Neuroimaging Predictors of Cognitive Resilience against Alzheimer's Disease Pathology

McKenna E. Williams, MS [1,2] Christine Fennema-Notestine, PhD,[1] Tyler R. Bell, PhD [1] Shu-Ju Lin, PhD,[1] Stephen J. Glatt, PhD,[3] William S. Kremen, PhD,[1] and Jeremy A. Elman, PhD,[1] for the Alzheimer's Disease Neuroimaging Initiative

Objective: Some individuals demonstrate greater cognitive resilience—the ability to maintain cognitive performance despite adverse brain-related changes—through as yet unknown mechanisms. We examined whether cortical thickness in several brain regions confers resilience against cognitive decline in amyloid-positive adults by moderating the effects of thinner cortex in Alzheimer's disease (AD)-related brain regions and of higher levels of tau.
Methods: Amyloid-positive participants from the Alzheimer's Disease Neuroimaging Initiative with relevant imaging data were included (n = 160,
observations = 473). Risk factors included an AD brain signature and cerebrospinal fluid phosphorylated tau. Cognitive measures were episodic memory and executive function composites. Mixed effects models tested whether region-specific cortical thickness moderated relationships between markers of AD risk and memory or executive function.
Results: Cross-sectionally, thicker cortex in 8 regions minimized the negative impact of thinner cortex/smaller volume in AD signature regions on executive function. Longitudinally, higher baseline thickness in a composite of these 8 regions predicted less memory decline ($p = 0.007$) and weakened negative effects of phosphorylated tau on memory decline ($p = 0.014$), independent of baseline cognition and risk markers.
Interpretation: We identified 8 cortical regions that appear to confer cognitive resilience cross-sectionally and longitudinally in the face of established indicators of AD pathology. Brain regions fostering executive function may enable compensation in later memory performance and confer cognitive resilience against effects of phosphorylated tau and AD-related cortical changes. These "resilience" regions suggest the value of focusing on brain regions beyond only those determined to be AD-related and may partially explain variability in AD-related cognitive trajectories.

ANN NEUROL 2025;97:1038–1050

Many older adults (10–44%) display significant levels of Alzheimer's disease (AD) pathology without known cognitive impairment.[1–6] Preserved cognitive functioning despite the presence of AD pathology has been the focus of a growing literature on cognitive reserve and resilience.[7–9] Here, we focus on cognitive resilience, which we define as the ability to maintain cognitive performance in the face of adverse brain-related changes.[8] Our definition of cognitive resilience corresponds to the definition of cognitive reserve proposed by the Collaboratory on Research Definitions for Reserve and Resilience in Cognitive Aging and Dementia.[10]

Several conceptual issues must be considered when investigating neural correlates of cognitive resilience. First, for resilience to be a useful concept it should provide

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.27186

Received Jul 19, 2024, and in revised form Jan 9, 2025. Accepted for publication Jan 9, 2025.

Address correspondence to Dr Williams, Center for Behavior Genetics of Aging, University of California, San Diego, 9500 Gilman Drive (MC 0738), La Jolla, CA 92093. E-mail: mewillia@health.ucsd.edu.

From the [1]Department of Psychiatry, University of California San Diego, La Jolla, CA; [2]Joint Doctoral Program in Clinical Psychology, San Diego State University/University of California San Diego, La Jolla, CA; and [3]Department of Psychiatry and Behavioral Sciences, Norton College of Medicine at SUNY Upstate Medical University, Syracuse, NY

Additional supporting information can be found in the online version of this article.

information that is independent of risk. For example, thicker cortex in certain brain regions may be associated with less cognitive decline; however, this finding would not necessarily reflect resilience, because it could be equivalently interpreted as lower risk (ie, thicker cortex) predicting less cognitive decline. Relatedly, although we are interested in identifying brain regions in which thicker cortex confers resilience against AD pathology, it is crucial that findings do not simply reflect that individuals in earlier disease stages have less progressed atrophy and correspondingly less cognitive decline. Furthermore, cognitive resilience should not reflect longstanding differences in individual cognitive abilities, a potential error to which the "residual method" is often prone.[11]

An approach to identifying resilience that addresses some of the issues described above is to test for an interaction between a risk factor and a factor that may confer resilience against that risk factor by attenuating negative effects of risk.[8,9,11] Importantly, this moderating effect is independent of expected main effects of the risk factor on cognition. This is particularly relevant when examining neurobiological substrates of risk and resilience that they evolve with disease progression. Prior work using this approach has shown that thicker cortex in a composite of AD-related brain regions (ie, an AD signature) was associated with less decline on a global cognitive screener, but did not confer resilience by moderating the negative effects of tau on cognitive decline.[9] This prior study examined the role of cortical thickness in regions identified a priori and associated with AD risk (eg, an AD signature); however, it is possible that cortical thickness in brain regions beyond those in an AD signature may confer cognitive resilience, although which specific regions is unknown.

Here, we sought to expand on previous work by identifying new brain regions beyond typical risk-associated regions that may demonstrate independent resilience effects, accounting for putative disease staging and other known factors that can contribute to resilience (eg, education, age). We hypothesized that thicker cortex in some brain regions would weaken the negative impacts of risk for AD-related cognitive decline on cognitive performance cross-sectionally and longitudinally. Risk metrics included an AD signature and cerebrospinal fluid (CSF) phosphorylated tau (p-tau). Through a series of models, we describe how analytic choices affect interpretation of results, and to what extent they address common conceptual issues that arise when studying cognitive resilience.

Methods

Participants

Data were downloaded from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu) in June 2023. The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether biological markers, clinical assessment, and neuropsychological measures can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. Participants with data from ADNI-GO, ADNI-2, and/or ADNI-3 were included in the present study if they: (1) had structural imaging and cognitive composite (memory or executive functioning) data at the same timepoint; and (2) were amyloid-positive (determined by positron emission tomography [PET] or CSF) at the timepoint for which they had imaging and cognitive data. All participants had CSF p-tau181 data as well as relevant imaging data for at least one timepoint. Data from ADNI-1 visits were not included given that the AD signature was created using ADNI-1 data, and we sought to minimize bias that may arise from the inclusion of these data. These selection criteria resulted in 160 participants with 473 observations across multiple timepoints (Table 1). Informed consent was obtained from all

TABLE 1. Demographic Characteristics

	Full sample (n = 160) Observations = 473
Age, yr (SD)	74.99 (7.29)
Education, yr (SD)	16.45 (2.64)
APOE-ε4, n (%)	300/473 (63)
Diagnosis, n (%)	
CN	123/473 (26)
MCI	246/473 (52)
AD	102/473 (22)
CSF Aβ42, pg/mL (SD), 349 obs	747 (296.46)
CSF PTAU, pg/mL (SD), 349 obs	33.34 (15.83)
Florbetapir-PET, SUVR (SD), 457 obs	1.37 (0.20)
Tau positive, n (%)	287/420 (68)
Length of follow-up, yr (SD)	1.45 (1.53)
Observations per participant, n (SD)	2.81 (1.46)

Abbreviations: Aβ42 = amyloid-beta 42; AD = Alzheimer's disease; CSF = cerebrospinal fluid; MCI = mild cognitive impairment; PET = positron emission tomography; PTAU = phosphorylated tau; SD = standard deviation; SUVR = standardized uptake value ratios.

participants and procedures were approved by the Institutional Review Board of participating institutions.

CSF and PET Imaging Measures of AD Pathology

CSF or PET amyloid-beta (Aβ)-positivity was used as an inclusion criterion for this set of analyses. CSF p-tau181 was collected at multiple timepoints and was included in models as a pathological measure of risk for AD-related cognitive decline. CSF p-tau181 has been shown to become abnormal around the same time as amyloid PET and also predicts tau PET changes, suggesting it may reflect both amyloid- and tau-related changes.[12,13] In the present analyses, we include CSF p-tau181 as a broad index of AD pathology and risk for AD-related cognitive decline. Methods for the collection and processing of CSF samples have been previously described.[14] Established cut-offs designed to maximize sensitivity in the ADNI study population were used to classify CSF Aβ positivity (defined as Aβ42 < 977 pg/mL).[15] PET Aβ data were processed according to previously published methods.[16] Mean standardized uptake value ratios (SUVRs) were taken from a set of regions including frontal, temporal, parietal, and cingulate cortices using the whole cerebellum as a reference region. Established cut-offs to determine Aβ positivity were used for florbetapir-PET (SUVR >1.11) and for florbetaben-PET (SUVR >1.08).[17]

Structural Neuroimaging Measures

Processed structural magnetic resonance imaging (MRI) data were downloaded from the ADNI database in June 2023. ADNI-GO and ADNI-2 data were processed using FreeSurfer version 5.1, and ADNI-3 data were processed using FreeSurfer version 6.0 (no FreeSurfer 6.0 data were available for ADNI-GO and ADNI-2). The Desikan-Killiany atlas was used for regional parcellation by all FreeSurfer versions. In cases where a participant's MRI data from the same visit were processed more than once, the image identification (ID) with the most complete data for that participant was selected. Quality control variables produced by FreeSurfer (FRONTQC, TEMPQC, LHIPQC, or RHIPQC) were used to exclude corresponding regions with poor data quality. Before analyses, all imaging variables were residualized for the effects of study protocol (ie, ADNI-GO, ADNI-2, or ADNI-3). Additional details regarding image acquisition and processing are provided elsewhere.[18]

We used our methods to calculate AD signature scores, a measure of risk for AD-related cognitive decline, as described previously.[19] The regions and weights used in this signature were derived using a data-driven approach to identify a pattern of regional atrophy specific to a group with mild AD compared to cognitively unimpaired individuals using ADNI-1 data.[20,21] The resulting signature is a weighted sum of thickness in 7 cortical regions (entorhinal cortex, middle temporal gyrus, banks of superior temporal sulcus, superior temporal gyrus, isthmus cingulate, lateral orbitofrontal cortex, and medial orbitofrontal cortex), plus hippocampal volume, with separate weights for left and right hemisphere regions. A strength of this signature is its use of weightings for each region of interest (ROI) that reflect each region's importance in discriminating between cases and controls. These weights can help offset any potential dilution of AD-related changes across the regions that comprise the signature. For example, the largest weights are given to the hippocampus and entorhinal cortex with regions that tend to be impacted later in the disease having smaller weights. The effects of age and scanner were regressed out of each ROI. Estimated intracranial volume was additionally regressed out for hippocampal volume. Standardized residuals of ROIs were then weighted according to their ability to discriminate between ADNI-1 AD cases and controls and summed together to form the AD signature scores. Lower AD signature scores are indicative of lower cortical thickness or volume in these AD-related regions.

Cognitive Measures

We used two harmonized composite scores (memory, PHC_MEM; executive functioning, PHC_EXF) generated by the Alzheimer's Disease Sequencing Project Phenotype Harmonization Consortium (ADSP-PHC).[22] These composites are co-calibrated across 10 other studies, facilitating cross-study comparison and replication, and incorporate all items available for each participant. The Consortium now recommends their use over the earlier ADNI_MEM and ADNI-EF scores, which were based only on ADNI-1 neuropsychological data, which have changed considerably in later ADNI phases.

Statistical Analysis

Linear mixed effects models were conducted using the *lme4* package[23] in $R^{v.4.3.0}$. Winsorization was applied to all values of MRI and CSF measures that were more than 3 standard deviations above or below the mean. In cross-sectional models, predictor variables were standardized according to the grand mean. In longitudinal models, baseline predictor variables were centered within the baseline timepoint. All models were tested using memory and executive functioning composite scores as separate outcomes. Table 2 displays the series of cross-sectional and longitudinal models tested and how terms of interest can be interpreted with respect to associations with cognitive decline.

TABLE 2. Cross-Sectional and Longitudinal Models of Cognitive Resilience

Cross-sectional models	Example interpretation of term of interest
1. Term of interest: **ROI*ADsignature** Covariates: Ptau, Age	Higher cortical thickness in a given ROI weakens the adverse effect of low AD signature scores on cognition, at average levels of covariates (p-tau, age). Pools across all observations, but tests within-timepoint associations.
2. Term of interest: ROI*Ptau Covariates: ADsignature, Age	Higher cortical thickness in a given ROI weakens the adverse effect of high p-tau on cognition, at average levels of covariates (AD signatures, age). Pools across all observations, but tests within-timepoint associations.
3. Term of interest: ROI*ADsignature*Ptau Covariates: Age	Low AD signature scores are associated with lower cognitive performance, particularly at high levels of p-tau, although the impacts of these factors are weakened at high levels of cortical thickness in a given ROI and average age. Pools across all observations, but tests within-timepoint associations.
Longitudinal models	**Example interpretation of term of interest**
4. Term of interest: **ResComposite_BL*Time** Covariates: ADsignature_BL, Ptau_BL, Age_BL, Education	Higher baseline resilience composite scores are associated with less cognitive decline over time, controlling for levels of baseline risk for AD-related cognitive decline and education. This interaction can be interpreted as resilience because the sample comprises individuals at-risk for AD-related cognitive decline (ie, all are amyloid-positive). However, this model does not account for the impact of covariates on decline over time. The resilience composite is correlated with AD signatures, so although the main effect of atrophy on cognition is controlled for by inclusion of the AD signature term, it is possible that the resilience composite effect on slope is simply capturing the effects of less atrophy in the AD signature associated with less decline over time. This is not ideal for capturing resilience.
5. Term of interest: **ResComposite_BL*Time** Covariates: ADsignature_BL*Time, Ptau_BL*Time, Age_BL*Time, Education*Time	Similar interpretation as model 4, but including interactions of other risk factors and education with time means that the resilience composite effect on slope is now independent of other covariates' impacts on slope. This model better identifies resilience that is not simply reflecting the effects of low risk. The two factors are independent, but have additive contributions to cognitive change.
6. Term of interest: **ResComposite_BL*Ptau_BL*Time** Covariates: ADsignature_BL*Time, Age_BL*Time, Education*Time	Higher baseline resilience composite scores weaken adverse effects of p-tau on cognition over time, beyond effects of age, education, and AD signatures on cognition over time. In contrast to model 5, the resilience composite does not operate through independent and additive contributions to cognitive change, but through weakening the impact of p-tau on cognitive change. Explicitly testing the moderating effect of the resilience composite on the association between pathology and cognitive decline provides stronger evidence of cognitive resilience than model 5.
7. Term of interest: ResComposite_BL*ADsignature_BL*Time Covariates: Ptau_BL*Time, Age_BL*Time, Education*Time	Similar interpretation as model 6, but with the resilience composite modifying the effects of AD signatures on cognition over time.
8. Term of interest: ADsignature_BL*Ptau_BL*Time Covariates: ResComposite_BL*Time, Age_BL*Time, Education*Time	Higher baseline AD signature scores weaken adverse effects of p-tau on cognition over time, beyond effects of resilience composite scores, education, and age over time. This model tests whether higher AD signature scores confer resilience in the same way as the resilience composite.

Note: All models were tested with memory and executive functioning composite scores as separate outcomes. Example interpretations of interaction terms that model cognitive resilience are provided, with the hypothesis that higher cortical thickness in ROIs or the resilience composite would confer resilience. Terms of interest with significant findings are bolded. Note that for each interaction term, there are at least two statistically equivalent interpretations; all interaction terms below are interpreted with the ROI or resilience composite as the primary moderator. Main effects for all variables specified in interaction terms are not displayed but were included in the model, such that significant interaction terms contribute to resilience against AD risk over and beyond any main effect of ROI, composite, or risk on cognition. All models additionally included a random intercept to account for repeated measurements within participants.

Abbreviations: AD = Alzheimer's disease; BL = baseline; p-tau = phosphorylated tau; ResComposite = resilience composite; ROI = region of interest.

One complicating factor in identifying neurobiological substrates of cognitive resilience is that measures such as cortical thickness change with disease progression. We wanted to avoid the tautological scenario in which we interpret less severe outcomes of disease (ie, thicker cortex) as evidence of resilience against disease effects. Because our measures of risk evolve with disease progression, they can also serve as putative indices of disease stage (ie, lower AD signatures and higher levels of p-tau are a risk factor for future cognitive decline and may also reflect more advanced disease progression). Therefore, to account for potential confounding effects of disease staging, we include both the AD signature and p-tau in all models as covariates, regardless of the interaction term of interest. This allows for the identification of ROIs that contribute to resilience over and beyond the main effects of AD-related atrophy and level of AD pathology.

Cross-Sectional Models

First, we examined cognitive resilience against cortical thinning in AD-related regions. We created bilateral ROIs for each of the 34 Desikan-Killiany cortical parcellations by averaging together left and right hemisphere data for each ROI to test if regions within and beyond the AD signature confer cognitive resilience. Multiple visits per participant were included in these models, but effects correspond to within-timepoint associations (ie, no interactions with time in these models). Models tested whether bilateral cortical thickness in each brain region moderated the relationship between the AD signature and concurrent cognitive functioning. A significant interaction term would suggest that, over and above the expected association of brain structure and cognitive performance (main effect), higher cortical thickness in a given ROI contributed to resilience against risk for AD-related cognitive decline by modifying the relationship between the AD signature and cognition. Separate models were used to test this interaction effect (ROI*ADsignature) for all 34 bilateral cortical ROIs and for the 2 cognitive outcomes (memory and executive functioning composite scores). Eight of these 34 ROIs comprise the AD signature itself. Given that the AD signature is a composite of multiple ROIs with potentially heterogeneous contributions to risk and resilience, we included these ROIs in analyses to allow for the possibility that relatively higher cortical thickness in one region may confer resilience despite lower cortical thickness across the AD signature as a whole. In these cross-sectional models, CSF p-tau and age were included as time-varying covariates. Because we used linear mixed models, if a participant did not have all covariates of interest at a given timepoint, they were not included in these models. Participant ID was included as a random intercept to account for repeated measurements within participants.

Next, we explored resilience against CSF p-tau. Specifically, we tested whether cortical thickness in each brain region modified the relationship between CSF p-tau and cognitive performance. We tested this interaction effect (ROI*p-tau) in the same way as described above and included the AD signature and age as covariates in these models (both time-varying).

Longitudinal Models

Finally, for use in longitudinal models, we created a resilience composite (unweighted average) based on all ROIs that significantly moderated the relationship between a form of risk for AD-related cognitive decline (AD signature or p-tau) and cognitive performance in the previously described cross-sectional models. Creation of this composite allowed for reduction in number of tests conducted. Composite measures can also increase measurement reliability by increasing the signal-to-noise ratio and are more easily incorporated into subsequent analyses. Moreover, we have found in prior work among an independent sample that use of a composite score may be more sensitive to cognitive change over time compared to using a smaller subset of regions or individual ROIs.[24] The Longitudinal models section of Table 2 lists the model specifications that incorporate the resilience composite and to what extent this provides evidence for resilience. For example, we note that although models 5–7 all assess resilience, models 6 and 7 test for stronger or more direct evidence by explicitly testing whether thicker resilience composite weakens the (modelled) association between p-tau and cognitive decline. In all longitudinal models, a random intercept was included to account for repeated measures across timepoints. We did not include random slopes in models as this resulted in unidentifiable models. Importantly, the random intercept term additionally accounts for differences in baseline cognitive performance across individuals. Years of education and baseline values of AD signatures, p-tau, and age were included in all longitudinal models as time-invariant main effects. Time was calculated as the interval in years between the first assessment with relevant data and each follow-up assessment. If available for a participant, multiple follow-up assessments were included.

A false discovery rate (FDR)-corrected value of $p < 0.05$ was used for each set of analyses to correct for multiple comparisons.[25] For cross-sectional models, FDR correction was applied to interaction terms of interest separately for each model (models 1–3) and for each cognitive outcome (memory, executive functioning; groups of 34 tests per model and outcome). For longitudinal models, FDR correction was applied to interaction terms of interest in models 5–7 predicting memory and

executive functioning outcomes (total of 6 tests). Interaction terms of interest in models 4 and 8 were not adjusted for multiple comparisons as they represent an illustration of poor model specification or a sensitivity analysis, respectively.

Results

Cross-Sectional Models (Models 1–3)

The sample included individuals who self-identified as Asian (<1%), Black (2.5%), multiracial (3.8%), and White (93.1%). Most (96.9%) were not Hispanic or Latino. The proportion of males and females was relatively equal (50.6% female). Figure 1 displays distributions of measures of interest by diagnostic group. In cross-sectional analyses controlling for p-tau and age, cortical thickness in 8 bilateral ROIs significantly moderated the relationship between the AD signature and executive functioning (model 1). Higher cortical thickness in these 8 resilience ROIs (lateral occipital, inferior parietal, banks of superior temporal sulcus, isthmus cingulate, inferior temporal, precuneus, middle temporal, and posterior cingulate) minimized the negative impact of thinner cortex in AD signature regions on executive functioning (Fig 2). Five of these 8 ROIs were regions that were not included in the AD signature. These significant interaction effects were independent of main effects of both ROI and AD signature on executive functioning. No ROIs significantly moderated the cross-sectional relationship between the AD signature and memory performance. There were no significant interactions predicting cross-sectional cognitive performance in model 2 (ROI*Ptau) or model 3 (ROI*ADsignature*Ptau). Full results for cross-sectional models are available in Tables S1 and S2.

Longitudinal Models (Models 4–7)

For use in longitudinal analyses, we created a resilience composite from these 8 bilateral ROIs that moderated the

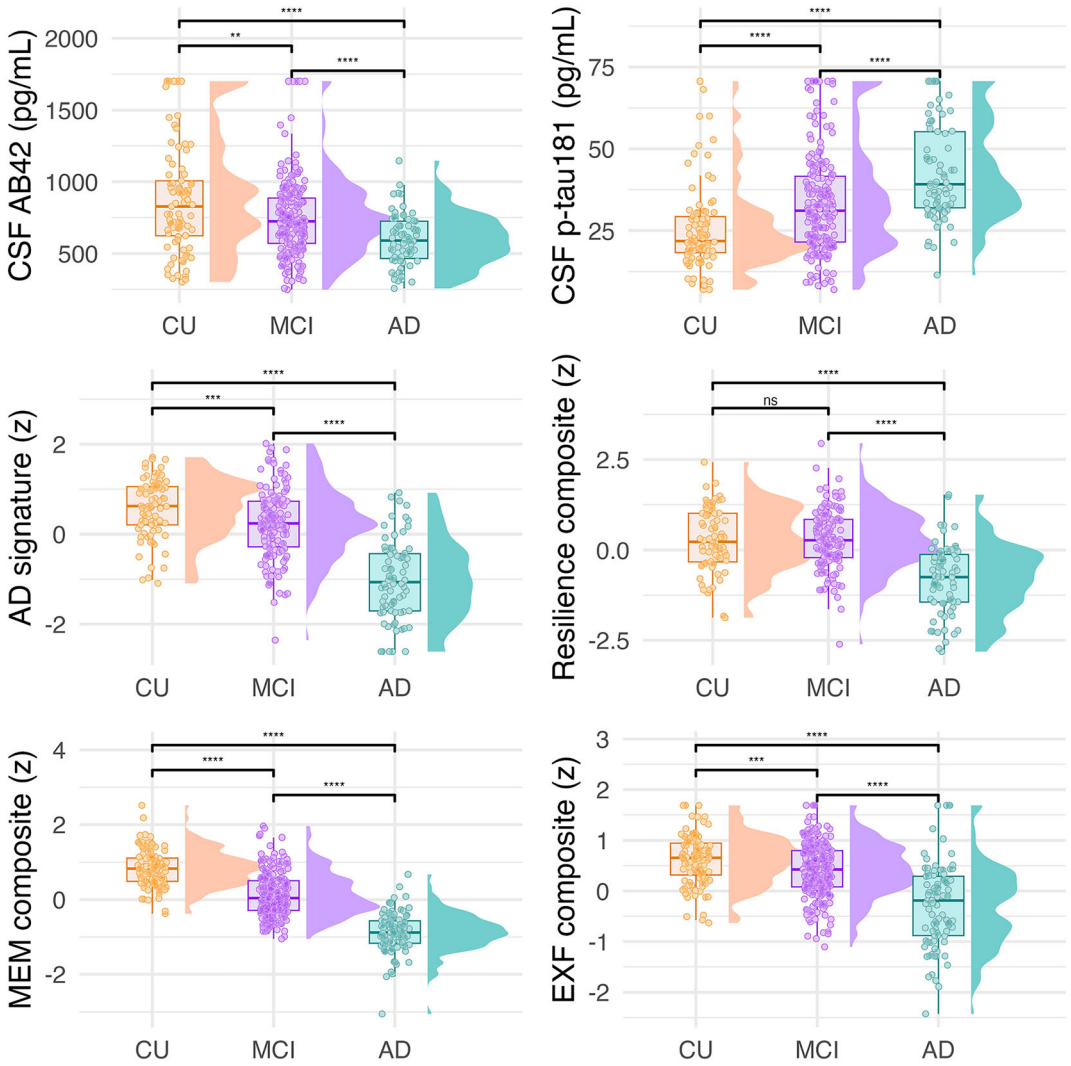

FIGURE 1: Distributions of cerebrospinal fluid (CSF), imaging, and cognitive measures by diagnostic group. ****$p < 0.0001$, ***$p < 0.001$, **$p < 0.01$, ns = not significant. [Color figure can be viewed at www.annalsofneurology.org]

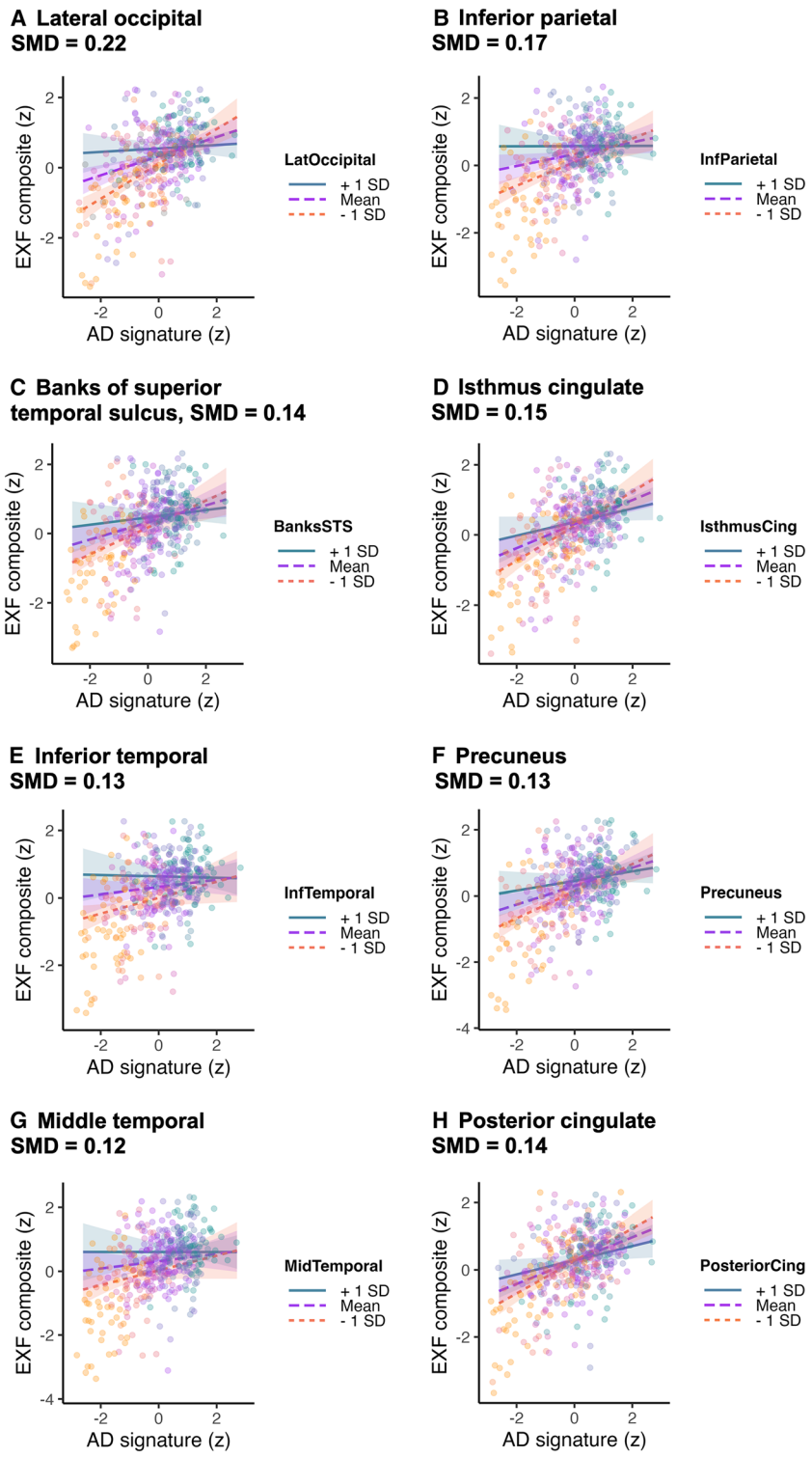

FIGURE 2: Cortical thickness regions of interest (ROIs) that significantly moderate relationship between Alzheimer's disease (AD) signatures and executive functioning performance in cross-sectional models. Models control for p-tau, age, and repeated assessments. Figures display model estimates for higher cortical thickness values (+1 standard deviation from the mean) depicted in blue/solid line, mean cortical thickness values in purple/large dashed line, and low cortical thickness values (−1 standard deviation from the mean) in orange/small dashed line. Lower AD signature values indicate lower cortical thickness in AD-related regions. Standardized mean difference (SMD) effect sizes are reported for each ROI. [Color figure can be viewed at www.annalsofneurology.org]

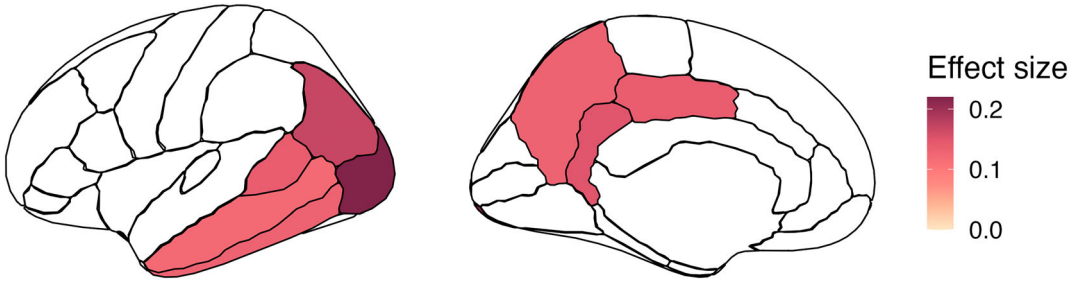

FIGURE 3: Cortical thickness regions of interest (ROIs) that significantly moderate relationship between Alzheimer's disease signatures and executive functioning performance. These ROIs comprise the resilience composite used in longitudinal analyses. Bilateral ROIs are used, only left hemisphere is displayed. Stronger effect sizes (standardized mean difference) of interaction terms for each ROI are depicted in darker shades of red. [Color figure can be viewed at www.annalsofneurology.org]

cross-sectional relationship between the AD signature and executive functioning (Fig 3). Resilience composite scores were positively associated with AD risk signature scores ($r = 0.83$, $p < 0.001$; Fig S1). That is, thicker cortex on one was associated with thicker cortex on the other. In model 4, controlling for AD signature, p-tau, education, and age as fixed effects, baseline resilience composite scores significantly moderated the relationship between time and cognitive performance such that higher baseline resilience composite scores were associated with less decline in both memory and executive functioning over time (p <0.001). However, the resilience composite is correlated with the AD signature. We controlled for the main effect of the AD signature at baseline, but not for its impact on cognitive slope (ie, the ADsignature*Time interaction is not in the model). This seemingly protective effect of the resilience composite on slope of cognitive performance is not independent of AD signature effects on slope of cognitive decline and could, therefore, reflect that those with worse AD signature scores (ie, more progressed atrophy) demonstrate greater cognitive decline. Therefore, we focus on results from model 5, which additionally accounts for the expected effects of baseline risk and education on cognitive performance over time (ie, here the ADsignature*Time and Ptau*Time interactions are included in the model). In model 5, the baseline resilience composite significantly moderated the relationship between time and memory performance ($p = 0.005$, $p_{adj} = 0.030$) such that higher baseline resilience scores were associated with slower memory decline over time (Fig 4). Importantly, this was independent of the effects of education and baseline measures of risk on cognitive decline. In model 5, baseline AD signature was associated with baseline memory performance ($p < 0.001$), but in contrast to the resilience composite, it did not significantly impact the slope of memory performance over time ($p = 0.806$). Therefore, in this model specification the resilience composite exerts an additive (and independent) effect on preserving memory function among a group of individuals harboring amyloid pathology. The interaction term of interest in model 5 (ResComposite_BL*Time) did not significantly predict executive functioning.

Beyond contributing an additive effect toward slowing cognitive decline, the resilience composite may exert an effect by modifying the relationships between risk factors and cognition over time. We tested this hypothesis using 3-way interactions in models 6 and 7. In model 6, accounting for the expected effects of education, AD signature, and age on cognitive change over time, baseline resilience composite scores significantly moderated the relationship between baseline p-tau and memory over time ($p = 0.013$, $p_{adj} = 0.039$). Higher baseline resilience composite scores were associated with slower decline in memory over time, particularly at lower levels of p-tau (Fig 5A). An alternate and statistically equivalent interpretation is that lower baseline p-tau was associated with slower decline in memory over time, particularly for those with high baseline resilience composite scores (see Fig 5B). The 3-way interaction term from model 6 did not significantly predict executive functioning. The baseline resilience composite score did not moderate the impact of baseline AD signature scores on cognitive performance over time (model 7).

Finally, model 8 tested whether the moderating effect of baseline resilience composite scores on the relationship between baseline p-tau and cognitive performance over time (interaction term of interest in model 6) was specific to the resilience composite, or if this effect was just capturing the extent of AD-related neurodegeneration. In model 8, baseline AD signature scores did not moderate the relationship between baseline p-tau and memory ($p = 0.343$) or executive functioning ($p = 0.808$) over time, suggesting that results from model 6 were specific to the resilience composite. That is, we did not find a similar, but opposite, effect of the AD signature as we found for the resilience composite in model 6. Full results for longitudinal models are available in Tables S3–S12.

Sensitivity analyses examined whether the moderating effects of the 8 ROIs identified in cross-sectional

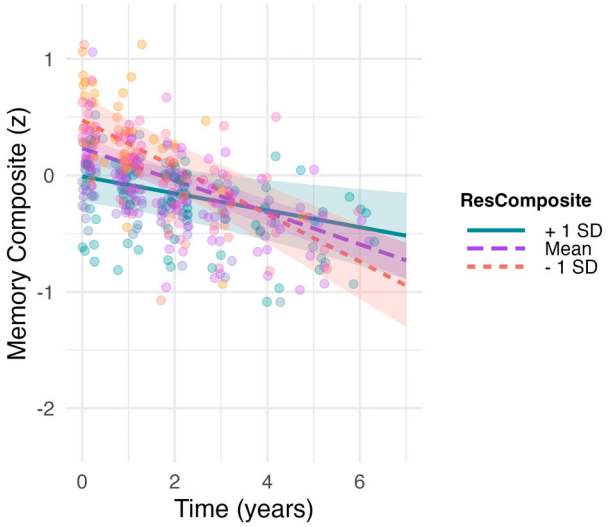

FIGURE 4: Higher baseline resilience composite scores are associated with slower memory decline. Model controls for the effects of risk (Alzheimer's disease [AD] signatures, p-tau, age) and education over time as well as repeated assessments within participants (model 5). Estimates for higher cortical thickness values (+1 standard deviation from the mean) are depicted in blue/solid line, mean cortical thickness values in purple/large dashed line, and low cortical thickness values (−1 standard deviation from the mean) in orange/small dashed line. Lower AD signature values indicate lower cortical thickness in AD-related regions. [Color figure can be viewed at www.annalsofneurology.org]

analyses or the results from longitudinal analyses differed by sex. In both cross-sectional models and longitudinal models, the moderating effects of ROIs or the resilience composite did not significantly differ across men and women (eg, nonsignificant ROI*ADsignature*Sex interaction term). Table S13 in Supporting information provides effect sizes for all models within female-only and male-only sub-samples.

Discussion

Cognitive resilience reflects dynamic relationships that exist across levels of risk, cognitive performance, and protective factors. We examined differences in cognitive resilience among at-risk (ie, amyloid-positive) adults by leveraging a careful selection of models that used interaction terms to test for the presence of cognitive resilience, with each model contributing insights into different forms of resilience and with varying degrees of evidence. In cross-sectional analyses, we identified 8 brain regions in which higher cortical thickness conferred cognitive resilience by weakening the negative impact of more AD-like brain signatures on concurrent executive functioning. In longitudinal analyses, higher cortical thickness in a composite score of these 8 resilience regions contributed to cognitive resilience as evidenced by (1) associations with slower memory decline over time among a group of at-risk (ie, amyloid-positive) individuals, and (2) weakening of the adverse effects of CSF p-tau on memory performance over time.

Interestingly, despite exhibiting a protective effect on concurrent executive functioning, baseline thickness of the 8 resilience-associated brain regions did not predict subsequent slowing of executive functioning decline over time. Instead, although not associated with concurrent memory performance, a composite of these 8 regions was associated with subsequent preservation of memory performance over time. These results may suggest the role of executive function abilities in enabling compensation in longitudinal memory performance. As a higher-order cognitive control function, executive function is a logical candidate for a mechanism underlying cognitive resilience. The domain captures a variety of abilities (eg, inhibition, set shifting, updating of working memory, organization and monitoring) that are involved in episodic memory tasks and have been found to mediate age-related differences in episodic memory performance.[26] In line with our findings, several of the resilience-associated regions identified in the current study have been previously linked to executive function performance (middle temporal, inferior temporal, and posterior cingulate regions)[27] or compensatory hyperactivation in the presence of amyloid pathology on a memory task (lateral occipital region).[28] Moreover, although episodic memory is typically the focus of AD-related cognitive deficits, there is evidence that executive function deficits may present as early or even earlier than memory deficits.[29–31] By examining specific cognitive domains as outcomes, our results lend new insight into individual variability in cognitive trajectories among individuals on the AD continuum.

Results from our longitudinal models showed that higher baseline cortical thickness in the resilience composite was associated with slower memory decline over time, particularly at lower levels of p-tau. Equivalently, among individuals with thinner cortex in resilience-associated regions, even low levels of p-tau may be sufficient to cause memory decline. Therefore, increased thickness in resilience-related regions may attenuate the deleterious effect of p-tau accumulation on cognitive decline. It may also be that at higher levels of p-tau, which in this sample correspond to values above a cut-off used to identify tau-positivity, this compensatory mechanism begins to fail. It should be noted, however, that the present sample displayed considerable levels of AD-related pathology, even at lower levels of p-tau (eg, all were amyloid-positive). Bocancea et al[9] reported a similar breakdown of the protective moderation effects of education on the relationship between tau-PET burden and cognitive decline at higher levels of tau pathology in an amyloid-positive sample. These findings are in line with prior work demonstrating that cognitive decline is linked

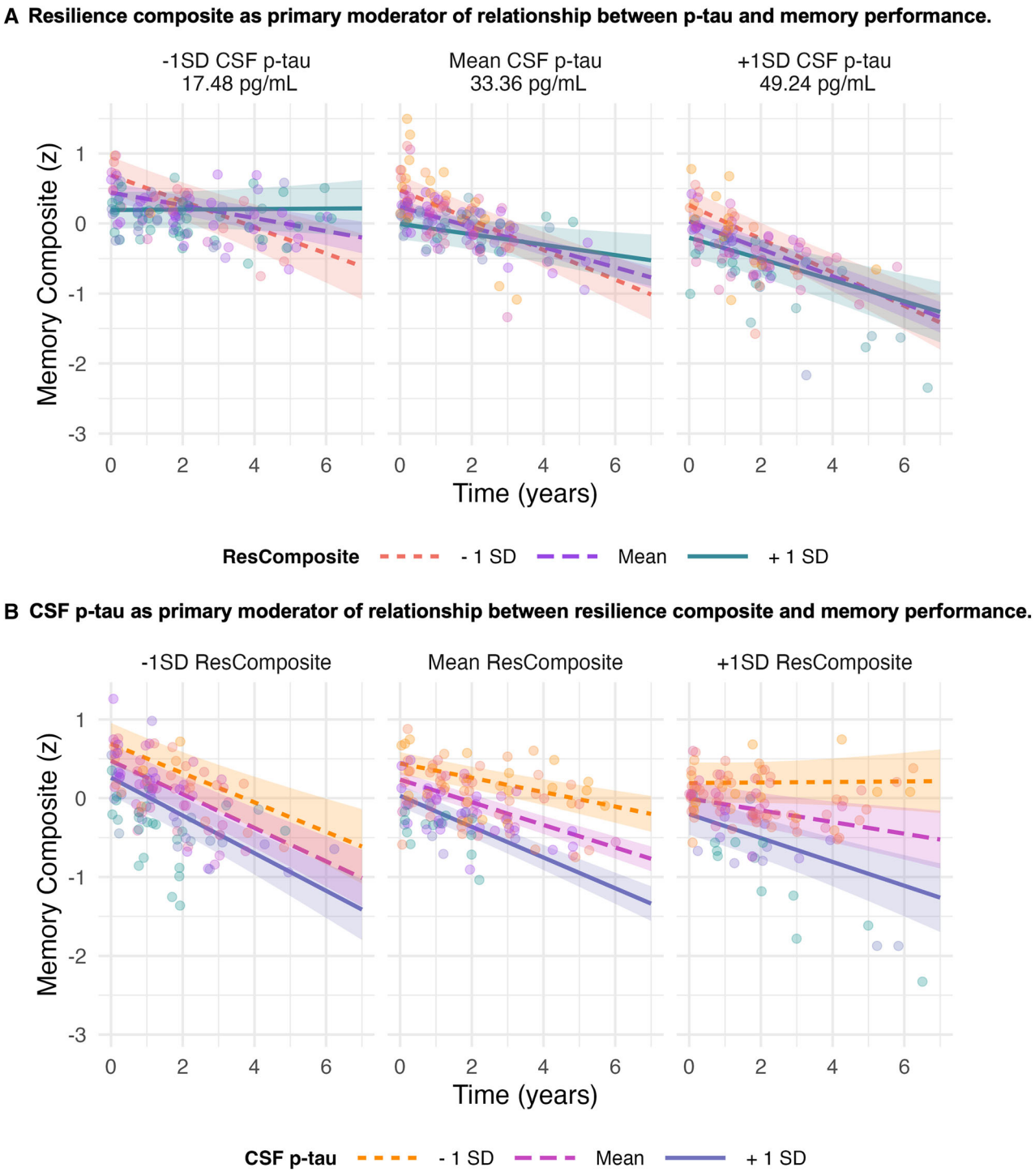

FIGURE 5: Baseline resilience composite and baseline cerebrospinal fluid (CSF) p-tau interact on memory performance over time. A and B depict the same interaction term, with differing primary moderators. Mean and +/− 1 standard deviation values of CSF p-tau for the longitudinal sample are reported. [Color figure can be viewed at www.annalsofneurology.org]

more consistently to levels of tau than to levels of Aβ.[32] However, even compensatory mechanisms contributing to resilience against amyloid accumulation have been shown to become reduced at high levels.[28]

Importantly, our sequential model testing enabled us to rule out alternate explanations related to cognitive resilience. For example, results from longitudinal model 4 tested whether baseline resilience composite scores moderated the rate of cognitive decline over time. However, because this model did not include interactions with time for other risk-related covariates, the finding might simply reflect the effects of low risk or earlier disease stage on

cognition over time, rather than true resilience. Results from model 5, in contrast, indicate combined and independent impacts of both risk and resilience factors on cognitive performance over time. Therefore, because higher resilience composite scores were associated with reduced memory decline over time independent of education and risk factors, model 5 differentiates resilience from low risk. Moreover, as these measures of risk for AD-related cognitive decline can also serve as putative indices of disease stage and are included as main effects in all models (ie, lower AD signatures and higher p-tau levels are a risk factor for future decline and may also reflect current disease progression), these interaction effects reflect evidence of cognitive resilience against memory decline beyond the effects of putative disease stage on cognition.

Of note, some of the 8 resilience regions identified in our study overlap with regions implicated in AD, specifically regions that show amyloid accumulation relatively early in the disease process.[33] Three of the 8 resilience regions (middle temporal, banks of superior temporal sulcus, and isthmus cingulate) are included in the AD signature itself (with different weightings), and the AD signature was highly correlated with the resilience composite. Yet, in cross-sectional analyses each individual region modified the relationship between the overall pattern of AD-related changes captured by the signature and executive function performance. To test whether the resilience composite captures unique variance, we examined whether the AD signature displayed similar effects compared to the resilience composite, albeit in the opposite direction. In contrast to the resilience composite, baseline AD signature scores did not significantly impact the slope of memory performance over time nor did the AD signature modify the negative impact of p-tau on memory performance over time, consistent with prior work.[9] However, our data-driven approach focused on identifying new brain regions that offset the impacts of cortical thinning in AD related regions, and accounted for risk-related effects in all models to differentiate risk from resilience effects. In contrast to the AD risk signature, we found that higher baseline resilience composite scores did significantly weaken the negative impact of p-tau on longitudinal memory performance. This novel finding highlights the value of focusing on brain regions beyond those associated with higher risk for AD. Although some risk-related variance is reflected in the resilience composite given the partially overlapping regions with the AD signature, results show that just having low risk does not demonstrate the same effects as this resilience composite. Findings also highlight heterogeneity within risk-related measures such as the AD signature. It may be that the average of cortical thickness in AD signatures obscures heterogeneity across regions that differentially contribute to risk and resilience, as suggested by our prior work.[34]

These findings are contextualized by several limitations. We demonstrated cognitive resilience against different forms of risk for AD-related cognitive decline, although there are many other plausible predictors of cognitive resilience or other forms of risk that we did not assess, and our models were not exhaustive. We also focused specifically on cortical thickness as a contributor to cognitive resilience, although future work would benefit from examining different types of imaging metrics (eg, diffusion in gray and white matter, functional imaging), genetic, or sociodemographic factors and their relationships to cognitive resilience.[35] With regard to imaging measures, there were differences in FreeSurfer versions across study protocols, which may result in differences in group-level estimates of cortical thickness across time. However, our primary interest was in the moderating effects of cortical thickness rather than group differences in means, which minimizes the influence of potential version-related bias on our results. The AD signature that we used was developed in the ADNI-1 sample, and some of the same participants that were used in the development of the signature may have contributed data at subsequent visits in the present analyses if they met our inclusion criteria. For this reason, we did not use ADNI-1 data, with the tradeoff of a smaller sample size. Generalizability of these results may be limited given that the ADNI sample is largely White, non-Hispanic, and highly educated. Additional work is required in more representative samples.

In conclusion, we found evidence that thicker cortex in several temporal, parietal, occipital, and limbic regions may confer cognitive resilience by weakening the adverse effects of risk for AD-related cognitive decline, both concurrently and longitudinally. The results highlight the value of focusing on brain regions beyond those associated with higher risk for AD, as well as variation within AD-related regions. Higher cortical thickness in these regions was associated with better concurrent executive functioning. Moreover, higher thickness in a composite of these regions predicted slower memory decline over time and reduced the negative effects of p-tau on memory performance over time, independent of the effects of an AD brain signature, p-tau, and education. Results suggest that better executive functioning may enable compensation in later memory performance. Our findings provide insight into individual variability in cognitive trajectories among individuals on the AD continuum and illustrate a clear analytic framework for studying neuroimaging predictors of cognitive resilience, with implications for improving prediction of clinical progression and elucidating

additional protective mechanisms against the impacts of AD pathology.

Acknowledgements

This work was supported by National Institute on Aging (grant R01 AG064955, S.J.G. and W.S.K.; R01 AG050595, W.S.K.; R01 AG076838, W.S.K.; and K01 AG063805, J.A.E.) Data used in preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf. Data collection and sharing for the ADNI is funded by the National Institute on Aging (National Institutes of Health Grant U19 AG024904). The grantee organization is the Northern California Institute for Research and Education. In the past, ADNI has also received funding from the National Institute of Biomedical Imaging and Bioengineering, the Canadian Institutes of Health Research, and private sector contributions through the Foundation for the National Institutes of Health (FNIH) including generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica; Biogen; Bristol-Myers Squibb Company; CereSpir; Cogstate; Eisai; Elan Pharmaceuticals; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche and its affiliated company Genentech; Fujirebio; GE Healthcare; IXICO; Janssen Alzheimer Immunotherapy Research and Development; Johnson and Johnson Pharmaceutical Research and Development; Lumosity; Lundbeck; Merck and Company; Meso Scale Diagnostics; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics.

Author Contributions

M.W., C.F., T.B., S.L., S.G., W.K., and J.E. contributed to the conception and design of the study; M.W., C.F., T.B., S.G., W.K., and J.E. contributed to the analysis and interpretation of data; M.W., C.F., T.B., S.G., W.K., and J.E. contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

Nothing to report.

Data Availability

The datasets analyzed in the current study are available in the ADNI database (adni.loni.usc.edu).

References

1. Bennett DA, Schneider JA, Arvanitakis Z, et al. Neuropathology of older persons without cognitive impairment from two community-based studies. Neurology 2006;66:1837–1844.
2. Riley KP, Snowdon DA, Desrosiers MF, Markesbery WR. Early life linguistic ability, late life cognitive function, and neuropathology: findings from the nun study. Neurobiol Aging 2005;26:341–347.
3. Schneider JA, Aggarwal NT, Barnes L, et al. The neuropathology of older persons with and without dementia from community versus clinic cohorts. J Alzheimers Dis 2009;18:691–701.
4. Corrada MM, Berlau DJ, Kawas CH. A population-based clinicopathological study in the oldest-old: the 90+ study. Curr Alzheimer Res 2012;9:709–717.
5. Jansen WJ, Ossenkoppele R, Knol DL, et al. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. JAMA 2015;313:1924–1938.
6. Gomez-Isla T, Frosch MP. Lesions without symptoms: understanding resilience to Alzheimer disease neuropathological changes. Nat Rev Neurol 2022;18:323–332.
7. Stern Y, Arenaza-Urquijo EM, Bartres-Faz D, et al. Whitepaper: defining and investigating cognitive reserve, brain reserve, and brain maintenance. Alzheimers Dement 2020;16:1305–1311.
8. Kremen WS, Elman JA, Panizzon MS, et al. Cognitive reserve and related constructs: a unified framework across cognitive and brain dimensions of aging. Front Aging Neurosci 2022;14:834765.
9. Bocancea DI, Svenningsson AL, van Loenhoud AC, et al. Determinants of cognitive and brain resilience to tau pathology: a longitudinal analysis. Brain 2023;146:3719–3734.
10. Stern Y, Albert M, Barnes CA, et al. A framework for concepts of reserve and resilience in aging. Neurobiol Aging 2023;124:100–103.
11. Elman JA, Vogel JW, Bocancea DI, et al. Issues and recommendations for the residual approach to quantifying cognitive resilience and reserve. Alzheimers Res Ther 2022;14:102.
12. Jack CR Jr, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association workgroup. Alzheimers Dement 2024;20:5143–5169.
13. Therriault J, Vermeiren M, Servaes S, et al. Association of Phosphorylated tau Biomarkers with Amyloid Positron Emission Tomography vs tau positron emission tomography. JAMA Neurol 2023;80:188–199.
14. Shaw LM, Vanderstichele H, Knapik-Czajka M, et al. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. Ann Neurol 2009;65:403–413.
15. Hansson O, Seibyl J, Stomrud E, et al. CSF biomarkers of Alzheimer's disease concord with amyloid-beta PET and predict clinical progression: a study of fully automated immunoassays in BioFINDER and ADNI cohorts. Alzheimers Dement 2018;14:1470–1481.
16. Landau SM, Breault C, Joshi AD, et al. Amyloid-beta imaging with Pittsburgh compound B and florbetapir: comparing radiotracers and quantification methods. J Nucl Med 2013;54:70–77.
17. Royse SK, Minhas DS, Lopresti BJ, et al. Validation of amyloid PET positivity thresholds in centiloids: a multisite PET study approach. Alzheimers Res Ther 2021;13:99.
18. Jack CR Jr, Bernstein MA, Fox NC, et al. The Alzheimer's disease neuroimaging initiative (ADNI): MRI methods. J Magn Reson Imaging 2008;27:685–691.

19. Williams ME, Elman JA, McEvoy LK, et al. 12-year prediction of mild cognitive impairment aided by Alzheimer's brain signatures at mean age 56. Brain Commun 2021;3.

20. McEvoy LK, Fennema-Notestine C, Cooper Roddey J, et al. Quantitative structural neuroimaging for detection and prediction of clinical and structural changes in mild cognitive impairment. Radiology 2009;251:195–205.

21. McEvoy LK, Holland D, Hagler DJ, et al. Baseline and longitudinal structural MR imaging measures improve predictive prognosis. Radiology 2011;259:834–843.

22. Mukherjee S, Choi SE, Lee ML, et al. Cognitive domain harmonization and cocalibration in studies of older adults. Neuropsychology 2023;37:409–423.

23. Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models Usinglme4. J Stat Softw 2015;67:1–48.

24. Williams ME, Elman JA, Bell TR, et al. Higher cortical thickness/volume in Alzheimer's-related regions: protective factor or risk factor? Neurobiol Aging 2023;129:185–194.

25. Li J, Ji L. Adjusting multiple testing in multilocus analyses using the eigenvalues of a correlation matrix. Heredity 2005;95:221–227.

26. McCabe DP, Roediger HL, McDaniel MA, et al. The relationship between working memory capacity and executive functioning: evidence for a common executive attention construct. Neuropsychology 2010;24:222–243.

27. Chang YL, Jacobson MW, Fennema-Notestine C, et al. Level of executive function influences verbal memory in amnestic mild cognitive impairment and predicts prefrontal and posterior cingulate thickness. Cereb Cortex 2010;20:1305–1313.

28. Elman JA, Oh H, Madison CM, et al. Neural compensation in older people with brain amyloid-beta deposition. Nat Neurosci 2014;17:1316–1318.

29. Gustavson DE, Reynolds CA, Hohman TJ, et al. Alzheimer's disease polygenic scores predict changes in episodic memory and executive function across 12 years in late middle age. J Int Neuropsychol Soc 2023;29:136–147.

30. Junquera A, Garcia-Zamora E, Olazaran J, et al. Role of executive functions in the conversion from mild cognitive impairment to dementia. J Alzheimers Dis 2020;77:641–653.

31. Harrison TM, Chadwick T, Pezzoli S, et al. Cognitive trajectories and Alzheimer disease biomarkers: from successful cognitive aging to clinical impairment. Ann Neurol 2024;96:378–389.

32. Aschenbrenner AJ, Gordon BA, Benzinger TLS, et al. Influence of tau PET, amyloid PET, and hippocampal volume on cognition in Alzheimer disease. Neurology 2018;91:e859–e866.

33. Jagust WJ, Landau SM. Alzheimer's disease neuroimaging I. Temporal dynamics of beta-amyloid accumulation in aging and Alzheimer disease. Neurology 2021;96:e1347–e1357.

34. Williams ME, Gillespie NA, Bell TR, et al. Genetic and environmental influences on structural- and diffusion-based Alzheimer's disease neuroimaging signatures across midlife and early old age. BiolPsychiatry 2022;8:918–927.

35. Hou J, Hess JL, Armstrong N, et al. Polygenic resilience scores capture protective genetic effects for Alzheimer's disease. Transl Psychiatry 2022;12:296.