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The impact of Aβ and tau on prospective cognitive decline in older individuals

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Abstract:

Objectives: Amyloid-beta (Aβ) and tau pathologies are commonly observed among clinically normal older individuals at post-mortem and can now be detected with *in vivo* neuroimaging. The association and interaction of these proteinopathies with prospective cognitive decline in normal aging and preclinical Alzheimer's disease (AD) remains to be fully elucidated.

Methods: One hundred and thirty-seven older individuals (age=76.3±6.22 years) participating in the Harvard Aging Brain Study underwent Aβ (^{11}C-Pittsburgh Compound B) and tau (^{18}F-Flortaucipir) positron emission tomography (PET) with prospective neuropsychological assessments following PET imaging (mean number of cognitive visits = 2.8±1.1). Tau and Aβ PET measures were assessed in regions of interest (ROI) as well as vertex-wise map analyses. Cognitive change was evaluated with Memory and Executive Function composites.

Results: Higher levels of Aβ and tau were both associated with greater memory decline, but not with change in executive function. Higher cortical Aβ was associated with higher tau levels in all ROI, independent of age, and very elevated levels of tau were observed primarily in CN with elevated Aβ. A significant interaction between tau and Aβ was observed in both ROI and map level analyses, such that rapid prospective memory decline was observed in participants who had high levels of both pathologies.

Interpretation: Our results are consistent with the supposition that both Aβ and tau are necessary for memory decline in the preclinical stages of AD. These findings may be relevant for disambiguating aging and early cognitive manifestations of AD, and to inform secondary prevention trials in preclinical AD.

Introduction

        The pathophysiologic process of Alzheimer's disease (AD) is thought to commence more than a decade before the stage of dementia.[1-3] The two hallmark pathologies of AD, amyloid-β (Aβ) and tau aggregates, are commonly observed at postmortem in clinically normal older individuals (CN) and can now be detected *in vivo* with PET imaging techniques.[4-7] In this study, we investigated the association of amyloid-β (Aβ) and tau imaging markers with prospective cognitive trajectories in CN participating in the Harvard Aging Brain Study (HABS).

        The late-life accumulation of these proteins may play a critical role in cognitive decline, and several secondary prevention trials are currently evaluating the efficacy of anti-Aβ interventions to slow tau accumulation and prevent cognitive decline in preclinical stages of AD. First, we sought to understand the relationships among age, *in vivo* measures of Aβ and regional tau pathology in CN. Specifically, we evaluate recently acquired PET data to assess the relationship of age and Aβ to tau pathology in the medial temporal lobe and neocortical regions. We further aimed to evaluate the association of Aβ and tau with prospective cognitive change, focusing on memory and executive function (EF) as these domains have been widely reported to decline in both aging and very early AD. Multiple studies have reported that CN with elevated Aβ demonstrate faster rates of cognitive decline in both memory and executive function domains,[8-12] but there are very limited reports to date evaluating the association of both Aβ and tau with longitudinal

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trajectories of cognitive performance in CN,[7, 13, 14] and these studies have primarily

examined cross-sectional or retrospective cognitive data.

Several related questions motivated our research. It has been posited that Aβ may

be necessary but not sufficient to predict future cognitive decline in the preclinical stages

of AD.[15] Previous studies have suggested that CN with abnormalities in both Aβ and tau

measures in cerebrospinal fluid (CSF) are more likely to demonstrate cognitive decline

over long-term follow-up.[16, 17] One potential advantage of tau PET over CSF is the

ability to investigate the relevance of specific anatomic regional tau deposition. Autopsy

reports suggest that tau deposition in the entorhinal cortex (EC) is nearly ubiquitous in

advanced aging, whereas spread into the surrounding temporal neocortex is less

commonly observed among clinically normal older individuals, particularly in the

absence of substantial Aβ pathology.[18] It remains unclear whether EC tau accumulation is

relatively "benign" and associated with "normal aging", such that neocortical tau is

required for cognitive decline. Although both memory and executive function decline

have been associated with elevated amyloid, the relative specificity of decline in these

cognitive domains related to tau has not yet been examined. Moreover, it is unknown

whether similar patterns of tau associated cognitive change are observed among CN with

low levels of cortical amyloid (Aβ-) compared to those with elevated levels of amyloid

(Aβ+). Finally, we modeled multiple factors that may influence longitudinal cognitive

performance, including age, APOE, sex, and education, to investigate the relative

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contributions of Aβ, regional tau, and the potential synergy of these pathologies in the prediction of prospective cognitive decline.

Methods

Participants

One hundred and thirty-seven participants from HABS were included in this study. HABS participants were recruited from the community through media and outreach events, and screened for major neurologic, psychiatric or unstable medical illnesses. At study entry, all HABS participants were clinically normal (CN), had a global Clinical Dementia Rating (CDR) =0, Mini Mental Status Examination (MMSE) ≥27 with educational adjustment, and performed within education-adjusted norms on Logical Memory Delayed Recall.

All participants provided written informed consent prior to undergoing any study procedures. The HABS protocol is approved annually by the Partners Human Research Committee.

Neuropsychological evaluations

Participants are evaluated annually with a battery of cognitive and functional assessments, including tests of episodic memory, executive function, global cognition, and the CDR. For this study, we combined several neuropsychological tests to create two composites, covering memory and executive function, to estimate change across several tests within each domain. Given the mid-entrance of tau PET into HABS, we focused on tests administered annually (as opposed to those administered only on selected years) to ensure that consistent composites were used across participants and time points. Individual tests were z-transformed using the baseline sample and averaged to form the composites.[19]

Episodic memory composite: The episodic memory composite included three measures: The Free and Cued Selective Reminding Test (FCSRT) is a multi-modal associative memory measure. Two primary FSCRT scores were included in the composite: 1) *Free Recall* is the sum of items freely recalled (up to a total of 48) and 2) *Total Recall* is the sum of *free* and *cued recall* (up to a total of 48). The 6-Trial Selective Reminding Test (SRT) is comprised of 12 words, learned over 6 trials. 3) Delayed Recall on the SRT assessed after a 10-minute delay was included in the composite.

Executive Function Composite: The executive function composite included three measures: 1) The Digit-Symbol Substitution test from the Wechsler Adult Intelligence Scale – Revised measures the ability to rapidly transcribe a geometric symbol to the correct corresponding number within 90 seconds. 2) Trails B measures the speed to

accurately connect letters and numbers in alternating sequence. Trails B is log-transformed and inverted so that higher values reflect better performance. 3) Phonemic Letter Fluency measures the number of words generated to three letters (F-A-S), each over 60 seconds.

Molecular Imaging

C^{11}-Pittsburgh Compound B (PiB) and F^{18}-Flortaucipir (FTP) (previously known as AV-1451 or T807) PET tracers were synthesized and administered at Massachusetts General Hospital (Siemens ECAT EXACT HR+ scanner). For both PiB and FTP-PET cerebellar grey matter was used as the reference region from the Freesurfer atlas as previously described.[7] For PiB, distribution volume ratio (DVR) images were created with Logan plotting (40-60min), and PiB values were extracted from a global cortical aggregate (given the very high degree of collinearity among neocortical regions) and normalized to cerebellar grey. Aβ was treated as a continuous variable in statistical models. Participants were dichotomized into Aβ- and Aβ+ groups using a DVR cut off of 1.20,[20] for additional analyses and visualization purposes.

FTP (tau) PET imaging was introduced mid-study into HABS as this technology was not available at study initiation. We utilized the first FTP scan acquired in HABS for each participant, and the corresponding PiB amyloid scan acquired closest in time (years between PiB and FTP, *M*=0.32, *SD*=0.44). FTP scans were acquired at Year 4 of HABS

or later for most participants, but a minority of participants who enrolled more recently in HABS underwent FTP at their earlier HABS visits (Table 1).

FTP-PET measures were computed as standardized uptake value ratios (SUVRs) in three individually defined anatomic regions of interest (using FreeSurfer 6.0): entorhinal cortex (EC), hippocampus (Hip), and inferior temporal (IT) cortex, which commonly exhibit early Tau pathology among CN.[7, 21-23] Because of reports of off-target binding in choroid plexus adjacent to the hippocampus, we residualized the Hip FTP values for mean choroid plexus signal.[24]

Statistical Analyses:

Cross-sectional relationships between age, Aβ (PiB), and tau (FTP) were examined with linear regression models. When predicting tau, we explored the independent effects of Aβ and age, as well as the interaction between Aβ and age.

To visually examine the associations between cognitive change as a function of both regional tau and Aβ, cognitive slopes for both memory and executive function were extracted from a simple linear mixed model with the cognitive variable as the outcome and a time term as the only predictor (by extracting the random slope term from this model for each participant). These slopes were plotted against regional tau, with individual data points additionally coded by Aβ group. Before plotting, cognitive slopes and regional tau were residualized by age, sex, education, and time of tau scan. These

plots enabled visualization of the overall pattern between these variables, whereas all associations were tested formally in linear mixed models (LMM, Supplementary Table 1).

LMM were conducted to examine prospective change in cognition following most recent tau and Aβ PET imaging, separately for memory and executive function composite scores. The time term in these models was relative to the neuropsychological testing session within one year of the date of the tau PET scan. The mean prospective follow up period was 2.04 years, with a mean number of cognitive visits = 2.8±1.1). Of the 137 participants, 12 had a single neuropsychological testing visit, 31 had two visits, 53 had three visits, and 41 had four visits. Thus, the majority of individuals (69%) had 3 or more visits. Although the 12 participants that had a single time point did not contribute directly to the model estimates of cognitive change over time in our LMMs, these data were included since they contribute to the estimation of the model main effects.

The same time term was used in models examining change related to Aβ PET imaging, since Aβ PET imaging for each participant was selected to be close in time to the tau scans All models included age at the tau scan, time (relative to the neuropsychological testing session closest to the tau PET scan), APOE status (ε4 carrier versus non-carrier), education, sex, time of tau scan relative to time of entry into the HABS Study (to account for the variance in when tau PET was first acquired across participants), as well as the interaction between time and all covariates (time x age, time x APOE, etc). Random intercepts were included in all models.

We first examined Aβ and regional tau as predictors of cognitive change in separate LMMs, by examining the interaction of each PET variable with the time term (Supplemental Table 1). We subsequently modeled Aβ and tau as simultaneous predictors within the same model (with the same covariates listed above). Then we added the three-way interaction between Aβ, tau and time to this model to determine whether the association between tau and cognitive decline was modified by Aβ levels (Aβ x Regional Tau x Time).

Exploratory, vertex-wise whole brain analyses to investigate associations across all brain regions were performed with GLM_Flex_Fast (mrtools.mgh.harvard.edu). Models were run examining the relationship between 1) PiB-PET burden and 2) FTP-PET with change on the Memory and EF composites (extracted from linear mixed models). Additionally, we explored vertex wise map analyses of PiB-PET interacting with tau R0I and FTP-PET vertex wise map interacting with Aβ ROI to assess the anatomic patterns of Aβ by tau interactions associated with memory decline. All analyses controlled for age and all maps are displayed at a t-value threshold of t=±3.362, or p<0.001.

All p values were 2-sided. We did not correct for multiple comparisons for the ROI analyses, as we examined only ROI of independent *a priori* interest, and used composite neuropsychological measures. However, we did require a stringent statistical threshold (p<0.001, as above) for the whole brain voxel wise analyses to account for multiple comparisons.

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We also repeated the primary analyses using partial volume correction (PVC) using the geometric transform matrix method, as implemented in Freesurfer 6.0,[25] assuming a uniform 6mm point spread function. Utilization of PVC values did not alter the overall pattern of results.

Results

Demographics at the time of PET scanning are presented for the entire group and by dichotomized Aβ groups (Table 1). As expected from other reports, CN who were classified as Aβ+ were slightly older (p=0.015) and more likely to be *APOE ε4* carriers (χ^2=31.9, p<0.001). At the time of tau scanning, logical memory scores were lower in the Aβ+ group (p=0.013). All participants were clinically normal (Global CDR=0) at entry into HABS. Three participants progressed to a diagnosis of Mild Cognitive Impairment (MCI) as determined by diagnostic consensus conference, within one year of their tau PET imaging (all three participants who transitioned to MCI were Aβ+). We repeated the analyses excluding these three participants, which did not alter any of the results presented below.

Age and Aβ *Influence Degree of Tau Pathology*

We first investigated the relationships of age (at time of PET scan), Aβ and tau using linear regression models. Older age was associated with higher continuous cortical Aβ (beta: 0.0067±0.0031, r=0.18, p=0.034). Older age was also significantly associated with elevated tau in EC (beta: 0.0044±0.0017, r=0.22, p=0.009) and IT (beta:

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0.0042±0.0012, r=0.28, p<0.001), but did not reach statistical significance for Hip (beta: 0.0024±0.0012, r=0.16, p=0.054).

We then examined the relationship between continuous Aβ levels and tau, controlling for age. Higher Aβ was associated with higher tau, independent of age, in all tau ROI (EC beta: 0.2458±0.0410, r_p= 0.46, p<0.001; Hip beta: 0.1329±0.0320, r_p= 0.34, p<0.001; and IT beta: 0.1675±0.0306, r_p= 0.43, p<0.001). The interaction between age and continuous Aβ was not significant for any Tau ROI (p-values>0.34). Across all participants, the three tau ROI showed significant correlations with each other (EC Tau versus Hip: r=0.626, EC versus IT: r=0.698, Hip versus IT: r=0.607; p-values<0.0001). An exploratory whole brain analysis, covarying PiB DVR into the vertex-wise FTP PET map, controlling for age, also demonstrated that higher Aβ was associated with higher tau in temporal regions bilaterally, with strongest correlations observed in the right medial temporal lobe (**Figure 1**).

Amyloid and tau are each associated with longitudinal memory decline

Visualization of cognitive change as a function of regional tau and Aβ group revealed a consistent pattern across ROI with respect to memory, such that Aβ+ individuals with greater tau showed the greatest memory decline (Figure 2A-C). Regional tau was not associated with memory change among Aβ- individuals, although it should be noted that Aβ- participants did not show very high levels of tau in these regions.

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Furthermore, regional tau was not associated with change in EF in either Aβ+ or Aβ-groups (Figure 2D-F).

We formally tested these associations between regional tau, Aβ, and cognitive change in a series of linear mixed models. We first investigated the association of prospective change in cognitive performance with Aβ and tau separately, controlling for age, education, APOE4, sex, and the time of tau scan. Continuous levels of Aβ were associated with greater longitudinal decline in the memory composite (beta: -0.641±0.163, p<0.001), whereas age was not related to change in memory (-0.0053±0.0053, p=0.32). Interestingly, age was significantly related to the EF composite (beta: -0.009±0.003, p<0.001), and we observed only a weak relationship between change in EF and continuous mean cortical Aβ (beta: -0.146±0.079, p=0.067). The pattern of results was very similar when Aβ was treated dichotomously rather than continuously.

Greater tau in all three anatomic ROI was related to greater decline in the memory composite (EC: -0.594±0.269, p=0.028; Hip: -1.117±0.393, p=0.005; IT: -0.889±0.369, p=0.017). In contrast, the relationships between tau and EF did not reach statistical significance and were considerably smaller in magnitude than those observed for memory, as evident by the model beta estimates for EF that are approximately 4 times smaller (EC: -0.144±0.130 p=0.28; Hip: 0.025±0.195, p=0.90; IT: -0.201±0.184, p=0.27) than the LMMs predicting memory shown above.

To evaluate relationships of amyloid and tau with memory or EF across a more extensive range of anatomy, we also examined the association of longitudinal cognitive slopes using whole brain map vertex-wise analyses of the PiB and FTP SUVr images. Higher levels of Aβ (PiB) in medial orbital and lateral prefrontal, posterior cingulate, precuneus, and lateral parietal regions were associated with worsening memory performance (p<0.001; Figure 3A). We note that the regions demonstrating this significant relationship nearly completely overlaps the set of regions in our cortical aggregate ROI and strongly resembles the Stage II of amyloidosis, described by Grothe and colleagues.[26] We found increasing tau (FTP) to be associated with longitudinal memory change in medial and inferior temporal regions (Figure 3B). The regions involved were spatially aligned with the FTP map that showed an association with increasing levels of PiB (as in Figure 1). Interestingly, the map level analyses suggested a stronger relationship between tau in right medial temporal regions with mean cortical Aβ, but demonstrated a particularly strong relationship between tau in the left medial temporal lobe and decline on the memory composite, perhaps because our memory composite is weighted towards verbal memory measures. Similar to ROI analysis results, we did not find evidence of a significant relationship between EF change and FTP in any region in the vertexwise analyses, using a similar threshold of p<0.001 (data not shown).

Amyloid and tau interact to influence cognitive decline

We then investigated the independent and synergistic effects of continuous values of Aβ and tau on memory and EF change, using both PiB and FTP values as simultaneous predictors (separately for each of the three FTP regions). In all models predicting memory change, the 3-way interaction terms between Aβ, tau in all ROI and time were significant (Table 2). Examination of EF models revealed that the only significant independent predictor of prospective change in EF across all tau regions was Age x Time (all ROI $p<0.002$). No other term (APOE, sex, education or time of tau scan) was significantly associated with change in memory or EF, once age and the 3-way interaction of Aβ by tau ROI by time were included in the models.

We also explored the interaction of Aβ and tau using whole-brain, vertex-wise PiB and FTP maps. The interaction of each of the tau ROI into the PiB map to predict longitudinal memory change revealed a similar pattern of to our aggregate Aβ ROI. Large areas of precuneus, lateral prefrontal (but limited orbital prefrontal), and lateral parietal cortex demonstrated significant interactions with inferior temporal tau ROI (Figure 3C), suggesting that multiple cortical regions with Aβ deposition contribute to the interaction with tau in predicting memory decline. We did not observe any regions on the PiB map that interacted with tau to predict change in EF. Conversely, the tau vertex-wise map interacting with the cortical aggregate Aβ ROI to predict memory change (Figure 3D) revealed medial and lateral temporal tau regions predicting memory decline. Interestingly, the FTP map with Aβ interaction revealed a similar pattern to the FTP map

alone (Figure 3B) but showed even stronger associations with memory change, again suggesting that higher tau in the setting of higher Aβ is associated with the greatest prospective memory decline.

Given the significance of the 3-way interaction in the memory models, the relationship of Aβ, tau and memory was therefore interpreted in the context of this interaction in all subsequent models. These models revealed consistent evidence for a synergistic association such that individuals with both elevated Aβ and tau levels showed the greatest memory decline. Figure 4 highlights that a negative relationship between Aβ burden as a continuous measure and memory change emerges around values of 1.1 SUVR in EC Tau. Likewise, the negative effect of EC Tau on memory emerges at around PiB DVR values of 1.4. This multiplicative effect of Aβ and tau was consistent across all examined tau regions, as indicated by the significant interaction term across all three models.

Finally, to further explore the interaction between Aβ and tau with memory decline, models were repeated treating amyloid as a dichotomous variable to estimate the effect of tau on memory change in Aβ- and Aβ+ groups (Table 3). These models provide further evidence that greater tau was significantly associated with greater decline in memory, specifically within the Aβ+ group, consistent with the visualization in Figure 2. We did not observe evidence of tau-related memory decline within the Aβ- group. In fact, the directionality of the relationship between EC tau and memory change among the

Aβ- was paradoxically positive, an effect that is likely spurious and driven by the more restricted range of EC tau values present in the Aβ- group (mean EC tau=1.084±0.087; range=0.933-1.298) compared to the Aβ+ group (mean EC tau=1.201±0.157; range=0.962-1.495).

Discussion:

This study assessed the association of Aβ and tau pathology, as estimated with *in vivo* imaging markers, with prospective longitudinal cognitive trajectories among a group of well-characterized CN. Our findings suggest that the hallmark pathologies of AD are synergistically associated with longitudinal memory decline. Specifically, the fastest rates of memory decline were observed in CN with higher levels of both Aβ and tau on PET imaging.

Our findings using neuroimaging markers are consistent with previous reports using CSF, suggesting that greater cognitive decline is observed in CN with abnormalities of both CSF Aβ and phospho-tau.[16, 17, 27-29] These findings are also consistent with laboratory work suggesting that tau is likely the primary mechanism of Aβ-related neurotoxicity,[30] and previous work using other imaging markers of neurodegeneration,[31-34] suggesting that Aβ pathology in isolation may be insufficient to drive imminent cognitive decline.

Our findings may also be relevant to the question as to whether tau, in the setting of low Aβ, might underlie age-related decline in episodic memory, given the nearly ubiquitous presence of tau pathology in the EC (Braak Stage 1-2) by age 80,[18] and the recent interest in "primary age-related tauopathy" (PART),[35] defined as early neocortical tau accumulation with absent or low Aβ pathology (Thal phase <3 corresponding approximately to PET Aβ-) in very elderly individuals (average ages 88-90). These PART studies have reported somewhat variable findings regarding the relationship to cognition, with one recent study finding no association between episodic memory measures and tau pathology, despite substantial hippocampal atrophy, in the setting of low Aβ pathology.[36] There have also been two reports of memory decline, using primarily retrospective cognitive trajectories, associated with elevated tau PET measures among Aβ- participants from the Berkeley Aging Cohort Study.[13, 14] Our overall results are consistent with the Berkeley group findings, however, we did not find supporting evidence for tau-associated cognitive decline among Aβ- in any region or in any cognitive domain. Our cohort included a somewhat larger number of participants, who were slightly younger overall, and were evaluated prospectively using somewhat different cognitive testing instruments. Furthermore, our Aβ- group did not show very elevated levels of tau. Our finding that memory decline requires the synergistic relationship of both elevated Aβ and tau was highly consistent across all analyses (i.e.,

using continuous Aβ, dichotomous Aβ groups, with or without partial volume correction in the tau ROI, and in whole-brain vertex-wise map analyses).

We replicated previous reports that Aβ and tau PET measures are correlated, even among CN.[1, 7, 37, 38] Furthermore, we show that it is only a subset of Aβ+, with higher levels of tau detected by PET imaging, who demonstrate prospective memory decline. Our results are consistent with the hypothetical model that accumulating Aβ may be associated with accelerated tau spreading, which in turn underlies cognitive decline in preclinical AD.[39] However, more direct evidence for the temporal ordering in this model will require evaluation of simultaneous change measures of both Aβ and tau biomarkers.

We wanted to ascertain whether tau PET signal in three specific anatomic regions that often demonstrate tau pathology in CN at postmortem[1, 18] exhibit differential relationships with Aβ and cognitive decline. While tau PET measures are generally consistent with the Braak staging scheme,[40] they are not necessarily equivalent to tangle counts (the basis of Braak staging), but rather correspond to the wider range of PET binding site substrates on tau pathology, including neuropil threads and the coronae of neuritic amyloid plaques observed in recent autoradiographic studies.[41] We measured tau signal in the EC, an early site of allocortical tau deposition;[18] the hippocampus because of its critical role in episodic memory function and early involvement presumably due to tau spread from EC,[42] and IT as a proxy region for early neocortical tau spreading.[1, 7, 13, 23, 43] We then investigated whether there were other regions that demonstrated similar

relationships with Aβ or cognitive decline using exploratory whole brain analyses, but found that our individual ROI well represented the areas showing significant tau associations.

Notably, we did not find differences among tau regions in the associations with age, Aβ, or memory decline. Indeed, EC tau, sometimes thought of as primarily age-related and more "benign", actually showed the strongest correlation with Aβ. Furthermore, all three regions, including the EC, demonstrated tau-related memory decline, that was only evident in the Aβ+ group, perhaps due to the finding that Aβ-showed lower levels of tau in all regions. Our results are consistent with early autopsy work by Price, Morris, and colleagues, highlighting evidence that elevated EC tau in CN, associated with Aβ plaques, represents preclinical AD.[1] Given the co-linearity among these regions wherein participants with high EC tau also demonstrate higher levels of hippocampal and neocortical tau, it is difficult to ascertain whether tau spreading beyond the EC is required for memory decline among Aβ+ CN. Using map-level analyses, we also found evidence that multiple cortical areas with Aβ deposition contributed to the interaction with tau associated with memory decline. Future studies with serial tau PET imaging in addition to longitudinal cognitive testing will further elucidate this question.

Interestingly, we did not observe a strong relationship between either Aβ or tau with EF, despite previous evidence of decline in EF associated with elevated Aβ in a larger sample from HABS[10] and other reports in the literature.[8, 9, 12] Thus, we may be

underpowered to detect change with the smaller sample size with both Aβ and tau imaging using this EF composite. However, the stronger and consistent relationship between both Aβ and tau and the memory composite is consonant with the hypothesis that episodic memory may be particularly vulnerable to early AD pathology.[44]

Limitations:

Tau FTP PET imaging was introduced mid-study to HABS, and thus we are able to investigate only relatively short trajectories of prospective longitudinal change. Because preliminary reports with longitudinal FTP PET suggest that tau accumulation may be much more dynamic than Aβ, we chose to investigate only prospective cognitive trajectories, as we did not have tau PET available at HABS baseline. Although over two-thirds of our participants had at least three cognitive testing visits, 31 percent of the participants in our analysis had only one or two neuropsychological testing visits, which may limit our ability to reliably measure longitudinal change. Nevertheless, we did find significant synergistic relationships between Aβ and tau predicting memory decline over this short time period, suggesting CN with elevated levels of both pathologies are at very high risk for imminent decline. Longitudinal studies with serial Aβ and tau PET are ongoing to investigate the relative rates of accumulation of these pathologies and the temporal proximity to cognitive decline.

It is important to acknowledge that FTP (AV-1451) and tau PET tracers in general, are relatively new, with reports of off-target binding with multiple tau tracers.[41] Most of the regions with reported off-target binding are outside the ROI investigated in this study. However, the choroid plexus, which is adjacent to the hippocampus, may be particularly susceptible to off-target FTP binding and thus we performed analyses residualizing the hippocampal signal using an anatomically defined choroid plexus region.[24]

Although we recruited the HABS cohort across strata based on age and socio-economic status, the majority of HABS participants have at least some advanced education, are overall healthy, and may have substantial cognitive reserve.[45] The neuropsychological tests utilized in HABS were chosen to be sensitive to decline associated with both "normal aging" and the earliest stages of AD. It is possible, however, that other neuropsychological measures would demonstrate evidence of decline in the setting of relatively low levels of Aβ or tau accumulation, or across a larger age range. Finally, it is notable, that even with age, education, gender, APOE, Aβ, tau, and their interactions in the models, we are still only explaining a fraction of the variance in the short-term trajectories of memory or EF change. Thus, there are likely other contributing factors, including cerebrovascular disease, accumulation of TDP-43, loss of dopaminergic projections, or the synergistic effects of these processes with early AD pathology, that are not fully captured with the current molecular imaging markers.

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Implications:

Our findings provide further evidence to support the hypothesis that both of the hallmark pathologies of AD, i.e. Aβ and tau, are required for rapid cognitive decline during the preclinical stages of AD. Thus, selecting individuals with evidence of higher levels of both pathologies might provide greater power in clinical trials to detect a therapeutic effect on rate of cognitive decline, particularly over a relatively short timeframe.[17, 46] However, it is possible that anti-Aβ monotherapy will have more limited efficacy once substantial tau pathology is present, especially if there is an uncoupling of these pathophysiological processes as the disease progresses.[47]

Given the association between Aβ and tau, and the observation that elevated levels of neocortical tau are primarily observed in the high Aβ group, it is possible that decreasing Aβ accumulation might slow memory decline through preventing further accumulation of tau. This hypothesis is being tested in several ongoing secondary prevention trials in both biomarker-at-risk[48] and in genetic-at-risk cohorts.[49, 50] Our findings do suggest the possibility, however, that once Aβ and tau have begun to accumulate, particularly if there is already subtle memory decline apparent, in the later stages of preclinical AD, combination therapies may be needed to maximally impact the clinical course of the disease.

Author Contributions

Conception and design of the study: R.A.S., E.C.M., R.A.B., K.A.J.; Acquisition and analysis of data, interpretation of results, and editing of manuscript: R.A.S., E.C.M., A.P.S., R.A.B., K.V.P, R.E.A., B.J.H., R.B., J.C., T.H., G.A.M., Y.T.Q., N.J.D., J.J.,

J.R.G., J.S.R., H.J., H.Y., M.P., K.R.K., D.M.R., K.A.J.; Drafting the text, preparing the figures, and final preparation of the manuscript: R.A.S., E.C.M., A.P.S., R.A.B., K.A.J.

Potential Conflicts of Interest

Drs. Sperling and Johnson are involved in public-private partnership clinical trials sponsored by NIH and Eli Lilly and Co. who owns the distribution rights to Flortaucipir (AV-1451), but they do not have any personal financial relationship with Eli Lilly.

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Figure Legends

Figure 1: Vertex-wise map of Flortaucipir tau (FTP) PET (threshold set at p<0.001) demonstrating regions with higher tau associated with higher levels of cortical amyloid (PiB), controlling for age. Left hemisphere is shown on the left side of the figure. The color bar represents T values, with warmer colors reflecting vertices with stronger associations between Aβ and tau.

Figure 2: Plots of tau vs. Memory and Executive (EF) Slope, with each plotted variable residualized by age, sex, education, APOE4, and time of tau scan. LOESS lines are fit in each plot. Participants are divided by dichotomous Aβ group for illustration purposes, as Aβ was considered as a continuous variable in the statistical models, for: (A, D) entorhinal cortex (EC), (B, E) hippocampus (Hip), and (C, F) Inferior Temporal cortex tau. No relationship between tau and memory was observed among the Aβ- group (black circles) in any ROI, however, the range of tau is more limited in the Aβ- group. The Aβ+ (red diamonds) demonstrate a negative association between tau and memory slope (top row) across all three regions. The three participants who progressed to a clinical diagnosis of MCI within one year of their tau scan date (all were Aβ+), are indicated in the green triangles. In addition, there were two participants who demonstrated substantial memory decline from their baseline but did not yet meet MCI criteria. The interaction

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analyses remained significant with these participants excluded. Neither Aβ group demonstrated clear evidence of a relationship between tau and EF.

Figure 3: Vertex-wise maps of 11-C-Pittsburg Compound B (PiB) and 18-F-Flortaucipir (FTP) tau PET imaging demonstrating relationship with memory slopes across all participants, thresholded at p<0.001. Left hemisphere is shown on the left side of the figure. Color bar represents T values with warmer colors connoting vertices with stronger relationship between higher FTP SUVR and memory decline. A) Map of PiB and memory change demonstrating multiple cortical regions, including orbital and lateral prefrontal, precuneus and posterior cingulate, and lateral parietal cortices, where higher Aβ burden is associated with decreasing memory performance: B) Map of FTP and memory change showing multiple regions in medial and inferior temporal cortices in which higher levels of FTP binding are associated with more rapid prospective decline in memory. C) Map of PiB interacting with inferior temporal tau ROI reveals areas of precuneus, posterior cingulate, lateral prefrontal, and lateral parietal cortices that demonstrate significant association with memory decline. D) Map of FTP interacting with cortical Aβ ROI demonstrates regions in medial and lateral temporal cortices, as well as limited areas of cingulate and prefrontal cortices associated with memory decline. Notably these tau regions interacting with Aβ (in D) show a stronger relationship than the tau regions alone (in B).

Figure 4: Demonstration of the three-way interaction between continuous Aβ x EC tau x Time predicting memory. The top row shows the effect of Amyloid on memory change at varying levels of EC tau. For reference, the distribution of EC tau values in the sample is shown to the left. The effect of Amyloid at different levels of tau is plotted on the right (for instance the green vertical line at left represents EC tau SUVR=1.0 and corresponds to the green point at right showing the multiplicative effect of Amyloid burden is 0.0 when EC tau SUVR is 1.0). This plot demonstrates that the effect of Amyloid increases at higher levels of EC tau, with a negative relationship between Amyloid and memory change emerging around values of 1.1 SUVR in EC tau (blue dot at right). Likewise, the bottom row shows the effect of EC tau at varying levels of global Amyloid (for instance the green point reflects the effect of EC tau when Amyloid DVR is 1.05). For reference, the distribution of global Amyloid DVR values in the sample is shown to the left. This plot shows that the negative effect of EC tau on memory emerges at higher levels of Amyloid (around DVR values of 1.4). This multiplicative effect of Aβ and tau was consistent across all examined tau regions, as indicated by the significant interaction term across all three models.

Tables

TABLE 1. Demographic and Cognitive Test Performance

	All Participants	Aβ-	Aβ+
N	137	97	40
Age at Tau PET scan#	76.32 (6.22) Range=65-90	75.54 (6.41) Range=65-90	78.20 (5.34) Range=68-88
Female Sex	79	55	24
Years of Education	15.85 (2.95)	15.75 (3.07)	16.10 (2.67)
APOE ε4 non-carrier/APOE ε4 carrier*	94/43	81/16	13/27
Total Prospective Follow Up Time (years)#	2.05 (0.74)	2.09 (0.72)	1.94 (0.76)
Total number of cognitive test visits	2.8 (1.1)	2.8 (1.2)	2.8 (1.1)
MMSE	29.18 (1.04)	29.29 (0.98)	28.92 (1.14)
Logical Memory Delayed Recall WMS IIa**	15.75 (3.92)	16.30 (3.81)	14.43 (3.93)

Table 1: Demographics and cognitive test performance (mean [S.D.]) at clinic visit corresponding to year of Tau and Aβ PET imaging for the entire sample and classified by dichotomous Aβ status. Mean and standard deviation are listed for continuous variables.

* Age difference p<0.05 between Aβ- and Aβ + groups. #Total prospective follow up time was defined using the neuropsychological testing session within one year of the Tau PET as the "baseline" visit and comparing that date to the date of the final subsequent neuropsychological testing session. Likewise, the tabulated MMSE and Logical Memory values reflect scores from the neuropsychological testing session within one year of the date of the tau scan. ** Logical Memory performance difference p<0.05 between Aβ- and Aβ + groups.

TABLE 2. Aβ and tau modeled as simultaneous predictors of memory and executive function change

	EC Tau	Hip Tau	IT Tau
Memory	**Age x Time**	**Age x Time**	**Age x Time**
	-0.008 (0.005) p=0.12	-0.007 (0.005) p=0.20	-0.009 (0.005) p=0.095
	Aβ cont x EC tau x Time	**Aβ cont x Hip tau x Time**	**Aβ cont x IT tau x Time**
	-4.261 (1.057) p<0.001	-7.044 (1.520) p<0.001	-5.160 (1.360) p<0.001
Executive Function	**Age x Time**	**Age x Time**	**Age x Time**
	-0.009 (0.003) p=0.0019	-0.009 (0.003) p<0.001	-0.009 (0.0028) p=0.002
	Aβ cont x EC tau x Time	**Aβ cont x Hip tau x Time**	**Aβ cont x IT tau x Time**
	0.065 (0.5449) p=0.91	0.623 (0.776) p= 0.42	-0.085 (0.7094) p=0.91

Table 2. Linear mixed models with Aβ and tau as simultaneous predictors of memory and executive function change, repeated for each tau region. Unstandardized betas and standard errors are listed. All models include the two-way interactions between Aβ x Time and tau x Time, as well as covariates for APOE4, education, sex, and time of tau scan, as well as their interactions with time. Significant effects are highlighted in gray (p<0.05).

TABLE 3. Relationship of Tau Regions to Memory Decline by Dichotomous Aβ group.

	Aβ-	Aβ+
EC Tau x Time	0.725 ± 0.472 p=0.13	-1.656 ± 0.657 p=0.012
Hip Tau x Time	0.013 ± 0.513 p=0.98	-2.310 ± 0.649 p<0.001
IT Tau x Time	0.676 ± 0.573 p=0.24	-1.643 ± 0.486 p<0.001

Table 3. Linear mixed models were repeated with Aβ treated as a dichotomous variable, and the effect of tau on memory change (Regional tau x Time) was estimated in Aβ- and Aβ+ groups from these models for Entorhinal cortex (EC), Hippocampus (Hip) and Inferior Temporal (IT) cortex. Unstandardized betas and standard errors are listed. All models additionally include covariates for APOE4, education, sex, and time of tau scan, as well as their interactions with time. A consistent pattern is observed, such that elevated regional tau is associated with greater memory decline over time across all regions only in the Aβ+ group. Significant effects are highlighted in gray (p<0.05).

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SUPPLEMENTAL TABLE 1: Equations for Linear Mixed Models

LMM with Aβ

$\text{Cognition}_{ij} = \beta_1 + \beta_2 \text{Age}_i + \beta_3 \text{APOE}_i + \beta_4 \text{Education}_i + \beta_5 \text{Sex}_i + \beta_6 \text{Time of Tau Scan}_i$
$\mathbf{+ \beta_7 A\beta_i} + \beta_8 \text{Time}_{ij} + [\beta_9 \text{Age}_i \times \text{Time}_{ij}] + [\beta_{10} \text{APOE}_i \times \text{Time}_{ij}] + [\beta_{11} \text{Education}_i \times \text{Time}_{ij}]$
$+ [\beta_{12} \text{Sex}_i \times \text{Time}_{ij}] + [\beta_{13} \text{Time of Tau Scan}_i \times \text{Time}_{ij}] \mathbf{+ [\beta_{14} A\beta_i \times \text{Time}_{ij}]} + b_{1i}$

LMM with regional Tau

$\text{Cognition}_{ij} = \beta_1 + \beta_2 \text{Age}_i + \beta_3 \text{APOE}_i + \beta_4 \text{Education}_i + \beta_5 \text{Sex}_i + \beta_6 \text{Time of Tau Scan}_i$
$\mathbf{+ \beta_7 \text{Regional Tau}_i} + \beta_8 \text{Time}_{ij} + [\beta_9 \text{Age}_i \times \text{Time}_{ij}] + [\beta_{10} \text{APOE}_i \times \text{Time}_{ij}] + [\beta_{11} \text{Education}_i$
$\times \text{Time}_{ij}] + [\beta_{12} \text{Sex}_i \times \text{Time}_{ij}] + [\beta_{13} \text{Time of Tau Scan}_i \times \text{Time}_{ij}] \mathbf{+ [\beta_{14} \text{Regional Tau}_i \times}$
$\mathbf{\text{Time}_{ij}]} + b_{1i}$

Cognition_{ij}=Memory or executive function composite score at each testing session

Age_i=Age at Tau scan

APOE_i=APOE4 carrier status (carrier versus non-carrier)

Education_i=Education (in years)

Sex_i=Male versus Female

$\text{Time of Tau Scan}_i$=Time of Tau scan relative to study baseline. Dichotomized into 2 levels (either early in the study, between the 1st and 3rd annual visit; or late in the study, during the 4th visit or later).

Time$_{ij}$=Time relative to the testing session up to one year before the tau PET scan (all

testing sessions more than one year before Tau PET were discarded to enable

examination of prospective change in cognition).

Aβ$_i$=Continuous levels of Aβ (from PiB scans closest to tau PET scan)

Regional tau$_i$= EC Tau$_i$, HV Tau$_i$, or IT Tau$_i$ values

b$_{1i}$=random intercept for each subject

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