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Regional Tau Effects on Prospective Cognitive Change in Cognitively Normal Older Adults

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Abstract

Studies suggest that tau deposition starts in the anterolateral entorhinal cortex (EC) with normal aging, and that the presence of β-amyloid (Aβ) facilitates its spread to neocortex, which may reflect the beginning of Alzheimer's disease (AD). Functional connectivity between the anterolateral EC and the anterior-temporal (AT) memory network appears to drive higher tau deposition in AT than in the posterior-medial (PM) memory network. Here, we investigated whether this differential vulnerability to tau deposition may predict different cognitive consequences of EC, AT, and PM tau. Using ^{18}F-flortaucipir (FTP) and ^{11}C-Pittsburgh compound-B (PiB) positron emission tomography (PET) imaging, we measured tau and Aβ in 124 cognitively normal human older adults (74 females, 50 males) followed for an average of 2.8 years for prospective cognition. We found that higher FTP in all three regions was individually related to faster memory decline, and that the effects of AT and PM FTP, but not EC, were driven by Aβ+ individuals. Moreover, when we included all three FTP measures competitively in the same model, only AT FTP significantly predicted memory decline. Our data support a model whereby tau, facilitated by Aβ, transits from EC to cortical regions that are most closely associated with the anterolateral EC, which specifically affects memory in the initial stage of AD. Memory also appears to be affected by EC tau in the absence of Aβ, which may be less clinically consequential. These findings may provide clarification of differences between normal aging and AD, and elucidate the transition between the two stages.

Key words: β-amyloid; aging; Alzheimer's disease; memory; positron emission tomography; tau

52 **Significance Statement**

53 Tau and β-amyloid (Aβ) are hallmarks of Alzheimer's disease (AD), but are also found in
54 cognitively normal people. It is unclear whether, and how, this early deposition of tau and Aβ
55 may affect cognition in normal aging and the asymptomatic stage of AD. We show that tau
56 deposition in the entorhinal cortex, which is common in advanced age, predicts memory
57 decline in older adults independent of Aβ, likely reflecting normal, age-related memory loss. In
58 contrast, tau in anterior temporal regions is most predictive of memory decline in Aβ+
59 individuals. These data support the idea that tau preferentially spreads to specific cortical
60 regions, likely through functional connections, and plays a primary role in memory decline in
61 the early stage of AD.

Introduction

The pathological changes in Alzheimer's disease (AD), including β-amyloid (Aβ) and tau deposition, start decades before the symptoms (Price et al., 2009; Jack et al., 2013). With positron emission tomography (PET) imaging, researchers can visualize the distribution of these two hallmark pathologies in the brain (Ossenkoppele et al., 2015; Johnson et al., 2016). Different from the diffuse accumulation of Aβ (Nordberg, 2004), tau starts focally in the early stages of AD, most commonly in the transentorhinal region, including the anterolateral entorhinal cortex (EC) (Braak and Braak, 1992, 1995). This early EC tau increases with age and has been reported in individuals without Aβ pathology (Sonnen et al., 2011; Jack et al., 2019; Schöll et al., 2019). This Aβ-independent tauopathy has recently been linked to age-related memory decline in normal aging (Maass et al., 2018). On the other hand, high Aβ facilitates tau spreading outside EC, likely through neural connections (Pooler et al., 2015; Cho et al., 2016), which may signal the transition to AD (Braak and Braak, 1997). This tau deposition outside EC may be responsible for the initiation of clinically significant memory decline related to AD pathology.

In this study, we were interested in the cognitive consequences of tau deposition in cognitively normal individuals, especially in regions where we expect tau deposits early. One model for examining early stage tau deposition presupposes that tau spreads via patterns of neural connectivity, and is based on the organization of large-scale memory networks (Hoenig et al., 2018). This includes an anterior-temporal (AT) network comprising anterior and inferior temporal regions, specialized for object processing and item memory, and a posterior-medial network (PM) of medial parietal regions involved in context and spatial recognition (Ranganath

and Ritchey, 2012). Recent evidence from our lab using the Berkeley Aging Cohort Study (BACS) suggests that tau preferentially deposits in the AT network, while Aβ preferentially deposits in the PM network (Maass et al., 2019). Preferential tau deposition in AT is likely due to its strong functional connection to EC, especially the anterolateral EC where tau initially deposits (Schröder et al., 2015; Adams et al., 2019). Meanwhile, the posteromedial subregion of EC also demonstrates connectivity to the neocortical regions of the PM network (Kerr et al., 2007; Schultz et al., 2012; Adams et al., 2019). While PM may also show tau deposition, it probably occurs later, since PM shows less tau burden in asymptomatic people compared to AT regions (Maass et al., 2019). This differential vulnerability to tau deposition allows us to examine the hypothesis that the earliest tau deposition outside EC, within AT regions, is a better predictor of subsequent memory change than tau in EC or PM regions.

Few studies have examined this potential regional difference in tau effects on cognition, although there is abundant evidence that tau has an adverse effect on memory (Aschenbrenner et al., 2018; Sperling et al., 2018; Hanseeuw et al., 2019; Pontecorvo et al., 2019; Ziontz et al., 2019; Betthauser et al., 2020). However, the role of Aβ in this association, especially in normal aging, is still unclear (Maass et al., 2018; Sperling et al., 2018; Schöll and Maass, 2020).

Therefore, we aimed to investigate regional tau effects on memory in cognitively normal older people as well as the effects of Aβ by evaluating multiple regions susceptible to tau deposition. Because tau in EC is common in normal aging, we hypothesized that EC tau may predict memory change independent of Aβ. We also hypothesized that tau in AT and PM regions would also affect memory change, but only in Aβ+ individuals, since the spread of tau into neocortex seems to be Aβ-dependent. Finally, while tau in EC, AT, and PM may each

predict memory, we hypothesized that AT tau would have the strongest effect: as tau is more likely to spread from the anterolateral EC to AT regions first, AT tau may be most predictive of AD-related decline in this early stage.

Materials and Methods

Participants

A total of 124 cognitively normal older individuals (74 females, 50 males) from BACS over age 65 were included in the study. All participants were cognitively normal when enrolled, and remained normal throughout the study, with Mini-Mental State Examination (MMSE) score greater than 25. Participants underwent structural 1.5T MRI, tau PET with ^{18}F-Flortaucipir (FTP), β-amyloid PET with ^{11}C-Pittsburgh Compound-B (PiB), and a standard cognitive assessment that included measures of episodic memory, language, visuospatial ability, working memory and executive function. Most subjects underwent repeated cognitive testing at one to two-year intervals and 108 participants had at least two cognitive visits following their tau PET scan: 39 had two visits, 21 had three visits, 22 had four visits, 18 had five visits, and eight had six visits. All participants provided written, informed consent. The study was approved by the Institutional Review Board at the Lawrence Berkeley National Laboratory (LBNL) and the University of California, Berkeley.

Cognitive Assessment

To examine prospective cognitive change, we only focused on cognitive assessments administered close to (180 days) and after the tau PET scan. The time interval between

cognitive assessment and tau PET scan was included as a covariate of no interest for all analyses. We used composite scores to examine cognitive performance over time. We calculated the composite score by first standardizing the raw measures based on the baseline mean and standard deviation. Then, for any task with multiple measures, we averaged measures of the same task to create a task score to minimize any task bias. Finally, we averaged across tasks of the same cognitive domain to form the composite score.

The primary cognitive domain studied was memory, which comprised five measures from three tasks, including short-delay free-recall and long-delay free-recall of the California Verbal Learning Test (Delis et al., 2000) and of Visual Reproduction (Wechsler, 1997), and total score of Logical Memory (Wechsler, 1997). We additionally explored the domain of executive function, using number correct in the Digit Symbol test (Smith, 1982), number correct in 60 sec in the Stroop Interference Test (Stroop, 1938), and "Trail B minus A" from the Trail Making Test (Reitan and Wolfson, 1985).

MRI Acquisition and Processing

Structural MRIs were acquired for PET preprocessing. Participants were scanned using a 1.5T Siemens Magnetom Avanto scanner at LBNL. High-resolution anatomical images were collected with T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) images (1 mm isotropic voxels, TR=2110ms, TE=3.58ms, FA=15). All MPRAGE images were processed using FreeSurfer v5.3 (http://surfer.nmr.mgh.harvard.edu/). We derived regions of interest (ROIs) in participant's native space using the Desikan-Killiany atlas (Desikan et al., 2006). These segmentations were later used to extract regional uptake values, perform partial volume

correction for the FTP data, and extract hippocampal volumetric, EC thickness, and white matter hypointensity measures used for supplementary analyses.

PET Acquisition and Processing

PET data acquisition was detailed previously (Ossenkoppele et al., 2016; Schöll et al., 2016; Adams et al., 2019). Both FTP and PiB were synthesized at the Biomedical Isotope Facility at LBNL and all PET imaging was conducted on a BIOGRAPH PET/CT scanner. For FTP scans, participants were first injected with 10 mCi of tracer and data acquired from 80-100 min post-injection were used for analysis. CT scans collected before the start of emission acquisition were used for attenuation correction. We reconstructed the FTP-PET images using an ordered subset expectation maximization algorithm with scatter correction and smoothed with a 4 mm Gaussian kernel.

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, as the reference region, to create FTP standardized uptake value ratio (SUVR) images. We performed partial volume correction (PVC) to account for partial volume effects related to atrophy and spillover signal, using the Rousset geometric transfer matrix method, as detailed previously (Rousset et al., 1998; Baker et al., 2017). Our primary interest was focused on three regions of interest (ROIs) – composite AT and PM regions, and the entorhinal cortex. Subregions for AT and PM were selected *a priori* based on the literature on AT and PM networks (Ranganath and Ritchey, 2012; Inhoff and Ranganath, 2017; Maass et al., 2019). Specifically, AT FTP SUVR was calculated using a weighted average of inferior temporal cortex, amygdala, and fusiform cortex. PM FTP SUVR

was calculated using a weighted average of parahippocampal gyrus, isthmus cingulate, and precuneus. EC FTP SUVR was based on the FreeSurfer parcellation of entorhinal cortex. The regional FTP SUVR of the left and right hemispheres were averaged to create the mean measure of regional FTP SUVR.

For PiB-PET imaging, participants were injected with 15 mCi of PiB tracer, and 90 min of dynamic acquisition frames began immediately after the injection. A CT scan was obtained before the injection and used for attenuation correction. PiB-PET images were also reconstructed using an ordered subset expectation maximization algorithm with scatter correction and smoothed with a 4 mm Gaussian kernel.

For PiB data processing, 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 whole cerebellar gray as the reference region. Global PiB was calculated using multiple FreeSurfer ROIs across the cortex, as previously described (Mormino et al., 2012). We used the threshold of 1.065 of global DVR to define Aβ positivity (Villeneuve et al., 2015). We did not perform PVC for PiB data, following the procedure used to define the Aβ positivity cutoffs in this cohort (Villeneuve et al., 2015). Aβ is widely distributed in association cortex so PVC on PiB data offers little benefit in quantitation of tracer retention.

Experimental Design and Statistical Analyses

Individual Effect of Tau in AT, PM, and EC on Prospective Memory Change

To examine regional tau effects on memory change, three linear mixed models (LMMs) were conducted with time, regional FTP SUVR, and FTP SUVR x time interaction as predictors

194 and the memory composite score as the outcome variable. Baseline age, sex, education (yrs),
195 *APOE* status (ε4 carrier or not) and the time interval between baseline cognitive assessment
196 and FTP PET were included as covariates, as well as the covariate x time interactions. Random
197 effects included subject intercept and time slope. Another set of LMMs examined if the tau
198 effect was different in Aβ− and Aβ+ groups, by additionally including Aβ positivity status and its
199 interactions with time and tau (i.e., Aβ status x time, FTP SUVR x Aβ status, and FTP SUVR x Aβ
200 status x time). We completed *post hoc* analyses examining the FTP SUVR level at which
201 longitudinal memory started to decline. To do so, for AT and PM regions separately, we
202 estimated the simple slopes of memory change at varying FTP SUVRs in Aβ+ individuals (Aiken
203 et al., 1991) and identified the specific FTP SUVR value associated with the initiation of negative
204 longitudinal memory change.

205 We then repeated the LMM analyses with continuous PiB DVR substituting for the
206 dichotomized Aβ status, while controlling for the same covariates. This allowed us to confirm
207 the reliability of our findings and explore the range of Aβ levels where a tau effect emerged: we
208 estimated the conditional effect of FTP SUVR on memory change slopes (extracted using a
209 simple LMM with only time as a predictor) at varying levels of Aβ, and identified the specific
210 global PiB DVR value at which FTP SUVR started to have a significant effect on memory change,
211 using the Johnson-Neyman procedure (Johnson and Fay, 1950; Aiken et al., 1991).

212 Multiple Regional Tau Measures Simultaneously Predicting Prospective Memory Change

213 To test whether AT tau had the strongest effect on memory change among the three
214 regions, using three LMMs, we examined the effects of (1) AT and EC FTP, (2) PM and EC FTP,
215 and (3) AT and PM FTP on longitudinal memory, as well as their interactive effect with Aβ status.

Finally, we included all three FTP measures simultaneously and explored their unique contributions when competitively examined in the same model. We included the same covariates as in previous analyses for these models.

All predictors were mean-centered to minimize multicollinearity. We also examined the variance inflation factor (VIF) for all models and found little evidence of problematic collinearity (James et al., 2013).

Results

Demographics

Participants' information at baseline is presented in Table 1. The within-subjects *t*-test revealed that FTP SUVR values were higher in AT ($p<.001$) and EC ($p<.001$), than the PM region, as expected. The independent sample *t*-test found no significant group difference in age, sex, testing interval, total duration of follow-up, number of longitudinal cognitive assessments, retention rate, hippocampal volume, entorhinal cortex thickness, baseline memory or executive function performance between Aβ– and Aβ+ groups. However, the Aβ+ group had fewer years of education ($p=.018$), higher percentage of *APOE* ε4 carriers ($p<.001$; in Aβ–, 14.3% ε2ε3, 77.1% ε3ε3 and 8.6% ε3ε4; in Aβ+, 2% ε2ε3, 6% ε2ε4, 48% ε3ε3 and 44% ε3ε4), and higher FTP SUVRs in all three tau ROIs (AT: $p<.001$, PM: $p=.001$, EC: $p<.001$).

236 ***AT, PM, and EC Tau Individually Predicts Prospective Memory Change***

237 Using three LMMs, we examined the individual effect of FTP SUVR in AT, PM, and EC
238 separately (Table 2: Model 1; see Table 2-1, 2-2, 2-3 for statistics of all predictors). In all three
239 regions, FTP showed a significant main effect on memory performance (AT: $p<.001$, PM: $p=.007$,
240 EC: $p<.001$) and a significant FTP x time interaction (AT: $p<.001$, PM: $p=.014$, EC: $p=.008$),
241 suggesting that higher FTP SUVR was associated with greater memory decline and worse
242 memory performance, as depicted in Figure 1.

243

244 ***Aβ Moderates AT and PM Tau Effect on Prospective Memory Change***

245 We next examined if the FTP effect differed in Aβ+ and Aβ− individuals (Table 2: Model 2;
246 see Table 2-1, 2-2, 2-3 for statistics of all predictors). We found a significant three-way
247 interaction of FTP x Aβ status x time for both AT ($p=.009$) and PM ($p=.023$) models, such that
248 higher FTP SUVR was more predictive of faster memory decline in the Aβ+ group (Figure 2). In
249 contrast, we did not find any statistical difference in EC FTP effect between Aβ+ and Aβ−
250 individuals ($p=.12$). Based on the predicted memory trajectories, we were able to identify the
251 AT and PM FTP SUVR value required to produce memory decline in the Aβ+ group. For AT FTP,
252 an SUVR greater than 1.29 was associated with a negative longitudinal memory slope; and for
253 PM FTP, the defining SUVR was 1.19. To further account for the effect of individual amyloid
254 burden on these relationships, we used continuous PIB DVR values (see next section below) in
255 the models. For individuals with an average Aβ+ group PIB DVR of 1.33, equivalent to a value of
256 48 on the centiloid (CL) scale (Klunk et al., 2015), the AT FTP SUVR associated with a negative
257 memory slope was 1.33, and for PM FTP the value was 1.24.

We also note that the paradoxical increase in memory performance at FTP SUVR=1 for the Aβ+ group in Figure 2 was a spurious effect. It occurred because model estimates are primarily driven by high FTP individuals due to very few individuals with FTP SUVR =1 in the Aβ+ group (see histograms in Figure 3). This results in a skewed relationship in the low FTP range that is not representative of actual trajectories in those people (Figure 3-1).

Figure 3 further illustrates the individual data depicting the relationship between FTP and memory change (slopes extracted using a simple LMM with only time as a predictor), while controlling for age, sex, education, *APOE* status, and cog-PET interval. The visualization confirms the above finding that AT and PM FTP effect was only evident in Aβ+ individuals, whereas the EC FTP effect was not statistically different in Aβ− and Aβ+ individuals. The scatter plots and the histograms also reveal that high FTP SUVRs were primarily Aβ+ cases and that the EC FTP effect was most different from AT and PM in the relatively low FTP range: a slight increase in EC FTP SUVR was associated with memory decline in both Aβ− and Aβ+ individuals, while increased FTP in AT or PM regions was not related to memory decline in Aβ− individuals.

Defining Values of PiB DVR for Tau Effects to Emerge

The results were replicated when using PiB DVR as the continuous measure of Aβ: AT and PM FTP showed a significantly greater effect on longitudinal memory change as PiB DVR increased (AT: p=.001, PM: p=.018), while the EC FTP x PiB DVR x time interaction was not statistically significant, although trending (p=.085).

Using a continuous Aβ measure also allowed us to explore the global PiB DVR value at which regional tau starts to affect memory as Aβ accumulates. We found that the effect of AT FTP on

memory change was significant after PiB DVR reached a value of 1.17, equivalent to 25 CL. Similarly, the PM FTP effect on memory change became significant as PiB DVR increased to 1.13 (19 CL). In contrast, the EC FTP effect was significant even at very low PiB DVRs (inflection PiB DVR=0.95, CL=-7), consistent with the finding suggesting a significant EC FTP effect on memory change across Aβ groups.

Regional Tau Measures Simultaneously Predict Prospective Memory Change

We examined whether tau in AT was the strongest predictor of memory change above and beyond EC and PM tau by simultaneously modeling multiple FTP measures (Table 3). In the model with AT and EC FTP, we found that AT FTP significantly predicted longitudinal memory change (p=.048), whereas EC FTP only had a main effect on memory performance (p<.001; see Table 3-1 for all statistics). When additionally including Aβ status in the model, AT FTP x time x Aβ status was significant (p=.025), revealing a stronger effect of AT FTP in Aβ+ individuals.

In contrast, we did not find any significant PM FTP effect (p=.33) when PM and EC FTP SUVRs were both included in the model. Including Aβ status did not change the result (p=.27; see Table 3-1 for statistics of all predictors).

When including both AT and PM FTP SUVRs in the model (see Table 3-3 for statistics of all predictors), AT FTP still had a significant effect on memory change (p=.011), whereas PM FTP did not (p=.36). This AT FTP effect was stronger in Aβ+ individuals (p=.035).

Finally, we simultaneously modeled all three FTP measures to explore their unique effects when they were competitively included in the same model (see Table 3-4 for statistics). As depicted in Figure 4, we found that while EC FTP SUVR was strongly related to cross-sectional

memory performance (p<.001), AT FTP SUVR was the only significant predictor of longitudinal memory change among the three FTP measures (p=.045). This strongest effect of AT FTP x time was primarily driven by Aβ+ individuals (p=.032).

Confirmatory Analyses of AT and PM Subregions, Hippocampal and EC Neurodegeneration, White Matter Lesion, and Executive Function

To further confirm and interpret our results, we conducted a series of supplementary analyses. First, we repeated the primary analyses for each subregion that constitutes the AT and PM ROIs. Higher FTP SUVR in inferior temporal and fusiform both predicted prospective memory decline beyond EC FTP, particularly in Aβ+ individuals (Inferior Temporal: p=.025, Fusiform: p=.018), whereas amygdala FTP was not significantly related to memory change when EC FTP was in the model (p=.76). For PM subregions, results largely replicated the primary finding: higher regional FTP SUVR was individually related to greater longitudinal memory decline for all three subregions (Parahippocampal: p=.002, Isthmus Cingulate: p=.037, Precuneus: p=.039), but the effect diminished when EC FTP SUVR was additionally included (Parahippocampal: p=.11, Isthmus Cingulate: p=.33, Precuneus: p=.46).

Next, we investigated if the FTP effect on memory decline was confounded by individual differences in neurodegeneration. We used hippocampal volume (adjusted for estimated total intracranial volume) and entorhinal cortex thickness as indices and examined whether their inclusion in the models changed any of the findings. We found that hippocampal volume did not predict memory change in any analysis and did not change any findings we reported. Thinner entorhinal cortex, on the other hand, was related to faster memory decline in several

models (*p*'s<.05). But FTP effects remained unchanged, suggesting a primary tau influence on memory decline beyond neurodegeneration.

We also considered the potential influence of the load of vascular insults (Kim et al., 2018) by examining the effect of white matter lesions on memory change. We incorporated the white matter hypointensity measure (Dadar et al., 2018; Wei et al., 2019) derived from FreeSurfer using the T1-weighted images. We found that white matter hypointensity was related to worse cross-sectional memory performance (*p*'s<.05), but did not predict longitudinal memory change, and did not change any of our findings.

Finally, we explored whether the reported FTP effects on memory also applied to executive function, and repeated the primary analyses using executive function as the dependent variable in the models. We did not find any significant effect of FTP in AT, PM or EC on executive function change (*p*'s >.1), suggesting a specific effect of early tau on memory in this healthy cohort.

Discussion

Our study investigated regional tau effects on prospective cognitive change in 124 cognitively normal older adults. We found that having greater tau predicted faster memory decline, consistent with previous findings of prospectively measured cognition (Hanseeuw et al., 2019; Sperling et al., 2019). Specifically, we found interesting regional differences in which tau burden in AT and PM regions was predictive of memory decline exclusively in individuals harboring Aβ, whereas the EC tau effect appeared to be independent of Aβ pathology. Moreover, AT tau had the strongest effect on memory change above and beyond EC and PM

346 tau effects. Altogether, our study suggests differential contributions of regional tau to memory
347 decline, potentially revealing a sequential influence of tau pathology in EC, AT and PM regions
348 on prospectively measured cognition.

349 High EC tau was found to be related to worse cross-sectional memory and greater memory
350 decline preceding Aβ deposition, suggesting an initial effect of EC tau on cognition in older
351 adults with little AD pathology. This finding is consistent with the concept of Primary Age
352 Related Tauopathy (PART) (Crary et al., 2014), which describes a common pathology in older
353 brains of high tau accumulation with little evidence of Aβ. Whether or not PART belongs on the
354 AD continuum is debated (Duyckaerts et al., 2015; Bell et al., 2019), and recent research on its
355 clinical consequences yielded mixed findings (Jefferson-George et al., 2017; Schöll and Maass,
356 2020; Teylan et al., 2020). Our findings seem to agree with previous pathological (Jefferson-
357 George et al., 2017; Josephs et al., 2017) and cross-sectional evidence (Shimada et al., 2017;
358 Groot et al., 2020; Weigand et al., 2020) that tau in EC may exert a detrimental effect on
359 memory without the necessity of Aβ (Maass et al., 2018). There have also been reports that EC
360 tau does not affect cognition in the absence of Aβ (e.g., Sperling et al., 2019). The contrast
361 between these findings and the present study can be illustrated by comparing results from
362 Sperling et al. (2019; e.g., Figure 2A) with ours (e.g., EC plot in Figure 3); results in the high tau
363 range are similar, while our results also show a relationship between EC tau and memory
364 change even in the low tau range where theirs did not. Our sample was slightly smaller, more
365 highly educated, and with a lower proportion of *APOE* ε4 carriers, none of which seem likely to
366 explain the differences. However, our sample, particularly the Aβ− group, appeared to have
367 more memory decline with greater variability, possibly due to their slightly older age and longer

368 follow-up time, which may contribute to the result differences. Altogether, we believe that
369 increases in EC tau are likely to affect memory without Aβ pathology, possibly underlying age-
370 related memory loss in normal aging. Elevated Aβ further accelerates this tau effect in
371 preclinical AD, possibly by increasing the toxicity of the accumulated tau and also facilitating its
372 further spread to the neocortex (Pooler et al., 2015).

373 We found that AT tau was the strongest predictor of prospective memory change among
374 the three regions we investigated, particularly in those harboring Aβ. This likely reflects a
375 transition from an age-related to an AD-related tau effect as the primary determinant of
376 memory in preclinical AD, following the spread of tau from EC to AT regions. Our finding that
377 the PM tau effect diminished when the stronger influence of AT tau was taken into account
378 may reflect the lower amount of tau accumulation in PM in cognitively normal older people.
379 This is consistent with the observation that a lower PM FTP SUVR than AT FTP SUVR was
380 associated with the initiation of negative memory change. It is likely that in later stages (e.g.,
381 MCI), PM tau may play a more important role in predicting cognitive decline in symptomatic
382 patients.

383 The thresholds for both FTP effects on memory (SUVR ≈ 1.3) and Aβ effects on tau (DVR ≈
384 1.17, 25 CL) are also informative. While there is no clear consensus on either brain regions or
385 threshold values defining a “positive” tau PET scan, the FTP SUVR value identified is in the range
386 of proposed thresholds albeit for other brain regions (Jack Jr et al., 2017; Maass et al., 2017).
387 This is perhaps not surprising since thresholds are often generated through comparisons of
388 impaired vs. normal individuals; nevertheless, this general range of FTP SUVRs seems to have
389 biological significance. We note that the identified SUVR values in this study were based on

PVC-corrected data, which may increase the values when compared to other non-PVC SUVR values. Similarly, the global Aβ at which neocortical tau starts to become behaviorally detrimental is approximately 19-25 CL, which falls within the range of Aβ thresholds for moderate neuropathology and Aβ positivity based on autopsy studies (Navitsky et al., 2018; La Joie et al., 2019; Amadoru et al., 2020). Studies have also shown that Aβ burden below positivity thresholds can still predict longitudinal cognitive decline in cognitively normal individuals (Farrell et al., 2018; Landau et al., 2018). It is important to recognize that the Aβ thresholds suggested here in the study indicate levels at which Aβ exerts effects on tau that are cognitively relevant; it is possible that Aβ may produce detrimental effects at lower levels because they are associated with undetectable increases in tau. Nevertheless, these findings are important for identifying individuals at most risk of prospective cognitive decline due to AD pathology, who may benefit most from Aβ lowering therapeutic interventions.

The AT and PM networks investigated in the study are both functionally connected to the entorhinal cortex, but to different subregions: the AT region to anterolateral EC and PM to posteromedial EC (Maass et al., 2015; Schröder et al., 2015). Accumulating evidence suggests that tau spreads through neural connectivity in AD (Liu et al., 2012; Hoenig et al., 2018; Franzmeier et al., 2019). Recently, investigating BACS participants that overlapped with this study, our lab reported that tau preferentially deposits in the AT network (Maass et al., 2019), and showed strong evidence that this is related to patterns of anterolateral EC connectivity (Adams et al., 2019). Cortical tau deposition likely initiates in the transentorhinal region (Braak and Braak, 1992, 1995), a site comprising anterolateral EC and the medial aspect of perirhinal cortex. We thus interpret our finding that AT tau affects cognition more strongly than EC or PM

412 tau as reflecting the earliest spread of tau out of the medial temporal lobe (MTL) to AT targets
413 from anterolateral EC. Other recent BACS data from our laboratory has shown that AT tau
414 appears to disconnect the hippocampus from other components of the MTL memory system,
415 which in turn is related to episodic memory decline (Harrison et al., 2019). Based on this
416 evidence and our current findings, we suggest that the pathophysiology of the progression from
417 normal aging to AD involves the spread of tau from anterolateral EC to AT regions,
418 disconnection of hippocampal function, and episodic memory decline. We found that these
419 events appear to be specific to memory, congruent with the typical initiation of AD as an
420 amnestic syndrome. Moreover, evidence has shown that difficulties in object processing are
421 prevalent in normal aging, while spatial memory is often better preserved; whereas impaired
422 individuals often have difficulties with both object and spatial processing (Binetti et al., 1998;
423 Reagh et al., 2016). This also supports the idea of a sequential impact of tau pathology in the AT
424 and PM memory networks. We suspect that as tau spreads into brain areas with different
425 functional specialization, or as the disease progresses to later stages (Koran et al., 2017; Visser
426 et al., 2020), other cognitive functions eventually become affected (Digma et al., 2019; Sun et
427 al., 2019).

428 While our study has many strengths, including its multimodal nature, the moderate period
429 of prospective follow-up, and the convergence of results consistent with previous findings, it
430 does have limitations. The FTP tracer has shown evidence of off-target binding and lack of
431 specificity in some regions (Marquié et al., 2015; Baker et al., 2019; Lowe et al., 2019). However,
432 the ROIs we investigated are not particularly susceptible to these effects, and we conducted
433 partial volume correction to further control for this problem. Although the follow-up time was

434 moderate by current standards, it is possible that some non-significant effects would become
435 significant with longer testing intervals. Finally, our cohort is highly educated and does not fully
436 represent the diversity of older individuals across the US.
437
438 In conclusion, our data support a model whereby tau transits from the MTL to cortical
439 targets that are most closely associated with anterolateral EC in a pattern facilitated by Aβ,
440 which has specific effects on prospective memory decline. This may represent the initial stage
441 of AD, and occurs when Aβ levels cross a general threshold of positivity. There appear to be
442 additional effects of EC tau on longitudinal memory decline that are not dependent on Aβ,
443 which may be less clinically consequential. Together, these findings provide clarification of
444 differences between normal aging and preclinical AD and elucidate the transitions between the
445 two stages.

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658

Figure legends

Figure 1. Higher AT, PM, and EC Tau Associated with Faster Prospective Memory Decline. Simple slopes of FTP effect on longitudinal memory are depicted while holding other variables fixed at the sample mean. Higher FTP SUVR in all three regions is associated with a steeper declining slope.

Figure 2. AT, PM, EC Tau Effects on Prospective Memory Change in Aβ- and Aβ+ Individuals. Simple slopes of FTP effect in Aβ- and Aβ+ groups on longitudinal memory are separately depicted while holding other variables fixed at the sample mean. The effect of tau in AT and PM is moderated by Aβ status: higher FTP SUVR is only associated with a steeper declining slope in the Aβ+ group.

Figure 3. Relationship between AT, PM, EC Tau and Memory Change (Slope) in Aβ- and Aβ+ Individuals after Controlling for Age, Sex, Education, and APOE Status. The individual memory change (slope) was extracted using a simple LMM with time as the only predictor. The covariate-regressed standardized residuals are plotted. Group lines are separately fit for Aβ- and Aβ+ individuals using generalized additive model (GAM) smoothing to show group trends. Histograms illustrate the distribution of regional FTP burden, separated by PiB status (top: negative; bottom: positive). See extended data Figure 3-1 for raw relationships.

Figure 3-1. Raw Relationships between FTP SUVR Burden and Memory Change (Slope) in Aβ+ and Aβ- Individuals. The individual memory change (slope) was extracted using a simple LMM with time as the only predictor.

Figure 4. AT Tau Effect on Longitudinal Memory Decline Above and Beyond PM and EC Tau.

680 Table 1: Participants' characteristics at baseline.

	All Participants (N=124)	Aβ− (N=72)	Aβ+ (N=51)	Aβ− vs Aβ+ *p*
Age	77.3 (5.9)	77.3 (6.9)	77.3 (4.2)	n.s.
Sex: Female (N)[1]	74 (59.7%)	41 (56.9%)	32 (62.7%)	n.s.
Education (yrs)	16.8 (1.9)	17.2 (1.8)	16.4 (1.9)	.018
Mean Testing Interval (yrs)	1.4 (0.6)	1.4 (0.6)	1.4 (0.6)	n.s.
Cognitive Follow-up Duration (yrs)	2.8 (1.2)	2.8 (1.3)	2.8 (1.2)	n.s.
Number of cognitive assessments	2.4 (1.3)	2.4 (1.4)	2.4 (1.3)	n.s.
Retained participants (N)[1]	15 (87.9%)	65 (90.3%)	43 (84.3%)	n.s.
APOE status (N of ε4 carriers)[1, 2]	31 (25.6%)	6 (8.6%)	25 (50%)	<.001
Global Aβ (DVR)[3]	1.15 (0.22)	1.02 (0.28)	1.33 (0.25)	<.001
AT Tau (SUVR)	1.27 (0.18)	1.22 (0.11)	1.35 (0.24)	<.001
PM Tau (SUVR)	1.17 (0.12)	1.14 (0.10)	1.21 (0.13)	.001
EC Tau (SUVR)	1.28 (0.23)	1.20 (0.17)	1.38 (0.27)	<.001
Hippocampal Vol (cm^3)	7.36 (0.99)	7.45 (0.98)	7.25 (1.00)	n.s.
Entorhinal Thickness (cm)	3.36 (0.37)	3.35 (0.35)	3.36 (0.40)	n.s.
Baseline episodic memory	0.01 (0.77)	0.10 (0.77)	-0.13 (0.77)	n.s.
Baseline executive function	0.00 (0.70)	0.08 (0.65)	-0.12 (0.77)	n.s.

681 [1] Sex is reported as number of female participants (%); *APOE* status is reported as number of
682 ε4 carriers (%); Retained participants is reported as number of participants remain
683 participating in Berkeley Aging Cohort Study (%); other variables are continuous and
684 reported as mean (SD).
685 [2] Data were not available for three participants.
686 [3] Data were not available for one participant.

Table 2: Regression statistics for the effects of FTP, FTP x Time, and FTP x Aβ Status x Time in individual effect models. See Table 2-1 (AT), 2-2 (PM), and 2-3 (EC) for statistics of all predictors.

		AT	PM	EC
Model 1: *Memory ~Sex + Age + Education + APOE + Cog-PET Interval + FTP + Time + Age x Time + Sex x Time + Education x Time + APOE x Time + Cog-PET Interval x Time + FTP x Time + random slope + random intercept*				
FTP	*b* (se)	-1.51 (0.36)	-1.47 (0.54)	-1.57 (0.26)
	p	<.001***	.007**	<.001***
FTP x Time	*b* (se)	-0.33 (0.10)	-0.28 (0.11)	-0.17 (0.06)
	p	<.001***	.014*	.008**
Model 2: *Memory ~Sex + Age + Education + APOE + Cog-PET Interval + FTP + Aβ Status + Time + FTP x Aβ Status + Age x Time + Sex x Time + Education x Time + APOE x Time + Cog-PET Interval x Time + Aβ Status x Time + FTP x Time + FTP x Aβ Status x Time + random slope + random intercept*				
FTP	*b* (se)	-1.49 (0.48)	-1.44 (0.58)	-1.50 (0.31)
	p	.002**	.014*	<.001***
FTP x Time	*b* (se)	-0.20 (0.11)	-0.22 (0.12)	-0.13 (0.07)
	p	.069†	.061†	.063†
FTP x Aβ Status x Time	*b* (se)	-0.55 (0.21)	-0.54 (0.23)	-0.22 (0.14)
	p	.009**	.023*	.12

*** p <.001, ** p <.01, * p <.05, † p <.1

690 Table 3: Regression statistic for the effects of FTP x Time and FTP x Aβ Status x Time in models
691 with multiple tau predictors. See Table 3-1 (AT and EC), 3-2 (PM and EC), 3-3 (AT and PM), and
692 3-4 (AT, PM, and EC) for statistics of all predictors.

		ROI_1: AT ROI_2: EC	**ROI_1: PM ROI_2: EC**	**ROI_1: AT ROI_2: PM**
Model 3: *Memory ~Sex + Age + Education + APOE + Cog-PET Interval + ROI_1 FTP + ROI_2 FTP + Time + Age x Time + Sex x Time + Education x Time + APOE x Time + Cog-PET Interval x Time + ROI_1 FTP x Time + ROI_2 FTP x Time + random slope + random intercept*				
ROI_1 FTP x Time	*b* (se)	-0.27 (0.14)	-0.15 (0.15)	-0.48 (0.19)
	p	.048*	.33	.011*
ROI_2 FTP x Time	*b* (se)	-0.04 (0.10)	-0.12 (0.08)	0.22 (0.23)
	p	.70	.13	.36
Model 4: Memory ~Sex + Age + Education + APOE + Cog-PET Interval + ROI_1 FTP + ROI_2 FTP + Aβ Status + Time + ROI_1 FTP x Aβ Status + ROI_2 FTP x Aβ Status + Age x Time + Sex x Time + Education x Time + APOE x Time + Cog-PET Interval x Time + Aβ Status x Time + ROI_1 FTP x Time + ROI_2 FTP x Time + ROI_1 FTP x Aβ Status x Time + ROI_2 FTP x Aβ Status x Time + random slope + random intercept				
ROI_1 FTP x Aβ Status x Time	*b* (se)	-0.63 (0.27)	-0.34 (0.31)	-0.91 (0.42)
	p	.025*	.27	.035*
ROI_2 FTP x Aβ Status x Time	*b* (se)	0.09 (0.17)	-0.11 (0.17)	0.48 (0.48)
	p	.62	.52	.32

693 * $p < .05$