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Longitudinal relationships between Aβ and tau to executive function and memory in cognitively normal older adults

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ABSTRACT

The early accumulation of AD pathology such as Aβ and tau in cognitively normal older people is predictive of cognitive decline, but it has been difficult to dissociate the cognitive effects of these two proteins. Early Aβ and tau target distinct brain regions that have different functional roles. Here, we assessed specific longitudinal pathology-cognition associations in seventy-six cognitively normal older adults from the Berkeley Aging Cohort Study who underwent longitudinal PiB PET, FTP PET, and cognitive assessments. Using linear mixed-effects models to estimate longitudinal changes and residual approach to characterizing cognitive domain-specific associations, we found that Aβ accumulation, especially in frontal/parietal regions, was associated with faster decline in executive function, not memory, whereas tau accumulation, especially in left entorhinal/parahippocampal regions, was associated with faster decline in memory, not executive function, supporting an "Aβ-executive function, tau-memory" double-dissociation in cognitively normal older people. These specific relationships between accumulating pathology and domain-specific cognitive decline may be due to the particular vulnerabilities of the frontal-parietal executive network to Aβ and temporal memory network to tau.

1. Introduction

Cognitive decline in preclinical Alzheimer's disease (AD) is predictive of future dementia and associated with the emergence of AD pathology prior to disease onset (Jack et al., 2018; Sperling et al., 2011). Using PET imaging in cognitively normal individuals, studies have shown that tau deposition predicts subsequent cognitive decline (Chen et al., 2021; Sperling et al., 2019) and that even low levels of Aβ deposition can predict tau deposition (Leal et al., 2018) and faster cognitive decline (Farrell et al., 2018; Landau et al., 2018). However, it has been difficult to disentangle the associations of Aβ and tau with cognition and track early cognitive decline related to the development of these two pathologies in cognitively normal older individuals.

Among various cognitive domains affected in AD, executive function and memory are especially vulnerable in early stages (Chen et al., 2001; Hedden et al., 2013). This may be related to how initial Aβ and tau are spatially distributed in the brain (Braak and Braak, 1991; Van Der Kant et al., 2020). Aβ pathology predominately begins in frontal and parietal regions and rapidly accumulates globally across the brain (Buckner et al., 2005; Grothe et al., 2017). Tau, on the other hand, accumulates in the medial temporal lobe (MTL) with increasing age before spreading to inferior and lateral temporal regions (Braak and Braak, 1995; Johnson et al., 2016). Meanwhile, the frontal-parietal regions comprise a functional network that is responsible for executive function (Fassbender et al., 2004; Witt et al., 2021), and the temporal especially MTL regions are especially critical for memory processes (Rugg and Vilberg, 2013; Squire and Zola-Morgan, 1991).

The selective vulnerability of frontal-parietal and temporal systems respectively to Aβ and tau, as well as their functional specificity in cognition, allows us to hypothesize that there may be specific pathology-cognitive associations that can explain the vulnerability of executive function and memory in cognitively normal older individuals: Aβ, primarily depositing in the medial parietal and frontal regions, may be more predictive of executive function decline, while tau in MTL may correlate better with memory decline.

Previous studies have shown indirect evidence suggesting the

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hypothesized associations. For example, Farrell et al. (Farrell et al., 2022) reported that in cognitively normal older individuals with slightly elevated Aβ, executive/speed decline was associated with faster Aβ, but not tau, accumulation. Tideman et al. (Tideman et al., 2022) using cross-sectional data found that Aβ in an early accumulating composite region was associated with worse executive function, while entorhinal tau was associated with worse memory. Building on these findings, the present study examined the specific longitudinal associations between Aβ and tau accumulation and cognitive declines in memory and executive function in cognitively normal older individuals.

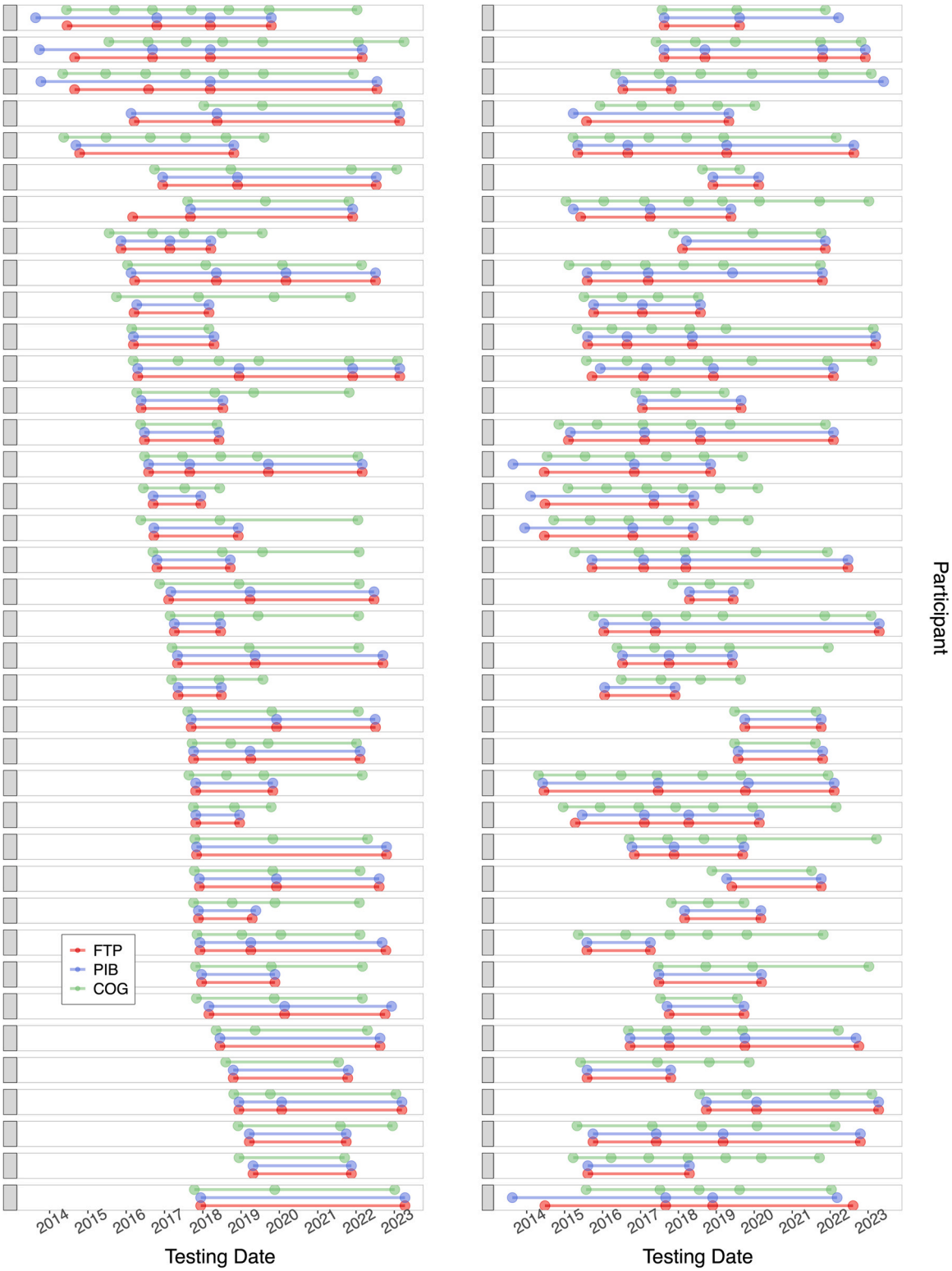

Fig. 1. Longitudinal testing of PET and cognitive assessment in the Berkeley Aging Cohort Study. Each box represents one participant. Red represents FTP PET visit for tau (FTP), blue represents PiB PET visit for Aβ (PIB), and green represents cognitive visits (COG). All cognitive measures are close to (within 6 months) of PET scans.

One challenge in studying AD-related cognitive deficits in cognitively normal older individuals is the common cognitive decline in normal aging. Cognitive aging research on healthy individuals has demonstrated that cognitive abilities tend to be de-differentiated in normal aging (Baltes and Lindenberger, 1997; de Frias et al., 2007; Li et al., 2004), meaning that different cognitive abilities decline together with increasing age in normal people. This dedifferentiation of cognitive aging reflects normative and generalized neuroanatomical and neurochemical deterioration that uniformly affects most cognitive domains (Raz et al., 2005; Tucker-Drob et al., 2019). On the other hand, a disproportionally faster decline in certain cognitive abilities is related to abnormalities and impairments beyond normal aging, such as Aβ pathology (McDonough et al., 2016) and terminal decline (Wilson et al., 2012). This suggestion of abnormality-related cognitive differentiation is also expected in pathological aging. Domain-specific cognitive decline that is more substantial than expected and independent of other cognitive abilities can reflect the presence of a particular pathology underlying the specific deficit.

To best characterize the variability associated with specific cognitive decline, we used residual-based measures representing the domain-specific variability in one cognitive domain after accounting for another, e.g., faster memory decline than expected given the degree of executive function decline. Despite some limitations (Elman et al., 2022), this approach is well accepted as an appropriate method for establishing meaningful individual variability that cannot be captured by traditional analyses (Bocancea et al., 2021; Dobyns et al., 2023). We focused on executive function and memory because they are particularly vulnerable and differentially related to the frontal-parietal and temporal functional networks. To best examine the specific relations of Aβ and tau accumulation to cognitive declines, we controlled for Aβ when examining tau associations (and tau when examining Aβ associations). We hypothesized that faster memory decline was related to greater tau accumulation and that faster executive decline was related to greater Aβ accumulation.

2. Material and Methods

2.1. Participants

This study included 76 cognitively normal older individuals ($\geq$ 60 yrs old) from the Berkeley Aging Cohort Study (BACS) who underwent longitudinal structural 1.5 T magnetic resonance imaging (MRI), Aβ PET with ^{11}C-Pittsburgh Compound-B (PiB), tau PET with ^{18}F-Flortaucipir (FTP), and cognitive assessments. All participants had a Mini-Mental State Examination (MMSE) $\geq$ 25 and normal cognition (within 1.5 standard deviations of age-, education-, and sex-adjusted means) and had no history of neurological, psychiatric, or other major medical illness. To study longitudinal change in cognition concurrent with and following pathology accumulation, we focused on cognitive assessments that were administered close to (within 6 months) and after PET. Figure 1 presents the testing timeline of all participants included in this study. Participants all provided written, informed consent. The study was approved by the Institutional Review Boards at the Lawrence Berkeley National Laboratory and the University of California, Berkeley.

2.2. Cognitive assessment

Participants on average had 4.3 cognitive visits, over an average of 4.9 years. Specifically, nine had two visits, 21 had three visits, 15 had four visits, 11 had five visits, 12 had six visits, seven had seven visits, and one had eight visits. Cognitive composites for memory and executive function were carefully constructed by iteratively comparing the internal reliability when different combinations of *a priori* domain-specific indicators were used (Supplemental Table 1 and 2). This procedure optimizes the psychometric validity and reliability of the cognitive constructs that are used to measure memory and executive function. The memory composite was based on five measures from three tasks, including short-delay free-recall and long-delay free-recall of the California Verbal Learning Test, Visual Reproduction, and total score on the Logical Memory scale (Cronbach's α =.720). The executive function composite was based on digit symbol substitution test, Stroop in 60 s, and mental control test (Cronbach's α =.715).

Table 1
Participant's characteristics and longitudinal visit information. Mean values are presented in the table and standard deviations are in parentheses.

	All (N=76)	Aβ- (N=48)	Aβ+ (N=28)	*p*
Age	76.5 (5.8)	76.1 (6.6)	77.1 (4.2)	.49
N of female (%)	45 (59 %)	27 (56 %)	18 (64 %)	.47
MMSE at baseline	28.9 (1.2)	28.9 (1.1)	29.0 (1.3)	.75
# of PiB PET visit	2.8 (0.8)	2.8 (0.8)	2.6 (0.8)	.38
PiB follow-up duration: yrs	4.1 (2.1)	4.3 (2.0)	3.9 (2.2)	.43
# of FTP PET visit	2.7 (0.7)	2.8 (0.8)	2.6 (0.8)	.24
FTP follow-up duration: yrs	3.8 (2.1)	4.0 (2.0)	3.5 (2.2)	.21
# of Cognitive visit	4.3 (1.6)	4.3 (1.7)	4.1 (1.6)	.63
Cognitive follow-up duration: yrs	4.9 (1.8)	5.0 (1.7)	4.5 (1.9)	.23
Baseline Cog-FTP interval: yrs	0.3 (0.3)	0.2 (0.2)	0.3 (0.4)	.24
Baseline Cog-PiB interval: yrs	0.3 (0.4)	0.3 (0.3)	0.4 (0.5)	.30
Baseline PiB-FTP interval: yrs	0.1 (0.3)	0.1 (0.4)	0.1 (0.2)	.35

To estimate the longitudinal change rate in cognition (see Figure 2 for raw cognitive scores at each visit), we extracted slopes for each individual using a linear mixed effects model including time as the only fixed predictor with subject intercept and slope as the random effects. This approach uses all longitudinal scores accounting for subject-specific longitudinal trend and baseline performance, minimizing the influence of random error on a change score. Next, to create measures that represent domain-specific variabilities in longitudinal cognitive change, we computed memory change residual scores by regressing out executive function change from memory change after adjusting for age and sex, as they are known factors that can influence the relationship between memory and executive function (e.g., Levine et al., 2021). Similarly, we regressed out memory change from executive function change, adjusted for age and sex, to calculate the executive function change residual score. The resulting residual values were the differences between the slope of one domain and the predicted slope based on the other domain of that individual, after adjusting for age and sex (Figure 3). Therefore, these values represent the domain-specific variability in memory change that is independent of executive function change, and the executive function change residual represents the variability in executive function change that is independent of memory change. Additionally, we performed control analyses with estimated cognitive slopes without using this residual approach to test if this approach indeed offers additional information that improves sensitivity (Elman et al., 2022).

2.3. MRI Acquisition and Processing

All participants underwent a 1.5 T T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) images (1 mm isotropic voxels, TR=2110ms, TE=3.58ms, FA=15) at each visit. MPRAGE images were processed using FreeSurfer v7.1.0 (http://surfer.nmr.mgh.harvard.edu/) to derive regions of interest (ROIs) in each participant's native space using the Desikan-Killiany atlas. These segmentations were later used to extract regional uptake values in PET analysis and perform partial volume correction for the FTP data.

2.4. PET acquisition and processing

PET data acquisition has been detailed previously (Chen et al., 2021). Briefly, both FTP and PiB were synthesized at the Biomedical Isotope Facility at the Lawrence Berkeley National Laboratory and all

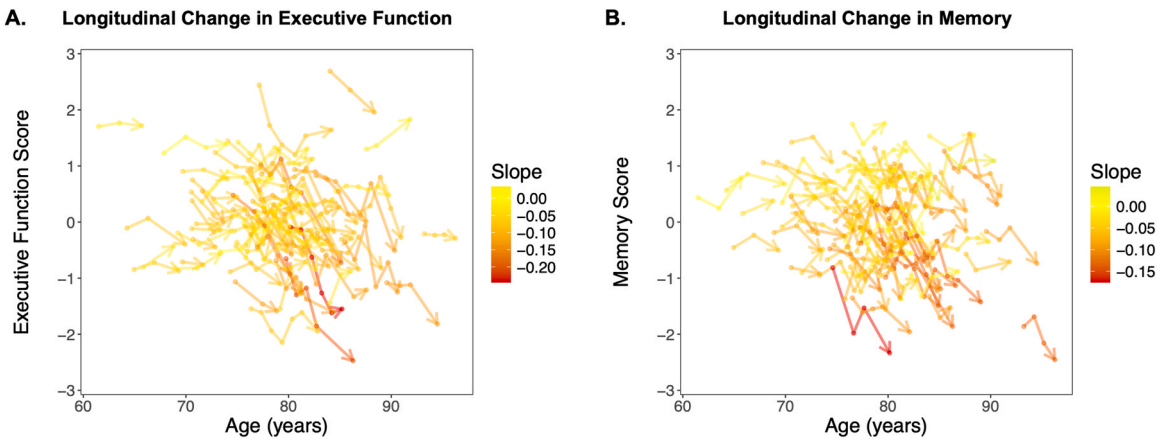

Fig. 2. Longitudinal change in executive function (A) and memory (B). Each line represents one participant and connects the cognitive score at each visit of the individual. The beginning of the line represents the baseline performance, and the arrow shows the last cognitive visit. Lines are color-coded based on estimated longitudinal slope – green means improvement; yellow means stability; red means decline.

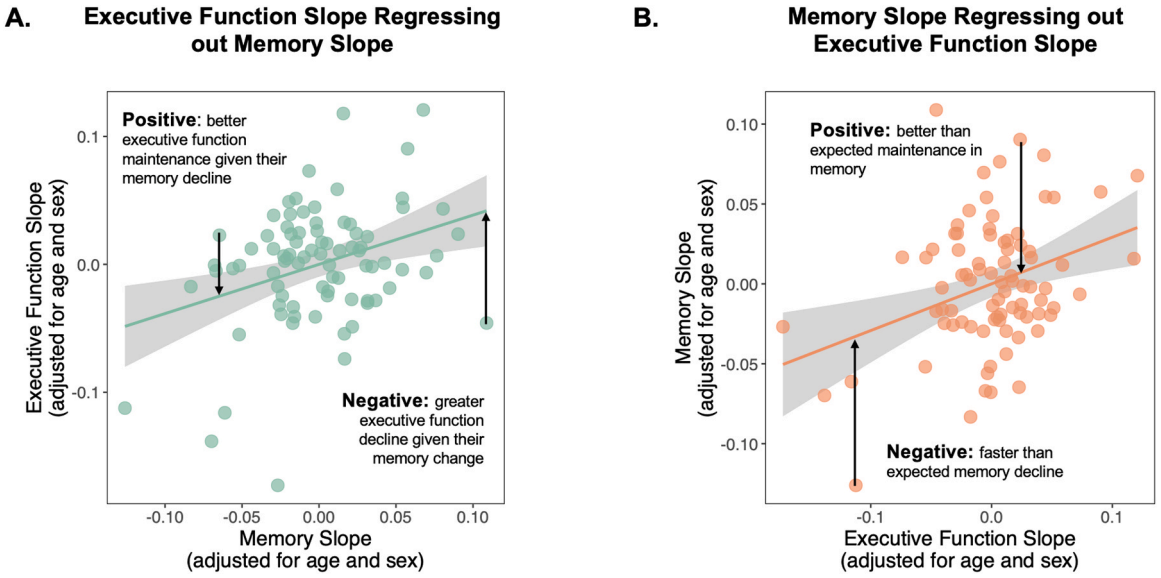

Fig. 3. Partial regression plots demonstrate the variability in cognitive slopes across domains. Arrows represent the deviation of the slope in one domain from the expected value based on the other domain; for example, one may have higher-than-expected maintenance in executive function given their decline in memory, after adjusting for their age and sex.

PET imaging was conducted on a BIOGRAPH PET/CT scanner, with PiB and FTP scans generally performed on the same day. For PiB, participants were injected with 15 mCi of PiB tracer, and 90 min of dynamic acquisition began immediately after the injection. For FTP, participants were first injected with 10 mCi of tracer, and data acquired from 80 to 100 min post-injection were used for analysis. For both PiB and FTP, CT scans collected before the start of emission acquisition were used for attenuation correction. PET images were reconstructed using an ordered subset expectation maximization algorithm with scatter correction and smoothed with a 4 mm Gaussian kernel.

For PiB data processing, a distribution volume ratio (DVR) was generated with Logan graphical analysis (Logan et al., 1996; Price et al., 2005) on frames over 35–90 min post-injection, and normalized using the cerebellar gray matter as the reference region. Mean DVR of each ROI at each time point was quantified. For FTP data processing, the mean tracer retention over 80–100 min post-injection was normalized by the mean tracer retention in the inferior cerebellar gray matter as the reference region, to create FTP standardized uptake value ratio (SUVR) images. Mean SUVR of each ROI at each time point was quantified and partial volume correction (PVC) was performed using the Rousset geometric transfer matrix method (Rousset et al., 1998), following the FTP analysis pipeline in BACS as detailed previously (Baker et al., 2019, 2017). We did not perform PVC on PiB data, following processing steps published previously (LaPoint et al., 2022), because PVC on PiB data provides very little benefit but introduces potential new sources of error (Minhas et al., 2018; Shidahara et al., 2017).

To measure longitudinal change of PiB and FTP for each ROI, we extracted slopes using linear mixed effects models including time as the only fixed predictor with subject intercept and slope as the random effects. For PiB DVRs, all Desikan-Killiany ROIs were examined. For FTP SUVRs, because the sample included only cognitively normal individuals, the tau-related analyses focused on the regions in parts of temporal lobe where tau is known to accumulate early (i.e, the temporal meta-ROI including entorhinal, amygdala, inferior temporal, parahippocampal, fusiform, middle temporal regions) (Jack et al., 2018, 2017).

2.5. Statistical analysis

Statistical analyses were performed using R v4.2.2. Linear mixed effects models were used to estimate longitudinal slopes for PiB, FTP, memory, and executive function. Regression was used to adjust effects related to age and sex and then compute the domain-specific residual scores for memory slope and executive function slope. Partial correlations were used to examine the relationship between regional Aβ/tau accumulation and executive function/memory change residual while adjusting for the other pathology. To confirm the reliability of our results, we conducted a set of control analyses where we used linear mixed effects model to replicate the primary findings. Significant associations were reported based on p value (<0.05) before and after FDR correction.

3. Results

Participant characteristics are shown in Table 1. Although we used continuous and regional Aβ measures in our primary analyses, participant information is separated by baseline Aβ status, defined by the global PiB DVR using a cut-off of 1.065 (Villeneuve et al., 2015). Figure 2 presents the raw longitudinal change in executive function and memory scores in this cognitively normal cohort over an average of 5 years.

3.1. Longitudinal Aβ accumulation associated with executive function decline, but not memory decline

The average estimated rate of regional accumulation for Aβ across the cortex is presented in Figure 4A. When correlating Aβ accumulation to executive function slope residual, while adjusting for the temporal meta-ROI FTP change, we found that greater Aβ accumulation was significantly related to executive function decline, primarily in right prefrontal and parietal regions (Figure 5; Supplemental Table 3 for r_p, uncorrected p and FDR-corrected p values). After FDR correction, the associations in right isthmus cingulate, right precuneus, right inferior and superior parietal, right caudal and rostral middle frontal, right superior frontal, and right precentral regions remained significant (p_{FDR}'s$<.05$). Controlling for regional FTP change in these regions, instead of temporal meta-ROI FTP change, yielded fewer regions but showed the same pattern where frontal-parietal Aβ change was associated with executive function change, but not memory (Supplemental Table 4). We found minimal associations between Aβ accumulation and memory even before FDR correction (Supplemental Table 3). We found similar but overall stronger associations before controlling for FTP change, where increasing Aβ was only statistically significantly associated with executive function change, with strongest associations in frontal and parietal regions, after FDR correction (Supplemental Figure 1).

3.2. Longitudinal tau accumulation associated with memory decline, but not executive function decline

The average estimated rate of accumulation for tau in the regions within the temporal meta-ROIs is presented in Figure 4B. When correlating temporal tau accumulation to memory slope residual, while adjusting for global PiB slope, we found greater temporal tau accumulation was significantly related to memory decline in entorhinal and parahippocampal regions (p's$<.05$; Supplemental Table 5). After FDR correction, the associations in left entorhinal and left parahippocampal regions were marginally significant (Figure 6; p_{FDR}'s$<.1$). Controlling for regional PiB slope, instead of global PiB slope, did not weaken the results (Supplemental Table 6). We did not find any significant associations with executive function even before FDR correction (Supplemental Table 5). We found similar but overall stronger associations before controlling for Aβ change, where increasing tau was only statistically significantly associated with memory change, with strongest associations in left entorhinal and parahippocampal regions, after FDR correction (Supplemental Figure 2). Using non-PVC FTP data, we found very similar results of significant associations between increasing tau, particularly in the left hemisphere, and declining memory (left entorhinal: r_p=-.299, p=.009; right entorhinal: r_p=-.301, p=.009; left parahippocampal: r_p=-.336, p=.003; left inferior temporal: r_p=-.264, p=.022), but not executive function change (p's$>.434$; Supplemental Table 7).

3.3. Control analyses

We first examined if using this residual approach improved the sensitivity to observe the specific dissociations. When using raw estimated cognitive slopes without the residual approach, we found stronger pathology-cognitive associations but with reduced specificity: Aβ and tau accumulations were both associated with memory and executive function decline (Supplemental Figure 3).

Finally, to confirm the reliability of our results, we replicated the analyses of the primary findings using equivalent linear mixed effects models. For example, to examine the effect of left entorhinal tau on memory, we included age, sex, executive function, time, left entorhinal tau slope, time x left entorhinal tau slope, global PiB slope, and time x global PiB slope as the fixed effects, and individual slope and intercept as the random effects. We found the results converged with our primary findings: left entorhinal (p=.002), left parahippocampal (p=.006) and left inferior temporal (p=.03) tau and right entorhinal tau (p=.018) was significantly associated with change in memory, but not executive function (p's$>.31$), whereas Aβ (right superior parietal: p=.012; right superior frontal: p=.045; right precuneus: p=.041; right caudal middle frontal: p=.039) was significantly associated with change in executive function, but not memory (p's$>.19$).

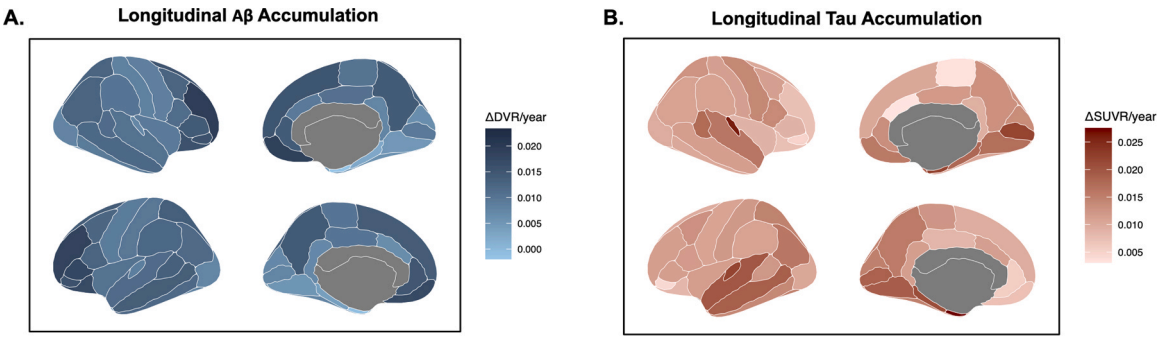

Fig. 4. A. Longitudinal Aβ accumulation, indexed as DVR change per year. **B.** Longitudinal tau accumulation, indexed as SUVR change per year.

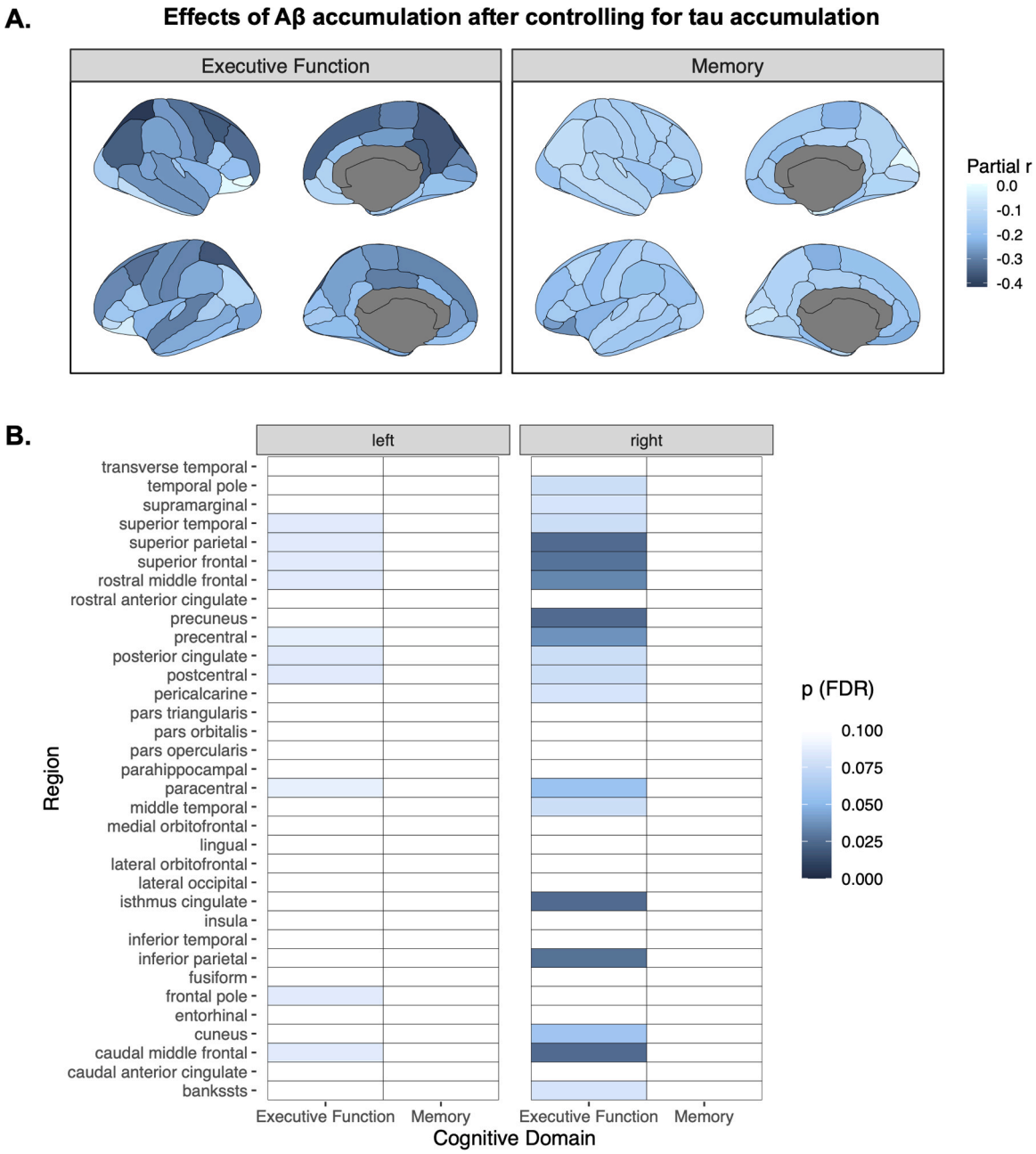

Fig. 5. Association between Aβ accumulation across the cortex and cognitive decline after controlling for tau accumulation. Multiple regions show significant associations with executive function change (*p*'s<.05), primarily in the frontal and parietal regions, whereas minimal associations were observed with memory (Supplemental Table 3). After FDR correction, Aβ accumulation is significantly related to executive function decline in right frontal and parietal regions (Supplemental Table 3).

4. Discussion

Recent AD clinical trials have shown promising outcomes when intervening in early disease stages and mildly impaired individuals (Sims et al., 2023; van Dyck et al., 2023). Detecting the first signs of emerging AD pathology in clinically normal individuals and intervening when subtle cognitive decline begins may be even more optimal to prevent significant, irreversible cognitive impairment. Our study sheds light on the early changes related to accumulating Aβ and tau in cognitively normal people. In cognitively normal older individuals, faster executive function decline, beyond the expected rate given the rate of memory decline, appears to be more associated with Aβ accumulation in the frontal and parietal regions. Faster memory decline, beyond its expected rate given executive function decline, tracks better with tau accumulation in the entorhinal and parahippocampal regions. This "Aβ-executive/tau-memory" pattern suggests specific associations between pathology and cognitive domain affected in the early stage of disease progression.

The key novel finding of this study is a double dissociation between accumulating Aβ/tau pathology and declining abilities in executive function/memory. These pathology-cognitive domain associations may reflect the functional specificity of the networks that are vulnerable to Aβ and tau pathology. Inspecting regional Aβ accumulation in the sample (Figure 4), frontal and parietal regions are among the fastest accumulating regions. They are also essential for performing tasks that require attentional and executive function (Witt et al., 2021). Our results indeed confirm that the strongest associations between Aβ accumulation and executive function decline are observed in middle and superior

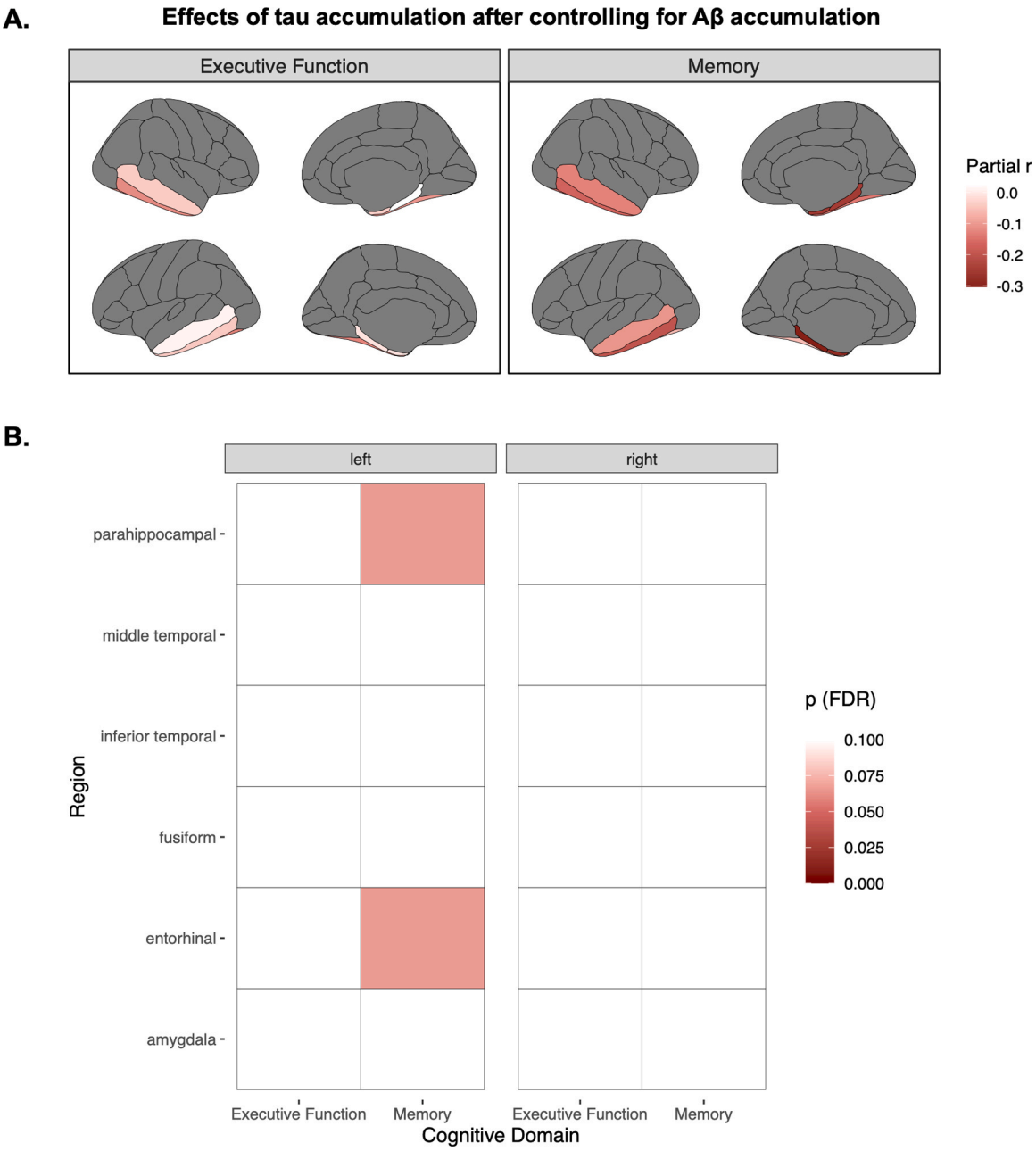

Fig. 6. Association between tau accumulation in the temporal meta-ROIs and cognitive decline after controlling for Aβ accumulation. Significant associations were observed with memory change in left and right entorhinal (left: r_p=-0.283, p=.022; right: r_p=-0.256, p=.040) and parahippocampal (left: r_p=-0.304, p=.014; right: r_p=-0.247, p=.047) regions (Supplemental Table 5). After FDR correction, tau accumulation in left entorhinal and parahippocampal regions is marginally significantly related to memory change (Supplemental Table 5).

frontal regions as well as inferior and medial parietal regions, suggesting that vulnerabilities of those regions to Aβ pathology may lead to regional dysfunction (Liu et al., 2023) that causes specific deficits in executive function.

Our findings indicate that the regional differences in Aβ accumulation in cognitively normal older individuals, though relatively small (LaPoint et al., 2022), are still important variabilities (Collij et al., 2022) that have meaningful consequences. Previous studies have demonstrated that focal Aβ in medial parietal regions is predictive of cognitive decline prior to global positivity (Ali et al., 2022; Farrell et al., 2018). A global threshold is useful to identify individuals with positive Aβ deposition, but may be too late to detect the emergence of the disease. Measuring regional Aβ in a subset of regions may be more sensitive in detecting early cognitive decline (Ali et al., 2022; Farrell et al., 2018; Guo et al., 2020). Meanwhile, these regions involved in early Aβ accumulation are particularly functionally specialized. Our findings further highlight that the regional differential vulnerability to different pathologies can explain individual differences in cognitive decline in cognitively normal older individuals.

The Aβ and executive function association also suggests that Aβ may have a direct association with cognition. Previous studies have reported that the association between Aβ and cognition is weak, and further diminished when including tau in statistical models, suggesting that the effect of Aβ may be mediated by higher tau deposition related to Aβ (Bloom, 2014; Hanseeuw et al., 2019). Our results, however, suggest that Aβ accumulation, particularly in fast accumulating regions, is related to cognitive decline after controlling for tau. It is likely that early Aβ accumulation in neocortical regions where tau rarely deposits in

cognitively normal older individuals could exert direct effects on certain cognition. The executive function measures in our study have a particular emphasis on inhibition (Stroop) and attention (Digit Symbol Substitution Test, Mental Control) where reaction time is part of the scoring. Although these are commonly used executive function tests, their performance is highly influenced by processing speed especially in older people (Albinet et al., 2012; Baudouin et al., 2009). It is challenging to completely disentangle the speed component in executive function. Nevertheless, the role of Aβ has been demonstrated in studies using speed-related (Farrell et al., 2022) and non-speed related indicators (Ali et al., 2022; Tideman et al., 2022) measuring executive function.

We found that longitudinal tau accumulation in the entorhinal and parahippocampal regions is associated with longitudinal memory decline, consistent with recent reports of longitudinal accumulation of medial temporal tau associated with memory decline (Farrell et al., 2022; Fonseca et al., 2024). Entorhinal and parahippocampal cortices play important roles for memory processes (Aminoff et al., 2013; Takehara-Nishiuchi, 2014) and their integrity is critical for maintaining memory function (Nassif et al., 2022; Rodrigue and Raz, 2004; Chen et al., 2024). These regions, however, are particularly vulnerable to tau pathology, which leads to faster memory decline.

These specific pathology-cognitive domain associations are consistent with previous suggestion that tau is a strong predictor of memory decline, but not executive function decline (Chen et al., 2021; Fonseca et al., 2024; Sperling et al., 2019). It is also consistent with previous observations that the initial focal Aβ is predictive of decline in executive measures, but not memory (Ali et al., 2022; Tideman et al., 2022). Taken together, we think that executive function and memory separately track Aβ and tau accumulation in cognitively normal older individuals. Although not directly examined, we suggest that the regional selectivity to Aβ and tau contributes to this observed pathology-cognitive association. During the initial emergence of AD, accumulating Aβ pathology is most evident in frontal and parietal regions, leading to subtle but measurable executive function decline while tau accumulation in entorhinal and parahippocampal regions is linked to memory decline. Soon thereafter, the accumulation of Aβ throughout cortex appears to be very rapid as it passes the global positivity threshold (LaPoint et al., 2022), and tau accumulation increases leading to dysfunction in multiple neural and cognitive systems (Chen et al., 2024). The subtle effect of Aβ becomes difficult to detect when tau is present as the primary pathology in neocortical regions, causing more severe decline in memory, executive function, and other cognitive domains that lead to dementia. The Aβ-related executive decline may therefore be particularly sensitive in reflecting very early changes in Alzheimer's disease prior to tau emergence. We believe the preferential distribution of Aβ and tau in this early stage before global deposition presents a particularly unique window to detect this double dissociation driving by functional specificity in those vulnerable regions.

One interesting observation in our study is that Aβ-executive function associations appear to be right-lateralized while tau-memory associations are left-lateralized. The left-lateralized tau association with memory has also been noted in our recent voxel-wise analysis (Chen et al., 2024). These lateralized associations may be due to higher representations of verbal-based measures in the memory composite and spatial-attentional measures in the executive function composite. This may further suggest regional functional specificity as the underlying mechanism contributing to the specific pathology-cognition associations. Another possibility is that Aβ and tau differentially accumulate in the two hemispheres, contributing to a lateralized association in the more vulnerable hemisphere. However, in our data, we did not find systematic differences in pathology change between left and right hemispheres, which would suggest a lateralized vulnerability to certain pathology. Future studies may analyze Aβ and tau in left and right hemispheres separately and further examine the preferential lateralization of AD pathology.

Our results also challenge the stereotypical view of early AD as an isolated amnestic syndrome. Although some studies suggested that executive function abilities were relatively preserved in early stages of AD (Petersen et al., 1994), this view has recently changed with increasing evidence of the presence of impairment in executive function in early AD (Guarino et al., 2019). Our study shows that even in cognitively normal individuals, there are early declines in executive function independently associated with Aβ. This highlights the importance of evaluating executive dysfunction in AD and recommends the use of a comprehensive examination of cognitive abilities beyond a single domain of memory.

We used a novel approach that defined "greater than expected" cognitive decline reflecting within-individual variability across different domains. This appears to be more sensitive than traditional measures of longitudinal change and shows specific relationships to different pathology. We believe that the examination of within-person variability could provide important information that is not captured by traditional neuropsychological measures.

While our study has many strengths, including extensive longitudinal data for PET and cognition and the development of domain-specific measures for cognitive decline, it does have limitations. The FTP tracer used has shown evidence of off-target binding and lack of specificity in some regions (Baker et al., 2019). However, the ROIs we investigated are not particularly susceptible to these effects, and we conducted partial volume correction to further control for this problem. Our residual approach, although shown to be useful in detecting domain-specific deviation in cognitively normal older people (Supplementary Figure 3), may not be as appropriate in measuring cognitive decline in later stages, as cognitive impairments across multiple domains become common. In addition, we focused our study on executive function and memory because they are most frequently studied and demonstrated to be particularly vulnerable in aging and early AD. A more comprehensive examination including additional cognitive domains would be ideal to better characterize cognitive variabilities in multiple domains. Similarly, the specific measures included in memory and executive function composites are also limited by the tests available. We created the cognitive constructs maximizing the internal reliability and thus were not able to include all subdomains of memory and executive function. Future studies should incorporate other non-speed related executive measures and other memory indicators that rely less on executive attention to better understand their differential association to pathology. Finally, our cohort, though deeply characterized, is highly educated and does not fully represent the diversity of older individuals in the US. Although very healthy, our participants' co-pathology such as vascular disease is not examined. Vascular changes have been associated with AD pathology (Nichols et al., 2021; Rodrigue et al., 2013) and directly and indirectly related to cognitive decline (Iadecola, 2017; Rabin et al., 2018; Villeneuve et al., 2015). Future research may explore the role of other pathologies in the relationship between emerging AD pathology and early cognitive decline.

5. Conclusion

We found a double dissociation where Aβ accumulation related to faster executive function decline while tau accumulation was related to memory decline in cognitively normal older individuals. This may reflect the selective vulnerabilities in the networks that are functionally responsible for those cognitive processes. Our findings are informative for developing sensitive behavioral markers for detecting specific AD pathology in the early stage and particularly highlight the importance of executive function evaluation in assessing early AD-related deficits in asymptomatic populations. The use of multi-domain cognitive assessment tracking domain-specific decline may improve prediction of disease progression in the asymptomatic stage of AD.

CRediT authorship contribution statement

Xi Chen: Writing – review & editing, Writing – original draft,

Visualization, Investigation, Formal analysis, Conceptualization. **Suzanne Mason:** Writing – review & editing, Data curation. **Alexis Juarez:** Writing – review & editing, Data curation. **Suzanne L Baker:** Writing – review & editing, Project administration, Methodology. **Sarah Kobayashi:** Writing – review & editing, Data curation. **Susan M Landau:** Writing – review & editing, Project administration, Methodology. **Theresa M Harrison:** Writing – review & editing, Project administration, Methodology. **William J Jagust:** Writing – review & editing, Supervision, Project administration, Funding acquisition.

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Verification

The authors have no conflict of interest to report for this paper. This work was funded by National Institute on Aging (W.J.J.: AG034570 and AG062542). Xi Chen was supported by the BrightFocus Foundation (A2021004F). Avid Radiopharmaceuticals enabled the use of the [18 F] flortaucipir tracer but did not provide direct funding and were not involved in data analysis or interpretation.

We confirm that this original work has not been published elsewhere nor is it currently under consideration for publication elsewhere. Participants all provided written, informed consent, approved by the Institutional Review Boards at the Lawrence Berkeley National Laboratory and the University of California, Berkeley.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neurobiolaging.2024.10.004.

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