that ApoE4 carriers may require earlier intervention to effectively attenuate tau spreading and associated clinical deterioration. Moreover, our results motivate further research into Aβ thresholds which determine clinical trial inclusion according to subject-specific characteristics such as ApoE4 so that AD progression can be targeted in time to prevent tau spreading.

REFERENCES

1. Scholl M, Lockhart SN, Schonhaut DR, et al. PET Imaging of Tau Deposition in the Aging Human Brain. *Neuron*. Mar 2 2016;89(5):971-982. doi:10.1016/j.neuron.2016.01.028
2. Vogel JW, Iturria-Medina Y, Strandberg OT, et al. Spread of pathological tau proteins through communicating neurons in human Alzheimer's disease. *Nature communications*. 2020;11(1):1-15.
3. Franzmeier N, Dewenter A, Frontzkowski L, et al. Patient-centered connectivity-based prediction of tau pathology spread in Alzheimer's disease. *Sci Adv*. Nov 2020;6(48)doi:10.1126/sciadv.abd1327
4. Franzmeier N, Neitzel J, Rubinski A, et al. Functional brain architecture is associated with the rate of tau accumulation in Alzheimer's disease. *Nat Commun*. Jan 17 2020;11(1):347. doi:10.1038/s41467-019-14159-1
5. Cope TE, Rittman T, Borchert RJ, et al. Tau burden and the functional connectome in Alzheimer's disease and progressive supranuclear palsy. *Brain*. Feb 1 2018;141(2):550-567. doi:10.1093/brain/awx347
6. Adams JN, Maass A, Harrison TM, Baker SL, Jagust WJ. Cortical tau deposition follows patterns of entorhinal functional connectivity in aging. *Elife*. 2019;8:e49132.
7. Jack CR, Jr., Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol*. Jan 2010;9(1):119-28. doi:10.1016/s1474-4422(09)70299-6
8. Jack Jr CR, Bennett DA, Blennow K, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimer's & Dementia*. 2018;14(4):535-562.
9. Biel D, Brendel M, Rubinski A, et al. Tau-PET and in vivo Braak-staging as prognostic markers of future cognitive decline in cognitively normal to demented individuals. *Alzheimer's Research & Therapy*. 2021/08/12 2021;13(1):137. doi:10.1186/s13195-021-00880-x
10. Ossenkoppele R, Smith R, Mattsson-Carlgren N, et al. Accuracy of Tau Positron Emission Tomography as a Prognostic Marker in Preclinical and Prodromal Alzheimer Disease: A Head-to-Head Comparison Against Amyloid Positron Emission Tomography and Magnetic Resonance Imaging. *JAMA Neurol*. Aug 1 2021;78(8):961-971. doi:10.1001/jamaneurol.2021.1858
11. La Joie R, Visani AV, Baker SL, et al. Prospective longitudinal atrophy in Alzheimer's disease correlates with the intensity and topography of baseline tau-PET. *Sci Transl Med*. Jan 1 2020;12(524)doi:10.1126/scitranslmed.aau5732
12. Biel D, Brendel M, Rubinski A, et al. Tau-PET and in vivo Braak-staging as prognostic markers of future cognitive decline in cognitively normal to demented individuals. *Alzheimers Res Ther*. Aug 12 2021;13(1):137. doi:10.1186/s13195-021-00880-x
13. Biel D, Luan Y, Brendel M, et al. Combining tau-PET and fMRI meta-analyses for patient-centered prediction of cognitive decline in Alzheimer's disease. *Alzheimers Res Ther*. Nov 7 2022;14(1):166. doi:10.1186/s13195-022-01105-5
14. Buckley RF, Mormino EC, Rabin JS, et al. Sex Differences in the Association of Global Amyloid and Regional Tau Deposition Measured by Positron Emission Tomography in Clinically Normal Older Adults. *JAMA Neurol*. May 1 2019;76(5):542-551. doi:10.1001/jamaneurol.2018.4693

15. Buckley RF, Scott MR, Jacobs HIL, et al. Sex Mediates Relationships Between Regional Tau Pathology and Cognitive Decline. *Annals of neurology*. Nov 2020;88(5):921-932. doi:10.1002/ana.25878
16. Rabin JS, Yang HS, Schultz AP, et al. Vascular Risk and beta-Amyloid Are Synergistically Associated with Cortical Tau. *Ann Neurol*. Feb 2019;85(2):272-279. doi:10.1002/ana.25399
17. Steward A, Biel D, Brendel M, et al. Functional network segregation is associated with attenuated tau spreading in Alzheimer's disease. *Alzheimers Dement*. Nov 25 2022;doi:10.1002/alz.12867
18. Franzmeier N, Ossenkoppele R, Brendel M, et al. The BIN1 rs744373 Alzheimer's disease risk SNP is associated with faster Abeta-associated tau accumulation and cognitive decline. *Alzheimers Dement*. Jun 1 2021;doi:10.1002/alz.12371
19. Franzmeier N, Rubinski A, Neitzel J, Ewers M. The BIN1 rs744373 SNP is associated with increased tau-PET levels and impaired memory. *Nat Commun*. 2019;
20. Baek MS, Cho H, Lee HS, Lee JH, Ryu YH, Lyoo CH. Effect of APOE epsilon4 genotype on amyloid-beta and tau accumulation in Alzheimer's disease. *Alzheimers Res Ther*. Oct 31 2020;12(1):140. doi:10.1186/s13195-020-00710-6
21. Hersi M, Irvine B, Gupta P, Gomes J, Birkett N, Krewski D. Risk factors associated with the onset and progression of Alzheimer's disease: A systematic review of the evidence. *Neurotoxicology*. 2017;61:143-187.
22. Benson GS, Bauer C, Hausner L, et al. Don't forget about tau: the effects of ApoE4 genotype on Alzheimer's disease cerebrospinal fluid biomarkers in subjects with mild cognitive impairment-data from the Dementia Competence Network. *J Neural Transm (Vienna)*. Jun 2022;129(5-6):477-486. doi:10.1007/s00702-022-02461-0
23. Hong YJ, Kim CM, Lee JH, Sepulcre J. Correlations between APOE4 allele and regional amyloid and tau burdens in cognitively normal older individuals. *Scientific reports*. Aug 22 2022;12(1):14307. doi:10.1038/s41598-022-18325-2
24. Montal V, Diez I, Kim CM, et al. Network Tau spreading is vulnerable to the expression gradients of APOE and glutamatergic-related genes. *Sci Transl Med*. Jul 27 2022;14(655):eabn7273. doi:10.1126/scitranslmed.abn7273
25. Farfel JM, Yu L, De Jager PL, Schneider JA, Bennett DA. Association of APOE with tau-tangle pathology with and without β-amyloid. *Neurobiology of aging*. 2016;37:19-25.
26. Crary JF, Trojanowski JQ, Schneider JA, et al. Primary age-related tauopathy (PART): a common pathology associated with human aging. *Acta neuropathologica*. 2014;128(6):755-766.
27. Sando SB, Melquist S, Cannon A, et al. APOE epsilon 4 lowers age at onset and is a high risk factor for Alzheimer's disease; a case control study from central Norway. *BMC Neurol*. Apr 16 2008;8:9. doi:10.1186/1471-2377-8-9
28. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. *New England Journal of Medicine*. 2022;
29. Ward A, Crean S, Mercaldi CJ, et al. Prevalence of apolipoprotein E4 genotype and homozygotes (APOE e4/4) among patients diagnosed with Alzheimer's disease: a systematic review and meta-analysis. *Neuroepidemiology*. 2012;38(1):1-17. doi:10.1159/000334607
30. Pichet Binette A, Franzmeier N, Spotorno N, et al. Amyloid-associated increases in soluble tau relate to tau aggregation rates and cognitive decline in early Alzheimer's disease. *Nat Commun*. Nov 4 2022;13(1):6635. doi:10.1038/s41467-022-34129-4

31. Hyman BT. Amyloid-dependent and amyloid-independent stages of Alzheimer disease. *Archives of neurology*. 2011;68(8):1062-1064.
32. Meisl G, Hidari E, Allinson K, et al. In vivo rate-determining steps of tau seed accumulation in Alzheimer's disease. *Science advances*. 2021;7(44):eabh1448.
33. Jack Jr CR, Wiste HJ, Weigand SD, et al. Defining imaging biomarker cut points for brain aging and Alzheimer's disease. *Alzheimer's & Dementia*. 2017;13(3):205-216.
34. Pichet Binette A, Franzmeier N, Spotorno N, et al. Amyloid-associated increases in soluble tau relate to tau aggregation rates and cognitive decline in early Alzheimer's disease. *Nature Communications*. 2022;13(1):6635.
35. Corder E, Saunders AM, Risch N, et al. Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. *Nature genetics*. 1994;7:180-184.
36. Navitsky M, Joshi AD, Kennedy I, et al. Standardization of amyloid quantitation with florbetapir standardized uptake value ratios to the Centiloid scale. *Alzheimer's & Dementia*. 2018;14(12):1565-1571.
37. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & dementia*. 2011;7(3):270-279.
38. Schaefer A, Kong R, Gordon EM, et al. Local-Global Parcellation of the Human Cerebral Cortex from Intrinsic Functional Connectivity MRI. *Cereb Cortex*. Sep 1 2018;28(9):3095-3114. doi:10.1093/cercor/bhx179
39. Ewers M, Luan Y, Frontzkowski L, et al. Segregation of functional networks is associated with cognitive resilience in Alzheimer's disease. *Brain*. Aug 17 2021;144(7):2176-2185. doi:10.1093/brain/awab112
40. de Leon MJ, Pirraglia E, Osorio RS, et al. The nonlinear relationship between cerebrospinal fluid Aβ42 and tau in preclinical Alzheimer's disease. *PloS one*. 2018;13(2):e0191240.
41. *R: A language and environment for statistical computing*. R Foundation for Statistical Computing; 2021. https://www.R-project.org/
42. Armstrong RA. When to use the B onferroni correction. *Ophthalmic and Physiological Optics*. 2014;34(5):502-508.
43. Fleisher AS, Chen K, Liu X, et al. Apolipoprotein E ε4 and age effects on florbetapir positron emission tomography in healthy aging and Alzheimer disease. *Neurobiology of aging*. 2013;34(1):1-12.
44. Maass A, Landau S, Baker SL, et al. Comparison of multiple tau-PET measures as biomarkers in aging and Alzheimer's disease. *Neuroimage*. Aug 15 2017;157:448-463. doi:10.1016/j.neuroimage.2017.05.058
45. Young CB, Johns E, Kennedy G, et al. APOE effects on regional tau in preclinical Alzheimer's disease. *Mol Neurodegener*. Jan 4 2023;18(1):1. doi:10.1186/s13024-022-00590-4
46. Therriault J, Benedet AL, Pascoal TA, et al. APOEepsilon4 potentiates the relationship between amyloid-beta and tau pathologies. *Mol Psychiatry*. Oct 2021;26(10):5977-5988. doi:10.1038/s41380-020-0688-6
47. La Joie R, Ayakta N, Seeley WW, et al. Multisite study of the relationships between antemortem [(11)C]PIB-PET Centiloid values and postmortem measures of Alzheimer's disease neuropathology. *Alzheimers Dement*. Feb 2019;15(2):205-216. doi:10.1016/j.jalz.2018.09.001

48. Amadoru S, Dore V, McLean CA, et al. Comparison of amyloid PET measured in Centiloid units with neuropathological findings in Alzheimer's disease. *Alzheimers Res Ther*. Mar 4 2020;12(1):22. doi:10.1186/s13195-020-00587-5
49. Weigand AJ, Bangen KJ, Thomas KR, et al. Is tau in the absence of amyloid on the Alzheimer's continuum?: A study of discordant PET positivity. *Brain Commun*. 2020;2(1):fcz046. doi:10.1093/braincomms/fcz046
50. Salvadó G, Grothe MJ, Groot C, et al. Differential associations of APOE-ε2 and APOE-ε4 alleles with PET-measured amyloid-β and tau deposition in older individuals without dementia. *European Journal of Nuclear Medicine and Molecular Imaging*. 2021/07/01 2021;48(7):2212-2224. doi:10.1007/s00259-021-05192-8
51. Oddo S, Billings L, Kesslak JP, Cribbs DH, LaFerla FM. Aβ immunotherapy leads to clearance of early, but not late, hyperphosphorylated tau aggregates via the proteasome. *Neuron*. 2004;43(3):321-332.
52. Lee WJ, Brown JA, Kim HR, et al. Regional Aβ-tau interactions promote onset and acceleration of Alzheimer's disease tau spreading. *Neuron*. 2022;110(12):1932-1943. e5.
53. Koelewijn L, Lancaster TM, Linden D, et al. Oscillatory hyperactivity and hyperconnectivity in young APOE-ε4 carriers and hypoconnectivity in Alzheimer's disease. *Elife*. 2019;8:e36011.
54. Pihlajamäki M, Sperling RA. Functional MRI assessment of task-induced deactivation of the default mode network in Alzheimer's disease and at-risk older individuals. *Behavioural neurology*. 2009;21(1-2):77-91.
55. Stephen TL, Cacciottolo M, Balu D, et al. APOE genotype and sex affect microglial interactions with plaques in Alzheimer's disease mice. *Acta Neuropathologica Communications*. 2019/05/21 2019;7(1):82. doi:10.1186/s40478-019-0729-z
56. Rodriguez GA, Tai LM, LaDu MJ, Rebeck GW. Human APOE4 increases microglia reactivity at Aβ plaques in a mouse model of Aβ deposition. *Journal of Neuroinflammation*. 2014/06/19 2014;11(1):111. doi:10.1186/1742-2094-11-111
57. Liu CC, Zhao N, Fu Y, et al. ApoE4 Accelerates Early Seeding of Amyloid Pathology. *Neuron*. Dec 6 2017;96(5):1024-1032 e3. doi:10.1016/j.neuron.2017.11.013
58. Bellaver B, Povala G, Ferreira PCL, et al. Astrocyte reactivity influences amyloid-beta effects on tau pathology in preclinical Alzheimer's disease. *Nat Med*. Jul 2023;29(7):1775-1781. doi:10.1038/s41591-023-02380-x
59. Weigand AJ, Edwards LE, Thomas KR, Bangen KJ, Bondi MW, Initiative AsDN. Comprehensive characterization of elevated tau PET signal in the absence of amyloid-beta. *Brain Communications*. 2022;4(6):fcac272.
60. Leal SL, Lockhart SN, Maass A, Bell RK, Jagust WJ. Subthreshold Amyloid Predicts Tau Deposition in Aging. *J Neurosci*. May 9 2018;38(19):4482-4489. doi:10.1523/JNEUROSCI.0485-18.2018
61. Therriault J, Benedet AL, Pascoal TA, et al. Association of apolipoprotein E ε4 with medial temporal tau independent of amyloid-β. *JAMA neurology*. 2020;77(4):470-479.
62. Leuzy A, Binette AP, Vogel JW, et al. Comparison of Group-Level and Individualized Brain Regions for Measuring Change in Longitudinal Tau Positron Emission Tomography in Alzheimer Disease. *JAMA Neurol*. Jun 1 2023;80(6):614-623. doi:10.1001/jamaneurol.2023.1067
63. Lemoine L, Leuzy A, Chiotis K, Rodriguez-Vieitez E, Nordberg A. Tau positron emission tomography imaging in tauopathies: the added hurdle of off-target binding. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*. 2018;10:232-236.

64. Lace G, Savva G, Forster G, et al. Hippocampal tau pathology is related to neuroanatomical connections: an ageing population-based study. *Brain*. 2009;132(5):1324-1334.
65. Mu Y, Gage FH. Adult hippocampal neurogenesis and its role in Alzheimer's disease. *Molecular neurodegeneration*. 2011;6(1):1-9.
66. Honey CJ, Sporns O, Cammoun L, et al. Predicting human resting-state functional connectivity from structural connectivity. *Proceedings of the National Academy of Sciences*. 2009;106(6):2035-2040.
67. Grandjean J, Zerbi V, Balsters JH, Wenderoth N, Rudin M. Structural basis of large-scale functional connectivity in the mouse. *Journal of Neuroscience*. 2017;37(34):8092-8101.
68. Abhinav K, Yeh F-C, Pathak S, et al. Advanced diffusion MRI fiber tracking in neurosurgical and neurodegenerative disorders and neuroanatomical studies: a review. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*. 2014;1842(11):2286-2297.
69. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology*. 1990:43-46.
70. Naslavsky MS, Suemoto CK, Brito LA, et al. Global and local ancestry modulate APOE association with Alzheimer's neuropathology and cognitive outcomes in an admixed sample. *Molecular Psychiatry*. 2022/11/01 2022;27(11):4800-4808. doi:10.1038/s41380-022-01729-x

FIGURES

Figure 1 *Group-average tau-PET SUVRs at baseline stratified by ApoE4 status and diagnostic group. Tau-PET SUVRs are showed as continuous values, white outlines define areas which surpass a pre-established pathological tau SUVR threshold of 1.3[44] in ADNI subjects (A) and A05 subjects (C). Number of subjects displayed under each group rendering, Group average tau-SUVR annual change rates defined by linear mixed models, stratified by ApoE4 carriership and diagnostic group in ADNI subjects (B) and A05 subjects (D). Tukey HSD (95% confidence level) post-hoc tests on ROI-wise ANCOVAs reveal mean-differences between tau-PET SUVR values of ApoE4 carriers minus non-carriers (E) and their annual tau-PET SUVR change (F) stratified by sample.*

Figure 2 *Global mediation analyses with ApoE4 status as predictor, centiloid as mediator, and the global annual tau SUVR rate of change (ROC) i.e. averaged across all 200 cortical Schaefer ROIs, as the dependent variable, p-values for each path are displayed on the respective arrow. The average causal mediation effect (ACME) and the average direct effect (ADE) are displayed under each mediation triangle as estimated from bootstrapped mediation models. The models are controlled for age and sex. Tested in ADNI (A) and A05 (B). Surface rendering of the Braak-staging ROIs by which longitudinal tau-PET changes were determined (C). Bar chart presenting ACME B-values of mediation analyses (ApoE4 Risk as predictor, Amyloid SUVR as mediator, and the annual tau SUVR rate of change across Braak stages as the dependent variable), asterisks reflect significant mediations and error bars represent 95%CI of mediation bootstrapping in ADNI (D) and A05 (E).*

Figure 3 *Scatterplots illustrating the interaction effect between ApoE4 status and centiloid on the annual rate of tau SUVR change through braak stages III to VI in ADNI (A, B, C, D) and A05 (E, F, G, H) and through connectivity stages Q1 to Q4 in ADNI (I, J, K, L) and A05 (M, N, O, P) showing that ApoE4 carriers show an amyloid-related increase in tau accumulation in early disease stages. Vertical dashed lines represent centiloid threshold of when groups diverge and converge, estimated according to a non-parametric bootstrapping technique with 1000 iterations identifying the point of where confidence intervals around regression lines diverge and converge, presented with shaded 95%CI threshold.*

Table 1. Mediation Results

613

	B	CI L	CI U	p-value
		ADNI		
Global	0.15	0.05	0.28	0.01*
Braak I	0.03	-0.09	0.14	0.68
Braak III	0.19	0.07	0.32	<0.001*
Braak IV	0.17	0.06	0.30	0.01*
Braak V	0.12	0.01	0.24	0.03*
Braak VI	0.09	-0.02	0.21	0.108
		A05		
Global	0.33	0.14	0.54	<0.001*
Braak I	-0.02	-0.17	0.13	0.78
Braak III	0.33	0.14	0.54	<0.001*
Braak IV	0.28	0.11	0.48	<0.001*
Braak V	0.34	0.15	0.55	<0.001*
Braak VI	0.27	0.10	0.46	<0.001*

CI L 95% Confidence interval lower, CI U 95% Confidence interval upper.
Values are ACME values derived from mediation analyses with ApoE4 risk as predictor, centiloid as mediator, and the annual tau SUVR rate of change (ROC) in the respective Braak stage as the dependent variable. The table displays beta-estimates and p-values.
* indicate p-values that fall below an FDR-corrected p-threshold of 0.05. The mediation models are controlled for age and sex. Additional mediation models correcting for diagnosis are shown in supplementary eTable 3.

Table 2. Interaction effects estimated by linear regression

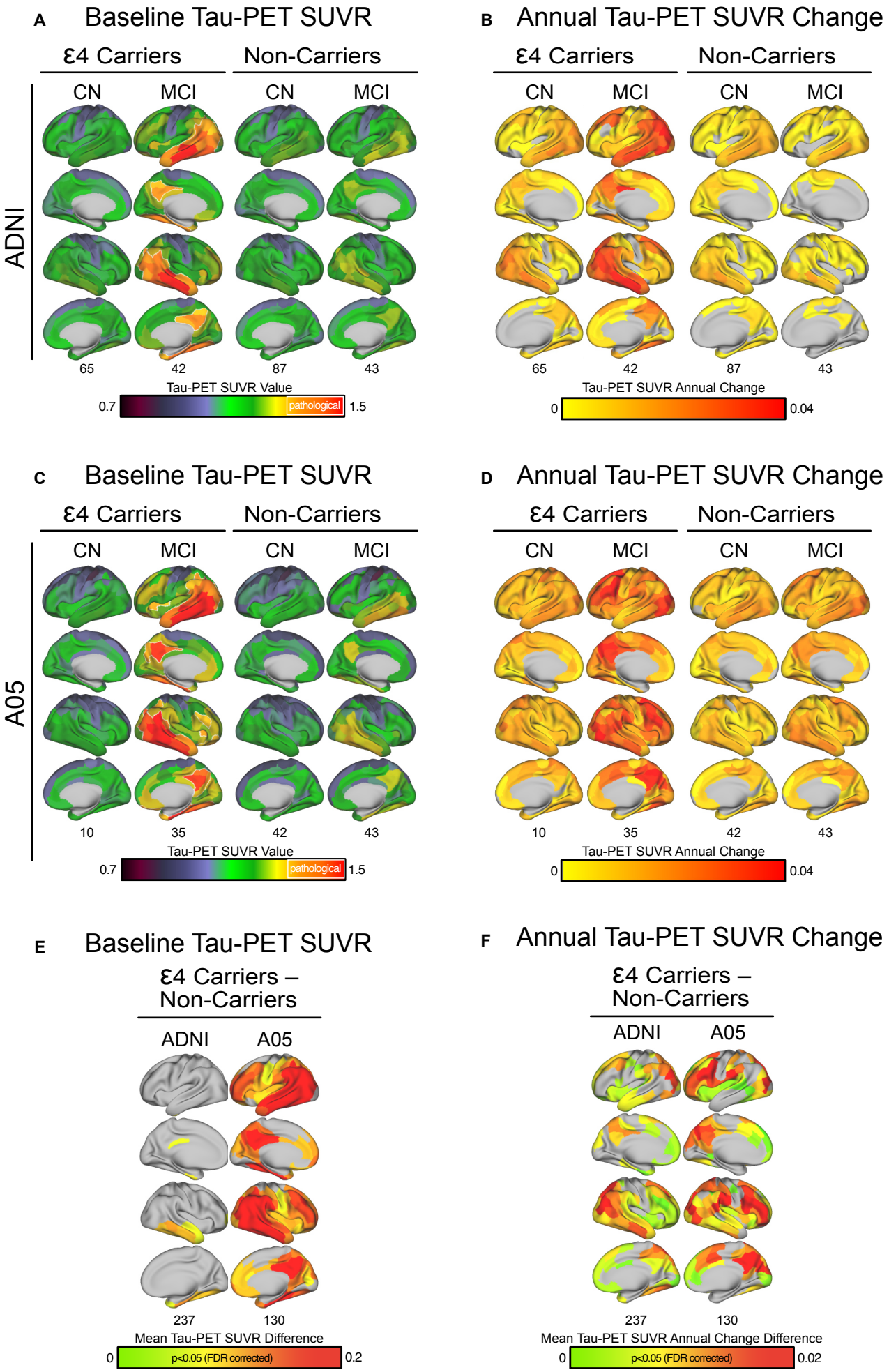
	β	t-value	p-value	Par. R^2	Lower cut-point			Upper cut-point		
					mean	CI L	CI U	mean	CI L	CI U
Braak Stages										
ADNI										
Braak III	-0.34	-3.35	<0.001*	0.05	16.10	15.43	16.76	75.90	75.05	76.75
Braak IV	-0.36	-3.51	<0.001*	0.05	12.44	11.74	13.15	74.20	73.33	75.06
Braak V	-0.28	-2.64	0.009*	0.03	12.43	11.43	13.42	79.80	78.76	80.84
Braak VI	-0.18	-1.63	0.104	0.01	–	–	–	–	–	–
A05										
Braak III	-0.27	-2.19	0.030	0.04	15.42	14.14	16.70	60.47	58.32	62.61
Braak IV	-0.16	-1.28	0.204	0.02	–	–	–	–	–	–
Braak V	-0.26	-2.23	0.028	0.05	11.03	9.89	12.17	63.96	61.82	66.10
Braak VI	-0.09	-0.71	0.480	0.03	–	–	–	–	–	–
Connectivity Stages										
ADNI										
Q1	-0.39	-3.78	<0.001*	0.06	11.20	10.61	11.80	83.60	82.74	84.45
Q2	-0.27	-2.66	0.008*	0.03	13.29	12.39	14.19	80.77	79.72	81.83
Q3	-0.20	-1.94	0.053	0.02	–	–	–	–	–	–
Q4	-0.14	-1.26	0.208	0.01	–	–	–	–	–	–
A05										
Q1	-0.23	-2.02	0.046	0.03	13.31	12.25	14.37	69.70	67.67	71.74
Q2	-0.31	-2.67	0.008*	0.07	11.93	10.86	12.99	56.48	54.38	58.57
Q3	-0.20	-1.67	0.098	0.04	–	–	–	–	–	–
Q4	-0.02	-0.15	0.884	0.02	–	–	–	–	–	–

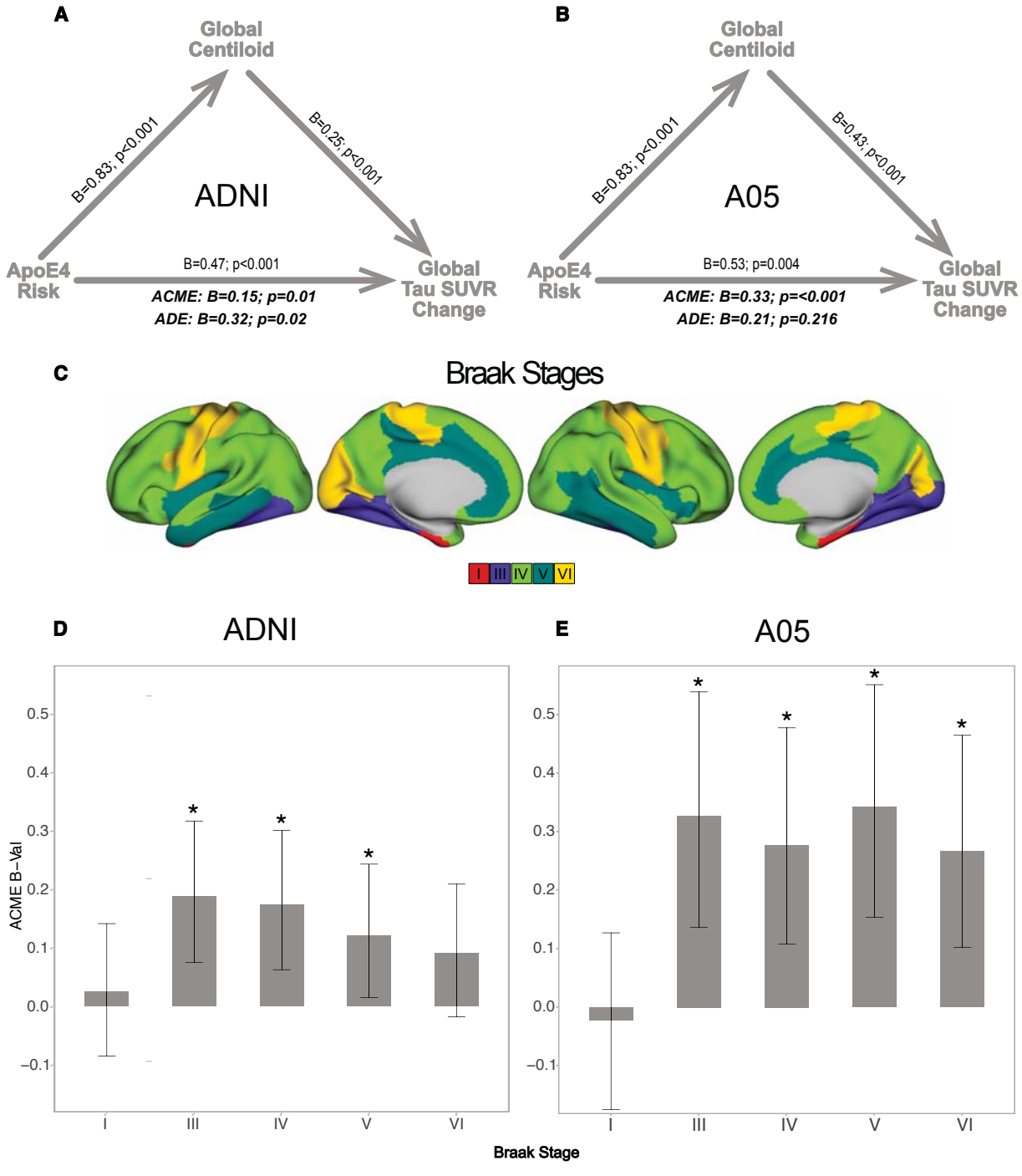
CI L 95% Confidence interval lower, CI U 95% Confidence interval upper

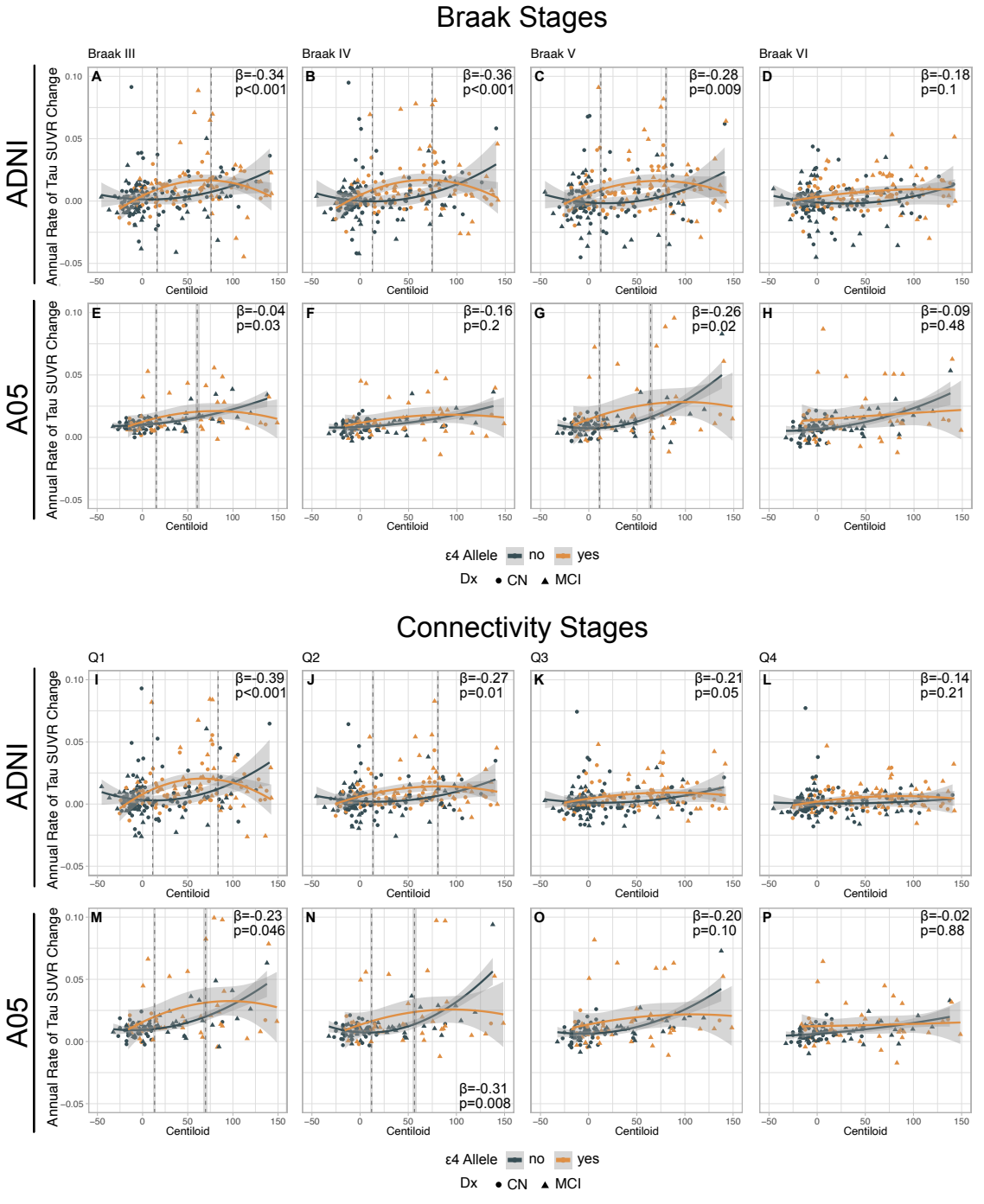
Values derived from regressions fitted with the interaction effect of ApoE4 risk and Centiloid^2 on the rate of annual tau accumulation in respective Braak stages and connectivity stages in ADNI and A05. Lower and upper cut-points means and CI values estimated through selecting the point of no overlap of 95% and re-overlap of confidence intervals of bootstrapped regressions. The table displays standardized β-estimates, T-values, p-values and partial R squared values. The regression models are controlled for age and sex. Additional regression models correcting for diagnosis are shown in supplementary eTable 4.

* indicate p-values that fall below an FDR-corrected p-threshold of 0.05.

614


A
Baseline Tau-PET SUVR
ε4 Carriers
Non-Carriers
CN
MCI
CN
MCI
ADNI
65
42
87
43
Tau-PET SUVR Value
0.7
pathological
1.5
B
Annual Tau-PET SUVR Change
ε4 Carriers
Non-Carriers
CN
MCI
CN
MCI
65
42
87
43
Tau-PET SUVR Annual Change
0
0.04
C
Baseline Tau-PET SUVR
ε4 Carriers
Non-Carriers
CN
MCI
CN
MCI
A05
10
35
42
43
Tau-PET SUVR Value
0.7
pathological
1.5
D
Annual Tau-PET SUVR Change
ε4 Carriers
Non-Carriers
CN
MCI
CN
MCI
10
35
42
43
Tau-PET SUVR Annual Change
0
0.04
E
Baseline Tau-PET SUVR
ε4 Carriers –
Non-Carriers
ADNI
A05
237
130
Mean Tau-PET SUVR Difference
0
p<0.05 (FDR corrected)
0.2
F
Annual Tau-PET SUVR Change
ε4 Carriers –
Non-Carriers
ADNI
A05
237
130
Mean Tau-PET SUVR Annual Change Difference
0
p<0.05 (FDR corrected)
0.02


A
Global Centiloid
B=0.83; p<0.001
B=0.25; p<0.001
ADNI
ApoE4 Risk
B=0.47; p<0.001
ACME: B=0.15; p=0.01
ADE: B=0.32; p=0.02
Global Tau SUVR Change
B
Global Centiloid
B=0.83; p<0.001
B=0.43; p<0.001
A05
ApoE4 Risk
B=0.53; p=0.004
ACME: B=0.33; p=<0.001
ADE: B=0.21; p=0.216
Global Tau SUVR Change
C
Braak Stages
I III IV V VI
D
ADNI
ACME B−Val
0.5
0.4
0.3
0.2
0.1
0.0
−0.1
I III IV V VI
E
A05
I III IV V VI
Braak Stage


Braak Stages
Braak III
Braak IV
Braak V
Braak VI
ADNI
A05
Annual Rate of Tau SUVR Change
Centiloid
A β=-0.34 p<0.001
B β=-0.36 p<0.001
C β=-0.28 p=0.009
D β=-0.18 p=0.1
E β=-0.04 p=0.03
F β=-0.16 p=0.2
G β=-0.26 p=0.02
H β=-0.09 p=0.48
ε4 Allele no yes
Dx CN MCI
Connectivity Stages
Q1
Q2
Q3
Q4
I β=-0.39 p<0.001
J β=-0.27 p=0.01
K β=-0.21 p=0.05
L β=-0.14 p=0.21
M β=-0.23 p=0.046
N β=-0.31 p=0.008
O β=-0.20 p=0.10
P β=-0.02 p=0.88