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An empirical measure of resilience explains individual differences in the effect of tau pathology on memory change in aging

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Abstract

Accurately measuring resilience to preclinical Alzheimer's disease (AD) pathology is essential to understanding an important source of variability in cognitive aging. In a cohort of cognitively normal older adults (n = 123, age 76.75 ± 6.15 yr), we built a multifactorial measure of resilience which moderated the effect of AD pathology on longitudinal cognitive change. Linear residuals-based measures of resilience, along with other proxy measures (education and vocabulary), were entered into a hierarchical partial least-squares path model defining a putative consolidated resilience latent factor (model goodness of fit = 0.77). In a set of validation analyses using linear mixed models predicting longitudinal cognitive change, there was a significant three-way interaction among consolidated resilience, tau and time on episodic memory change (P = 0.001) such that higher resilience blunted the effect of tau pathology on episodic memory decline. Interactions between consolidated resilience and amyloid pathology on non-memory cognition decline suggested that resilience moderates pathology-specific effects on different cognitive domains.

The neuropathological markers of Alzheimer's disease (AD), amyloid-beta (Aβ) and hyperphosphorylated tau, accumulate in the brain decades before the onset of cognitive decline[1]. A model of the temporal sequence of preclinical pathology describes initial A– deposition, followed by tau deposition, then tau-mediated neuronal injury and dysfunction[2].

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Author contributions

T.M.H., D.M. and W.J.J. contributed to the conception and design of the study. L.D., K.Z., S.L.B. and T.M.H. contributed to the acquisition, curation and analysis of the data. L.D. and T.M.H. wrote the original manuscript draft. All authors contributed to drafting the final manuscript and figures.

Competing interests

The authors have no competing interests.

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Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Next, as AD moves from the preclinical to the clinical phase, structural brain atrophy progresses, memory function declines and finally patients experience generalized cognitive impairment. This general model does not, however, capture the individual heterogeneity that exists at each phase.

Cognitive aging trajectories are heterogenous, and differing capacity to cope with preclinical AD pathology is one source of variability in cognitive performance in older adults. Evidence that there is not a one-to-one correspondence between pathology and cognition initially came from autopsy studies that showed some older adults who are cognitively healthy at the time of death have substantial AD pathology, sometimes similar to those with dementia[1,3]. Several terms have been used to describe this variability in clinical expression of AD pathology including cognitive reserve and cognitive resilience[4-6]. These terms are overlapping and precise definitions can be difficult to operationalize, though there are coordinated efforts to do so[7]. The concept of resilience encompasses aspects of cognitive reserve and is often applied as relating to an individual's ability to cope with pathology, which can be measured in neuropathological studies or with specific imaging or fluid biomarkers. The crucial idea behind both resilience and reserve is that individuals with higher reserve and/or resilience perform better than expected given their pathological burden whereas individuals with lower reserve and/or resilience will experience greater decline than expected. In other words, despite various measurement approaches in the literature, greater reserve and resilience is associated with reduced risk of progression to mild cognitive impairment or AD[8,9].

Using a resilience framework and positron emission tomography (PET) neuroimaging biomarkers of Aβ and tau, the variability in cognitive performance relative to preclinical AD pathology can now be assessed in vivo. Measures of resilience in the literature are often indirect proxies of the concept, such as years of education or IQ, which are hypothesized to capture neural advantages underlying resilience[10]. Evidence suggests that proxy measures such as education capture early life experiences that cannot be modified in later life[11]. Another approach to measuring resilience is to use linear models to predict cognition with relevant predictors and use the residuals of the model as a measure of resilience because they represent the variance in cognition that cannot be explained with available data[12]. Residual measures may be better suited for capturing current resilience and have been shown to vary over time in older adults[13]. Finally, latent factor modeling approaches can be used to combine multiple putative measures of resilience into a single latent factor[14,15]. Here, we combine these approaches in a theory-driven manner, using a latent factor framework with both proxy-based (early-life) and residuals-based (later-life) measures, to attempt to best capture the concept of resilience in a single factor, which we refer to as 'consolidated resilience'. Combined with PET measures of Aβ and tau in the same individuals, we can explore relationships among resilience, AD pathology and cognition in our cohort of cognitively normal older adults.

Accurate, quantitative measurement of resilience on the individual level is essential to uncovering factors related to successful aging outcomes. One approach to assessing the construct validity of a resilience measure is to test for an interaction between the measure and pathology on cognition[7]. For a valid measure, higher resilience should be related

to less pathology-associated cognitive decline. Another consideration is how resilience is related to decline in different cognitive domains[16]. Here, we address both of these issues by (1) assessing how resilience affects the relationship between pathology and cognition and (2) examining two domain scores weighted by confirmatory factor analysis (CFA), one composed of episodic memory tests and another composed of tests of executive functioning, processing speed and fluency (non-memory cognition).

The objective of the present study was to create a theory-driven, consolidated resilience score and validate this measure by examining its relationship with AD pathology and longitudinal cognitive trajectories. We deliberately chose to call our score a resilience measure because our aim was to assess cognitive resilience to AD pathology measured with PET imaging. A key validation step was the assessment of whether consolidated resilience moderated the relationship between pathology and cognitive decline[7]. We hypothesized that our consolidated resilience score would be associated with less cognitive decline over time in the episodic memory domain. Finally, we predicted that there would be a significant interaction between AD pathology and consolidated resilience on episodic memory decline such that individuals with higher resilience would show a blunted relationship between tau pathology and memory decline.

Results

Overview

We used latent variable modeling to create a consolidated resilience score and then related it to AD pathology and cognitive trajectories. Study participant data were obtained from the longitudinal, observational Berkeley Aging Cohort Study (BACS). All participants underwent neuropsychological testing, [11 C] Pittsburgh Compound B (PiB) PET scans to measure Aβ pathology, [18 F] flortaucipir (FTP) PET scans to measure tau pathology and magnetic resonance imaging (MRI) scans to measure brain structure and create regions of interest (ROIs). We focused on two cognitive domain scores, episodic memory and non-memory cognition, based on CFAs of our neuropsychological data (Fig. 1). CFAs were completed using all BACS participants. CFA-weighted episodic memory and non-memory cognition domain scores were used to calculate a residuals-based measure of resilience. Separately, we used years of education and premorbid IQ (vocabulary score) to create a proxy-based measure of resilience. Together, our proxy-based and residuals-based measures were entered into a partial least-squares (PLS) path model to generate consolidated resilience scores for each individual participant (Fig. 2). The PLS path model was built using only BACS participants who had undergone MRI and PET imaging. Consolidated resilience scores were then entered into linear mixed effects models, which revealed moderating effects of consolidated resilience on the association between PET measures of tau and Aβ pathology and longitudinal change in episodic memory and non-memory cognition domain scores.

Participants

Demographic characteristics of the BACS participants included in each analysis are summarized in Table 1. The average age of the imaging cohort participants (n = 123) at

the cognitive session used in the PLS path model (closest to FTP-PET) was 76.75 ± 6.15 years with 58% females and an average of 16.88 ± 1.88 years of education. The larger cohorts used for the CFAs did not differ from the imaging cohort in sex or years of education (all $P > 0.05$), but they were slightly younger (both $P < 0.001$). In the imaging cohort, 23% of participants carried the apolipoprotein ε4 allele, 42% of participants were PiB positive, and the average cognitive follow-up time was 5.81 ± 3.98 years with an average of 5.58 ± 3.34 cognitive sessions. One participant did not have usable PiB data, so this participant was excluded from models including global PiB distribution volume ratio (DVR). A total of 18 (out of 1,599) cognitive test scores closest to the baseline FTP-PET were imputed for the primary cohort. A total of 50 scores (out of 8,840) were imputed due to missingness across all cognitive sessions for all participants.

CFA-generated cognitive domain scores

Using CFA, episodic memory and non-memory cognitive domains were modeled; 493 participants were included in the episodic memory CFA and 515 participants included in the non-memory cognition CFA based on our criteria requiring complete neuropsychological test data within each domain. The episodic memory model had a Comparative Fit Index (CFI) value of 0.998, a Tucker-Lewis Index (TLI) of 0.995, a root mean square error of approximation (RMSEA) value of 0.032 and a standardized root mean square residual (SRMR) value of 0.014, which all indicate that this model was a good fit for the data. This CFA model generated standardized factor loadings of 0.737 for California Verbal Learning Test Short Delay Free Recall (CVLT SDFR), 0.765 for California Verbal Learning Test Long Delay Free Recall (CVLT LDFR), 0.570 for visual reproduction I (VR I), 0.630 for visual reproduction II (VR II), 0.656 for logical memory and 0.642 for verbal paired associates (Fig. 1a). The factor loadings were then used as weights to calculate episodic memory domain scores for each participant. The non-memory cognition model generated through the CFA had a CFI value of 0.982, a TLI of 0.969, an RMSEA value of 0.052 and an SRMR value of 0.031, which all indicate that this model was a good fit for the data. This CFA model generated standardized factor loadings of 0.722 for Stroop in 60 s, 0.815 for digit symbol, −0.550 for Trail B-A, −0.564 for Trail Making Test A, 0.388 for backwards digit span, 0.535 for animal naming and 0.547 for vegetable naming (Fig. 1b). These factor loadings were then used as weights to calculate composite non-memory cognition scores for each participant.

Estimating a residuals-based measure of cognitive resilience

We used the residuals from multiple linear regressions predicting cognition (episodic memory domain and non-memory cognition domain separately) to create a residuals-based measure of resilience[12]. The results of these multiple linear regression models are shown in Supplementary Table 1. We observed a significant effect of hippocampal volume (β=0.018, $P = 0.008$) in predicting episodic memory. We observed significant effects of hippocampal volume (β=0.013, $P = 0.03$) and whole cortex thickness (β=63.540, $P = 0.003$) in predicting non-memory cognition. Residuals from these models were entered into the PLS path models as a residuals-based measure of cognitive resilience (Fig. 2).

PLS path models

To calculate participant-specific consolidated resilience scores we built a PLS path model combining the residuals-based measures of cognitive resilience and common proxy-based measures from the literature. The PLS path model and corresponding loadings are shown in Fig. 2. The goodness-of-fit score of 0.77 indicates a good-fitting model. No indicator cross-loaded onto another first-order latent trait (all crossloadings <0.46). Each first-order latent trait demonstrated clear unidimensionality (Dillon-Goldstein's rho >0.78, first eigenvalue >1.28, second eigenvalue <0.79). Factor scores for the second-order latent factor were extracted from the PLS path model and used as our measure of consolidated resilience.

Consolidated resilience and AD pathology

We first examined cross-sectional relationships between consolidated resilience and measures of AD pathology to ensure these measures were not colinear. There was a nonsignificant trend negative correlation between consolidated resilience and ERC FTP SUVR across the whole imaging cohort ($r = -0.164$, $P = 0.07$; Supplementary Fig. 1a) and no significant associations in PiB^+ participants ($r = -0.117$, $P = 0.41$) or PiB^- participants ($r = -0.134$, $P = 0.27$) separately. The interaction between PiB status and consolidated resilience was not significant ($P = 0.82$). Associations with consolidated resilience were not significant for FTP measured in IT (whole cohort: $r = -0.104$, $P = 0.25$; PIB^+: $r = -0.052$, $P = 0.71$; PiB^-: $r = -0.066$, $P = 0.59$) or the temporal MetaROI (whole cohort: $r = -0.085$, $P = 0.35$; PIB^+: $r = 0.00$, $P = 1$; PiB^-: $r = -0.075$, $P = 0.54$). Similarly, the correlation between consolidated resilience and global PiB DVR was negative but not significant in the whole cohort ($r = -0.168$, $P = 0.06$; Supplementary Fig. 1b) or in either PiB status subgroup (PIB^+: $r = -0.112$, $P = 0.43$; PiB^-: $r = -0.212$, $P = 0.08$).

Consolidated resilience, AD pathology and longitudinal cognition

We posited that higher resilience scores should be related to better longitudinal cognitive outcomes and should moderate the effect of AD pathology on cognitive decline. We used linear mixed effects models to test for these relationships using our consolidated resilience measure. Longitudinal cognitive domain data are plotted in Supplementary Fig. 2. In the model predicting episodic memory with ERC FTP SUVR, age and consolidated resilience showed significant main effects ($p < 0.001$; full model output is shown in Table 2a). In addition, the two-way interaction of ERC FTP SUVR with time was significant ($P < 0.001$), as well as our main predictor of interest, the three-way interaction between ERC FTP SUVR, consolidated resilience and time ($P = 0.001$). To illustrate this three-way interaction effect, we plotted the relationship between episodic memory and higher or lower ERC FTP SUVR over time in the context of higher or lower consolidated resilience (Fig. 3a). These plots reveal that high resilience is associated with a blunted effect of ERC FTP SUVR on episodic memory decline. The 2- and 3-way interactions were not significant in the model predicting longitudinal non-memory cognition (Table 2a and Fig. 3b). The results from both episodic memory and non-memory cognition models were similar using IT or MetaROI FTP SUVR values as the tau pathology measure, except episodic memory models also showed a significant two-way interaction between consolidated resilience and time ($P = 0.02$; Supplementary Table 2). Additionally, the two-way interaction between IT FTP SUVR

values and consolidated resilience was significant for the non-memory cognition model (P = 0.02; Supplementary Table 2).

Next, models predicting cognition (episodic memory and non-memory cognition) with global PiB DVR as the AD pathology measure showed significant main effects of age and consolidated resilience ($P \leq 0.01$; Table 2b), a significant two-way interaction of global PiB DVR with time ($P \leq 0.01$) as well as the three-way interaction between global PiB DVR, consolidated resilience and time ($P < 0.02$). An additional significant main effect of sex was found in the non-memory cognition model ($P = 0.002$). To illustrate the three-way interaction, we plotted the relationship between both episodic memory or non-memory cognition with higher or lower global PiB DVR over time in the context of higher or lower consolidated resilience (Fig. 4).

Finally, as an exploratory analysis to better understand the interactions between consolidated resilience and Aβ and tau pathology on cognition, we ran mixed effects models that included a four-way interaction term: global PiB DVR, ERC FTP SUVR, consolidated resilience and time. Full model results are shown in Supplementary Table 3. In the model predicting non-memory cognition, but not episodic memory, the four-way interaction term was significant ($P = 0.03$).

Discussion

Using a multifactorial latent variable model, we created a measure of consolidated resilience that moderated the effect of AD pathology on cognitive decline in cognitively healthy older adults. Consolidated resilience interacted with tau measures and time in linear mixed effects models, demonstrating that greater consolidated resilience buffered the effect of tau pathology on episodic memory decline. In addition, we found that consolidated resilience interacted with Aβ pathology to predict non-memory cognitive decline over time. An exploratory model showed a four-way interaction accounting for Aβ, tau and resilience effects on cognitive decline was significant only for the non-memory cognition domain.

We interpret our results based on established findings that episodic memory declines early in aging and is strongly associated with pathological tau[17-19]. Given this, results demonstrating that consolidated resilience moderates the negative association between tau and memory are evidence that our measure captures information about functional resilience to tau pathology in older adults. Indeed, a recent consensus paper highlighted the importance of demonstrating that putative resilience measures moderate the effect of brain injury or pathology on cognition[7]. By using a rich, longitudinal cognitive dataset, we showed that the moderation of tau pathology by consolidated resilience affects cognitive trajectories, not just cross-sectional performance. Furthermore, consolidated resilience moderated the effect of tau on cognition regardless of which ROI was used to measure tau. It is remarkable that these findings were observed using a cohort of cognitively healthy older adults, and the finding suggests that there is sufficient variability in consolidated resilience in cognitively normal older adults to observe key moderation effects between pathology and cognitive decline.

Previous studies have demonstrated moderating effects of reserve or resilience measures on cross-sectional relationships between tau and memory. One of these studies also found an attenuation of the relationship between tau and cross-sectional episodic memory based on the reserve proxy IQ, similar to the interaction effect we observe here with longitudinal cognitive data in cognitively healthy older adults[20]. In another study, a measure of brain resilience (for example, residuals from models predicting brain structure) interacted with tau pathology to predict MMSE scores in a group of mild cognitive impairment and AD patients[21]. Finally, several studies have examined left frontal functional connectivity as mechanism of resilience[22,23], including in moderating the effect of tau on memory performance in cognitively normal older adults and patients with mild cognitive impairment[24]. These studies highlight the diverse approaches applied to studying resilience and demonstrate that there is likely a myriad of sources and substrates of resilience to tau pathology. Compared to the literature, our study is different in several ways, including (1) the use of longitudinal cognitive domain-specific performance data, (2) a cohort comprising only cognitively healthy older adults and (3) a composite measure of resilience that integrates published approaches.

Measures of reserve and resilience have also been shown to attenuate the relationship between Aβ and cognition in cohorts of older adults and AD patients[25,26] and predict Aβ pathology burden in cognitively normal older adults[27]. In the present study, consolidated resilience moderated the relationship between global Aβ and episodic memory decline, but we interpreted this Aβ effect as being driven by the correlation between tau and Aβ pathology[20], especially given the strength of the interaction between consolidated resilience and tau on episodic memory decline. Our interpretation is supported by a model including both Aβ and tau where the 4-way interaction term Aβ*tau*consolidated resilience*time did not significantly predict episodic memory. In contrast, our findings suggest that Aβ pathology may interact with consolidated resilience to predict non-memory cognition performance over time. A significant effect of Aβ*consolidated resilience*time was observed that was not likely to be explained by tau which, in a separate model, did not interact with consolidated resilience to predict non-memory cognition change. In line with this, the four-way interaction term Aβ*tau*consolidated resilience*time did significantly predict non-memory cognition change. The interpretation of this contrast in findings in the two cognitive domains is not entirely clear. First, it may be that Aβ pathology, which has a widespread spatial pattern of accumulation occurring across much of cortex simultaneously, is associated with more distributed cognitive functions, including executive function and processing speed[28]. Indeed a large meta-analysis showed the Aβ pathology is associated with decline in multiple cognitive domains and in global cognition in cognitively normal older adults[29]. Second, given the early expression of memory decline in aging and the close association with early tau pathology in the medial temporal lobe, it may be that relationships between resilience, pathology and executive function can only be observed in individuals with AD pathological change, or who are Aβ positive[30].

Our consolidated resilience score predicted change in cognition above and beyond baseline performance, which was a major goal in developing a valid consolidated resilience score. Baseline cognitive performance predicts future performance such that individuals with higher baseline performance generally experience less decline compared to those

whose baseline performance was poorer, even in cognitively healthy older adults[31,32]. The consolidated resilience measure we constructed with a PLS path model included residuals from a linear model predicting cross-sectional episodic memory. As these residuals likely were correlated with cross-sectional episodic memory[33,34], it was critical that our consolidated resilience measure was not simply a proxy of cross-sectional cognitive performance. In our mixed effects models, we included a random effect of participant intercept that adjusts the model for differences in baseline performance. Thus, the significant interactions we report from these models represent effects above and beyond the effect of baseline performance. Another key feature of a latent factor approach is that it allowed us to create a single consolidated resilience measure rather than separately conducting repeated tests to explore different proxy measures that likely capture small amounts of nonoverlapping variance in resilience. Finally, the consolidated resilience score is comprised of data available in many longitudinal observational cohort studies and may be easily replicated by other groups and related to different biomarkers.

FTP-PET was introduced into this present longitudinal observational study protocol when it became available in 2014. Here, we chose to build the PLS path model using cross-sectional cognitive domain scores closest in time to the FTP-PET (and corresponding PiB-PET) scan because we were interested in associations between consolidated resilience and pathology. In our mixed effects models, however, we thought it was important to use all the cognitive data available so for some participants the baseline cognitive session in the mixed effect model does not correspond to the session used in the PLS path model.

To ensure that this was not influencing our results, we ran PLS path models to create consolidated resilience scores using true baseline cognitive data and confirmed that our main findings remained consistent (Supplementary Table 4).

This study had several limitations. First, the cohort is relatively homogenous in regards to race/ethnicity, education and socioeconomic status. This homogeneity may limit the generalizability of our findings and is a pervasive limitation in human subjects research. We also observed increasing cognitive performance slopes in some of our participants indicative of practice effects which are common in longitudinal cognitive data in healthy older adults[35]. However, even in our relatively homogenous, cognitively normal sample, our results show that there was sufficient variability to generate meaningful consolidated resilience scores. Second, we encountered conceptual limitations in the choice of variables to include in the PLS path model. Variables included in the model cannot be used in later validation steps. As cognition, brain structure, pathology and demographic characteristics are all interrelated, there may exist circularity in the model between variables included and variables used to validate it. We attempted to reduce this by using variables to validate the model (AD pathology, change in cognition) that were not included in the model calculation. Finally, the use of proxy measures to capture abstract constructs such as reserve and resilience is inherently limited, and certain proxies may be related to other unmeasured factors. For example, having higher years of formal education likely confers many advantages over one's peers, including factors not measured in the present study. In addition, there are other measures that were not available in the present cohort, such as occupational complexity and late-life social stimulation, that would have strengthened

our conceptual model of consolidated resilience. Using the data available in BACS, our approach attempted to consolidate different aspects of resilience across multiple measures to create a single factor that captured resilience across the constituent measures. Finally, the exploratory model examining the four-way interaction between Aβ, tau, consolidated resilience and time (Supplementary Table 3) may be underpowered given our sample size.

In summary, we created a single measure of consolidated resilience that moderates the effect of AD pathology on cognitive decline in a cohort of cognitively normal, older adults. Our findings provide evidence that latent factor models are a useful way to measure consolidated resilience and that moderation of pathology–cognition relationships can be observed in unimpaired individuals. In future work, we will further refine our approach with longitudinal AD pathology measures and data arising from a more diverse cohort. Given further refinement and study, a multifactorial modeling approach to defining resilience could act as an early screener tool for cognitively healthy older adults who are at higher risk for cognitive decline.

Methods

Participants

The BACS is an ongoing cohort study that has enrolled over 500 cognitively normal older adults and is composed of volunteers who were recruited into the cohort via advertisements and word of mouth. Recruitment for the cohort began in 2005 and is ongoing. BACS enrollment criteria include a Mini-Mental State Examination score ≥25, normal daily function, and scores on the California Verbal Learning and Visual Reproduction tests within 1.5 standard deviations of age, sex, and education-adjusted norms. Exclusion criteria include history of neurological disease, mental illness that could affect cognition, history of substance abuse, depression, or neuroimaging contraindications. In this study we examined BACS participants aged 60 or older who had demographic and neuropsychological data available. Additional requirements for the imaging cohort were completed FTP-PET and structural MRI scans. No statistical methods were used to predetermine sample sizes. We used the number of cumulative BACS participants who met our inclusion criteria for each analysis. Demographic variables were compared between analysis cohorts using two-sided independent *t*-tests for continuous variables and Fisher's exact test for categorical variables.

Written informed consent was obtained from all participants and participants were compensated for their time ($75 for cognitive sessions, $150 for combined PiB- and FTP-PET scanning session). The study protocols have been approved by the University of California, Berkeley and Lawrence Berkeley National Laboratory (LBNL) institutional review boards (073H004-22AP23).

Image acquisition and processing

Radiotracers for the PiB- and FTP-PET scans were prepared at LBNL and the data were acquired on a Siemens Biograph PET/computerized tomography scanner. DVR values for PiB-PET images were generated with Logan graphical analysis on frames corresponding to 35–90 min after injection using a cerebellar gray matter reference region[36,37]. Participants'

global PiB DVR (Supplementary Fig. 3) was calculated as the mean in FreeSurfer-derived frontal, temporal, parietal and posterior cingulate ROIs as previously described[38,39]. A global PiB DVR > 1.065 defined PiB positivity.

FTP standardized uptake value ratio (SUVR) measures were based on mean tracer uptake 80–100 min after injection normalized by mean inferior cerebellar gray matter[40]. Image processing was completed using SPM12 and MATLAB vR2019b. SUVR measures in FreeSurfer-derived ROIs[41] were partial volume (PV) corrected using the Geometric Transfer Matrix approach[42]. PV-corrected ROI SUVR values were re-normalized by PV-corrected inferior cerebellar gray reference region. Tau pathology was measured using PV-corrected SUVR values for entorhinal cortex (ERC; Supplementary Fig. 3), inferior temporal gyrus (IT) and a MetaROI composed of temporal regions (entorhinal, amygdala, parahippocampal, fusiform, inferior temporal and middle temporal gyri)[43]. We chose ERC because this is the earliest cortical site of tau accumulation and it is related to memory, IT because it is an early region of tau spread outside the MTL and the MetaROI because it has been shown to best differentiate between AD patients and controls[19,43].

Structural MRIs were collected for defining structural ROIs. MRI data were acquired on a Siemens 1.5 T Magnetom Avanto scanner at LBNL. Each participant received a structural, whole-brain three-dimensional T1-weighted magnetization prepared rapid gradient echo sequence with the following parameters: sagittal slice orientation, repetition time = 2,110 ms, echo time = 3.58 ms, flip angle = 15°, and voxel size = 1 mm isotropic. MRIs were segmented into ROIs, including ERC, IT, subregions of the tau-PET MetaROI, whole hippocampus volume and mean cortex thickness, using FreeSurfer (v. 5.3).

Statistics and reproducibility

CFA-generated cognitive domain scores.—BACS participants undergo a standard neuropsychological battery that includes tests of verbal and visual memory, language, frontal/executive function and verbal memory. Using these data in all available participants, we completed a series of CFAs (using ‘lavaan’ in R v4.0.3) initially evaluating domains for episodic memory, executive functioning, processing speed, language and working memory. We determined neuropsychological tests optimally loaded onto two factors, one representing episodic memory and one representing non-memory cognition, including tests of executive function, processing speed, fluency and working memory.

CVLT SDFR, CVLT LDFR, VRI, VRII, logical memory total score, and verbal paired associates data were included in a single-factor solution to quantify the episodic memory composite (Supplementary Fig. 3). Additional covariance terms were included a priori in the model between CVLT SDFR and CVLT LDFR as well as between VRI and VRII to account for correlations expected between subscores of the same test (Fig. 1a). Stroop in 60 s, digit symbol, Trail Making Test A subtracted from Trail Making Test B (Trails B-A), Trail Making Test A, Backward digit span, animal naming, and vegetable naming data were included in a single-factor solution to quantify the non-memory cognition composite (Supplementary Fig. 3). Additional covariance terms were included a priori in the model between animal naming and vegetable naming as well as between Trails B-A and Trails Making Test A (Fig. 1b).

All BACS participants (≥60 years) who had neuropsychological testing data were initially included in CFAs. If a participant was missing one cognitive testing score in either the episodic memory or non-memory cognition domains, these data were imputed by using the average respective test score across all baseline BACS participants (≥60 years). A total of 18 (out of 1,599) cognitive test scores closest to the baseline FTP-PET were imputed for the imaging cohort. A total of 50 scores (out of 8,840) were imputed due to missingness across all cognitive sessions for all participants. Eight participants with two or more missing test scores were excluded from the CFAs. The fit statistic cutoffs used to determine the validity of a standalone CFA model were: CFI value >0.95, TLI > 0.95, RMSEA value <0.06 and an SRMR value <0.08 (ref.[44]). These are commonly reported fit statistics which have been reported in previous factor analyses of neuropsychological batteries[45,46].

Standardized factor loadings were used as numerical weights and multiplied to the corresponding cognitive test score for each cognitive domain. We then summed these weighted test data together to create episodic memory and non-memory cognition domain scores for every cognitive session for each participant in the imaging cohort. This is a common approach that correlates highly with factor scores ($r > .92$ for both episodic memory and non-memory cognition domain scores) and allows for application of weights to data not used in the original model construction[47].

For all analyses, data collection was not randomized nor blinded. All data were modeled continuously. Data distribution was assumed to be normal, but this was not formally tested.

Residuals-based measures of resilience with linear models.—Linear models were used to calculate a residuals-based measure of resilience. In this approach, episodic memory and non-memory cognitive domain scores were regressed against age, sex, mean bilateral ICV-normalized hippocampal volume and mean bilateral whole cortex thickness. An individual with a positive residual from the regression model would indicate better-than-expected cognition.

Because we were interested in the relationship between resilience and pathology, we focused on cross-sectional episodic memory and non-memory cognition domain scores from the cognitive session closest to baseline FTP-PET scan to estimate a residuals-based score. An average of 2.84 ± 1.69 months took place between the cognitive test session and the FTP-PET scan.

Residuals-based measure linear regression equation:

$$cog\_score = \beta_0 + \beta_1 age + \beta_2 sex + \beta_3 hippo\ vol + \beta_4 thickness + \varepsilon \ldots,$$

where *cog_score* is either the episodic memory score or non-memory cognition score, *age* is the age of the participant, sex is the sex of the participant, *hippo vol* is the mean bilateral hippocampal volume normalized to intracranial volume, *thickness* is the mean bilateral whole cortex thickness, and ε is the residual term.

The residual term was used as a residuals-based measure of cognitive resilience in the hierarchical model used to capture consolidated resilience (Fig. 2).

PLS path modeling to estimate consolidated resilience.—To create a consolidated resilience score, we used a multivariate PLS path model ('plspm' in R v. 4.0.3), an approach related to structural equation modeling that is used to model relationships between groups of variables[48]. One key feature of the PLS path model is that there is an assumption that the variables loading onto a single latent variable are related or correlated. This makes the PLS path model a good option for modeling data that are collinear. We built our PLS path model using a residuals-based measure of cognitive resilience (residuals terms described above) and a proxy-based measure. Years of education and score on the WAIS Vocabulary test (a putative measure of premorbid IQ) were used to form the proxy-based factor. The PLS path model was composed of an inner and outer model[14]. The outer model of the PLS path model used reflective measurement to derive latent variables from the residuals-based and proxy-based measures. For the inner model, the residuals-based factor and proxy-based factor contributed to a consolidated resilience latent variable. A repeated indicators approach was used to derive the consolidated resilience second-order latent variable from the two outer model latent variables. The model's overall goodness of fit was assessed using both the average communality score and the average r^2 value. A goodness of fit > 0.7 is generally accepted as a good model[48]. Additionally, to assess a good-fitting model, no indicator should cross-load onto another first-order latent trait at a greater value than the loading on the intended latent trait. Finally, to ensure model unidimensionality we expect the Dillon-Goldstein's rho > 0.7, the first eigenvalue > 1, and the second eigenvalue < 1 (ref.[48]). The distribution of the consolidated resilience score in the Imaging cohort is shown in Supplementary Fig. 3.

Validating the consolidated resilience score.—To evaluate the consolidated resilience measure, we tested whether it was associated with AD pathology and longitudinal decline in neuropsychological performance. First, Pearson correlations were used to test the association between consolidated resilience and pathology measures. These bivariate correlations between consolidated resilience and pathology were used as a check that the resilience scores were not just proxies of tau or amyloid. Linear mixed effects models were used to explore effects of consolidated resilience and pathology on change in episodic memory and non-memory cognition domain scores across all available neuropsychological testing sessions while modeling random effects (varies by individual) of participant intercept and slope with sex and age as fixed effect covariates. Continuous independent variables were centered at their sample means. Our primary predictor of interest was a three-way interaction between consolidated resilience, ERC FTP SUVR and time.

R syntax for the linear mixed-effects model:

$$cog\ scores = AD\ pathology\ measure * consol\ resil * time + sex + age + (time \mid participant)\ldots,$$

where *cog_scores* are repeated episodic memory scores or repeated non-memory cognition scores; *AD pathology measure* is the ERC FTP SUVR, global PiB DVR, temporal MetaROI

FTP SUVR, or IT FTP SUVR; *consol resil* is the consolidated resilience score; *time* is years since baseline cognitive session; sex is *sex* of the participant; *age* is age of the participant; and *participant* is the participant ID. (Note: R package 'lme4' (function: lmer).)

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Data availability

Data used in this study (PET images, magnetic resonance images and cognitive data) will be shared by request from any qualified investigator subject to the negotiation of a data use agreement. Controlled access to human subjects data is required by the reviewing IRB and only deidentified data may be shared. Requests for data will be answered promptly and should be directed to W.J.J. (jagust@berkeley.edu).

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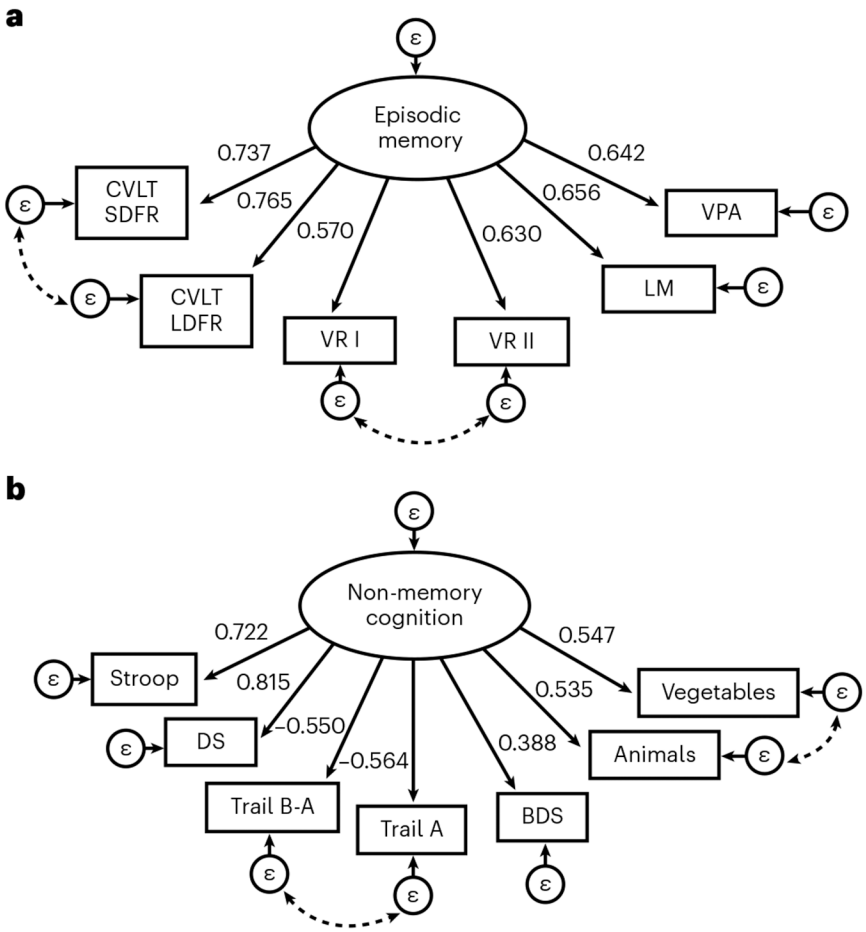

Fig. 1 |. CFA of two cognitive domains.

A graph of the CFA models used to generate episodic memory (**a**) and non-memory cognition (**b**) factors. Latent variables are shown in ovals and the measured neuropsychological tests are shown in rectangles, all which have unique error terms, Σ. Numbers next to the arrows indicate standardized factor loadings between measured variables and first-order latent variables. Double-headed, dashed arrows show covariances between different variables that are subscores on the same test. CVLT SDFR, California Verbal Learning Test Short Delay Free Recall; CVLT LDFR, California Verbal Learning Test Long Delay Free Recall; VR I, visual reproduction I; VR II, visual reproduction II; LM, logical memory; VPA, verbal paired associates; Stroop, Stroop in 60 s; DS, digit symbol; Trail B-A, Trail Making Test A subtracted from Trail Making Test B; Trail A, Trail Making Test A; BDS, backwards digit span; Animals, animal naming; Vegetables, vegetable naming.

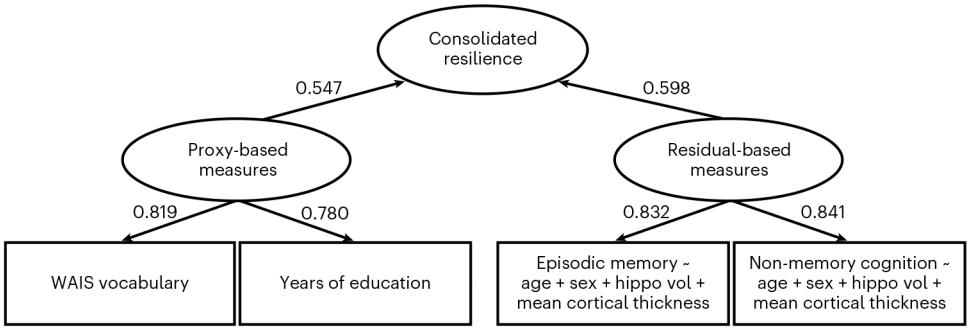

Fig. 2 |. PLS path model defining consolidated resilience.

A graph of the PLS path model used to generate consolidated resilience scores. The goodness of fit is 0.77. The variables included in each latent trait are represented as rectangles (measurement variables), and the factor loadings are represented as the numbers next to the arrows. The second-order latent variable (consolidated resilience) and the first-order latent variables (proxy-based measures, residuals-based measures) are depicted as ovals. Arrows pointing away from the first-order latent variables toward the measurement variables indicate reflective measurement. Arrows pointing away from the first-order latent variable towards the second-order latent variable indicate constructive measurement. The loadings for each first-order latent variable are presented above the arrows pointing to consolidated resilience. WAIS, Weschler Adult Intelligence Scale; hippo vol, bilateral hippocampal volume normalized by intracranial volume; mean cortical thickness, mean bilateral whole cortex thickness.

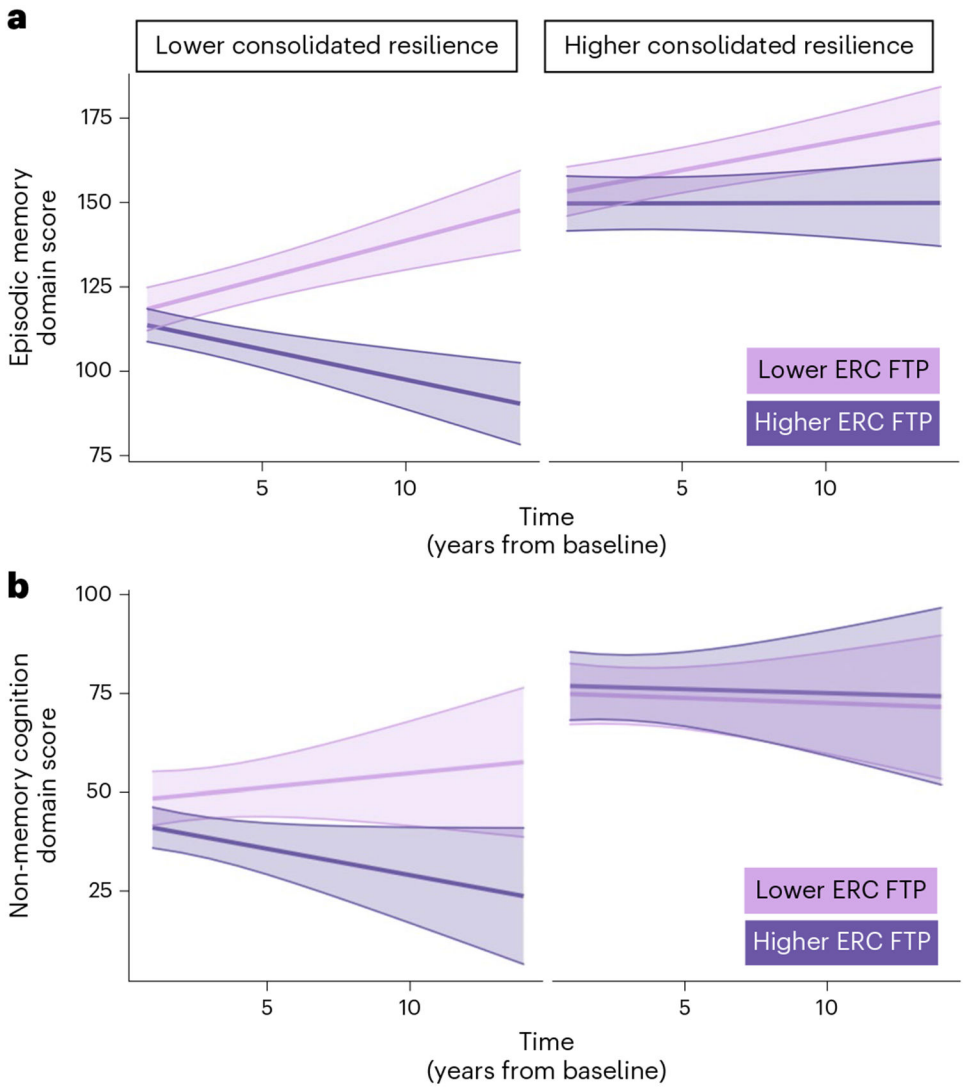

Fig. 3 | Consolidated resilience and ERC FTP interact to predict change in episodic memory. Fitted longitudinal change in cognitive domain scores for episodic memory (**a**) and non-memory cognition (**b**) are plotted for lower and higher levels of consolidated resilience defined by the values that correspond to 1 standard deviation (s.d.) below and above the group mean factor score (−0.75, 1.13). Lower and higher ERC FTP groups were created similarly using 1 s.d. below and above the group mean SUVR (1.04 and 1.50). Shaded regions represent 95% confidence intervals. **a**, The plot demonstrates that greater consolidated resilience protects against ERC FTP-related episodic memory decline (consolidated resilience*ERC FTP*time; $P = 0.001$). **b**, The plot shows that consolidated resilience does not significantly protect against ERC FTP-related non-memory cognition decline (consolidated resilience*ERC FTP*time; $P > 0.05$). ERC, entorhinal cortex.

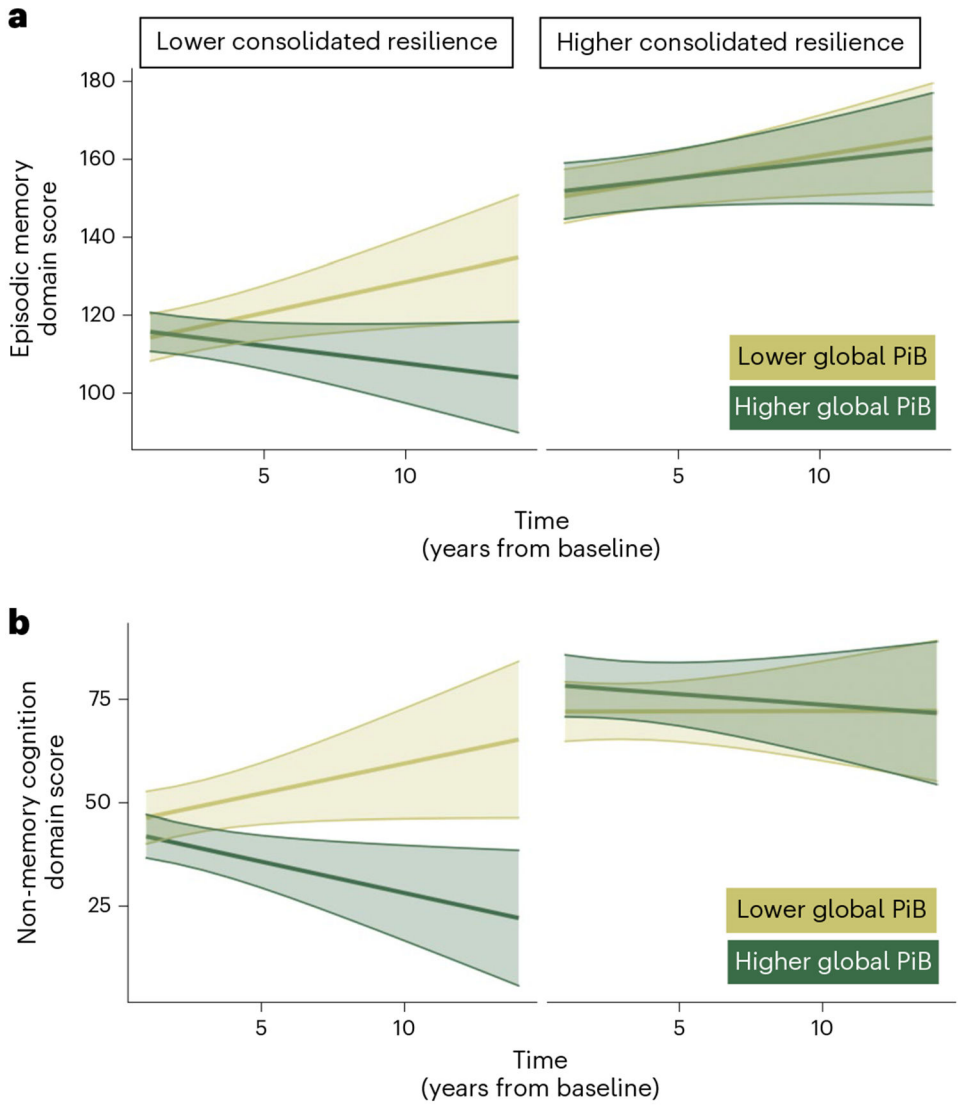

Fig. 4 |. Interactive associations of consolidated resilience and global PiB DVR on cognitive domain scores.

Fitted longitudinal change in cognitive domain scores for episodic memory (**a**) and non-memory cognition (**b**) are plotted for lower and higher levels of consolidated resilience defined by the values that correspond to 1 s.d. below and above the group mean (−0.75, 1.13). Lower and higher global PiB DVR groups were created similarly using 1 s.d. below and above the group mean DVR (0.94, 1.36). Shaded regions represent 95% confidence intervals. **a**, The plot demonstrates that greater consolidated resilience protects against PiB-related episodic memory decline (consolidated resilience*PiB DVR*time; $P = 0.009$). **b**, The plot shows that greater consolidated resilience protects against PiB DVR-related non-memory cognition decline (consolidated resilience*PiB DVR*time; $P = 0.02$).

Table 1 |

Analysis-specific cohort characteristics

	Episodic memory CFA cohort (*n* = 493)	**Non-memory cognition CFA cohort (*n* = 515)**	**Imaging cohort (*n* = 123)**
Age (yr)	74.04 (6.80)	74.01 (6.88)	76.75 (6.15)
Sex (M/F)	193/300	201/314	51/72
Education (yr)	16.74 (2.18)	16.76 (2.19)	16.88 (1.88)
MMSE	28.62 (1.52)	28.57 (1.57)	28.71 (1.23)
APOE ε4 (C/NC)	–	–	27/92 (4 NA)
PIB^{+}/PiB^{-}	—	—	52/70 (1 NA)
Cross-sectional episodic memory	127.32 (29.85)	126.83 (30.11)	132.89 (30.04)
Cross-sectional non-memory cognition	50.08 (40.61)	48.53 (42.69)	58.35 (26.82)
Cognitive follow-up (yr)	—	—	5.81 (3.98)

Global PiB DVR index >1.065 is classified as PIB^{+}. F,female; M,male; MMSE, Mini Mental State Exam; NA, not available;–,not applicable.

Table 2 |

Predicting longitudinal cognition: consolidated resilience with ERC FTP and global PiB DVR

Parameter	Episodic memory			Non-memory cognition		
	Estimate	**s.e.**	***P***	**Estimate**	**s.e.**	***P***
A: ERC FTP						
(Intercept)	133.668	2.710	*<0.001*	64.704	2.903	*<0.001*
Age	−1.025	0.303	*<0.001*	−0.583	0.319	0.07
Sex (male ref.)	−1.205	3.220	0.71	−10.227	3.364	*0.003*
ERC FTP	−2.970	7.736	0.70	−3.643	8.527	0.67
Consol Resil	18.579	1.671	*<0.001*	16.459	1.843	*<0.001*
Time	0.506	0.355	0.16	−0.273	0.488	0.58
ERC FTP*Consol Resil	−1.481	7.606	0.85	8.382	8.361	0.32
ERC FTP*time	−6.103	0.800	*<0.001*	−2.159	1.596	0.18
Consol Resil*time	0.302	0.207	0.15	0.049	0.394	0.90
ERC FTP*Consol Resil*time	2.870	0.824	*0.001*	2.412	1.637	0.15
B: Global PiB						
(Intercept)	133.040	2.707	*<0.001*	64.275	2.843	*<0.001*
Age	−1.159	0.301	*<0.001*	−0.793	0.310	*0.01*
Sex (male ref.)	−1.595	3.327	0.63	−10.813	3.404	*0.002*
Global PiB	6.689	7.741	0.39	6.225	8.353	0.46
Consol Resil	18.883	1.716	*<0.001*	16.550	1.854	*<0.001*
Time	0.677	0.397	0.09	−0.127	0.466	0.78
Global PiB*Consol Resil	−2.862	6.338	0.65	10.451	6.815	0.13
Global PiB*time	−3.352	1.235	*0.008*	−4.167	1.594	*0.01*
Consol Resil*time	0.341	0.285	0.24	−0.122	0.374	0.75
Global PiB*Consol Resil*time	2.712	1.010	*0.009*	3.099	1.304	*0.02*

A: number of observations = 680 (123 participants). B: number of observations = 673 (122 participants). Italicized *P* values indicate significance at < 0.05. Longitudinal analyses of cognitive domains (episodic memory and non-memory cognition) were performed using linear mixed-effects regression models with centered variables. Models assessed three-way interaction between a pathology measure, consolidated resilience (Consol Resil) and time. ERC,entorhinal cortex; s.e.,standard error.