Determinants of cognitive and brain resilience to tau pathology: a longitudinal analysis

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Abstract

Mechanisms of resilience against tau pathology in individuals across the Alzheimer's disease spectrum are insufficiently understood. Longitudinal data are necessary to reveal which factors relate to preserved cognition (i.e. cognitive resilience) and brain structure (i.e. brain resilience) despite abundant tau pathology, and to clarify whether these associations are cross-sectional or longitudinal. We employed a longitudinal study design to investigate the role of several demographic, biological and brain structural factors in yielding cognitive and brain resilience to tau pathology as measured with PET.

In this multicenter study, we included 366 amyloid-β-positive individuals with mild cognitive impairment or Alzheimer's disease-dementia with baseline [^{18}F]flortaucipir-PET and longitudinal cognitive assessments. A subset (n=200) additionally underwent longitudinal structural MRI. We used linear mixed-effects models with global cognition and cortical thickness as dependent variables to investigate determinants of cognitive resilience and brain resilience, respectively. Models assessed whether age, sex, years of education, *APOE*-ε4 status, intracranial volume (and cortical thickness for cognitive resilience models) modified the association of tau pathology with cognitive decline or cortical thinning.

We found that the association between higher baseline tau-PET levels (quantified in a temporal meta-region of interest) and rate of cognitive decline (measured with repeated Mini-Mental State Examination) was adversely modified by older age ($St\beta_{interaction}$=-0.062, P=0.032), higher education level ($St\beta_{interaction}$=-0.072, P=0.011) and higher intracranial volume ($St\beta_{interaction}$=-0.07, P=0.016). Younger age, higher education and greater cortical thickness were associated with

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better cognitive performance at baseline. Greater cortical thickness was furthermore associated with slower cognitive decline independent of tau burden. Higher education also modified the negative impact of tau-PET on cortical thinning, while older age was associated with higher baseline cortical thickness and slower rate of cortical thinning independent of tau. Our analyses revealed no (cross-sectional or longitudinal) associations for sex and *APOE*-ε4 status on cognition and cortical thickness.

In this longitudinal study of clinically impaired individuals with underlying Alzheimer's disease neuropathological changes, we identified education as the most robust determinant of both cognitive and brain resilience against tau pathology. The observed interaction with tau burden on cognitive decline suggests that education may be protective against cognitive decline and brain atrophy at lower levels of tau pathology, with a potential depletion of resilience resources with advancing pathology. Finally, we did not find major contributions of sex to brain nor cognitive resilience, suggesting that previous links between sex and resilience might be mainly driven by cross-sectional differences.

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Abbreviations: Aβ = Amyloid-β; APOE = Apolipoprotein E; AD = Alzheimer's Dementia; ICV = Intracranial volume; MCI = Mild Cognitive Impairment; MMSE = Minimental State Examination; PET = Positron Emission Tomography; ROI = Region Of Interest

Introduction

Of the two neuropathological hallmarks of Alzheimer's disease (AD), i.e., amyloid-β (Aβ) plaques and tau neurofibrillary tangles, tau pathology is more strongly associated with clinical disease severity[1-6] and neurodegeneration[7-9]. Although tau pathological changes, as measured with positron emission tomography (PET), explain substantial variance in cognitive decline[10,11] and brain

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atrophy[9,12], considerable interindividual differences remain. Cognitive resilience (CR) and brain resilience (BR), defined as the relative preservation of function (e.g. cognition) or brain structure (e.g. cortical thickness) in the face of AD pathology (e.g. tau pathology) [13-15] may explain these interindividual differences. Research on resilience to AD neuropathology has expanded in the past decade, given the limited success of pharmacological interventions and, thus, the demand for other avenues to promote successful cognitive aging. Resilience is a robust finding in the literature, yet its underlying mechanisms and/or associated factors are insufficiently understood. Current hypotheses involve several potential mechanisms, including a larger pre-existing neurobiological capital[16], a more efficient use of brain resources[17] and/or the additional recruitment of brain networks through compensatory processes[17,18].

Although there is a relatively large body of research on resilience determinants in AD, a substantial amount of it relies on cross-sectional data. Cross-sectional measures of cognitive performance and brain structure reflect the current (functional and structural) state of the brain. This state, however, is determined by each individuals' premorbid level (e.g. starting at a higher cognitive level or with more brain capital) and rate of cognitive decline or atrophy over time. For any factor associated with resilience cross-sectionally (i.e. doing better than expected at any given point in time), it is unclear through which pathway this is achieved. Longitudinal studies are needed to gain insight into whether determinants of resilience yield a baseline advantage (i.e., "difference in intercepts") or provide a longitudinal advantage (i.e., "difference in slopes"). These two pathways have also been described as "preserved differentiation" (i.e., intercepts differ but slopes are similar) versus "differential preservation" (i.e., slopes are [also] different) [19,20]. The importance of longitudinal designs has been recently emphasized in the consensus framework and guidelines elaborated by the Collaboratory on Research Definitions for Reserve and Resilience in Cognitive Aging and Dementia (https://reserveandresilience.com/framework/). Disentangling these relationships is important to fill the gaps in our current knowledge on mechanistic processes through which CR/BR factors facilitate resilience.

In the past years, the relationship of demographic (age and sex), genetic (*APOE*-ε4 genotype), neuroimaging (brain atrophy) and reserve-related (education, intracranial volume (ICV)) variables with cognitive performance, neuropathology and brain atrophy in AD has been thoroughly investigated. For example, previous studies showed a negative relationship between age and tau-PET load in clinically impaired individuals, with younger individuals presenting

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increased tau burden across neocortical regions[21-24] and higher tau accumulation rates[25,26]. Similarly, females showed increased tau burden (for different biomarkers), particularly at elevated amyloid levels or in the presence of an *APOE*-ε4 allele[27-29], and faster rates of tau accumulation[26]. In Aβ-positive individuals with symptomatic AD, *APOE*-ε4 carriership was associated with greater entorhinal cortex tau load[30,31] but with reduced neocortical tau and cortical thickness[30]. A higher level of education has been associated with an increased (and more widespread) tau-PET tracer uptake in AD individuals with similar cognitive impairment levels[32]. Nonetheless, to examine resilience mechanisms more definitively, it is important to investigate the role of these factors in the mismatch between pathologic burden, brain structure and cognition.

Therefore, in this longitudinal study we investigated whether age, sex, *APOE*-ε4 status, education, ICV and cortical thickness (in CR analyses only) relate to cognitive and brain resilience, with a focus on disentangling longitudinal from cross-sectional effects. Specifically, we evaluated (i) whether these variables moderate the association of baseline tau burden with longitudinal cognitive decline or cortical thinning and (ii) in the absence of moderation, whether they are directly related to rates of change above and beyond the effects of tau, or rather, to cross-sectional cognition and cortical thickness.

Materials and methods

Participants

The present longitudinal study comprises a convenience sample from an ongoing multicenter study[33]. A total of 371 participants were included across 5 cohorts, i.e. the Swedish BioFINDER-1 study at Lund University (BF1, n=70), the University of California San Francisco AD Research Center (UCSF, n=30), the Alzheimer Disease Neuroimaging Initiative (ADNI, n=120) and the Avid Radiopharmaceuticals studies (participants from A05, n=72 and LLCF, n=79). All selected participants underwent a ^{18}F-flortaucipir PET (tau-PET) scan between November 2014 and May 2019, a medical history assessment and neurological examination, structural MRI and neuropsychological assessments including the Mini-Mental State Examination (MMSE). We included Aβ-positive individuals with mild cognitive impairment [MCI], n=152) and AD-type dementia (n=219) >50 years at time of tau-PET. Aβ-positivity was defined using either CSF or Aβ-

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PET, according to previously established thresholds[26,33] (**Supplementary Table-1**). For the CR analyses, we selected individuals who had at least two MMSE cognitive assessments available, with the first assessment within 12 months from the tau-PET scan (CR sample, n=366). A sub-sample that underwent at least two MRI scans (with the first scan within 12 months from tau-PET) was used to investigate brain resilience (BR sub-sample, n=200, all but 5 overlapped with the CR sample). Written informed consent was obtained from all participants within each study and studies were approved by local institutional review boards for human research at each site.

PET acquisition and processing

Tau-PET images with [^{18}F]flortaucipir were acquired on different PET scanners across cohorts, including Discovery 690 PET scanner (GE Healthcare) in BioFINDER-1 (http://biofinder.se), Biograph 6 Truepoint PET/CT scanner (Siemens) in UCSF[34] and multiple scanners in the multicenter ADNI (http://adni.loni.usc.edu) and the AVID Radiopharmaceuticals studies[35]. At each site, PET data were reconstructed into 4x5-minute frames within the 80- to 100-minute interval after bolus injection of the tracer and images were resampled to a standard size (128x128x63 matrix with voxel size 2x2x2 mm). PET images were then centrally processed at Lund University[33], undergoing motion correction with AFNI 3d volume registration[36], calculation of mean time and rigid coregistration to the skull-stripped MRI scan[37]. Standardized uptake value ratio (SUVR) images were calculated by normalizing to uptake in the gray matter of the inferior cerebellum reference region. The cross-sectional FreeSurfer parcellation of the T1-weighted MRI scan in the participants' native space was used to extract mean regional SUVRs in 68 cortical regions-of-interest (ROIs) delineated in the Desikan-Killiany atlas. For our main analyses, we calculated a measure of tau uptake in a temporal meta-region of interest (temporal meta-ROI)[38] as the volume-weighted average SUVR of amygdala, entorhinal, parahippocampal, fusiform, inferior and middle temporal regions, and a measure of global tau uptake[39] as the volume weighted-average SUVR across the whole cortex. We selected these two regions as we expect them to provide complementary information. The temporal meta-ROI captures tau in earlier stages, however, with the possibility to become saturated in more advanced cases, whereas the global composite is at risk of signal dilution across the entire cortex, especially in individuals in the lower tau-PET range. We used partial volume (PV)-uncorrected data in the analyses reported in the main text, and PV-corrected data in sensitivity analyses. Briefly, we used the Geometric Transfer Matrix[40] partial

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volume correction with a 5mm FWHM Gaussian kernel across all the FreeSurfer ROIs. Furthermore, in a secondary analysis, we explored regional effects using tau-PET SUVR across all 68 cortical ROIs.

MRI acquisition and processing

As described in previous studies[26,33], structural T1-weighted MRI scans were acquired on a 3-T Tim Trio or Skyra scanner (Siemens) in BioFINDER-1, a 3-T Tim Trio or Prisma scanner (Siemens) at UCSF and multiple scanners in the multicenter ADNI and AVID Radiopharmaceuticals studies. MP-RAGE images were processed centrally (at Lund University) with a previously described[30] FreeSurfer-based image analysis pipeline (http://surfer.nmr.mgh.harvard.edu/; v6.0). Briefly, images underwent correction for intensity homogeneity, removal of non-brain tissue and segmentation into gray matter and white matter. Cortical thickness was calculated as the distance from the GM/WM boundary to the corresponding pial surface. Cortical thickness was extracted for the Desikan-Killiany atlas-based regions of interest[41]. Segmented data were visually inspected for accuracy and segmentation errors were corrected. Cross-sectional measures of cortical thickness and ICV were calculated from the processed baseline MRI scans. Two MRI measures of cortical thickness, comparable to the tau-PET composite ROIs, were used as predictors in the CR models (i.e. cortical thickness as determinant of CR). An "AD-signature" ROI was calculated by averaging cortical thickness across bilateral entorhinal, fusiform, inferior and middle temporal cortices[38]. A measure of global cortical thickness was calculated as the surface area-weighted average across all cortical ROIs[39]. Additionally, we explored regional effects in a secondary analysis using cortical thickness in all 68 cortical ROIs.

For the study of brain resilience, we used longitudinal MRI scans collected for the individuals in the BR sub-sample to derive longitudinal cortical thickness measures. These longitudinal variables serve as outcomes in the BR models (i.e. see Statistical analysis section). Images were processed with the longitudinal FreeSurfer pipeline[42]. We calculated the two composite measures described above, AD-signature and global cortical thickness, for all available time points.

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Cognitive data

We selected MMSE[43] for global cognition, the only test that was consistently administered across all included cohorts. All available longitudinal MMSE scores were collected for the participants in the CR sample (i.e., with at least one follow-up after the baseline assessment). We considered the MMSE score closest in time to the tau-PET scan as baseline (median time lag: 0.0±2.2 months, IQR: 1 month, range: -12–+9 months).

Cognitive resilience and brain resilience

We operationalized CR and BR as the degree to which either cognition or cortical thickness showed relative preservation over time given the degree of tau pathology observed at baseline. Our operationalization closely follows the definitions of cognitive reserve/brain maintenance proposed by the Collaboratory on Research Definitions for Reserve and Resilience in Cognitive Aging and Dementia (https://reserveandresilience.com/framework/), however, we call it "resilience" for two reasons. First, we aim to conceptualize resilience as the "response" of the brain (or rather the relative lack of response in the measured outcomes) to accruing neuropathology, while remaining agnostic to the underlying mechanism. Second, resilience is a "relative" term that implies a continuum, which is in line with how our statistical models (explained below) infer resilience as the deviation in outcome from a normative curve of "expected decline/cortical thinning" for a given level of pathology. Furthermore, in this manuscript we investigate resilience to tau pathology, hence, the use of "resilience" in later sections of this manuscript refers to tau pathology specifically. To examine the role of different variables, i.e. age, sex, *APOE*-ε4 status, education, ICV and cross-sectional cortical thickness (for cognition), we followed the recommended analyses in the framework. First, we assessed whether the effect of tau load on rate of change in cognition (in CR) or cortical thickness (in BR) was moderated by the possible determinant. In absence of moderation, we further investigated whether the determinant/predictor of interest was associated with the rate of change in cognition or cortical thickness "over and above" tau pathology.

Determinants

Socio-demographic and genetic variables were collected at the time of enrollment in each cohort. For the current study, age (in years) was defined as the age at the time of the tau-PET scan and self-reported sex was a dichotomous variable (female/male). Education represents the number of

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years of formal education. APOE-ε4 status was defined as a binary variable indicating the presence or absence of at least one ε4-allele. Intracranial volume (expressed in dm3) was generated through FreeSurfer (i.e. estimated eTIV) from the baseline MRI. Cortical thickness (as a determinant in CR analyses) was measured as the baseline cortical thickness (in mm) in the AD-signature composite region.

Statistical analysis

All statistics were done using R (v4.0.3, The R Foundation for Statistical Computing) and statistical significance was set at $p<0.05$, two-sided.

Primary analyses

We used linear mixed-effects models to investigate the association of determinant variables with cognitive and brain resilience, as these models can handle differences in follow-up times among participants. To examine determinants of CR, we fitted (separate) models with longitudinal MMSE as outcome and age, sex, *APOE*-ε4 status, education, ICV and AD-signature cortical thickness as predictors-of-interest. First, a full model was assessed that included a three-way interaction between time (defined as years from each participant's tau-PET scan), tau-PET SUVR and the predictor-of-interest, as well as all the lower-order and cross-sectional terms (see models in **Supplementary Table-2**). The three-way interaction term (time*tau*predictor) tests whether the predictor-of-interest moderates the effect of tau load at baseline on cognitive decline, in other words, whether the association between baseline tau-PET and rate of change in cognition is different at different levels of the hypothesized CR determinant variable. In the absence of a moderation effect (defined as a statistically non-significant [i.e., $p>0.05$] three-way interaction coefficient), we subsequently removed this term and instead assessed the association of each predictor-of-interest with cognitive decline in the presence of tau, by evaluating the time*predictor interaction term. Moreover, in the final models, we also evaluated the cross-sectional association of each predictor with cognition, by examining its conditional main effect (i.e. the association of the predictor with MMSE for an average tau-PET level at baseline). We fitted separate models for temporal meta-ROI tau-PET and global tau-PET. Similarly, we investigated the association of age, sex, *APOE*-ε4 status, education and ICV with brain resilience in the BR sub-sample, fitting linear mixed-effects models with longitudinal cortical thickness as outcome variable and following the same approach described for CR. We fitted separate models for temporal and global composite

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regions, i.e. we used AD-signature cortical thickness in models that included the temporal meta-ROI tau-PET as measure of pathology, and global cortical thickness in models with global cortical tau-PET. All CR and BR models were adjusted for cohort (i.e., they included a time*cohort term) and were fitted with the restricted maximum likelihood estimation using the lme4 package in R. The full models included a random intercept per patient and we tested whether the inclusion of a random slope for time was the best fit to the data using the likelihood ratio test (note that this was the case for all except the BR models with longitudinal global cortical thickness as outcome variable). Confidence intervals were calculated with Wald statistics using the Satterthwaite approximation for denominator degrees of freedom. Models were initially fitted with continuous predictors centered (except time). In order to have a more comparable effect size across determinants, we estimated standardized coefficients by standardizing (i.e. z-scoring) dependent variables (i.e. MMSE and cortical thickness) and continuous predictors (i.e. tau SUVR, age, education, ICV, cortical thickness) using the mean and standard deviation of each variable at baseline.

For visualization purposes, we estimated the annual change in MMSE (points per year) and the annual change in cortical thickness (mm per year) for each individual via a linear regression fitted across their respective repeated measurements over time. These individual-level slopes were used in descriptive figures and to display interactions (where indicated in the figure legend). To visualize model-estimated interactions stratified for different tau burden and determinant levels, we used the fitted models to predict trajectories of decline for representative values (i.e. low/intermediate/high, selected as the mean value within tertiles of each variable).

Secondary analyses

Additionally, we performed a regional analysis in which we explored possible interactions of our determinants of interest with regional tau pathology across all 68 cortical ROIs from the Desikan-Killiany atlas (i.e. we repeated the primary analysis with tau-PET in each ROI). To assess localized effects on CR, we fitted (separate) linear mixed-effects models with MMSE as outcome and a three-way interaction between time, tau-PET uptake in a given ROI and the predictor of interest, adjusted for cohort, including random intercepts and random slopes. For the BR analyses, we paired the outcome with the tau-PET ROI, therefore using as outcome variable longitudinal cortical thickness in the same ROI. We applied a correction for multiple comparisons per outcome (CR/BR)

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across all predictors and regions, using the Benjamini-Hochberg procedure with a false discovery rate Q value of 5%[44]. We present the regions that survived the multiple comparison correction in the main text and report all uncorrected results in supplementary material.

Sensitivity analyses

We reanalyzed the main models with several variations: using PV-corrected tau-PET data, adjusting additionally for sex, follow-up time and diagnosis (MCI or AD) alongside cohort, and restricting the sample to only those individuals followed for more than 18 months. These analyses were performed and plotted in the form of specification curves[45] and their main purpose is to assess whether the primary results are robust to these methodological decisions.

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Results

Participant characteristics

Characteristics of the CR sample participants are presented in **Table-1**, while the BR sample participants are presented in **Supplementary Table-3**. Additionally, histograms/bar plots of relevant variables stratified per cohort are shown in **Supplementary Figure-1**. Raw associations of the determinant variables with tau-PET burden, cognitive decline rate and cortical thinning rate are illustrated in **Supplementary Figure-2**. The CR sample included a total of 366 individuals across all cohorts (average age 73.2[8.5] years, 49.5% male, average MMSE score 24.2[4.2]), of which 41.3% were diagnosed with MCI and 58.7% with AD dementia. The BR sub-sample demographics were broadly representative of the larger CR sample (average age 72.5[8.8)] years, 52.5% males, average MMSE score 24.9[4.1]), although individuals with longitudinal MRI were in less advanced disease stages (i.e., 56.5% MCI and 43.5% AD dementia participants) and therefore showed less pathology and decline (**Supplementary Table-3**). Median follow-up was 18 months (range: 8-72 months) for the CR sample (i.e. MMSE follow-up) and 18 months (range:9-63 months) for the BR sub-sample (i.e. MRI follow-up) (**Supplementary Figure-3**).

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Cognitive resilience

Linear mixed-effects models with a three-way interaction between time, tau and each predictor tested whether the variables under investigation moderate the relationship between tau pathology and cognitive decline, as well as their main cross-sectional effects at average levels of tau burden (i.e. conditional main effects). Tau uptake in the temporal meta-ROI showed a significant negative association with cognitive decline ($p<0.001$ in all models, **Figure-1**). Significant interaction terms indicated that older age (stβ[95%CI]=-0.062[-0.118 – -0.006], p=0.032), higher education (stβ[95%CI]=-0.072[-0.127 – -0.017], p=0.011) and higher ICV (stβ[95%CI]=-0.07[-0.126 – -0.014], p=0.016) were associated with a stronger (more negative) effect of temporal meta-ROI tau burden on longitudinal decline in MMSE (**Table-2, Figure-2 A,C,E;**. these effects were additionally plotted as a function of tau level in **Figure-2 B0,D,E)**. All three variables also moderated the association of global tau-PET SUVR with cognitive decline (**Supplementary Table-4**). These models additionally revealed a conditional main effect of age (stβ[95%CI]=-0.16[-0.265 – -0.054], $p<0.01$) and education (stβ[95%CI]=0.217[0.114 – 0.319], $p<0.001$) on cross-sectional (i.e. baseline) levels of cognitive performance. Thus, at a given level of tau pathology (i.e. average level), being older at the time of the tau-PET was associated with worse cognitive performance (**Figure-2B**). In contrast, higher education was associated with better cross-sectional cognition (**Figure-2D**), while higher ICV was not related to cognitive performance at baseline (**Figure-2F**). There was no significant interaction with tau burden for cortical thickness, sex and *APOE*-ε4 status. In models in which these interaction terms were removed, greater cortical thickness was related to better cross-sectional cognition and slower longitudinal cognitive decline, above and beyond tau. Sex and *APOE*-ε4 status did not contribute to (cross-sectional nor longitudinal) cognition independent of tau (**Table-2**).

Using linear mixed models we explored interactions of predictors-of-interest with regional tau burden across 68 ROIs on cognitive decline. After multiple comparison correction, age interacted with tau burden in the left isthmus and posterior cingulate cortex, as well as left frontal and parietal regions (ROIs and statistics reported in **Figure-4**, **Supplementary Table-6**), indicating a greater impact of regional tau on cognitive decline in older individuals (**Figure-4B**). The regional analysis additionally revealed a positive interaction effect of *APOE*-ε4 status with tau burden in the entorhinal cortex, with carriers of the ε4-allele having an attenuated effect of regional

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tau on global cognitive decline (**Figure-4C**). For the other ROIs and factors investigated, no associations were found that survived FDR correction (**Supplementary Table-6**, **Supplementary Figure-4**).

Brain resilience

Linear mixed-effects models with longitudinal cortical thickness as outcome and a three-way interaction (time*tau*predictor) investigated moderating determinants of BR. Tau uptake in the temporal meta-ROI was significantly negatively associated with cortical thinning in the AD-signature composite region ($p<0.001$ in all models, **Supplementary Figure-5**). Models fitted for each determinant-of-interest revealed a significant moderation effect of education (stβ[95%CI]=-0.037[-0.065 – -0.008], p=0.013) on the relationship between temporal meta-ROI tau and AD-signature cortical thinning (**Table-3**). Higher education was associated with a stronger effect of tau burden on atrophy (**Figure-3**). None of the other investigated variables moderated this relationship. In models that estimated main effects (i.e. after removing the three-way interaction term), older age was related to thinner cross-sectional AD-signature cortex (stβ[95%CI]=-0.49[-0.613 – -0.366], $p<0.001$) and to accelerated cortical thinning (stβ[95%CI]=-0.051[-0.083 – -0.02], $p<0.01$) independent of temporal meta-ROI tau. None of the other variables showed a statistically significant association with longitudinal cortical thinning or cross-sectional cortical thickness (**Table-3**). Results of analyses with global tau burden were consistent with these findings (**Supplementary Table-5**).

In the region-wise analysis, after multiple comparison correction, none of the predictors investigated showed a localized interaction between cortical tau burden and cortical thinning in the same region (**Supplementary Table-7**, **Supplementary Figure-6**).

Sensitivity analyses

We performed a series of sensitivity analyses and report the results in **Supplementary Figures-7,8**. Main effects reported in the manuscript remained the same when using partial volume corrected tau-PET data, and when additionally adjusting our linear mixed-effect models for sex or diagnosis, demonstrating the robustness of the results.

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Discussion

The current study investigated determinants of cognitive and brain resilience to tau pathology in symptomatic AD using a longitudinal design. The primary analyses revealed that, in our sample of Aβ-positive MCI and AD-type dementia individuals, older age, higher education and higher intracranial volume exacerbated the impact of (temporal and neocortical) tau burden on subsequent decline in global cognition. In other words, and as depicted in **Figure-2B,D,F**, this interaction signifies that the differential association of these determinant variables with rate of cognitive decline becomes (more) negative with increasing levels of tau pathology. Younger age and higher education were, however, associated with better cognitive performance at baseline. Greater cortical thickness at baseline was associated with both better cross-sectional cognition and slower longitudinal cognitive decline, contributing to these outcomes above and beyond tau pathology. Education also moderated the effect on longitudinal cortical thinning, with higher education enhancing the negative impact of tau load on subsequent brain atrophy. While there was no evidence for age as a moderator in BR models, older age was associated with lower cortical thickness at the time of the tau-PET scan, and with faster cortical thinning over time. Importantly, we did not find major contributions of sex and *APOE*-ε4 status to neither brain nor cognitive resilience.

Determinants of resilience can facilitate the preservation of cognition/brain structure through two pathways. Firstly, they may provide a baseline (cross-sectional) advantage, likely reflecting a combination of genetic and developmental factors that results in higher pre-morbid cognitive performance (for CR) and thicker neocortex (for BR). This initial advantage may lead to a longer runway of decline, simply because there is a greater quantity of cognitive ability and brain integrity to lose. Secondly, protective factors could act by modifying the rate of change in the outcome, potentially involving more active mechanisms of preservation (e.g. compensatory mechanisms). These two hypothetical models are represented in **Figure-5A,B**. An initial difference in intercepts in the outcome variable that is preserved over time (i.e. with advancing pathology) constitutes the "preserved differentiation" model, while a differential rate of decline for low vs. high levels of the determinants represents the "differential preservation" model[19,20]. We further propose two additional theoretical scenarios (**Figure-5C,D**) based on the current findings. In the "enhanced differentiation" model, an initial difference in intercepts is enhanced over time given

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also a (positive, i.e. protective) differential association of the determinant with the decline rate (e.g. the relationship observed for age). On the other hand, a positive association with the intercept but a negative association with the rate of decline would suggest a "reduced differentiation" model (e.g. education).

Education

One of our main findings is the adverse moderating role of education on the impact of tau pathology on longitudinal decline in global cognition. Education is widely known in the resilience literature as it has been consistently associated to better outcomes in AD and is, therefore, the most commonly used proxy to index the related construct of cognitive reserve[16,17,46]. Multiple studies have related a higher educational attainment to reduced risk of dementia[47,48] and mortality[49], to delayed symptom onset[50] and to an attenuated effect of neuropathology on cognitive performance[51], suggesting an initial protective effect in the disease continuum. This protective effect seems to be, however, reversed with advancing disease trajectory, with higher education being associated with steeper declines[49,52-54]. While previously described for brain atrophy[49], the current study shows this paradoxical effect with tau pathology quantified with *in vivo* tau-PET imaging. In line with previous literature, our results revealed a positive association between education and cross-sectional cognition at similar levels of tau (i.e. difference in intercepts), but a detrimental interactive association between education and tau burden on cognitive decline (i.e. also a difference in slopes). Higher educational attainment strengthened the (negative) effect of tau pathology on rate of decline. In other words, higher educated individuals seem to be on an accelerated decline path compared to lower educated individuals at similar tau pathology levels. Our results are consistent with a study in which education similarly adversely moderated the impact of brain atrophy on cognitive change[55]. Given the positive baseline association but the negative moderation effect, the association of education with cognition and decline in the presence of tau pathology can be best summarized as "reduced differentiation" (**Figure-5D**). We note, however, that the current literature remains somewhat mixed, as other studies did not find an interactive association between education, neuropathology and cognitive trajectories[56,57]. Our results suggest, together with extensive literature, that education may be a protective factor in earlier phases of the disease, e.g. likely before substantial accumulation and spread of tau pathology, but not in advanced disease stages. This protection is presumably achieved through a combined effect of genetics,

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developmental and life-style factors, given that education is highly correlated with variables such as premorbid IQ[58,59], socioeconomical status[60], more favorable lifestyle choices or better access to healthcare[61], resulting in a higher premorbid level of cognitive performance and in a compression of morbidity.

Education also modified the association of tau burden with cortical thinning, though the role of education in brain resilience is less straightforward. According to our results, education enhanced the negative impact of tau pathology on longitudinal brain atrophy. In other words (and as observed in **Figure-3B**), a higher educational level was associated with faster cortical thinning at higher levels of tau pathology. This association is reminiscent of a differential preservation scenario (**Figure-5B**), given that there was no difference in intercepts but there was a differential association with rate of cortical thinning (with the higher educated however declining faster at higher levels of pathology). The lack of an association with atrophy rate at low levels of pathology are in line with studies that have disputed education being related to slower rates of gray matter volume loss in normative aging[62,63]. Nonetheless, our results suggest a detrimental association at high levels of tau pathology. This is in contrast to a study[64] that found a protective effect of education on the cross-sectional metabolic neuronal function in response to pathological tau. Still, previous literature on the relationship between education, pathology and brain atrophy remains scarce.

Intracranial volume

Alongside education, intracranial volume has received ample attention as a measure of premorbid brain size[16,65], as it is presumed to reflect maximal neurobiological capital available (e.g. number of neurons or synapses) before the emergence of neuropathology and associated brain changes. Previous literature has suggested a protective role of ICV in cognitive resilience to AD, with some studies showing more positive clinical outcomes with larger premorbid brain size[66]. In our models, a larger ICV was associated with a more negative impact of tau burden on cognitive decline. Furthermore, at average levels of tau, ICV was not associated with baseline cognition, in contrast to other studies that have shown an association between ICV and higher premorbid cognition in the presence of brain atrophy[16,49]. Our results are, therefore, most suggestive of an inverted version of the differential preservation pattern shown in **Figure-5B.**

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Sex

Sex differences in AD neuropathology burden and its subsequent clinical manifestation have been previously reported. Women, and more specifically amyloid-positive or *APOE*-ε4 carriers, show higher burden of pathological tau and faster accumulation rates measured with either CSF[67,68] or tau-PET[69] than men. Furthermore, female sex has also been associated with a faster CSF tau-mediated cognitive decline and hippocampal atrophy over time[70]. Another study, though, suggested that at similar levels of tau-PET burden, women showed higher cortical thickness across the neocortex, indicative of a protective role in brain resilience[39]. In the current study, while there was an overall difference in tau burden in line with previous literature, with females showing more tau-PET signal than males (**Supplementary Figure-3**), sex was not a determinant of either cognitive or brain resilience. In other words, our models did not support a moderation by sex of tau burden on either cognitive decline or cortical thinning. Furthermore, we did not observe cross-sectional nor longitudinal associations with the two outcomes.

Age and cortical thickness

Age and cortical thickness also contributed to CR, in line with expectations. Younger age and higher cortical thickness at the time of tau-PET were associated with better baseline cognition and slower rate of decline among individuals with similar pathological tau burden. Also longitudinally, younger age attenuated the impact of tau burden on cognitive decline rate. This moderation was also observed in the regional analysis, where younger age attenuated the effects of tau pathology in left-hemisphere cingulate and parietal regions on global cognition decline. Our results also suggest that age also plays a role in preserving brain structure in the face of tau pathology. While we previously reported on the baseline association of age with brain resilience[39], in this study we extend those findings by showing a longitudinal additive (but not interactive) effect of age in BR. Despite the robust negative cross-sectional association of age with tau burden[24,25] in cognitively impaired populations, indicative of more severe tau pathology in individuals with earlier disease onset, we found that younger age was associated with both higher baseline cortical thickness and slower rate of cortical thinning at similar levels of tau burden. The association of age and cortical thickness with both longitudinal cognition and atrophy is best conceptualized by the enhanced differentiation model (**Figure-5C**). These findings are not surprising, as age and cortical thickness likely capture aging-related and other pathological-processes[71] that result in a faster atrophy rate

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and worsened cognition and subsequent decline. Furthermore, younger individuals may present more preserved cellular repair mechanisms[72] contributing to their increased resilience level.

APOE-ε4 status

While we found no significant differential associations with resilience between the *APOE* genotype groups (ε4 carriers vs. ε4 non-carriers) in our main analyses, *APOE*-ε4 carriers showed an attenuated effect of local tau in multiple medial-temporal regions (of which the entorhinal cortex survived FDR-correction) on cognitive decline in the region-wise analysis. This seems counterintuitive as carriers of an ε4 allele have been reported to harbor more tau pathology in the entorhinal cortex compared to non-carriers[30,73]. However, the same study showed that ε4 non-carriers tend to have more widespread tau pathology in neocortical regions such as the parietal lobe[30]. We speculate that the observed interaction effect could reflect that, at high entorhinal cortex tau burden, the *APOE*-ε4 negative group likely also has more widespread tau pathology resulting in accelerated cognitive decline (**Supplementary Figure-9**).

Strengths of this study include the availability of longitudinal cognitive and neuroimaging data to investigate and disentangle longitudinal vs. cross-sectional effects of different determinants and their role in cognitive and brain resilience to tau pathology. There are also several limitations. First, we used MMSE to measure cognition, as this was the only test available across cohorts. The MMSE is prone to ceiling effects and shows a curvilinear sensitivity to change[74]. Other neuropsychological tests with better psychometric properties could be used in the future to replicate these findings. Nonetheless, our sample consists of clinically impaired individuals potentially reducing the ceiling effect. Second, both a strength and a limitation is the inclusion of the BR sub-sample. Including individuals with at least two MRI scans allowed investigation of moderators of and factors associated with cortical thinning over time beyond tau pathology. However, this sub-sample is smaller than the main CR sample, resulting in possible differences in cognitive or pathological severity. Third, selecting MCI and AD individuals means excluding subjects with substantial neuropathology that were still cognitively unimpaired, leading to a potential selection bias towards less resilient participants. Furthermore, we did not select based on tau burden level, which means that our sample spans a wide range of tau load. While this is desired to ensure sufficient variance in the tau-PET variable, it means that we likely included subjects with no tau pathology. However,

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including only Aβ-positive cognitively impaired participants maximizes the probability of tau pathology being incipient/present. Additionally, compared to previous literature, this study includes a well-characterized sample regarding the underlying neuropathology with *in vivo* longitudinal assessments of brain atrophy and cognitive performance. Fourth, we used cross-sectional tau burden instead of longitudinal tau accumulation, a missing element to have a fully longitudinal design. Nonetheless, cross-sectional tau-PET uptake mirrors closely Braak staging of post-mortem tau neuropathology[75] and is also predictive of tau accumulation rate[25,35]. Additionally, we quantified tau burden in both a temporal ROI (capturing tau pathology in intermediated Braak stages) and a global composite ROI (reflecting the later-stage spread of tau pathology to neocortex). Fifth, this study's results suggest differential associations between the determinants and the degree of resilience with increasing levels of tau pathology, but we note that our sample included relatively few individuals in the high tau-PET range. Therefore, replication in larger populations with a wider range of tau-PET burden over longer time periods is needed. Similarly, we acknowledge that the available follow-up duration was relatively short on average, with differences among individuals. Nonetheless, we investigated that individuals with longer follow-up did not bias the results. Sixth, the relatively small sample of each cohort precluded proper investigation of effect heterogeneity across studies. Nonetheless, we note that all models were covaried for cohort. Seventh, we acknowledge that, although comparable across cohorts, the measure of years of education is not ideal as it does not accurately represent the quality and complexity of educational experience. Finally, we recognize that the relationship of the determinants with pathology and the outcomes of this study are complex (i.e., while some variables, e.g., age, APOE-e4 carriership, increase the risk of AD, they may behave differently as prognostic factors within symptomatic AD), challenging the interpretation of the results and the translation of these findings outside of symptomatic AD.

Understanding the relation (or lack thereof) of the factors investigated in this study with future cognitive decline and brain atrophy in AD has implications for clinical trials. With the advent of tau-targeted therapeutics, ongoing and future trials recruit individuals that already harbor (some) tau pathological changes in the brain. Being able to more accurately predict progression and decline, especially for the duration of the trial, is important in order to observe the potential benefits of medication on clinical outcomes and chose appropriate covariates in the efficacy analyses.

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Conclusion

In this longitudinal multi-cohort study of a clinically impaired sample with underlying AD neuropathology, we found that age, education, ICV and cortical thickness play a role in cognitive resilience, while age and education contribute to brain resilience. Of note, we show that level of education is positively associated with baseline cognitive performance while it negatively moderates the impact of tau burden (measured with in vivo tau-PET) on cognitive decline, in line with the paradoxical effect that has previously been documented with brain atrophy[55]. While previous literature suggested a role of sex in cognitive/brain resilience, we did not find major contributions of sex to neither of the two resilience phenotypes, suggesting that previous links might be driven by cross-sectional differences.

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Competing interests

D. Bocancea, A.L. Svenningsson, R. Smith, R. La Joie, H. Rosen report no competing interests.

OH has acquired research support (for the institution) from ADx, AVID Radiopharmaceuticals, Biogen, Eli Lilly, Eisai, Fujirebio, GE Healthcare, Pfizer, and Roche. In the past 2 years, he has received consultancy/speaker fees from AC Immune, Amylyx, Alzpath, BioArctic, Biogen, Cerveau, Fujirebio, Genentech, Novartis, Roche, and Siemens.

MJP is an employees of Avid Radiopharmaceuticals a wholly owned subsidiary of Eli Lilly and Company and a minor stockholder in Eli Lilly.

FB is in the Steering committee or iDMC member for Biogen, Merck, Roche, EISAI and Prothena, consultant for Roche, Biogen, Merck, IXICO, Jansen, Combinostics, has research agreements with Merck, Biogen, GE Healthcare, Roche, and is Co-founder and shareholder of Queen Square Analytics LTD.

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Supplementary material

Supplementary material is available at *Brain* online.

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Figure Legends

Figure 1 Association of baseline tau-PET burden with rate of cognitive decline, stratified per determinant of interest. For visualization purposes, annual change in MMSE (points/year) was calculated for each participant through an individual-level regression of all available MMSE observation on time (in years). Continuous determinants were divided in tertiles.

Figure 2 Cognitive resilience moderating determinants. This figure illustrates the statistical interaction of age (first row), education (second row) and ICV (third row) with temporal meta-ROI tau-PET burden on rate of cognitive decline. Model-predicted associations and trajectories for representative values (low, intermediate, high) are shown, where the three levels of tau burden and of determinants variables were defined as the average value within the tertiles for each variable (note that the linear mixed models with continuous predictors were used to predict the decline trajectories; the tertile mean representative values were selected as that allowed plotting of raw individual trajectories within each level of tau burden). Older age at baseline (**A, B**), higher education (**C, D**) and higher ICV (**E, F**) adversely modified the negative effect of tau-PET burden on rate of cognitive decline. Temporal meta-ROI tau uptake levels: higher = 2.2 SUVR, intermediate = 1.6 SUVR, lower = 1.2 SUVR. Age levels: higher = 82 years old, intermediate = 74 years old, lower = 64 years old. Education levels: higher = 18 years, intermediate = 15 years, lower = 11 years. ICV levels: higher = 1.64 dm3, intermediate = 1.45 dm3, lower = 1.29 dm3. Bars with star in panels **A**, **C** and **E** indicate regions of temporal meta-ROI tau-PET uptake values for which age, education and ICV were significantly associated with rate of cognitive decline, as derived from a Johnson-Neyman analysis on simplified models of MMSE slopes regressed onto the interaction between tau burden and each determinant. Note that this figure shows model-predicted relationships, in contrast to Figure 1 that plots relationships based on the raw data.

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Figure 3 Brain resilience moderating determinants. This figure illustrates the statistical interaction of education with temporal meta-ROI tau-PET burden on rate of cortical thinning in the AD-signature composite region. Model-predicted associations and trajectories for representative values (low, intermediate, high) are shown, where the three levels of tau burden and of education were defined as the average value within the tertiles for each variable (note that the linear mixed models with continuous predictors were used to predict the decline trajectories; the tertile mean values were selected as that allowed plotting of raw individual trajectories within each level of tau burden). (**A, B**) Higher education adversely modified the negative effect of tau-PET burden on rate of cognitive decline. Temporal meta-ROI tau uptake levels: higher = 2.1 SUVR, intermediate = 1.5 SUVR, lower = 1.2 SUVR). Education levels: higher = 18 years, intermediate = 16 years, lower = 12 years. Bar with star in panel **A** indicate regions of temporal meta-ROI tau-PET uptake values for which education was significantly associated with rate of cortical thinning, as derived from a Johnson-Neyman analysis on simplified models of cortical thinning slopes regressed onto the interaction between tau burden and education.

Figure 4 Regional interaction effects of investigated determinants with localized tau-PET uptake on rate of global cognitive decline. (**A**) Significant associations ($p<0.05$ uncorrected and FDR<0.05 corrected for multiple comparisons) between regional tau tracer binding and rate of change in MMSE. (**B**) Coefficients of the three-way interaction of age with local tau burden and time from (separate) linear mixed models across the 68 Desikan-Killiany atlas-based cortical regions of interest. Older age at baseline was associated with a strengthened negative effect of tau burden in the regions highlighted in blue on cognitive decline. (**C**) Coefficients of the three-way interaction of APOE-e4 genotype with local tau burden and time from (separate) linear mixed models across the 68 cortical ROIs. APOE-e4 positivity was associated with an attenuated effect of tau burden in the entorhinal cortex (region highlighted in red) on cognitive decline.

Figure 5 Theoretical scenarios depicting the relationship of the determinant variable (low/high) and rates of cognitive decline/atrophy. (**A**) Preserved differentiation is observed if an existing baseline difference in intercepts is preserved over time (i.e. slopes for the low/high groups

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are the same). (**B**) Differential preservation is observed, on the other hand, when, rather than a difference in intercepts, there is a differential association of the determinant with the decline rate. (**C**) Enhanced differentiation depicts the scenario in which the initial difference in intercepts is further enhanced (the lines diverge further) given also a "protective" relationship of the determinant with the slope. (**D**) Reduced differentiation illustrates the opposite case, in which the group starting higher at baseline declines faster with accumulating tau pathology, closing the gap between the two lines.

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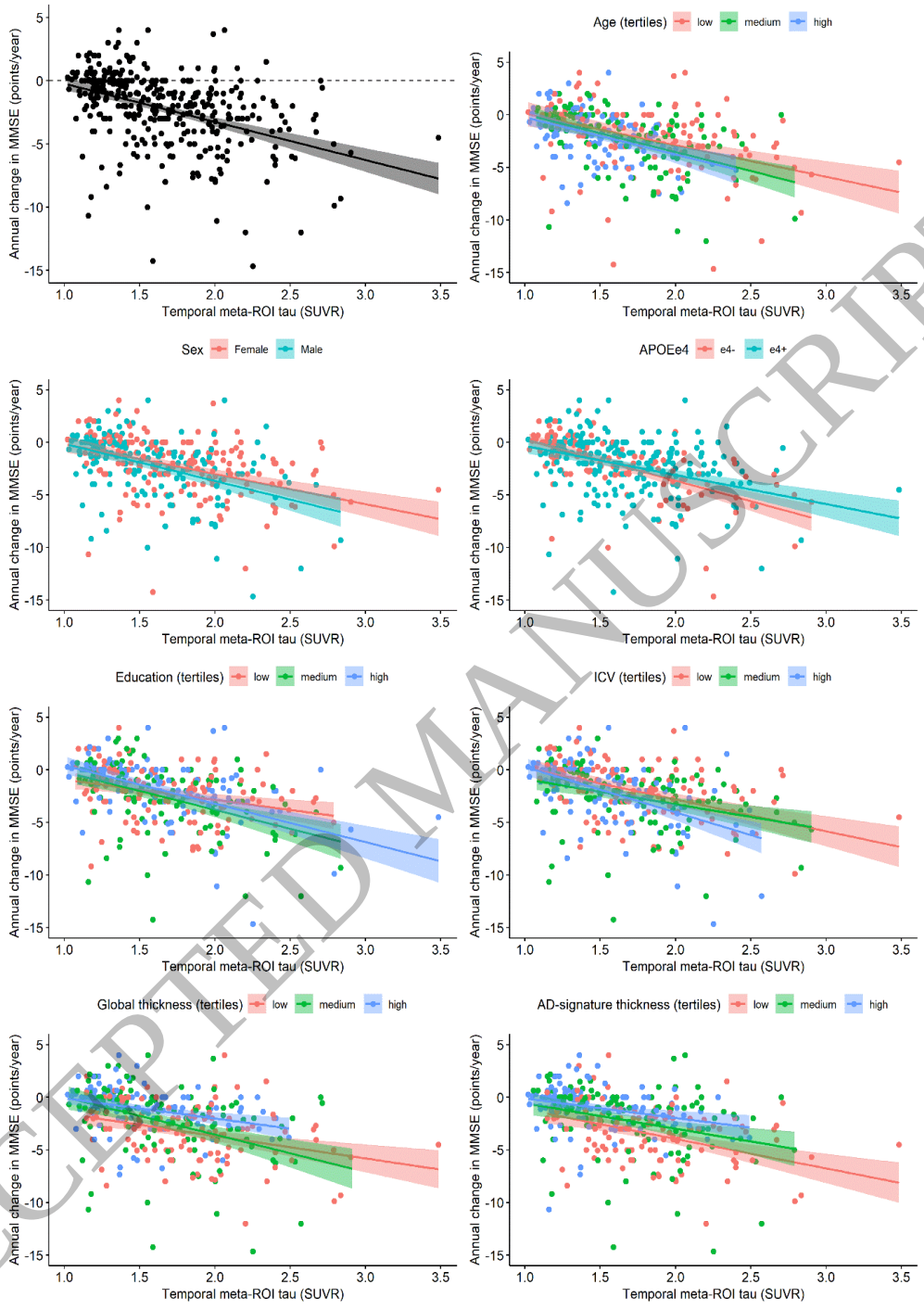

Figure 1
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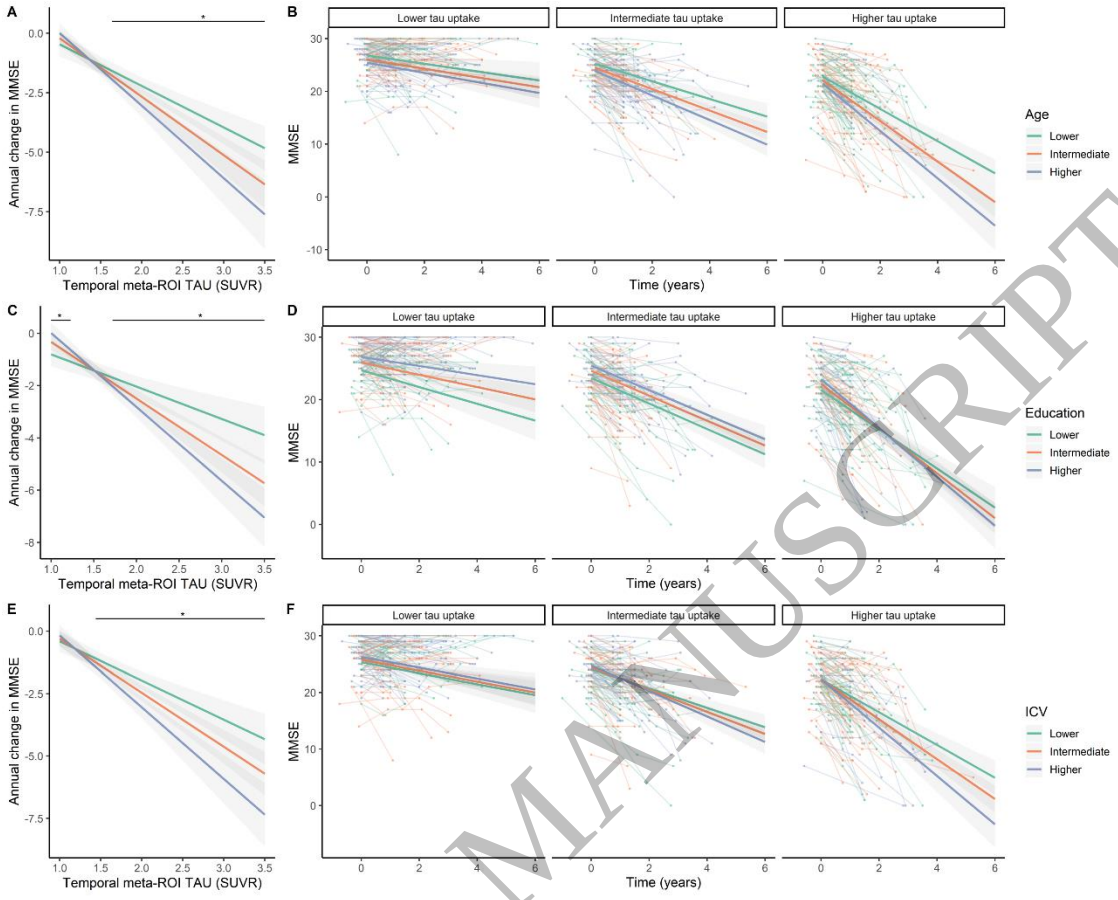

Figure 2
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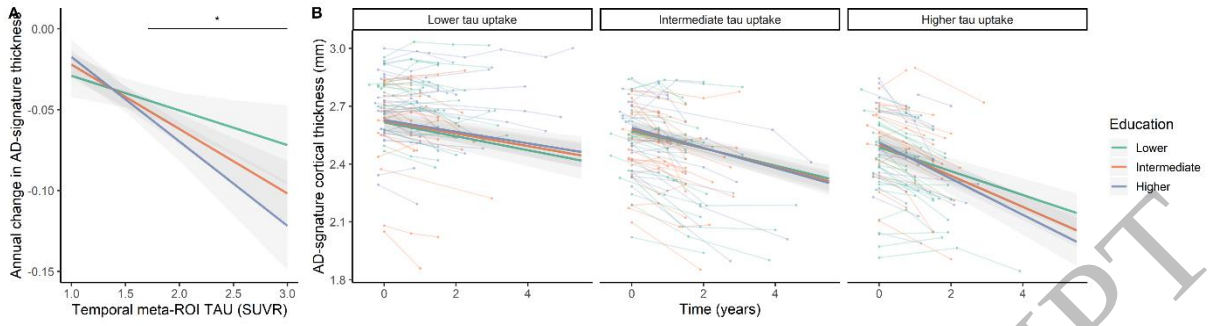

Figure 3
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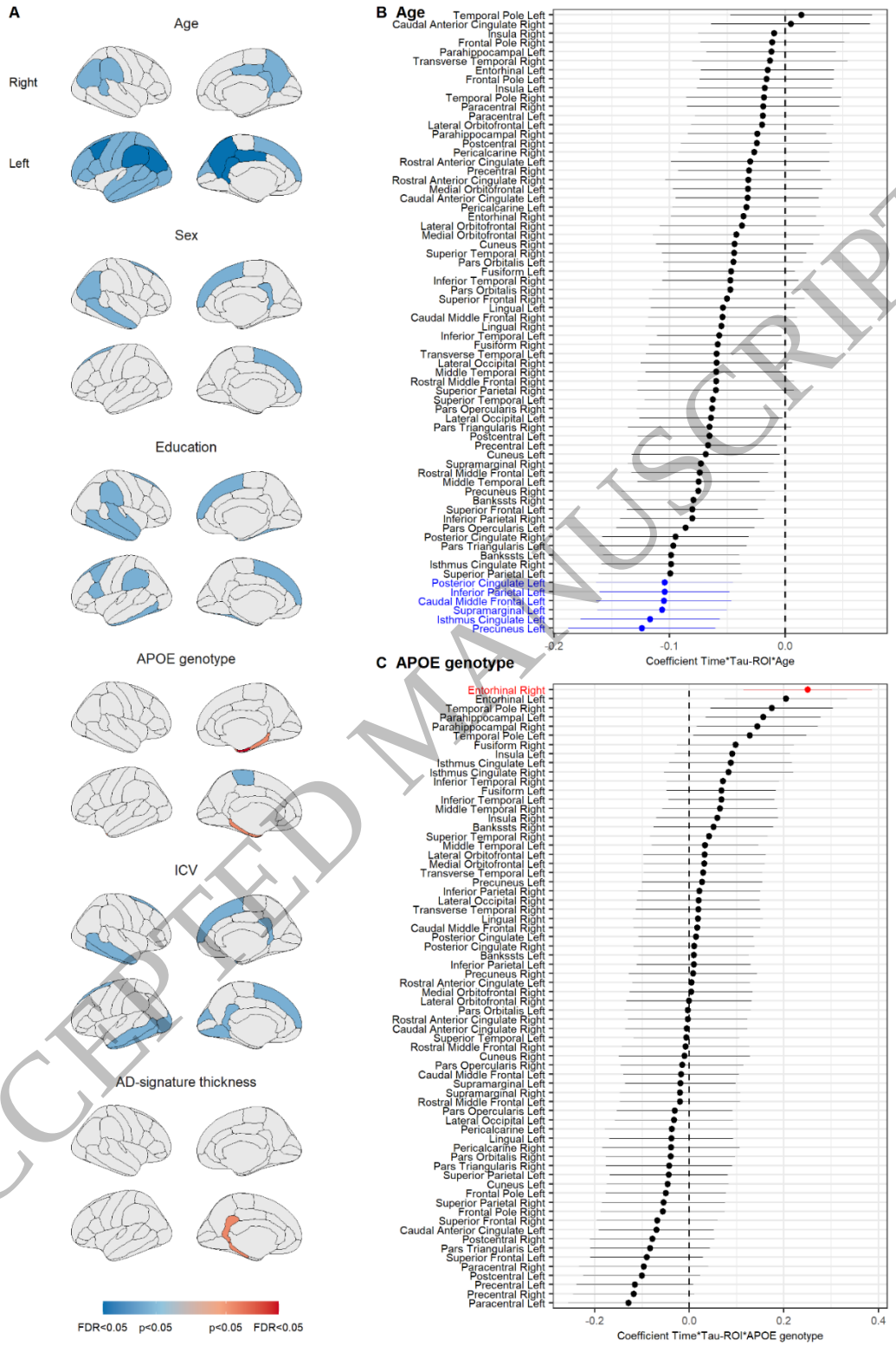

Figure 4
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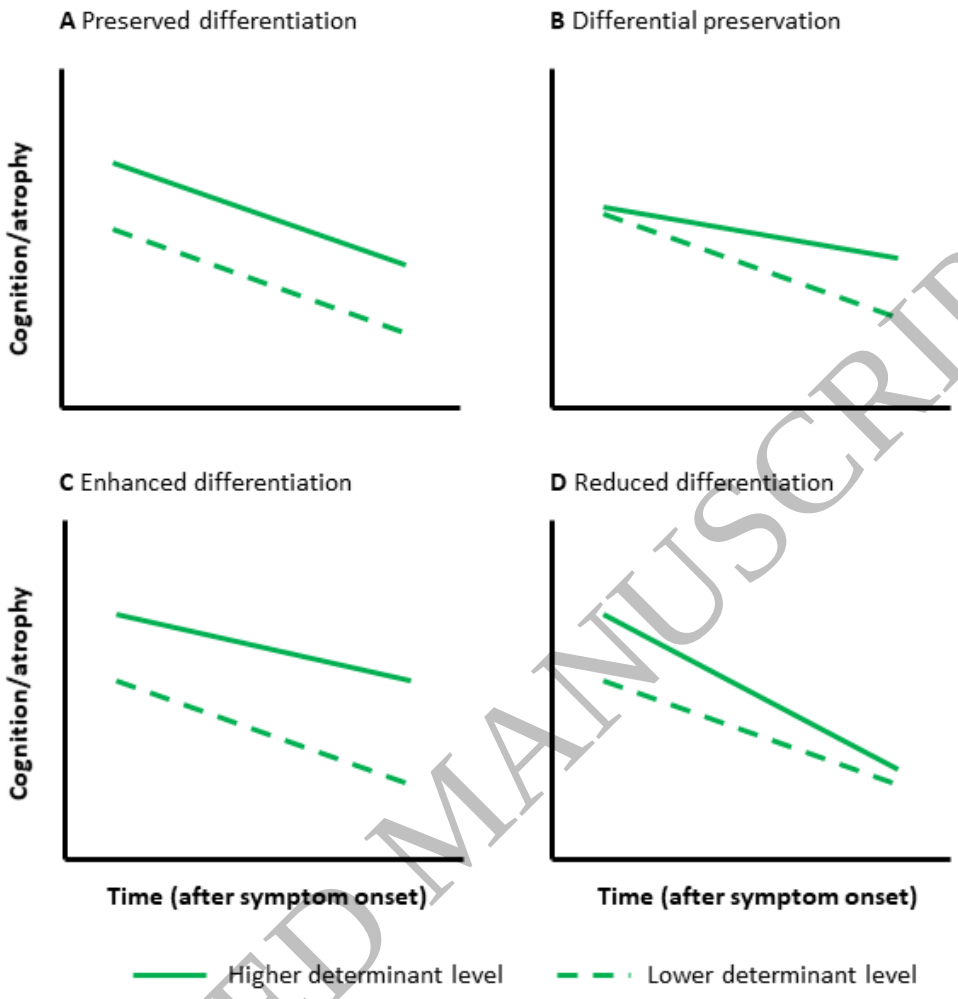

Figure 5
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Table 1 Demographic and clinical characteristics of the total sample (CR sample)

	CR sample
Total N	366
Study, n (%)	
ADNI	120 (32.8%)
AVID	147 (40.1%)
BFI	69 (18.9%)
UCSF	30 (8.2%)
Diagnosis, n (%)	
Mild cognitive impairment	151 (41.3%)
AD-type dementia	215 (58.7%)
Age (years)	73.22 ± 8.47
Sex (% males)	49.5%
APOE-ε4 status (% e4+)[a]	62.6%
APOE genotype, n (%)[a]	ε2/ε3 n = 5 (1.4%) ε2/ε4 n = 12 (3.4%) ε3/ε3 n = 115 (33%) ε3/ε4 n = 146 (41.8%) ε4/ε4 n = 71 (20.4%)
Education (years)[b]	15.0 ± 3.3
ICV (dm^3)	1.46 ± 0.16
MMSE, baseline score	24.15 ± 4.17 [range: 7–30]
MMSE, annual change (points/year)	−2.23 ± 2.99
Temporal meta-ROI tau, SUVR	1.66 ± 0.42
Global tau (SUVR)	1.38 ± 0.32
AD-signature cortical thickness (mm)	2.51 ± 0.23
Global cortical thickness (mm)	2.20 ± 0.12
Follow-up (months)[c]	18 (12, 30) [range: 5–72]
Follow-up (visits)[c]	3 (2, 3) [range: 2–8]
Time lag tau PET – first MMSE (months)	0 (−1, 0) [range: −12, 9]

Mean ± *SD*. Characteristics of the BR sub-sample is presented in Supplementary Table 2.
[a]APOE-ε4 status available for 349/366 of individuals.
[b]Education available for 363/366 of individuals.
[c]Median (IQR)

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Table 2 Results of linear mixed-effect models investigating determinants of cognitive resilience to tau burden in the temporal meta-ROI

	Cognitive resilience (MMSE)											
	Time*Tau*Variable β (CI)				Time*Variable β (CI)				Variable β (CI)			
Variable	**Unstandardized**	**Standardized**	**t**	**p-val**	**Unstandardized**	**Standardized**	**t**	**p-val**	**Unstandardized**	**Standardized**	**t**	**p-val**
Age [b]	−0.072 (−0.138 – −0.007)	−0.062 (−0.118 – −0.006)	−2.156	**0.032**	−0.042 (−0.072 – −0.012)	−0.085 (−0.146 – −0.024)	−2.729	**0.007**	−0.079 (−0.13 – −0.027)	−0.16 (−0.265 – −0.054)	−2.963	**0.003**
Sex [a]	−0.726 (−1.853 – 0.400)	−0.073 (−0.187 – 0.04)	−1.264	0.208	−0.273 (−0.74 – 0.193)	−0.066 (−0.178 – 0.046)	−1.148	0.252	−0.218 (−1.036 – 0.6)	−0.052 (−0.249 – 0.144)	−0.522	0.602
Education [b]	−0.215 (−0.380 – −0.051)	−0.072 (−0.127 – −0.017)	−2.561	**0.011**	−0.008 (−0.081 – 0.064)	−0.007 (−0.064 – 0.051)	−0.222	0.824	0.273 (0.144 – 0.403)	0.217 (0.114 – 0.319)	4.144	**<0.001**
APOE-ε4 status [a]	0.754 (−0.389 – 1.897)	0.076 (−0.039 – 0.191)	1.292	0.198	0.086 (−0.396 – 0.568)	0.021 (−0.095 – 0.136)	0.349	0.727	0.228 (−0.616 – 1.071)	0.055 (−0.148 – 0.257)	0.529	0.597
ICV [b]	−4.383 (−7.917 – −0.85)	−0.070 (−0.126 – −0.014)	−2.431	**0.016**	−1.786 (−3.261 – −0.312)	−0.068 (−0.124 – −0.012)	−2.375	**0.018**	1.145 (−1.415 – 3.705)	0.043 (−0.054 – 0.141)	0.877	0.381
AD-signature [a]	0.533 (−1.8 – 2.866)	0.012 (−0.041 – 0.066)	0.448	0.655	2.686 (1.555 – 3.817)	0.147 (0.085 – 0.209)	4.655	**<0.001**	7.296 (5.428 – 9.164)	0.399 (0.297 – 0.501)	7.657	**<0.001**

β = model coefficient, CI = 95% Confidence Intervals, ICV = Intracranial volume. Model with interaction: *Outcome ~ Time + Tau + Variable + Cohort + Time*Tau + Time*Variable + Time*Cohort + Tau*Variable + Time*Tau*Variable + (Time | ID).* Model without interaction: *Outcome ~ Time + Tau + Variable + Cohort + Time*Tau + Time*Variable + Time*Cohort + (Time | ID).* Sex [female as reference] and APOE-e4 status [e4- as reference] were two-level factors. Time (years), temporal meta-ROI tau (SUVR), age at baseline (years), educational level (years of education), ICV (dm^3) and AD-signature cortical thickness (mm) were centered and used in continuous form, each in their respective units (for the unstandardized coefficients) or standardized (z-scored) with respect to baseline standard deviation in the total group (for the standardized coefficients).
[a]The "Time*Variable β" and "Variable β" coefficients are main effects from models where the non-significant interaction term was removed.
[b]The "Time*Variable β" and "Variable β" coefficients are conditional main effects from the full model. These coefficients therefore represent the relationship between each variable and longitudinal decline or cross-sectional cognition, respectively, at average levels of tau PET.

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Table 3 Results of linear mixed-effect models investigating determinants of brain resilience to tau burden in the temporal meta-ROI

	Brain resilience (AD-signature cortical thickness)											
	Time*Tau*Variable β (CI)				Time*Variable β (CI)				Variable β (CI)			
Variable	**Unstandardized**	**Standardized**	**t**	**p-val**	**Unstandardized**	**Standardized**	**t**	**p-val**	**Unstandardized**	**Standardized**	**t**	**p-val**
Age[a]	0.001 (−0.001 – 0.002)	0.009 (−0.021 – 0.038)	0.566	0.572	−0.001 (−0.002 – 0)	−0.051 (−0.083 – −0.02)	−3.182	**0.002**	−0.012 (−0.015 – −0.009)	−0.49 (−0.613 – −0.366)	−7.774	**<0.001**
Sex[a]	0.003 (−0.029 – 0.034)	0.005 (−0.055 – 0.066)	0.177	0.86	−0.006 (−0.018 – 0.006)	−0.027 (−0.083 – 0.029)	−0.942	0.348	0.01 (−0.044 – 0.064)	0.047 (−0.205 – 0.299)	0.363	0.717
Education[b]	−0.006 (−0.011 – −0.001)	−0.037 (−0.065 – −0.008)	−2.517	**0.013**	−0.002 (−0.004 – 0)	−0.023 (−0.052 – 0.006)	−1.569	0.119	0.003 (−0.007 – 0.012)	0.04 (−0.095 – 0.176)	0.581	0.562
APOE-ε4 status[a]	−0.004 (−0.036 – 0.028)	−0.008 (−0.068 – 0.053)	−0.244	0.807	−0.004 (−0.016 – 0.009)	−0.017 (−0.075 – 0.041)	−0.579	0.564	0.02 (−0.035 – 0.076)	0.095 (−0.164 – 0.354)	0.72	0.472
ICV[a]	0.032 (−0.061 – 0.124)	0.010 (−0.019 – 0.039)	0.669	0.504	0.014 (−0.025 – 0.054)	0.011 (−0.019 – 0.042)	0.715	0.475	−0.052 (−0.215 – 0.111)	−0.04 (−0.166 – 0.086)	−0.623	0.534

β = model coefficient, CI = 95% Confidence Intervals, ICV = Intracranial volume. Model with interaction: *Outcome ~ Time + Tau + Variable + Cohort + Time*Tau + Time*Variable + Time*Cohort + Tau*Variable + Time*Tau*Variable + (Time | ID).* Model without interaction: *Outcome ~ Time + Tau + Variable + Cohort + Time*Tau + Time*Variable + Time*Cohort + (Time | ID).* Sex [female as reference] and APOE-e4 status [e4- as reference] were two-level factors. Time (years), temporal meta-ROI tau (SUVR), age at baseline (years), educational level (years of education) and ICV (dm^3) were centered and used in continuous form, each in their respective units (for the unstandardized coefficients) or standardized with respect to standard deviation in the total group at the time of tau-PET (for the standardized coefficients).

[a]The "Time*Variable β" and "Variable β" coefficients are main effects from models where the non-significant interaction term was removed.

[b]The "Time*Variable β" and "Variable β" coefficients are conditional main effects from the full model. These coefficients therefore represent the relationship between each variable and longitudinal cortical thinning or cross-sectional thickness, respectively, for an individual of average level of tau.

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