


## RESEARCH ARTICLE

# Tau accumulation and atrophy predict amyloid independent cognitive decline in aging

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## Abstract

**INTRODUCTION:** Amyloid beta ( $A\beta$ ) and tau pathology are cross-sectionally associated with atrophy and cognitive decline in aging and Alzheimer's disease (AD).

**METHODS:** We investigated relationships between concurrent longitudinal measures of  $A\beta$  (Pittsburgh compound B [PiB] positron emission tomography [PET]), tau (flortaucipir [FTP] PET), atrophy (structural magnetic resonance imaging), episodic memory (EM), and non-memory (NM) in 78 cognitively healthy older adults (OA).

**RESULTS:** Entorhinal FTP change was correlated with EM decline regardless of  $A\beta$ , but meta-temporal FTP and global PiB change were only associated with EM and NM decline in  $A\beta+$  OA. Voxel-wise analyses revealed significant associations between temporal lobe FTP change and EM decline in all groups. PiB and FTP change were not associated with structural change, suggesting a functional or microstructural mechanism linking these measures to cognitive decline.

**DISCUSSION:** Our results show that longitudinal  $A\beta$  is linked to cognitive decline only in the presence of elevated  $A\beta$ , but longitudinal temporal lobe tau is associated with memory decline regardless of  $A\beta$  status.

## KEYWORDS

aging, Alzheimer's disease, amyloid, episodic memory, magnetic resonance imaging, non-memory cognition, positron emission tomography, tau

## Highlights

- Entorhinal tau change was associated with memory decline in older adults (OA), regardless of amyloid beta ( $A\beta$ ).
- Greater meta-region of interest (ROI) tau change correlated with memory decline in  $A\beta+$  OA.
- Voxel-wise temporal tau change correlated with memory decline, regardless of  $A\beta$ .
- Meta-ROI tau and global amyloid change correlated with non-memory change in  $A\beta+$  OA.
- Tau and amyloid accumulation were not associated with structural change in OA.

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## 1 | INTRODUCTION

Alzheimer's disease (AD) is characterized by the accumulation of pathological proteins in the form of amyloid beta ( $A\beta$ ) plaques and neurofibrillary tau tangles, both of which can be detected in the brain decades before the onset of clinical symptoms.<sup>1-3</sup> Though tau is more closely linked to cognitive decline and neurodegeneration than  $A\beta$ , animal and human studies suggest that tau spread is influenced by the presence of  $A\beta$ .<sup>4-6</sup> Thus, understanding the relative contributions of early  $A\beta$  and tau accumulation to cognitive decline in older adults is critical for identifying who may develop AD and could potentially benefit from early therapeutic interventions. Current in vivo neuroimaging approaches now allow us to track the accumulation of these pathological proteins in older adults and evaluate their relationship to changes in brain structure and cognition over time, even before cognitive impairment occurs.<sup>7,8</sup>

Though the co-occurrence of  $A\beta$  and tau is thought to underlie the development of AD, *post mortem* and in vivo neuroimaging studies have shown that they follow distinct spatiotemporal patterns of accumulation.  $A\beta$  appears to accumulate multifocally across association cortices, whereas tau begins in the transentorhinal cortex of the medial temporal lobe (MTL) and is present in most older adults.<sup>1,9,10</sup> While tau accumulation in the MTL is characteristic of typical aging, tau accumulation beyond the MTL in the presence of widespread neocortical  $A\beta$  suggests the onset of AD<sup>1,11,12</sup> and is generally believed to be associated with a period of more rapid tau accumulation and cognitive decline. However, given the functional importance of the temporal structures that are targeted by early pathological tau for cognition, particularly for episodic memory, it is important to investigate the relationships between early tau pathology accumulation and both brain atrophy and cognition in cognitively healthy older adults (OA) in conjunction with  $A\beta$ .

Positron emission tomography (PET) studies from our laboratory and others have shown that tau accumulation is associated with structural atrophy in both cognitively healthy OA and patients with AD.<sup>13-15</sup> Although current models of AD pathogenesis suggest a sequential pattern in which  $A\beta$  is an initiating factor that precedes tau accumulation and structural atrophy, which ultimately leads to cognitive decline,<sup>16</sup> evidence suggests that there are important nuances. First, cross-sectional studies show that greater baseline MTL tau is predictive of worse cognitive performance and future cognitive decline in OA regardless of  $A\beta$  status.<sup>17,18</sup> Further,  $A\beta$  accumulation in both OA and AD is only weakly associated with atrophy and cognition,<sup>19,20</sup> and a recent study of cognitively healthy OA demonstrated that while both  $A\beta$  and tau are associated with general cognitive decline, tau is a better predictor.<sup>21</sup> Second, several studies examining the relationship between tau and cognition indicate that a substantial portion of the link between tau and cognition is not moderated by brain structure.<sup>14,21</sup> Yet, it remains unclear whether longitudinal  $A\beta$  and tau accumulation measured in vivo are associated with concurrent cognitive changes in cognitively normal OA and to what extent concurrent structural atrophy plays a role in explaining variability in cognitive change.

### RESEARCH IN CONTEXT

- 1. Systematic review:** The authors used PubMed to identify previous studies examining longitudinal tau- and amyloid positron emission tomography, brain structure, and domain-specific cognitive change in cognitively healthy older adults (OA). Relationships among longitudinal tau, amyloid beta ( $A\beta$ ), structure, memory, and non-memory have not been previously investigated in OA.
- 2. Interpretation:** Longitudinal entorhinal tau was associated with memory decline, regardless of  $A\beta$  status. Longitudinal global amyloid was associated with non-memory decline in  $A\beta+$  OA. Tau and  $A\beta$  change were not associated with structural change. These findings extend cross-sectional studies showing tau and memory associations and provide new insight into relationships among longitudinal tau, amyloid, brain structure, and domain-specific cognition in OA.
- 3. Future directions:** Given that tau accumulation was associated with memory decline independent of structural change or  $A\beta$  status, tau may affect memory through another mechanism. Future studies should examine specific mechanisms linking tau and cognition, including microstructural and functional changes in OA.

To date no study has investigated the relationships between longitudinal  $A\beta$  and tau accumulation and domain-specific cognitive changes in cognitively healthy OA. Our aim was to use longitudinally collected imaging and cognitive data to explore these relationships within typical aging and preclinical AD. In the present study, we investigated the in vivo relationships between concurrent longitudinal  $A\beta$  and tau pathology accumulation, structural change, and domain-specific cognitive decline in cognitively healthy OA with and without elevated cortical  $A\beta$ .

## 2 | METHODS

### 2.1 | Study participants

Seventy-eight cognitively healthy OA were recruited through the Berkeley Aging Cohort Study (BACS), an ongoing longitudinal study of typical cognitive aging in community-dwelling older adults. Participants underwent longitudinal 1.5T magnetic resonance imaging (MRI), Pittsburgh compound B (PiB) PET, flortaucipir (FTP) PET, and cognitive assessments. Participants were included in the present study if they met the following criteria: (1) aged  $\geq 60$  years; (2) had two or more structural MRI (sMRI), FTP PET, and PiB PET scans; (3) had two or more neuropsychological assessment sessions; (4) had a Mini-Mental State Examination (MMSE)  $\geq 25$  and normal cognition at baseline (within 1.5 standard deviations of age-, education-, and sex-adjusted means);

and (5) no neurological, psychiatric, or other major medical illness. To assess the impact of elevated A $\beta$  on relationships between longitudinal measures, the full cohort was also divided into two groups based on the PiB scan closest to the baseline FTP scan (PiB-  $n = 44$ , PiB+  $n = 34$ ; distribution volume ratio [DVR] threshold  $> 1.065$  [equivalent to  $> 10$  Centiloids]).<sup>22</sup> Most participants had a PiB scan on the same day as their baseline FTP scan ( $n = 52$ ). For the remainder of the subjects ( $n = 26$ ), the average gap between the PiB scan that was used to determine PiB status and FTP baseline was  $0.54 \pm 0.72$  years.

## 2.2 | Longitudinal measures

Longitudinal slopes for cognitive domain scores, MRI measures, PiB, and FTP were calculated separately using linear mixed effects models with a fixed effect of time and random effects for participant slope and intercept. For many participants, while all time points of cognitive assessment, MRI, and PiB were largely overlapping, collection of these modalities began several years before FTP scanning, which started in 2014. On average, cognitive baseline data collection began  $3.8 \pm 3.7$  (range: 0–12.8) years before baseline FTP scanning. MRI baseline scans were collected  $2.7 \pm 3$  (range: 0–11.4) years before baseline FTP scanning. PiB baseline scans were collected  $2.7 \pm 3$  (range: 0–11.4) years before baseline FTP scanning. However, we used the closest PiB scan to baseline FTP to determine A $\beta$  positivity. For most participants, these scans occurred on the same day but for those who did not have PiB scan on the same day as their baseline FTP scan, the average time lag was  $0.54 \pm 0.72$  years. Because data collection for each other modality began several years before FTP scanning, we estimated cognitive and structural slopes using two approaches: first, using all available time points to maximize the signal to noise in the slope estimates themselves and second, using cognitive and structural sessions that were concurrent to and after tau baseline (occurred at or after baseline FTP scanning) to explore only change subsequent to our first measurement of tau burden (see sections 2.3 and 2.4 for average follow-up time for each type of slope estimate).

## 2.3 | Neuropsychological assessment

All BACS participants undergo a standard battery of neuropsychological assessment at baseline and at each follow-up time point to assess cognition including verbal and visual memory, working memory, language, executive function, and processing. The present study examined composite scores for episodic memory (EM) and a non-memory domain (NM) that were calculated using a confirmatory factor analysis, which has been previously published.<sup>23</sup> The EM composite score included California Verbal Learning Test Short Delay Free Recall (CVLT SDFR), California Verbal Learning Test Long Delay Free Recall (CVLT LDFR), Visual Reproduction I (VRI), Visual Reproduction II (VR II), Logical Memory Total Score, and Verbal Paired Associates data. The NM composite score included measures of executive function and processing speed such as Stroop in 60 seconds, 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. To calculate the composites, standardized factor loadings were used as numerical weights and multiplied by the corresponding cognitive test score within each cognitive domain. The weighted test data were then summed to create EM and NM domain composite scores for each cognitive session for each participant. To measure longitudinal change in each cognitive domain, slopes were extracted from linear mixed effects models. The average follow-up for all available cognition time points and time points concurrent to and after baseline FTP scan was  $8.2 \pm 3.9$  years and  $4.5 \pm 1.8$  years, respectively.

## 2.4 | Imaging

### 2.4.1 | MRI acquisition

Each participant underwent a 1.5T T1-weighted magnetization-prepared rapid acquisition gradient echo scan at baseline and at each follow-up time point with the following parameters: sagittal slice orientation, repetition time (TR) = 2110 ms, echo time (TE) = 3.58 ms, flip angle = 15°, voxel size = 1 mm isotropic. All structural MRI data were collected on a Siemens Magnetom Avanto scanner at Lawrence Berkeley National Lab (LBNL).

### 2.4.2 | PET acquisition

All PET scans were acquired at LBNL on a Siemens Biograph 6 Truepoint PET/CT scanner. Both PiB and FTP were synthesized at the LBNL Biomedical Isotope Facility according to previously published protocol.<sup>7,24</sup> PiB scans were acquired dynamically for 90 minutes post-injection (tracer injection of 15 mCi; 35 frames). FTP scans were acquired from 80 to 100 minutes post-injection (tracer injection of 10 mCi; four 5-minute frames). PET images were reconstructed using an ordered subset expectation maximization algorithm with weighted attenuation correction, scatter correction, and 4mm<sup>3</sup> smoothing (image resolution  $6.5 \times 6.5 \times 7.25$  mm<sup>3</sup>).

### 2.4.3 | MRI processing

Structural MRI data were processed using the FreeSurfer 7.1.1 (surfer.nmr.mgh.harvard.edu) cross-sectional pipeline to derive volume and cortical thickness for each region of interest (ROI) in the Desikan–Killiany atlas. For the present study, we were interested in the entorhinal cortex (EC), hippocampal volume, and the temporal meta-ROI (meta-ROI), which included the entorhinal cortex, parahippocampal gyrus, inferior temporal gyrus, middle temporal gyrus, fusiform, and amygdala (volume only).<sup>3</sup> Regional volume and cortical thickness slopes were extracted from linear mixed effects models. The average follow-up for all available MRI time points was  $6.2 \pm 3.9$  years and  $3.1 \pm 0.23$  years for time points concurrent to and after baseline FTP scan.

## 2.4.4 | PET processing

PiB DVR images were generated with Logan graphical analysis over 35 to 90 minute data and were normalized by a cerebellar gray matter reference region. Global PiB DVR was calculated at each time point as the mean of FreeSurfer-derived frontal, temporal, parietal, and posterior cingulate ROIs. Global PiB slopes were extracted from linear mixed effects models. The average follow-up time for all available time points was  $5.6 \pm 3.6$  years. Baseline A $\beta$  status was determined using the closest PiB scan to the baseline FTP scan and calculated by using a global DVR threshold of 1.065.<sup>22,25</sup>

FTP scans were processed using a previously described longitudinal pipeline and were normalized using a white matter reference region.<sup>15,26</sup> Briefly, sMRI scans from baseline and follow-up visits were used to create an average sMRI image using SPM12's serial registration.<sup>27</sup> FTP standardized uptake value ratio (SUVR) images from baseline and follow-up were then registered to this average subject space. Each participant's white matter (WM) segmentation, including cerebral, cerebellar, and brainstem, from their midpoint sMRI was thresholded at 0.95 and then eroded by 1 voxel. The WM ROI was used to normalize the baseline and follow-up FTP data in subject-specific space. This region was used because it resulted in more stable estimates of change in FTP over time in OA in a pilot analysis performed for a previous study.<sup>15</sup> For ROI analyses, average MRIs were processed with FreeSurfer 7.1.1 and the resulting parcellations were applied to FTP SUVR images in the same space. Mean SUVR of each ROI at each time point were quantified and partial volume corrected (PVC) using a modified Geometric Transfer Matrix approach to reduce the effects of off-target FTP binding on SUVR estimates in MTL.<sup>28,29</sup> Partial volume effects in specific ROIs can be particularly influential when examining the relationships between regional PET and structure given the limited spatial resolution of PET, which can underestimate local radiotracer retention in regions with high atrophy. ROIs for the present study included the EC and meta-ROI. These regions were chosen because they are the earliest sites of tau accumulation and tau spread in aging and early AD.<sup>1</sup> To measure longitudinal change, FTP SUVR slopes for each ROI were extracted from linear mixed effects models using all available time points. The average follow-up time for FTP scans was  $2.8 \pm 1.5$  years.

To investigate the relationships between whole-brain FTP change, cognitive change, and structural change, we generated voxel-wise FTP slope images. For each participant, voxel-wise FTP slope images (non-PVC) were created by fitting linear regressions (FTP  $\approx$  years from baseline) at each voxel. Voxel-wise linear mixed effects models were not used due to failure of model convergence in voxels with low variability. The slope images for each participant were then warped to Montreal Neurological Institute space for group-level analyses.<sup>15,26</sup>

## 2.5 | Statistical analysis

Statistical analyses were completed using R (v 4.0.0; <https://www.Rproject.org>). Demographic variables were compared between PiB

groups using two-sample t tests and Fischer exact tests. Linear mixed effects models were run using the lme4 R package to estimate longitudinal slopes for PiB, FTP, MRI measures, EM, and NM using all available time points. This process was repeated for PiB, MRI, EM, and NM measures to calculate slopes using only time points that were concurrent with FTP time points. Pearson correlations and multiple linear regression models were used to assess the relationships between longitudinal slope measures and demographic variables. To better understand which longitudinal imaging measures were the best predictors of cognitive change in each domain, we ran an elastic net model within the whole sample and in A $\beta$  status groups separately. Elastic net regression models, which apply simultaneous variable penalization and feature selection, were run using the glmnet and caret R packages to identify the best predictors of EM and NM decline. The elastic net regression combines ridge regression and lasso regression, which aims to minimize the root mean squared error (RMSE) loss function.<sup>30</sup> Each model used a mixing parameter ( $\alpha$ ), which applies penalties between ridge ( $\alpha = 0$ ) and lasso ( $\alpha = 1$ ), and a regularization penalty parameter ( $\lambda$ ). Parameter optimization for elastic net models used the leave-one-out training approach within the caret package to minimize the RMSE. The optimal parameters for EM decline models were as follows: full group:  $\alpha = 0.55, \lambda = 0.26$ ; PiB- group:  $\alpha = 1, \lambda = 0.19$ ; and PiB+ group:  $\alpha = 1, \lambda = 0.19$ . NM decline model optimal parameters were as follows: full group:  $\alpha = 0.55, \lambda = 0.16$ ; PiB- group:  $\alpha = 1, \lambda = 0.06$ ; and PiB+ group:  $\alpha = 1, \lambda = 0.21$ . Voxel-wise regressions were performed using SPM12 to assess the relationships among PiB, structure, and cognitive slopes and voxel-wise FTP slope in the entire cohort and in baseline A $\beta$  status groups separately (gray matter explicit mask, voxel/cluster level uncorrected thresholds of  $P < 0.005/P < 0.05$ , respectively).

## 3 | RESULTS

### 3.1 | Study participants

The mean age of the full cohort was  $76.4 \pm 5.6$  years and 41% were female with a mean of  $16.9 \pm 1.8$  years of education. Twenty-one participants were apolipoprotein E (APOE)  $\epsilon 4$  allele carriers and 34 were PiB+. The A $\beta$  status groups were not significantly different in age, sex distribution, average years of education, or average years of follow-up in imaging or cognitive assessments. The PiB+ group had significantly more APOE  $\epsilon 4$  carriers, significantly higher EC and meta-ROI FTP SUVR at baseline, and significantly higher global composite PiB DVR at the time point closest to baseline FTP scan compared to PiB- (Table 1).

### 3.2 | Longitudinal measures of A $\beta$ and tau are not associated with structural rates of change

Global PiB, EC FTP, and meta-ROI FTP slopes were not significantly associated with hippocampal volume slopes or EC or meta-ROI cortical thickness slopes in the full group or in groups separated by A $\beta$  status. To ensure these analyses were unaffected by PVC, we tested relationships

**TABLE 1** Participant characteristics.

Characteristic	Fulln = 78	PiB-n = 44	PiB+n = 34	P
Age, years	76.4 ± 5.6(64–93)	76.4 ± 6.5(64–93)	76.6 ± 4.2(69–86)	0.88
Sex, M/F n	46/32	25/19	21/13	0.82
Education, years	16.9 ± 1.8	17.0 ± 1.9	16.9 ± 1.8	0.41
APOE ε4, ± (N/A) n	54/21 (3)	39/3 (2)	15/18 (1)	<b>0.00001</b>
Baseline EC FTP SUVR	1.08 ± 0.16	1.04 ± 0.13	1.13 ± 0.19	<b>0.011</b>
Baseline Meta-ROI FTP SUVR	1.07 ± 0.10	1.03 ± 0.09	1.11 ± 0.11	<b>0.002</b>
Global PiB DVR (for PiB status)	1.15 ± 0.22	1.02 ± 0.03	1.32 ± 0.24	<b>0.000001</b>
Number of FTP scans, 2/3/4+ n	50/22/6	28/12/4	22/10/2	0.88
FTP scans follow-up, years	2.9 ± 1.5	2.9 ± 1.7	2.9 ± 1.3	0.60
Number of PiB scans, 2/3/4+ n	33/15/30	20/8/16	13/7/14	0.91
PiB scans follow-up, years	5.6 ± 3.6	5.3 ± 3.5	5.8 ± 3.8	0.53
Number of MRI scans, 2/3/4+ n	23/17/38	14/11/19	10/6/18	0.70
MRI scans follow-up, years	6.2 ± 3.9	6.0 ± 3.8	6.4 ± 3.9	0.69
Number of cognition tps, 2/3/4+ n	7/9/62	4/8/32	3/1/30	0.53
Cognition follow-up, years	8.2 ± 3.9	7.7 ± 3.8	8.8 ± 4.1	0.23

Note: Group count (n) or mean with standard deviation is shown. Range is shown for age. There was a significant difference between number of APOE ε4 carriers, global PiB DVR, and baseline FTP SUVR in the PiB– and PiB+ groups. Number of available time points for each longitudinal measure are also shown. Follow-up time is shown in average years.

Abbreviations: APOE, apolipoprotein E genotype; DVR, distribution volume ratio; SUVR, standard uptake value ratio; FTP, flortaucipir; MRI, magnetic resonance imaging; N/A, not available; PiB, Pittsburgh compound B (threshold DVR > 1.065), tps, time points.

between FTP change and structural change without PVC and results were similar (Table S1 in supporting information). The relationship between regional FTP slopes and structural slopes were similar when structural slopes were restricted to concurrent to and after baseline tau time points.

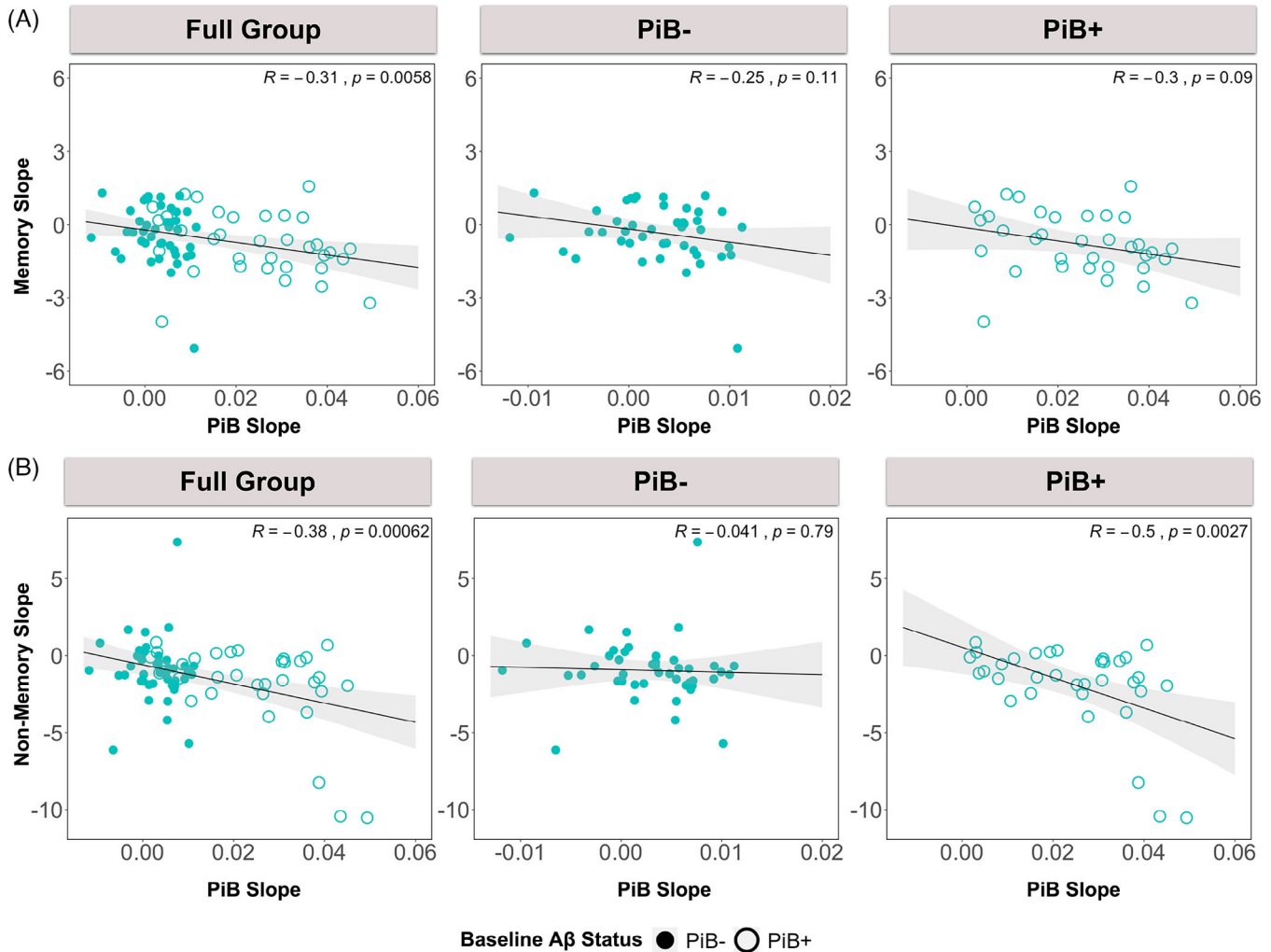
### 3.3 | Longitudinal Aβ is independently related to non-memory cognitive decline but not episodic memory decline

In the full group, greater PiB slope was significantly associated with steeper EM and NM decline (EM:  $r = -0.31$ ,  $P = 0.005$ ; NM:  $r = -0.38$ ,  $P < 0.001$ ). Dividing the full group by baseline Aβ status, the relationship between greater PiB slope and EM decline was not significant in the PiB– group but was trending in the PiB+ group (PiB–:  $r = -0.25$ ,  $P = 0.11$ ; PiB+:  $r = -0.30$ ,  $P = 0.09$ ). Similarly, there was no relationship between PiB slope and NM slope in the PiB– group ( $r = -0.041$ ,  $P = 0.79$ ) but greater PiB slope was significantly associated with steeper NM decline in the PiB+ group ( $r = -0.50$ ,  $P = 0.003$ ; Figures 1A,B). Additionally, all relationships between PiB slope and cognition slopes were similar after controlling for age, education, and sex. Because tau pathology is associated with both cognition and Aβ, we tested whether PiB slope associations with EM and NM decline were still significant after adjusting for EC FTP slope. Interestingly, the relationship between PiB slope and EM slope in the full group was no longer significant when including EC FTP slope in the model ( $r = -0.14$ ,  $P = 0.17$ ). However, relationships between PiB slope and NM slope in the full group and PiB+ group remained significant when including EC

FTP slope in the models (full:  $r = -0.31$ ,  $P = 0.007$ ; PiB+:  $r = -0.46$ ,  $P = 0.006$ ).

### 3.4 | Longitudinal entorhinal tau is associated with episodic memory decline regardless of Aβ status but longitudinal meta-temporal tau is associated with cognitive decline only in Aβ+ participants

Greater EC FTP slope was significantly related to steeper EM decline in the full group and in both baseline Aβ status groups when analyzed separately (full:  $r = -0.5$ ,  $P < 0.001$ ; PiB–:  $r = -0.44$ ,  $P = 0.003$ ; PiB+  $r = -0.5$ ,  $P = 0.003$ ; Figure 2A). Higher EC FTP slope was also significantly associated with steeper NM decline in the full group ( $r = -0.29$ ,  $P = 0.009$ ). Greater EC FTP slope was not correlated with NM decline in the PiB– group but was trending toward significance in the PiB+ group (PiB–:  $r = -0.18$ ,  $P = 0.25$ ; PiB+  $r = -0.3$ ,  $P = 0.08$ ; Figure 2B). When restricting cognitive slopes to time points concurrent to and after tau baseline, EC FTP slope was significantly associated with EM slope in the full group and PiB+ group but was reduced to a trend in the PiB– group (full:  $r = -0.35$ ,  $P = 0.002$ ; PiB–:  $r = -0.27$ ,  $P = 0.08$ ; PiB+:  $r = -0.36$ ,  $P = 0.04$ ). However, this relationship in the PiB– group was made significant in the restricted slopes when removing one influential participant higher EC FTP slope ( $r = -0.36$ ,  $P = 0.02$ ). Greater EC FTP slope was significantly associated with steeper NM decline in the full group and PiB+ group but not in the PiB– group (full:  $r = -0.35$ ,  $P = 0.002$ ; PiB–:  $r = -0.23$ ,  $P = 0.13$ ; PiB+:  $r = -0.38$ ,  $P = 0.02$ ). In the meta-ROI, FTP slope was significantly associated with steeper EM decline when using all time points in the full group and PiB+ group but not in the



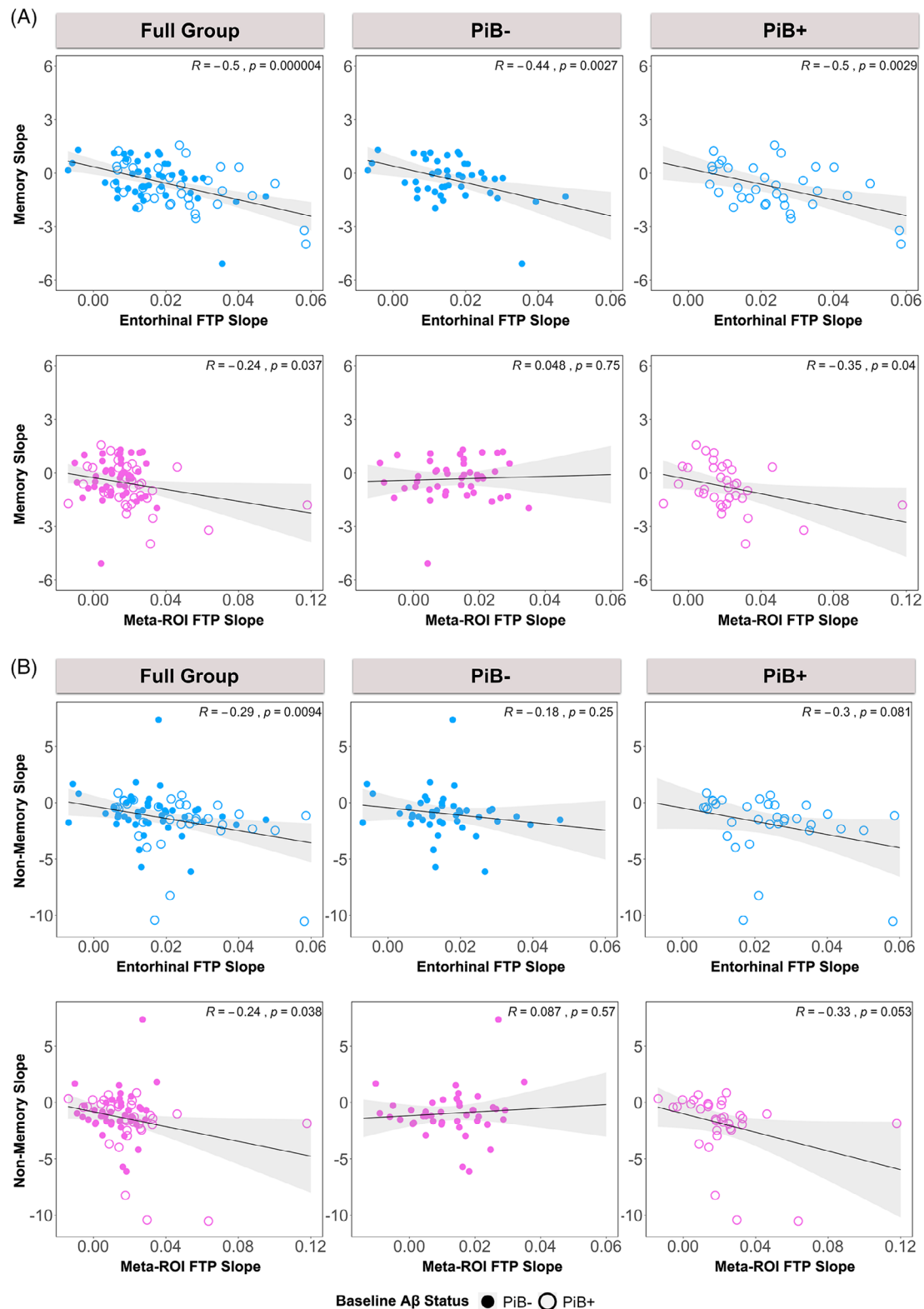
**FIGURE 1** Linear relationships between PiB slope and cognitive slopes by group. Bivariate relationships between PiB slope and cognitive slopes are shown. A, PiB slope was significantly associated with memory slope in the full group and was trending toward significance in the PiB+ group. B, PiB slope was significantly associated with non-memory slope in the full group and the PiB+ group but showed no relationship in the PiB- group. Aβ, amyloid beta; PiB, Pittsburgh compound B.

PiB- group (full:  $r = -0.24$ ,  $P = 0.04$ ; PiB-:  $r = 0.048$ ,  $P = 0.75$ ; PiB+:  $r = -0.35$ ,  $P = 0.04$ ; Figure 2A). Higher meta-ROI FTP slope was significantly correlated with steeper NM decline using all time points in the full group ( $r = -0.24$ ,  $P = 0.04$ ) but was not associated with NM slope in the PiB- group ( $r = 0.048$ ,  $P = 0.75$ ). The significant relationship in the full group was made stronger when removing one PiB+ subject with high FTP slope ( $r = -0.30$ ,  $P = 0.009$ ). In the PiB+ group, the relationship between greater meta-ROI slope and steeper NM decline was trending toward significance ( $r = -0.33$ ,  $P = 0.053$ ; Figure 2B). This relationship was made stronger and reached significance when removing one subject with high FTP slope ( $r = -0.52$ ,  $P = 0.002$ ). Restricting cognitive slopes to time points concurrent to and after tau baseline, meta-ROI FTP slope was significantly associated with EM slope in the full group and PiB+ group but not in the PiB- group (full:  $r = -0.36$ ,  $P = 0.001$ ; PiB-:  $r = -0.23$ ,  $P = 0.13$ ; PiB+:  $r = -0.41$ ,  $P = 0.01$ ). Greater meta-ROI FTP slope was significantly associated with steeper NM decline in the full group but not in the PiB groups separately (full:  $r = -0.26$ ,  $P = 0.02$ ; PiB-:  $r = -0.10$ ,  $P = 0.52$ ; PiB+:  $r = -0.28$ ,  $P = 0.11$ ). All relationships

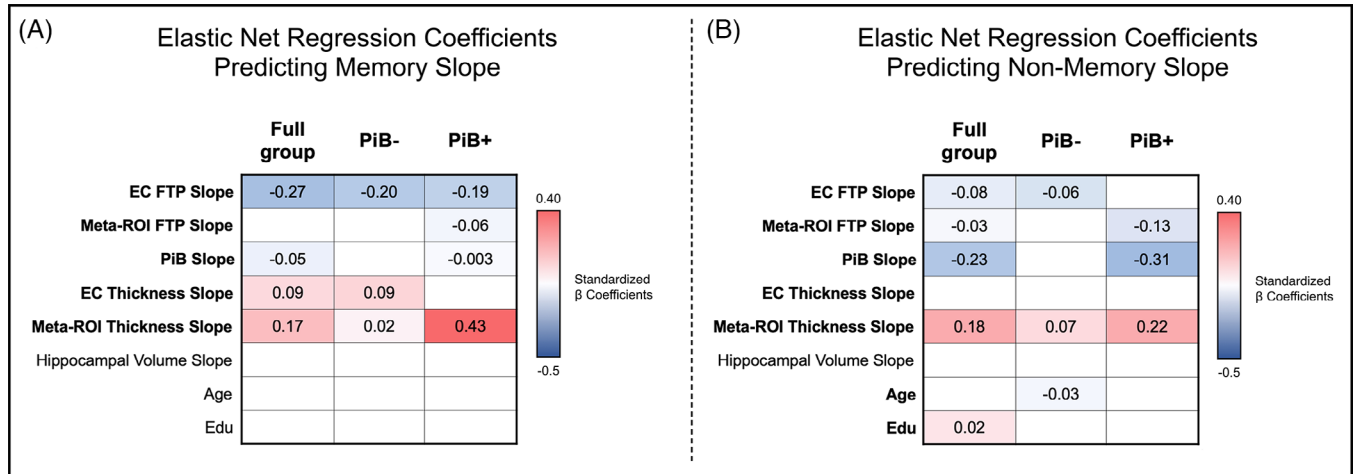
were similar after controlling for age, sex, and education. When adding PiB slope to the models, the relationship between FTP slopes and EM slope remained similar. However, the relationships between EC FTP slope and NM slope (using all time points) in the full group and meta-ROI FTP slope and NM slope in models that contained PiB+ subjects were no longer significant or reduced to a trend (EC full:  $r = -0.18$ ,  $P = 0.12$ ; meta-ROI full:  $r = -0.14$ ,  $P = 0.22$ ; meta-ROI PiB+:  $r = -0.28$ ,  $P = 0.06$ ). Results were similar when using PVC and non-PVC regional FTP slopes (Table S2 in supporting information).

### 3.5 | Elastic net models suggest EC tau slope and meta-ROI thickness slope are key predictors of cognitive change

For EM decline, EC FTP slope along with meta-ROI cortical thickness slopes were selected in all models. Change in thickness of the EC was selected as an important predictor in the full group and PiB- group



**FIGURE 2** Linear relationships between FTP slope and cognitive slopes. Bivariate relationships between FTP slope and cognitive slopes are shown. A, Greater entorhinal FTP slope was significantly associated with memory decline in the full group as well as PiB groups separately. Greater meta-ROI FTP slope was only significantly associated with memory decline in the full group and PiB+ group\*. B, Greater entorhinal FTP slope was significantly associated with non-memory decline in the full group and was trending toward significance in the PiB+ group but showed no significant relationship in the PiB- group. Greater meta-ROI slope was significantly associated with non-memory decline in the full group\*\*. While there was no relationship between meta-ROI FTP slope and non-memory slope in the PiB- group, the relationship between greater meta-ROI FTP slope and non-memory slope was approaching significance in the PiB+ group\*\*; \*Reduced to a trend when removing high FTP PiB+ participant; \*\*Significant when removing high FTP PiB+ participant. Aβ, amyloid beta; FTP, flortaucipir; ROI, region of interest; PiB, Pittsburgh compound B.



**FIGURE 3** Elastic net regression selected predictors of memory and non-memory decline. Elastic net regression models predicting cognitive slope were run for the full group and groups subset by baseline PiB status for each cognitive domain. Models were trained using a leave-one-out approach. Standardized beta coefficients for each model are shown. A, Greater entorhinal FTP slope and lower meta-ROI thickness slope were selected in models predicting memory decline in the full group as well as PiB groups separately. Meta-ROI FTP slope was selected only in the PiB+ group model. Global PiB slope was selected for the full group and PiB+ models. EC thickness slope was selected in the full group and PiB- group. Hippocampal volume slope and demographic measure coefficients were reduced to zero in all models. B, Greater entorhinal FTP slope was selected only in the full group and PiB- group when predicting non-memory decline. Greater meta-ROI FTP and lower thickness slopes were selected in the full group as well as PiB groups separately. PiB slope was selected in the full group and PiB+ group only. Although the coefficient was almost reduced to zero, age was selected in the PiB- group. All other measure coefficients were reduced to zero. EC, entorhinal cortex; FTP, flortaucipir; ROI, region of interest; PiB, Pittsburgh compound B.

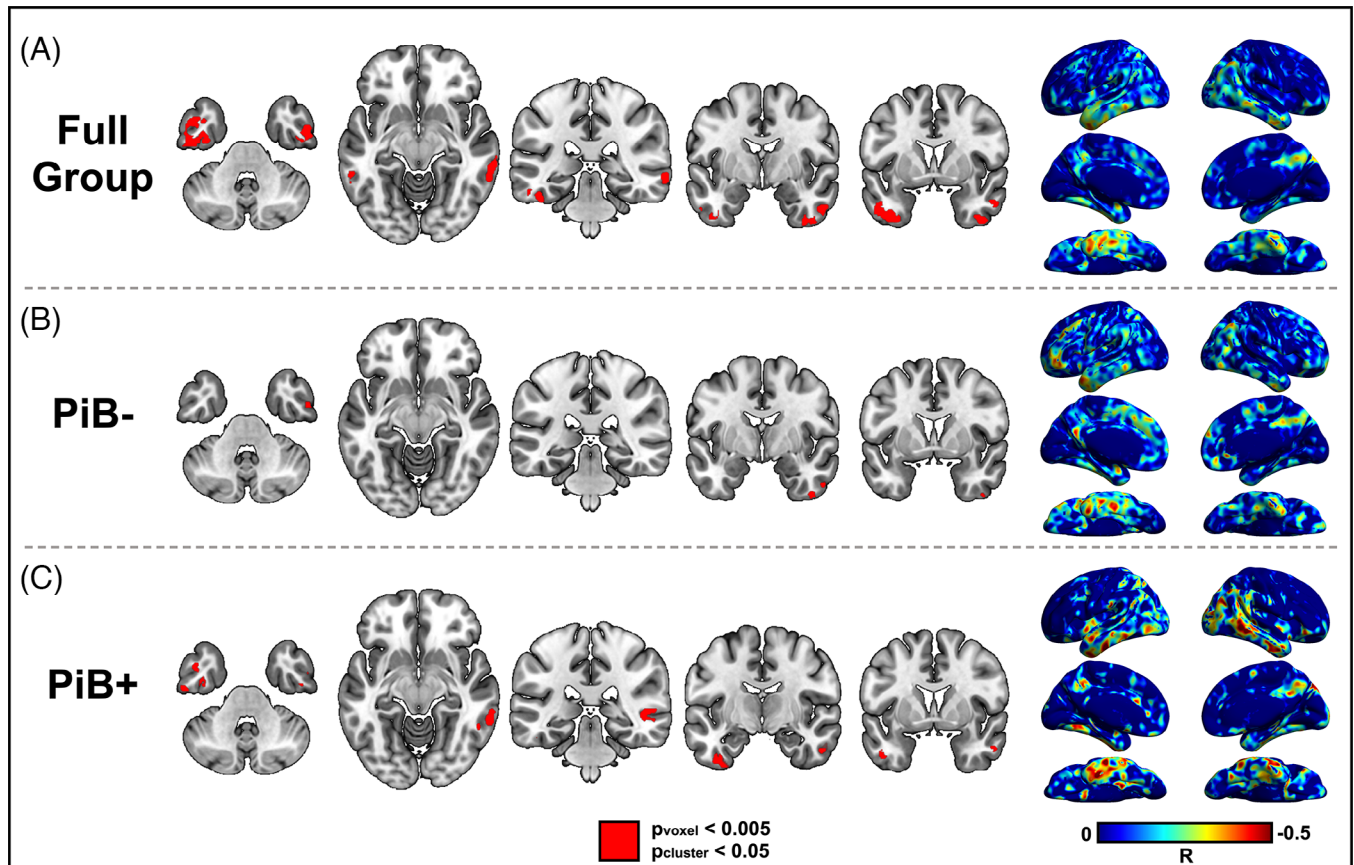
only. Meta-ROI FTP slope was selected in the PiB+ group only and PiB slope was selected only in groups with PiB+ subjects (full and PiB+ groups). All other predictors' coefficients in each model of EM decline were reduced to zero (Figure 3A). For NM decline, EC FTP slope was selected in the full group and PiB- group whereas meta-ROI FTP slope and PiB slope were selected only in groups that contained PiB+ participants. As with EM decline, meta-ROI cortical thickness slope was selected in all models. Education was selected in the full group and age was selected only in the PiB- group. Finally, EC thickness slope and hippocampal volume slope coefficients were reduced to zero in all models predicting NM decline (Figure 3B). Although we did not observe associations between PiB or FTP PET slopes and structural change, these models suggest that change in cortical thickness is an important independent predictor of cognitive change. To better quantify these relationships in our sample, we performed a post hoc bivariate correlation between structural slopes. These analyses showed a significant relationship between entorhinal cortical thickness slope and memory slope in the full group and PiB- group ( $r = 0.32$ ,  $P = 0.004$ ;  $0.34$   $P = 0.02$ , respectively). Meta-ROI thickness slope was associated with memory slope in the full group and PiB- group ( $r = 0.37$ ,  $P < 0.001$ ;  $0.64$   $P < 0.001$ , respectively; Figure S1A in supporting information). Hippocampal volume was not associated with memory slope in any group. While meta-ROI thickness slope was associated with non-memory slope in the full group and PiB+ group ( $r = 0.29$ ,  $P = 0.01$ ;  $0.48$   $P = 0.004$ , respectively; Figure S1B), entorhinal cortical thickness and hippocampal volume slopes were not associated with non-memory slope in any group (Table S3 in supporting information).

### 3.6 | Steeper memory decline is associated with greater voxel-wise tau change in the temporal lobe regardless of baseline A $\beta$ status

Voxel-wise FTP change was not associated with structural or NM slopes nor EM slopes using all available time points (thresholds:  $P_{\text{voxel}} < 0.005$ ,  $P_{\text{cluster}} < 0.05$ ). However, when restricting EM slopes to concurrent to and after tau baseline cognitive change, greater EM slope was associated with significant clusters of FTP change in the left fusiform gyrus, right inferior temporal, and right middle temporal gyri in the full group ( $P_{\text{voxel}} < 0.005$ ,  $P_{\text{cluster}} < 0.05$ ; Figure 4A). When separating the groups by A $\beta$  status, the clusters in the right inferior gyrus remain significant in both groups as well as the right superior, middle, fusiform, and left inferior temporal gyri in the PiB+ group (Figure 4B-C; for peak voxel coordinates see Table S4 in supporting information). There were no significant relationships between voxel-wise FTP change and NM slopes of time points concurrent to and after tau baseline.

## 4 | DISCUSSION

This study examined the relationships among longitudinal measures of AD pathology, structural atrophy, and domain-specific cognitive change. This is the first study to show that in vivo measures of longitudinal tau accumulation, particularly in the MTL, are related to longitudinal memory decline in cognitively healthy OA. Importantly,



**FIGURE 4** Voxel-wise relationships between memory slope and FTP slope. Volumetric maps of significant voxel-wise clusters are shown at a voxel threshold of  $P < 0.005$  and cluster threshold  $P < 0.05$  (left). Uncorrected correlation coefficient surface renderings are shown to demonstrate the whole-brain spatial relationships between memory slope and FTP slope (right). Volumetric maps and surface renderings are in neurological orientation. A, Significant clusters of higher voxel-wise FTP slope emerged in left inferior temporal, right fusiform, and right middle temporal gyri as associated with faster memory decline in the full group when restricted to concurrent to and after tau baseline memory slopes. B–C, Smaller but significant clusters in the right inferior temporal region emerged in groups subset by baseline PiB status as well as clusters in the right superior, middle, fusiform, and left inferior temporal gyri in the PiB+ group. FTP, flortaucipir; PiB, Pittsburgh compound B.

our results suggest that MTL tau change is related to memory even when  $A\beta$  pathology is not present or is very low, as measured by PET. Our findings also suggest that this relationship appears to be exacerbated in the presence of elevated  $A\beta$ , which is in line with current models of AD pathogenesis. Longitudinal tau accumulation outside of the MTL was associated with memory and non-memory decline in models that contained OA with elevated global  $A\beta$  at baseline ( $A\beta+$  OA). This finding is consistent with early AD pathology staging patterns that may represent a transition to preclinical AD.<sup>1,11,12</sup> In contrast, longitudinal  $A\beta$  was associated with both memory and non-memory decline, but post hoc analyses revealed that this relationship was no longer significant when rate of MTL tau accumulation was included in the same model. This suggests that the association between rate of  $A\beta$  accumulation and memory is indirect but also highlights an interesting relationship between  $A\beta$  and non-memory. Together, our results both expand on previous literature and provide new insight on the effects of longitudinal  $A\beta$  and tau accumulation on domain-specific cognitive decline in both typical aging ( $A\beta-$  OA) and preclinical AD ( $A\beta+$  OA).

A key finding was that greater rates of tau accumulation in the EC were consistently associated with steeper EM decline regardless of baseline  $A\beta$  or structural change. This finding was also robust to approach for estimating EM slope (using all time points vs. time points after tau baseline; Table S5 in supporting information), suggesting we can see this relationship over even a relatively short period of time. These relationships were also reflected in elastic net regression models in which longitudinal EC tau was consistently selected as an important predictor of EM decline. This finding expands on cross-sectional *post mortem* and PET studies of unimpaired  $A\beta-$  and  $A\beta+$  OA that show a relationship between MTL tau and lower memory performance.<sup>31–33</sup> Though EM decline is one of the first clinical symptoms of AD, it is also common with advanced age. Our results suggest that over time, memory may be independently affected by greater tau accumulation in MTL regions. These regions are critical to memory function, and this pattern of tau aggregation in  $A\beta-$  individuals may represent a distinct age-related pathological process referred to as primary age-related tauopathy (PART).<sup>34</sup> Greater meta-ROI tau accumulation was only associated with EM decline in groups with  $A\beta+$  OA, which was also

reflected in elastic net models. These relationships indicate a divergence between age-related tau pathology in the MTL and advancing, extra-MTL temporal tau pathology in the presence of elevated  $A\beta$ . Although our data cannot reveal whether unimpaired OA with elevated  $A\beta$  will develop cognitive impairment associated with AD, the relationship between memory decline and tau spread outside of the MTL with elevated global  $A\beta$  may reflect a transition to early stages of AD.<sup>35</sup>

Greater EC tau accumulation was only significantly associated with steeper NM decline in the full group and trended toward significance in the  $A\beta+$  group. Similarly, greater meta-ROI tau accumulation were associated with steeper NM decline in models that contained  $A\beta+$  participants. Post hoc multiple regression analyses revealed that these significant relationships were not independent of rates of  $A\beta$  accumulation, suggesting an important role of  $A\beta$  on NM decline. Previous studies have linked baseline  $A\beta$  deposition to both memory and non-memory decline in unimpaired OA.<sup>20,36,37</sup> However, some studies suggest that non-memory measures may be more sensitive to longitudinal  $A\beta$  than measures of memory.<sup>38,39</sup> Specifically, longitudinal  $A\beta$  accumulation has been linked to measures of executive function and processing speed,<sup>38</sup> which may be related to the multifocal pattern of  $A\beta$  accumulation, particularly in the medial frontal and medial parietal lobes.

Using longitudinal voxel-wise tau change maps, we found that EM decline, but not NM decline, was associated with greater tau change in the temporal lobes in the full group, with inferior temporal areas remaining significant in the  $A\beta$  groups separately. This indicates that the association between EM decline and greater tau change in the temporal lobe is robust to methodological approach and this relationship is best detected in inferior temporal areas. The inferior temporal gyrus has been shown to be the region that can best discriminate tau-PET tracer uptake between cognitively healthy OA and AD patients.<sup>40</sup> Larger clusters in the  $A\beta+$  group likely reflects greater tau spread out of the MTL to inferior temporal regions influenced by elevated  $A\beta$ . The uncorrected spatial maps representing the correlation between memory and tau change generally follow expected patterns of tau accumulation in OA and AD shown in a previous study.<sup>15</sup> Although the whole-brain analyses did not identify significant clusters in the MTL, we did see non-significant correlations between EM decline and greater MTL voxel-wise tau change across the groups. However, the stringent statistical thresholding necessary for voxel-wise regression did not capture a significant relationship between FTP within voxels of the MTL and memory that we saw in the averaged ROIs. Nonetheless, these findings go beyond our ROI-based analyses by presenting whole-brain evidence of the strongest spatial relationships between longitudinal memory and tau accumulation in the temporal lobes.

Although longitudinal global  $A\beta$  was associated with EM decline in the full group, multiple regression analyses showed that this relationship was not significant when accounting for longitudinal MTL tau accumulation. This finding highlights the specificity for the relationship between MTL tau accumulation and memory decline. This is consistent with a previous study that showed that concurrent tau accumulation attenuated the relationship between longitudinal  $A\beta$  and memory decline in OA with and without elevated  $A\beta$  at baseline.<sup>38</sup>

Another study found a significant mediation effect of tau on the relationship between  $A\beta$  accumulation and memory decline.<sup>41</sup> Together, these findings suggest that  $A\beta$  may be indirectly affecting memory and that tau may have more of a direct effect of memory decline in aging and preclinical AD.

Although current models of AD suggest that atrophy facilitates the relationship between pathology and cognitive decline, longitudinal  $A\beta$  and tau were not associated with concurrent rates of structural change in cognitively healthy OA in the present study. This is in contrast to previous cross-sectional work showing a relationship between tau and temporal lobe volume.<sup>33,42</sup> Although cortical thickness slope in the temporal meta-ROI was an important predictor of memory and non-memory cognitive decline, structural change did not moderate the relationship between pathology and cognition. The longitudinal  $A\beta$ , tau, and structural measures in the present study overlapped substantially in time and it is possible that structural changes related to longitudinal AD pathology are not detectable in largely concurrent structural atrophy slopes of OA who are not cognitively impaired. It may be that  $A\beta$  and tau toxicity affect future rates of brain structure change in typical aging or preclinical AD.<sup>42-44</sup> This is in line with a previous prospective longitudinal study of symptomatic patients showing that patterns of tau pathology more closely resembled future rather than concurrent patterns of atrophy.<sup>45</sup>

It is possible that there are mechanisms other than atrophy through which early AD pathology accumulation can affect cognitive decline in OA. Previous literature in aging and AD suggests that early pathological tau interacts with functional memory circuits in the MTL to drive memory decline.<sup>46,47</sup> Our laboratory has shown a link between functional memory pathways and early tau accumulation in which greater hippocampal activation was associated with greater local tau accumulation in cognitively healthy OA.<sup>26</sup> This work supports hypotheses positing that early tau production and propagation occur in an activity-dependent manner, which has been observed in humans and animals.<sup>48-50</sup> In contrast, a functional mechanism underlying the effects of cortical  $A\beta$  on non-memory cognition may be related to the disruption of functional network connectivity associated with higher level cognitive processes such as executive function. Human neuroimaging studies have shown that  $A\beta$  deposition is associated with altered connectivity and hypometabolism of the default mode network, which is highly connected to regions involved in executive function.<sup>51,52</sup> In line with animal models,  $A\beta$  toxicity may also contribute to the slowing of synaptic transmission in frontal regions that are associated with processing speed.<sup>53</sup>

#### 4.1 | Strengths and limitations

The main strength of this study was the availability of longitudinal data for each key measure. This study, however, also has some limitations. First, our sample of cognitively healthy OA, though deeply characterized, consisted of mostly White and highly educated OA, which may limit the generalizability of our findings. Future studies should examine the predictive utility of longitudinal imaging measures along with other

sociocultural factors in predicting cognitive decline in more diverse samples of OA. Second, though our sample size was reasonable, this was reduced when dividing the full cohort by baseline A $\beta$  status. Additionally, elastic net parameters were estimated using a leave-one-out approach rather than two separate cohorts, which may limit interpretability. Continued longitudinal data collection in aging and early AD cohorts in our laboratory and others will allow future studies to take advantage of multiple cohorts with larger sample sizes and longer follow-up time periods. Last, although our findings show a relationship between longitudinal tau accumulation and cognitive decline not fully explained by structural atrophy, we cannot draw final conclusions about specific mechanisms underlying this relationship. Though unlikely to make a significant difference in our cognitively healthy cohort, another limitation of our study is that we used cross-sectional MRI processing to calculate structural measures at each time point and that were subsequently used to derive structural slopes. Longitudinal structural MRI processing pipelines may be able to estimate more subtle changes in brain structure than cross-sectional pipelines by reducing intra-subject variability over time. Future studies should examine these relationships among longitudinal PET, MRI, and cognition in the context of functional mediators that may explain the influence of tau on cognition.

## 5 | CONCLUSION

The aim of this study was to investigate the relationships among longitudinal measures of A $\beta$ , tau, brain structure, and cognition in cognitively healthy OA. To our knowledge, this is the first study to show that longitudinal tau accumulation is related to concurrent memory decline, but not atrophy, in cognitively healthy OA regardless of baseline A $\beta$  status. Our findings suggest that there may be different downstream effects of longitudinal A $\beta$  and tau accumulation on domain-specific cognitive decline. These effects may be associated with typical aging or preclinical AD trajectories and potentially mediated by mechanisms other than structural atrophy. This study provides further evidence that in vivo tau pathology is a useful biomarker for predicting memory decline in both aging and preclinical AD.

## AUTHOR CONTRIBUTIONS

Designed research: Corrina S. Fonseca, Theresa M. Harrison, William J. Jagust; analyzed data: Corrina S. Fonseca, Suzanne L. Baker, Lindsey Dobyns, Mustafa Janabi, Theresa M. Harrison; wrote the paper: Corrina S. Fonseca & Theresa M. Harrison; edited the paper: all authors.

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## CONFLICT OF INTEREST STATEMENT

Dr. Jagust has served as a consultant to Biogen, Genentech, Clario, Roche, Prothena, and Bioclinica. Dr. Baker serves as a consultant to Genentech. The remaining authors have no declaration of interest. Author disclosures are available in the [supporting information](#).

## CONSENT STATEMENT

Written informed consent was obtained from participants under protocols approved by the institutional review boards of UC Berkeley and Lawrence Berkeley National Laboratory.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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