RESEARCH ARTICLE

Association of Emerging β-Amyloid and Tau Pathology With Early Cognitive Changes in Clinically Normal Older Adults

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Abstract

Background and Objectives

Alzheimer disease (AD) clinical trials are moving earlier in the disease process according to emerging signs of β-amyloid (Aβ) and tau pathology. If early treatment is the right time for intervention, it is critical to find the right test to optimize cognitive outcome measures for clinical trials. We sought to identify cognitive measures associated with the earliest detectable signs of emerging Aβ and tau pathology.

Methods

One hundred twelve clinically normal adults with longitudinal Pittsburgh compound B (PiB)-PET, ^{18}F-flortaucipir (FTP)-PET, and cognitive data for ≥7 years were included from the Harvard Aging Brain Study (HABS). Analyses assessed those initially classified as PiB− (less than Centiloid [CL] 20) and then expanded to include PiB+ individuals up to CL40, the approximate threshold beyond which neocortical tau proliferation begins. Separate linear mixed-effects models assessed the effects of emerging global Aβ (PiB slope) and tau (baseline FTP level and FTP slope) in the entorhinal and inferior temporal (IT) cortices on multiple cognitive tasks and the Preclinical Alzheimer's Cognitive Composite (PACC) over time.

Results

Steeper PiB slopes were associated with declining processing speed (Digit Symbol Substitution Test [DSST], Trail Making Test Part A) in those <CL20 and expanded to include learning/memory retrieval (FCSRT-FR], Selective Reminding Test Total Recall [SRT-tr], Logical Memory Immediate Recall) in the <CL40 group. FTP had limited effects under CL20, with only rising right IT FTP slope related to declining FCSRT-FR and SRT-tr learning/memory retrieval. When we expanded to include those initially <CL40, rising FTP level or slope was related to declines across all tasks, and PiB slope effects on memory retrieval but not DSST score were reduced. A composite measure of processing speed and memory retrieval tasks provided the strongest prediction of decline under CL40, while PACC score remained optimal at high levels of Aβ (>CL40).

Discussion

Early, Aβ-mediated cognitive slowing was detected for processing speed measures, while early memory retrieval declines were associated with emerging Aβ and tau pathology. Composites of these measures may help determine whether anti-Aβ or anti-tau therapies administered at the first signs of pathology might preserve cognitive function.

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Glossary

Aβ = β-amyloid; **AD** = Alzheimer disease; **CL** = Centiloid; **DSST** = Digit Symbol Substitution Test; **DVR** = distribution volume ratio; **ERC** = entorhinal cortex; **FCSRT** = Free and Cued Selective Reminding Test; **FCSRT-FR** = FCSRT Free Recall; **FDR** = false discovery rate; **FLR** = frontal, lateral temporal, and retrosplenial; **FTP** = 18F-flortaucipir; **HABS** = Harvard Aging Brain Study; **IT** = inferior temporal cortex; **LM** = Logical Memory; **LM-dr** = LM Delayed Recall; **LM-immed** = LM Immediate Recall; **LME** = linear mixed-effects; **MEM** = immediate memory retrieval composite; **PACC** = Preclinical Alzheimer Cognitive Composite; **PiB** = Pittsburgh compound B; **PS** = processing speed; **PSMEM** = PS/memory composite; **SE** = standard error; **SRT** = Selective Reminding Test; **SRT-dr** = SRT Delayed Recall; **SRT-tr** = SRT Total Recall; **Trails** = Trail Making Test.

Classification of Evidence

This study provides Class I evidence that in clinically normal older adults, emerging PET-detected AD pathology is associated with declining processing speeds and memory retrieval.

Alzheimer disease (AD) clinical trials are moving earlier in the disease process, with secondary prevention trials currently underway[1-3] in clinically normal older adults with elevated β-amyloid (Aβ) and tau pathology. However, moving even earlier, closer to primary prevention, by intervening at the first signs of emerging Aβ before extensive tau proliferation[4-6] may be optimal. Cognitive measures sensitive to the earliest stages of AD pathogenesis[7] may not be the same as those sensitive to high Aβ and spreading neocortical tau pathology, including specific declines in delayed recall[8-13] and composites such as the Preclinical Alzheimer Cognitive Composite (PACC).[14,15] If early intervention is necessary to successfully slow AD progression, it is critical to find the right test for the right time by identifying which cognitive tests are associated with emerging Aβ and tau pathology.

Recent studies indicate an early link between Aβ and memory, demonstrating that the first detectable signs of increasing Aβ in those initially below PET positivity thresholds are associated with worsening performance on memory composites.[16-18] However, it remains unclear what specific aspects of memory are vulnerable at this early stage and whether other cognitive processes may also be related to emerging Aβ pathology. Furthermore, while neocortical tau drives cognitive decline in individuals with high Aβ,[19-22] it is unclear to what extent tau contributes to the subtle cognitive changes associated with emerging Aβ. In the present study, we used longitudinal Aβ-PET, tau-PET, and multiple domains of cognitive data from clinically normal individuals with initially subthreshold to intermediate Aβ from the Harvard Aging Brain Study (HABS) and assessed which cognitive tasks were associated with emerging Aβ accumulation and the extent to which tau contributes to these early Aβ-cognition relationships.

Methods

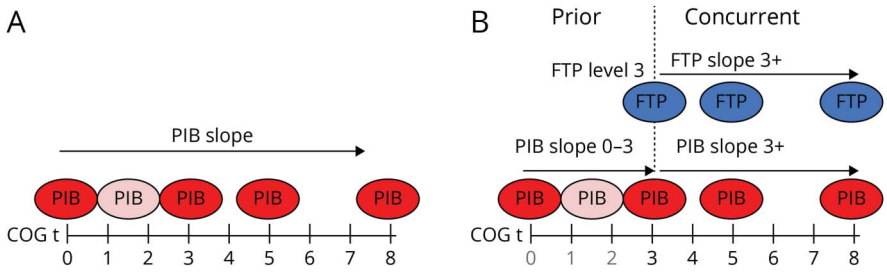
Sample

To evaluate cognitive changes appearing as Aβ and tau pathology first become detectable with PET, analyses were focused primarily on a subset of 112 individuals with initially low Pittsburgh compound B (PiB)-PET levels. Two thresholds for low PiB were selected. The lower threshold at 20 Centiloids (CL) is approximately the threshold for detection of global PiB positivity.[23,24] Because differentiating Aβ and nonspecific binding is difficult below the positivity threshold, starting subthreshold and exhibiting high rates of PiB accumulation constitutes the first reliable marker of early Aβ with PET. A second threshold at CL40 was included to select those with detectable but still low to intermediate Aβ at baseline; these individuals are the current targets of clinical trials such as the AHEAD study aimed at intervening as close as possible to the onset of amyloidosis. These trials selected CL40 as an upper limit on the basis of evidence that it corresponds to approximate CL threshold beyond which rapid tau proliferation is observed.[25] Participants falling into the critical CL20 to CL40 range are scarce in the population and the present sample (n = 10) due to the rapid rate of accumulation, but this range may represent the optimal window for intervention. An additional 31 participants over the CL40 threshold at baseline were included for comparison.

Cognitive testing was performed annually and PiB-PET at years 0, 1.5 in a small subset, 3, 5, and 8. ^{18}F-flortaucipir (FTP)-PET was introduced after the start of HABS, with most participants undergoing their first FTP scan at year 3 (±1 year) and repeated at years 5 and 8. Figure 1 shows the HABS timeline.

All HABS participants had a baseline Clinical Dementia Rating score of 0 and Mini-Mental State Examination score ≥27 with educational adjustment. Participants with evidence of clinical depression (Geriatric Depression Scale score ≥10), neurologic disorders, and head trauma were excluded. Detailed inclusion criteria have been published previously.[26] One extreme outlier (>10 SD from the mean change on all cognitive measures), a participant with CL28 at baseline who progressed to mild cognitive impairment within the first 2 years, was excluded from analyses to focus on the early stages of preclinical AD. No other participants <CL40 at baseline had progressed to mild cognitive impairment by their final follow-up.

Figure 1 HABS Timeline



Harvard Aging Brain Study (HABS) timeline and its adaptation for the present study are shown, with all participants completing annual cognitive (COG) visits starting at t = 0. (A) Design for analyses, including Pittsburgh compound B (PiB)-PET only. PiB-PET was completed at baseline and years 3, 5, and 8. A small subset also had a PiB-PET scan at 18 months. These analyses used extracted slopes for each participant from the individual's PiB scans over time. (B) Modified timeline for the analyses assessing both PiB and ^{18}F-flortaucipir (FTP) effects. Because FTP was added after HABS baseline for most participants, these analyses are anchored to year 3. Analyses were also split into PiB/FTP effects at or before year 3 visit (PiB slope years 0–3, FTP distribution volume ratio level at year 3) and those concurrent with cognitive visit from year 3 onward (PiB slope years 3–5, FTP slope years 3+).

Standard Protocol Approvals, Registrations, and Patient Consents

The procedures for this study were approved by the Partners Human Research Committee and the Institutional Review Board for the Massachusetts General Hospital and Brigham and Women's Hospital. All participants provided written consent.

PiB-PET Imaging

PiB-PET acquisition parameters for HABS have been published previously.[20,26] In brief, PET images were acquired on a Siemens (Erlangen, Germany) ECAT EXACT HR+ scanner with a 60-minute dynamic acquisition starting immediately after injection. For baseline scans, each participant's MRI was processed cross-sectionally with FreeSurfer 6.0, and PiB-PET scans were coregistered to MRI. Distribution volume ratios (DVRs) were calculated via Logan plotting over 40 to 60 minutes with a cerebellar gray matter reference region and a global PiB aggregate including frontal, lateral temporal, and retrosplenial (FLR) regions for the target, as previously reported.[12,20,23,27,28]

The baseline FLR PiB DVR was converted to the CL scale[30,31] with the use of a previously published linear transformation[23,29] to provide a generalizable context for the range of Aβ tracer retention being evaluated.

While baseline thresholds were set with the CL scale used for generalizability, we measured Aβ accumulation using a modified pipeline to favor longitudinal reliability on the basis of evidence that standard cross-sectional approaches are suboptimal for measuring longitudinal change in Aβ.[32,33] PiB-PET scans were realigned to the baseline PET image and coregistered to an averaged MRI across all time points with FreeSurfer version 6.0. DVRs were calculated via Logan plotting over 40 to 60 minutes with the same FLR target region but with a composite reference region composed of the cerebellum and eroded cortical white matter (similar to previously recommended longitudinal reference regions[32]). Longitudinal PiB reliability was higher without partial volume correction, so PiB data are not corrected. To measure Aβ accumulation, PiB slopes were extracted from each individual's linear regression of PiB FLR DVR over time, with PET time measured as the years between each visit and PET baseline. PiB slope indicates the rate of change per year in global PiB DVR in the FLR aggregate region of interest. Data were restricted to those with at least 3 PiB scans to focus on those with PiB data both before and after the inclusion of FTP data.

FTP-PET Scan

FTP-PET acquisition parameters for HABS have been published previously.[20,26,27] Due to the more recent development of tau tracers, no consensus has yet been reached on optimal longitudinal change methods for FTP. At present, longitudinal reliability is highest in HABS with the use of our existing cross-sectional PET pipeline with partial volume correction using the geometric transfer matrix method to adjust for longitudinal atrophy, as published previously.[20] However, FTP requires a longer wait after injection than PiB before approaching a steady state; therefore, the standardized uptake value ratio was computed from summed frames from 80 to 100 minutes. Analyses were conducted with and without partial volume correction, but the pattern of the results remained the same. To reduce the number of comparisons, only the left and right hemispheres of 2 early tau-accumulating regions were selected as regions of interest, representative of Braak I to II (entorhinal cortex [ERC]) and Braak III to IV (inferior temporal cortex [IT]) tau stages, as in previous HABS FTP studies.[19,20,34]

Cognition

From the larger HABS cognitive battery,[26] the present study evaluated 8 tasks (with 11 measures) that assess episodic memory, processing speed (PS), executive function, and language. Three episodic memory tasks were investigated: the Free and Cued Selective Reminding Test (FCSRT), WMS Wechsler Memory Scale-Revised Logical Memory (LM) and

the 6-trial Selective Reminding Test (SRT). From each, a measure of immediate free recall (FCSRT-FR, Logical Memory Immediate Recall [LM-immed], SRT Total Recall [SRT-tr]) was included as an indicator of learning and memory retrieval, and delayed recall (SRT-dr, LM-dr) and cued recall (FCSRT-total) were collected to assess delayed recall and memory consolidation. Three measures of PS/executive function were included: Wechsler Adult Intelligence Scale–Revised Digit Symbol Substitution Test (DSST) and Trail Making Test (Trails) Parts A and B. Finally, 2 measures of language were collected: category fluency (total from animals/vegetables/fruit) and verbal fluency (F-A-S). Each measure was standardized by computing z scores using the mean and SD from the full HABS sample at baseline, as previously reported.[20,23,26,27] For further comparison, the PACC5,[14,15] which is sensitive to high Aβ, was computed by averaging the FCSRT-total, LM-dr, DSST, category fluency, and Mini-Mental State Examination scores.

Statistical Analysis

All analyses were conducted in R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria). To account for the large number of comparisons, the p values for the estimate of interest (time × PiB slope and time × FTP level/slope) from all planned analyses were pooled, and a false discovery rate (FDR) correction was applied. Results were reported with both unadjusted $p < 0.05$ and FDR-adjusted p values. To focus on cognitive declines occurring early as Aβ pathology and tau pathology emerge, individuals were grouped into those with <CL 20 at baseline, <CL40 at baseline, only between CL20 and CL40 at baseline, and >CL40 at baseline. Mann-Whitney U and Kruskal-Wallis tests were conducted to compare groups on sample descriptives, including age, sex, education, *APOE* status, and length of follow-up.

For the primary analyses assessing whether each cognitive measure was associated with the earliest detectable Aβ accumulation, separate linear mixed-effects (LME) models were computed of the effect of the extracted PiB slopes over time (PiB slope × time) on each cognitive measure in individuals initially falling below the positivity threshold of CL20. Time was measured as a continuous variable computed as years from cognitive baseline (Figure 1A). Each model covaried for the main effects and interactions with time for baseline age, sex, and education and allowed for random effects of participant intercept and slopes. Baseline age and education were mean-centered at the means of the <CL40 group. To assess which cognitive tasks may change as individuals with low to intermediate Aβ are added, these analyses were repeated including individuals up to CL40.

To further explore the idea of selecting the right test at the right time, all individuals (including those >CL40 at baseline) were grouped according to where they fell along the Aβ continuum at the final PET scan: initially <CL20 and remained < CL20 at final follow-up, initially <CL20 and moved up to the CL20–40 group, initially <CL40 and moved up to >CL40 group, and >CL40 at baseline. Contrasting those who remain PiB– (<CL20) with each of the PiB+ groups allows estimation of group differences in cognitive change over time between those who are not accumulating Aβ and those moving through the early, intermediate, and later stages of amyloidosis. LME models assessed the change over time in each composite as a function of the final CL group (time × final CL group), with the same covariates and random effects as above.

Last, we evaluated the extent to which early tau deposition and accumulation in the ERC and IT may drive early Aβ-related cognitive changes within the baseline <CL20 group and the baseline <CL40 group. Because tau PET imaging was introduced later, within a year of the cognitive visit at year 3, analyses including tau were anchored to year 3 (Figure 1B) and included only cognitive data from year 3 onward. To reduce multicollinearity and differences due to the number of PET scans, analyses were split into LME analyses of prior Aβ and tau at year 3 and concurrent effects of Aβ and tau on cognition after year 3. Specifically, the prior analyses tested whether PiB $\text{slope}_{Y0\text{-}3}$ and FTP level_{Y3} predict cognitive decline year 3 onward. For concurrent analyses, PiB slope_{Y3+} and FTP slope_{Y3+} were computed for each cognitive task year 3+. Analyses were conducted separately for left and right ERC and IT FTP standardized uptake value ratio. Of note, no Aβ × tau × time interactions reached significance, so only Aβ× time and tau × time effects are reported. Furthermore, due to the smaller number of follow-up data points available after the introduction of FTP-PET, models including both random intercept and slope terms did not converge for some cognitive variables; therefore, only the random effect for participant intercept was included for all tests.

Data Availability

HABS data are available online.[35]

Results

Sample Descriptives

Table 1 reports the baseline sample descriptives for the <CL20 and <CL40 groups, as well as for those who fell between CL20 and CL40 at baseline (n = 10) and those already in later stages of amyloidosis (>CL40) at baseline. While small, the only significant differences between the 20 < CL < 40 group and the <CL20 group were for higher PiB slope ($W = 40$, $t = 6.30$, $p < 0.001$) and a higher proportion of *APOE* ε4 carriers in the 20 < CL < 40 group ($\chi^2 = 19.0$, $p < 0.001$). It is notable that the PiB slope was comparable between the 20 < CL < 40 group and the >CL 40 ($p > 0.10$).

Cognitive Changes Associated With Emerging Aβ Accumulation

In participants initially <CL20, DSST and Trails A score decline was associated with higher PiB slopes (Figure 2A). If the sample is expanded to include individuals with up to CL40 at baseline (Figure 2B), PiB slope effects over time remained significant for DSST and Trails A scores and expanded to

Table 1 Sample Descriptives

	<CL20	20 < CL < 40	<CL40	>CL40
No.	102	10	112	31
PiB scans, n	3.62 (0.76)	3.3 (0.67)	3.60 (0.75)	3.61 (0.84)
PiB follow-up, y	6.19 (1.66)	5.45 (1.47)	6.12 (1.66)	6.05 (1.56)
FTP scans, n	2.31 (0.78)	2 (1.05)	2.29 (0.81)	2.35 (0.88)
FTP follow-up, y	3.63 (1.63)	3.01 (1.65)	3.59 (1.63)	3.27 (1.79)
Cognitive follow-up, y	7.66 (1.18)	7.82 (1.07)	7.68 (1.17)	7.54 (1.22)
Age, y	71.9 (6.06)	73.0 (5.54)	72.0 (6.00)	74.5 (5.50)
Female, n (%)	61 (60)	6 (60)	67 (60)	16 (52)
Education, y	16.2 (2.99)	15.9 (2.77)	16.2 (2.96)	17.3 (2.55)
***APOE* ε4 carriers, n (%)**	16 (15.8)	7 (70)	23 (20.7)	17 (55)
PiB slope	0.004 (0.007)	0.020 (0.013)	0.022 (0.009)	0.005 (0.008)
ERC FTP level at year 3	1.31 (0.20)	1.42 (0.24)	1.31 (0.20)	1.68 (0.44)
IT FTP level at year 3	1.44 (0.12)	1.47 (0.17)	1.44 (0.12)	1.62 (0.23)
BL PACC score	0.19 (0.59)	−0.01 (0.57)	0.16 (0.59)	0.13 (0.60)
BL DSST *z* score	0.03 (0.99)	−0.28 (1.27)	0.00 (1.01)	0.02 (0.97)
BL Trails A *z* score	0.06 (0.94)	−0.18 (0.80)	0.04 (0.93)	−0.13 (1.25)
BL Trails B *z* score	−0.02 (1.05)	−0.01 (1.16)	−0.02 (1.05)	0.09 (0.81)
BL LM-immed *z* score	0.00 (1.03)	0.19 (0.98)	0.02 (1.02)	-0.05 (0.95)
BL LM-dr *z* score	0.00 (1.04)	0.06 (0.88)	0.00 (1.03)	0.00 (0.95)
BL SRT-dr *z* score	0.05 (0.97)	−0.14 (0.94)	0.03 (0.97)	-0.10 (1.12)
BL SRT-tr *z* score	0.10 (0.94)	0.15 (1.04)	0.10 (0.95)	-0.32 (1.08)
BL FCSRT-FR *z* score	0.03 (0.99)	−0.31 (0.72)	0.00 (0.97)	0.00 (1.14)
BL FCSRT Cued *z* score	0.02 (0.90)	0.07 (0.63)	0.03 (0.88)	-0.13 (1.42)
BL F-A-S *z* score	−0.05 (1.04)	−0.28 (0.71)	−0.07 (1.02)	0.27 (0.91)
BL CAT *z* score	0.00 (1.02)	−0.34 (0.93)	-0.03 (1.01)	0.13 (0.97)

Abbreviations: BL = baseline; CAT = category fluency; CL = Centiloid; DSST = Digit Symbol Substitution Test; ERC = entorhinal cortex; FCSRT = Free and Cued Selective Reminding Test; FCSRT-FR = FCSRT Free Recall; FTP = ^{18}F-flortaucipir; IT = inferior temporal cortex; LM-dr = Logical Memory Delayed Recall; LM-immed = Logical Memory Immediate Recall; PACC = Preclinical Alzheimer's Cognitive Composite; PiB = Pittsburgh compound B; SRT-dr = Selective Reminding Test Delayed Recall; SRT-tr = Selective Reminding Test Total Recall; Trails = Trail Making Test.
Data are mean (SD) for continuous variables and number (percent) for categorical. Analyses focused on the <CL20 and <CL40 subgroups, although those falling into the 20 < CL < 40 group and the >CL40 group at baseline are shown for comparison.

include all measures of retrieval (LM-immed and SRT-tr after correction for multiple comparisons, FCSRT-FR uncorrected). To ensure that PS effects were not confounded by rapid decline in the oldest-old or cardiovascular risk, analyses were repeated while also controlling for the quadratic effect of age and the Framingham Heart Study general cardiovascular disease risk score,[36,37] but the effects remained highly significant for DSST and Trails A scores.

Right Test, Right Time

To further assess the idea that different tests may be appropriate at different points along the Aβ continuum, individuals were grouped according to their final CL group. In addition, because tests appeared to act along domain lines, DSST and Trails A scores were combined into a PS composite; FCSRT-FR, SRT-tr and LM-immed scores were combined into a memory retrieval composite; and all these were combined into a PSMEM composite. Figure 3, A and B demonstrates the differing individual trajectories of cognitive change for the PS and immediate memory retrieval (MEM) composites, with changes in PS predominant as individuals cross the CL20 threshold, while the MEM composite becomes more consistently a decline as individuals cross the CL40 threshold. LME models using the final CL group further demonstrated that

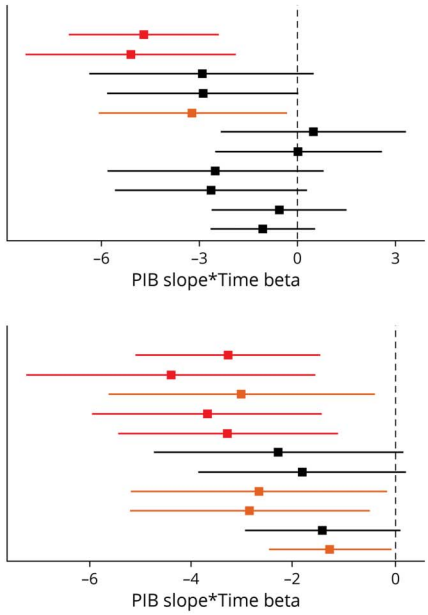
Figure 2 Effects of Emerging PiB Slope on Different Cognitive Tasks Over Time

A. Participants initially under CL 20

Task	β	se	*p*	*p* adjusted
DSST	−4.708	1.168	<0.001	0.003
Trails A	−5.088	1.639	0.003	0.018
FCsrt-FR	−2.922	1.749	0.098	0.196
SRT_tr	−2.890	1.495	0.057	0.139
LM-immed	−3.212	1.464	0.031	0.088
FCsrt-cued	0.492	1.440	0.733	0.788
SRT_dr	0.023	1.301	0.986	0.986
LM-delay	−2.507	1.691	0.142	0.249
Trails B	−2.635	1.504	0.084	0.172
CAT	−0.545	1.046	0.604	0.701
FAS	−1.056	0.821	0.202	0.319

B. Participants initially under CL 40

Task	β	se	*p*	*p* adjusted
DSST	−3.277	0.934	<0.001	0.006
Trails A	−4.396	1.459	0.003	0.021
FCsrt-FR	−3.005	1.343	0.028	0.083
SRT_tr	−3.687	1.158	0.002	0.015
LM-immed	−3.277	1.105	0.004	0.021
FCsrt-cued	−2.283	1.254	0.071	0.152
SRT_dr	−1.809	1.043	0.086	0.175
LM-delay	−2.660	1.294	0.043	0.110
Trails B	−2.848	1.209	0.021	0.069
CAT	−1.405	0.786	0.077	0.162
FAS	−1.252	0.617	0.045	0.114



Results of the linear mixed-effects models in the group <20 Centiloids (CL) (A; n = 102) and <CL40 group (B; n = 112) are shown. Unstandardized β, standard error (SE), and *p* value for the Pittsburgh compound B (PiB) slope × time interaction term are tabulated for each task on the left and plotted on the right. Age and educated are mean centered, so a 0.01 distribution volume ratio per year rate of accumulation is associated with a modest decline of 0.03 SD/y on the Digit Symbol Substitution Test (DSST) for a 72-year-old woman with 16.2 years of education. Significant effects at $p < 0.05$ are plotted in orange and in red if they also survive correction for multiple comparisons with false discovery rate ($p_{adj} < 0.05$). Rising PiB slope was associated with declining DSST and Trail Making Test (Trails) A scores. Expanding to those <CL40 at baseline, rising PiB slope was at least marginally associated with decline on all tasks, with strongest effects in measures of memory retrieval and processing speed/executive function. CAT = category fluency; FCSRT = Free and Cued Selective Reminding Test; FCSRT-FR = FCSRT Free Recall; LM = Logical Memory; PiB = Pittsburgh compound B; SRT-dr = Selective Reminding Test Delayed Recall.

the PS composite declined more in those initially <CL20 that accumulated and moved up to the CL20–40 group compared with those who remained <CL20 (β = −0.061, standard error [SE] = 0.030, p = 0.046) but did not differ for the MEM composite (β = −0.037, SE = 0.031, p = 0.245). Combining PS and MEM into a PSMEM composite (Figure 3C) reduced the difference between the final <CL20 and CL20–40 groups (β = −0.045, SE = 0.027, p = 0.091) but provided a slightly stronger marker of decline in those with initially low to intermediate Aβ who moved above CL40 by their final follow-up (β = −0.10, SE = 0.032, p = 0.001) than the PACC5 score (β = −0.010, SE = 0.042, p = 0.010) due to less error. In those with high Aβ already above CL40 at baseline, the PACC5 exhibited the most decline (β = −0.17, SE = 0.028, p < 0 .001).

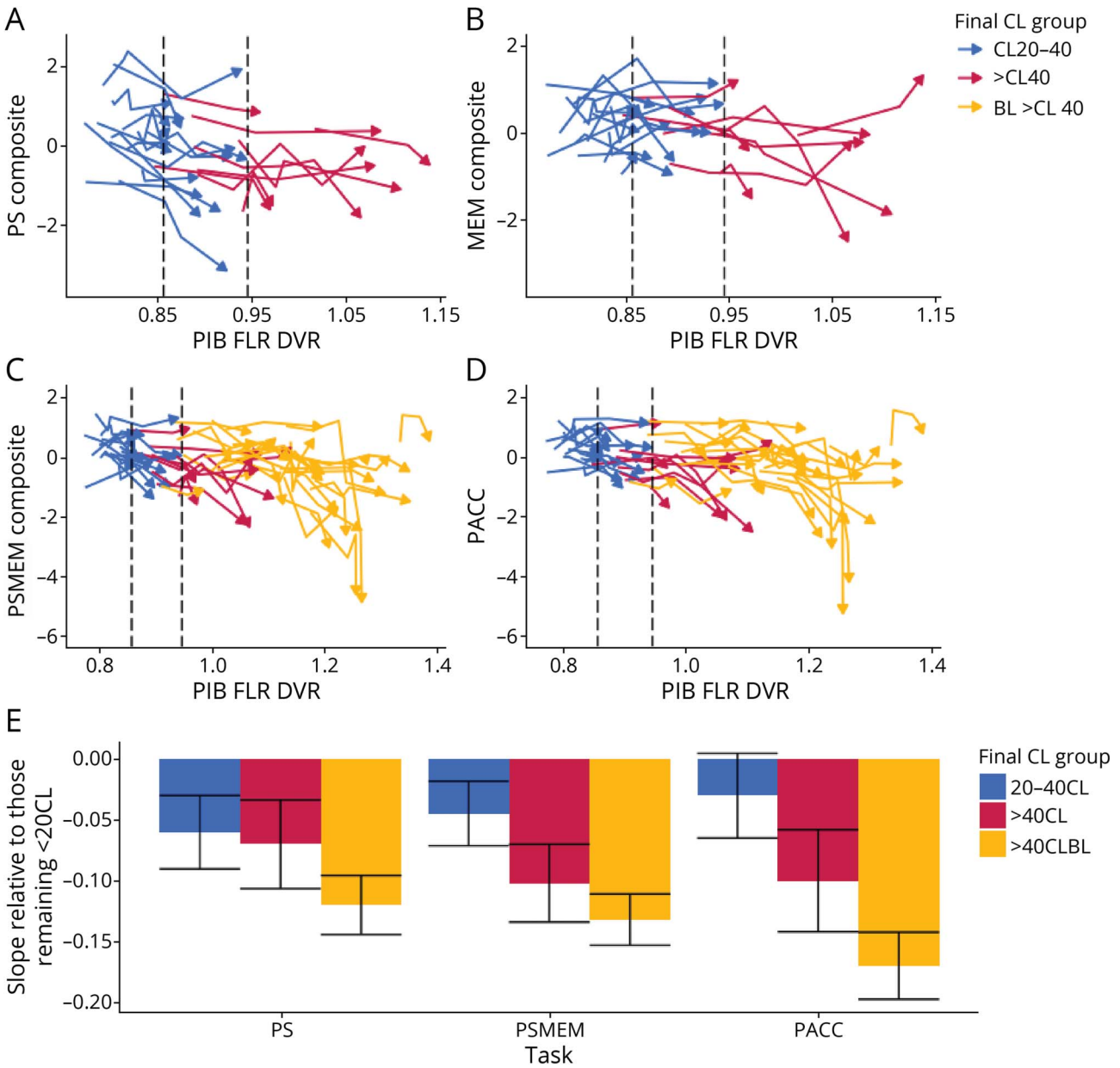
Role of ERC and IT Tau in Early Aβ-Related Cognitive Changes

Because FTP was introduced later, at year 3 for most participants, we first repeated the PiB only analyses focusing only on cognitive data acquired from tau baseline onward and split PiB slope into PiB slope before tau baseline, year 0 to 3, and PiB slope concurrent with tau data collection, year 3+. In both the <CL20 and <CL40 groups, prior PiB accumulation year 0 to 3 was associated with subsequent decline on the DSST (<CL20: β = −5.83, SE = 1.682, p < 0.001; <CL40: β = −3.79, SE = 1.43, p = 0.009), FCSRT-FR (<CL20: β = −7.41, SE = 3.12, p = 0.02; <CL40: β = −6.51, SE = 2.55, p = 0.012), and SRT-tr (<CL20: β = −5.19, SE = 2.04, p = 0.013; <CL40: β = −3.94, SE = 1.71, p = 0.023). Concurrent associations between PiB slope and cognitive decline were observed in both the <CL20 and <CL40 groups for DSST (<CL20: β = −2.77, SE = 1.18, p = 0.021; <CL40: β = −2.73, SE = 1.10, p = 0.015), Trails A (<CL20: β = −2.95, SE = 1.38, p = 0.035; <CL40: β = −4.77, SE = 1.94, p = 0.016), and Trails B (<CL20: β = −3.78, SE = 1.85, p = 0.045; <CL40: β = −5.04, SE = 1.87, p = 0.009). In addition, concurrent associations between decline and PiB slope year 3+ were observed in the <CL40 group for FCSRT-FR (β = −4.74, SE = 2.05, p = 0.023), SRT-tr (β = −3.56, SE = 1.35, p = 0.01), LM-immed (β = −2.46, SE = 1.24, p = 0.047), and SRT-dr (β = −3.025, SE = 1.21, p = 0.014) scores.

To establish the extent to which these amyloid-cognition relationships may be explained by emerging tau, we next added FTP level to our models of prior biomarker effects on subsequent cognitive decline and FTP slope to models of concurrent biomarker and cognitive changes. Table 2 provides a summary of findings across multiple sets of analyses. In those initially <CL20, prior tau level was not a significant predictor after FDR correction for any task, and prior PiB $slope_{Y0\text{-}3}$ remained a significant predictor of subsequent DSST, FCSRT-FR, and SRT-tr score decline with FTP level in the model. Moving to contemporaneous changes, PiB $slope_{Y3+}$ remained associated with DSST score decline while accounting for ERC/IT FTP. In contrast, the PiB slope effect was mitigated to a trend for FCSRT-FR, SRT-tr, and Trails B scores due to the presence of an association with increasing right IT FTP slope. The relationship between PiB slope and Trails A score was not significant when FTP level or slope was included in the models, although significant effects were also not observed for FTP.

When expanded to the <CL 40 group, FTP effects became more predominant. Higher bilateral IT FTP level at tau baseline was associated with subsequent FCSRT-FR score

Figure 3 PS and Memory Retrieval Composites Indicative of Emerging Aβ



To select individuals who started with lower Pittsburgh compound B (PiB) and accumulated over time, we subsetted the baseline below 40 Centiloids (CL) group to include only those who had progressed to >CL20 by their final PET scan. Then individual trajectories of change in the (A) processing speed (PS) composite and (B) memory retrieval composite (MEM) as PiB frontal, lateral temporal, and retrosplenial (FLR) distribution volume ratio (DVR) increases were plotted were grouped by their final CL group. (A) Increasing PiB FLR DVR over time is associated with declining PS, particularly as individuals cross the CL20 threshold (left dashed line in A–D). (B) Increasing PiB FLR DVR is associated with declining memory retrieval, although individual change is highly variable near the CL20 threshold but becomes more consistently negative as individuals surpass the CL40 threshold (right dashed line in A–D). (C) PS and memory retrieval (MR) tasks were combined into a single PSMEM composite that captures individuals with early changes better than the Preclinical Alzheimer Cognitive Composite (PACC) (D). Individuals who were already >CL40 at baseline (BL) are included in C–E for comparison as individuals reach high levels of β-amyloid (Aβ). (E) Estimated slopes and standard error are plotted of the change in PS, PSMEM, and PACC composites over time, comparing those who remained <CL20 at final follow-up to those who increased to CL20–40 or >CL40 or those already >CL40 at baseline. These results suggest early Aβ-related cognitive changes (blue, red) are best measured with the PS or PSMEM composite, while later changes in those already >CL40 at baseline are better measured with PACC (yellow).

decline in accordance with prior PiB slope$_{Y0\text{-}3}$. Similar links between FTP level$_{Y3}$ and memory decline were observed between right IT FTP and FCSRT-Cued score and between left ERC FTP level and LM-immed, LM-dr, and SRT-dr scores. DSST score decline remained associated primarily with both prior PiB slope$_{Y0\text{-}3}$ and concurrent PiB slope$_{Y3+}$ after adjustment for the strongest FTP predictor. Prior PiB slope$_{Y0\text{-}3}$ continued to be a significant contributor to memory retrieval decline for FCSRT-FR and SRT-tr in the <CL40 group, but concurrent PiB slope$_{Y3+}$ effects became non-significant when accounting for IT FTP slope$_{Y3+}$. Concurrent FTP slope$_{Y3+}$ exhibited widespread memory effects in the

Table 2 Summary of PiB and FTP Effects on Cognition Over Time (Years 3–8) for Multiple Tasks

		<CL20				<CL40			
		Prior		Concurrent		Prior		Concurrent	
		PiB	FTP	PiB	FTP	PiB	FTP	PiB	FTP
DSST	β (SE)	−5.59 (1.38)	lrERC: −0.06 (0.05)	−3.98 (0.28)	rIT: −0.55 (0.43)	−3.64 (1.06)	lrIT: −0.25 (0.09)	−3.78 (1.08)	rIT: −0.73 (0.37)
	p_{adj}	<0.001[b]	0.34	0.010[b]	0.34	0.006[b]	0.054[a]	<0.001[b]	0.125
Trails A	β (SE)	−2.14 (2.30)	rIT: -0.07 (0.15)	−1.46 (2.25)	rERC: -0.41 (0.28)	−2.94 (2.14)	rIT: −0.42 (0.16)	−4.21 (2.21)	lrIT: −2.44 (0.84)
	p_{adj}	0.51	0.75	0.65	0.27	0.30	0.040[b]	0.14	0.021[b]
FCSRT-FR	β (SE)	−7.78 (2.65)	lrIT: -0.47 (0.18)	−4.74 (2.46)	rIT: −3.07 (0.83)	−6.69 (1.95)	lrIT: −0.69 (0.16)	−3.78 (2.06)	rIT: −2.93 (0.70)
	p_{adj}	0.010[b]	0.053[a]	0.14[a]	0.003	0.006[b]	<0.001[b]	0.15	<0.001[b]
SRT-tr	β (SE)	−5.10 (1.81)	rERC: −0.10 (0.06)	−3.72 (1.79)	rIT: −2.06 (0.59)	−3.39 (1.47)	lrERC: −0.14 (0.06)	−2.53 (1.46)	rIT: −2.22 (0.52)
	p_{adj}	0.025[b]	0.19	0.10[a]	0.006[b]	0.014[b]	0.26[a]	0.18	<0.001[b]
LM- immed	β (SE)	−3.06 (1.99)	lERC: −0.32 (0.12)	−1.93 (1.90)	lrIT: −1.54 (0.65)	−2.24 (1.57)	lERC: −0.16 (0.06)	−1.55 (1.58)	lrIT: −1.55 (0.60)
	p_{adj}	0.24	0.11[a]	0.47[a]	0.061[a]	0.27	0.032[b]	0.48	0.042[b]
FCSRT-Cued	β (SE)	−0.31 (2.64)	lERC: -0.09 (0.08)	−1.42 (2.58)	rIT: −1.02 (0.85)	−4.27 (2.27)	rIT: −0.49 (0.17)	−3.27 (2.41)	lrIT: −1.37 (0.89)
	p_{adj}	0.94	0.43	0.72	0.37	0.14	0.026[b]	0.30	0.24
SRT-dr	β (SE)	−1.70 (1.69)	lERC: −0.08 (0.05)	1.60 (1.65)	rIT: −1.28 (0.76)	−2.77 (1.35)	lERC: −0.13 (0.05)	−2.05 (1.36)	rIT: −1.52 (0.48)
	p_{adj}	0.46	0.24	0.48	0.06[a]	0.36	0.033[b]	0.25	0.013[b]
LM-dr	β (SE)	−1.67 (2.30)	lERC: −0.15 (0.07)	−0.54 (2.20)	lrIT: −1.63 (0.54)	−1.02 (1.79)	lERC: −0.20 (0.07)	−1.41 (1.84)	lrIT: −1.75 (0.70)
	p_{adj}	0.61	0.12[a]	0.87	0.19	0.70	0.021[b]	0.66	0.049[b]
Trails B	β (SE)	−1.43 (2.25)	lrIT: −0.41 (0.16)	−5.07 (2.20)	rERC: −0.95 (0.28)	-0.25 (1.78)	lrIT: −0.66 (0.15)	−5.96 (1.85)	rIT: −1.83 (0.66)
	p_{adj}	0.60	0.057[a]	0.067[a]	0.006[b]	0.95	<0.001[b]	0.011[b]	<0.001[b]

Continued

Table 2 Summary of PiB and FTP Effects on Cognition Over Time (Years 3–8) for Multiple Tasks *(continued)*

		<CL20				<CL40			
		Prior		Concurrent		Prior		Concurrent	
		PiB	FTP	PiB	FTP	PiB	FTP	PiB	FTP
CAT	β (SE)	−0.53 (1.71)	rIT: −0.14 (0.11)	−2.63 (1.61)	rERC: −0.53 (0.20)	0.13 (1.31)	rIT: −0.19 (0.10)	−2.95 (1.27)	lERC: −0.66 (0.25)
	p_{adj}	0.84	0.34	0.30	0.051[a]	0.95	0.13	0.067[a]	0.032[b]
F-A-S	β (SE)	−0.81 (1.30)	lIT: −0.15 (0.08)	−2.12 (1.22)	rIT: −0.74 (0.41)	−1.05 (1.01)	rIT: −0.17 (0.08)	−2.23 (1.02)	rIT: −0.38 (2.34)
	p_{adj}	0.58	0.23	0.18[a]	0.16	0.45	0.083[a]	0.12[a]	0.424

Abbreviations: CAT = category fluency; CL = Centiloid; DSST = Digit Symbol Substitution Test; ERC = entorhinal cortex; FCSRT = Free and Cued Selective Reminding Test; FCSRT-FR = FCSRT Free Recall; FTP = ^{18}F-flortaucipir; IT = inferior temporal cortex; LM-dr = Logical Memory Delayed Recall; LM-immed = Logical Memory Immediate Recall; PiB = Pittsburgh compound B; SE = standard error; SRT-dr = Selective Reminding Test Delayed Recall; SRT-tr = Selective Reminding Test Total Recall; Trails = Trail Making Test.

β Estimates, standard error, and false discovery rate–adjusted *p* values are reported ([a]$p < 0.05$ uncorrected, [b]$p_{adj} < 0.05$) and reflect the effect of a 1-unit change in slope (or standardized uptake value ratio for prior FTP level$_{Y3}$) per year on the change in the cognitive task per year for a 72-year-old woman with 16.2 years of education. The FTP region of interest (left IT/ERC, right IT/ERC, or bilateral lrIT/ERC) with the strongest prediction of each respective cognitive test over time is reported for FTP effects, and corresponding PiB slope of that model is reported for PiB effects. Separate analyses were conducted evaluating prior biomarker effects on cognition (PiB slope$_{Y0\text{-}3}$, FTP level$_{Y3}$) and the concurrent association between changing biomarkers and changing cognition (PiB slope$_{Y3+}$, FTP slope$_{Y3+}$). DSST score was significantly related to prior and concurrent PiB slopes in <CL20 and <CL40 adults and was minimally associated with FTP. Memory retrieval measures (FCSRT-FR, SRT-tr, and, to a lesser extent, LM-immed) were associated with prior PiB slope and FTP level and slope, most often with right IT, especially when everyone <CL40 at baseline was included. Delayed recall measures of memory consolidation (FCSRT-Cued, SRT-dr, LM-dr) were predominately associated with FTP and significant at $p_{adj} < 0.05$ when those with low to moderate β-amyloid at baseline are included. Language measures (CAT, F-A-S) exhibited limited PiB and FTP effects after adjusting for multiple comparisons. Trails B was associated with concurrent PiB slope and FTP slope.

<CL40 group between right IT FTP slope$_{Y3+}$ and declines on FCSRT-FR, SRT-tr, and SRT-dr and between bilateral IT FTP slope and LM-immed and LM-dr. Both Trails A and B scores were associated with increasing IT FTP level/slope, although concurrent PiB slope$_{Y3+}$ remained a significant contributor to Trails B score.

Classification of Evidence

This study provides Class I evidence that in clinically normal older adults, emerging PET-detected AD pathology is associated with declining PS and memory retrieval.

Discussion

More refined detection of the earliest subtle cognitive changes associated with emerging Aβ and tau pathology is critical to understand the earliest stages of AD and to design efficient clinical trials aiming to get closer to primary prevention. Using longitudinal PiB and FTP PET data in clinical normally older adults with initially low but increasing AD pathology, we were able to detect a consistent pattern of early Aβ accumulation–related declines in measures of PS and executive function (especially DSST) and memory retrieval. As individuals continued to accumulate Aβ and tau spread into the neocortex, tau became a strong driver of decline across a broad range of cognitive tasks, particularly memory. Overall, these findings indicate that observational research and clinical trials attempting to intervene at the earliest possible point in AD pathologic progression (i.e., primary prevention) may hone detection and tracking of the subtle cognitive changes associated with the emerging AD pathology by measuring PS and learning/memory retrieval.

A key finding of the present study is the demonstration of an early and concurrent association between accumulating Aβ and measures of PS, most robustly with the DSST. While more research is needed to elucidate the mechanisms underlying this observed decline, it may reflect a general slowing of synaptic transmission in response to accumulating Aβ. Furthermore, because evidence indicates that the Aβ plaques quantified with PET are mostly in equilibrium with the soluble Aβ oligomers,[38,39] it is possible that this slowing of performance over time may reflect neurotoxic effects of soluble Aβ on synaptic transmission, as has been demonstrated in animal models and in vitro.[40,41] DSST and Trails A and B showed contemporaneous changes in Aβ and cognitive decline, further supporting the possibility of direct, neurotoxic effects of Aβ on synaptic transmission.

Alternatively, the particular sensitivity of the DSST to rising Aβ may be explained by its psychometric properties. The DSST has long been recognized as highly sensitive to change across multiple forms of neurologic injury.[42] Its sensitivity to change is attributed to its reliance on coordination across multiple cognitive processes,[43] including speed, attention, and visuospatial and executive functions. In older adults, DSST is known to be highly dependent on processing and motor speed,[42-44] which is supported by the similarity in the Aβ effects observed for DSST and Trails A. High performers on DSST often use memory encoding/retrieval, learning the paired associates of the task to increase speed.[45] Consequently, the DSST alone may be particularly sensitive to rising Aβ because it combines both speed and memory retrieval. However, its multidomain properties and sensitivity to change also make it less specific to preclinical AD. By combining the DSST with memory measures more specific to preclinical AD, the resulting composite may optimize detection of the subtle cognitive changes associated with emerging Aβ.

Our findings indicate that immediate measures of memory retrieval, which provide insight into whether items were initially learned, also begin changing in response to emerging Aβ and tau pathology. A common observation in longitudinal studies of Aβ and memory in clinically normal adults is that memory change is often characterized by diminishing practice effects rather than outright decline, as was also observed in our study most clearly for SRT-tr (Fig 3D) and to a lesser extent for LM-immed and FCSRT-FR. Mounting evidence suggests that this diminished practice effect may reflect an Aβ-related reduction in learning and retrieval[46] rather than the frank impairment in delayed recall and consolidation that characterizes later stages of the Alzheimer continuum and is strongly associated with abnormal tau.[47] While prior studies in subthreshold adults demonstrated a consistent link between rising Aβ and memory using composites, the associations detected in these studies may have been driven by a more specific decline on measures of learning and immediate retrieval that were included in the memory composites.[16-18] Furthermore, FCSRT-FR score was shown cross-sectionally in 4,432 adults screened for the A4 trial to subtly decrease as clinically normal adults approach the PET positivity threshold.[48] Thus, while practice effects may make detection of early Aβ-related declines in memory retrieval more challenging than detecting DSST score decline, there is consistent evidence across multiple studies of an early link with Aβ. It is also clear, however, that once neocortical tau enters the picture, its debilitating impact on cognitive decline far outweighs the subtle changes associated with Aβ. Further studies elucidating the mechanisms underlying early effects of Aβ and tau on PS, learning, and memory retrieval will help to elucidate AD pathogenesis and provide meaningful cognitive outcome measures in clinical trials aiming to intervene at the earliest possible point in the AD continuum.

While individuals with emerging Aβ pathology may be >2 decades from dementia onset, these results suggest that trials targeting them may still be able to detect treatment effects on cognition. The A3 trial, for example, is testing anti-Aβ treatments in individuals between CL20 and CL40 at baseline and seeks to demonstrate disease-modifying reductions in downstream AD biomarkers, especially tau pathology. At the present time, amyloidosis is the only step in the AD pathway that is reversible, and if it is the case that once neocortical tau proliferation and neurodegeneration are initiated they are irreversible and self-perpetuating, then intervention in those with amyloid but without significant tau may be the only feasible option to reduce the risk of developing future clinical symptoms. Our findings suggest that PS and memory retrieval measures could provide a more sensitive indicator than a

traditional composite such as the PACC5 of whether anti-Aβ therapies applied early can preserve cognitive function. However, these results are preliminary and will require replication in additional samples.

The HABS sample is composed predominantly of White, highly educated individuals with relatively low cardiovascular risk, and future studies with more representative samples are needed. Because the present study focused on individuals with longitudinal PiB and FTP data available, it is possible that selection bias may result in underestimation of the effect of emerging Aβ and tau on cognitive decline. It should also be noted that a small number of participants fell between the CL20 and CL40 threshold; this is a period of rapid Aβ accumulation, and future studies combining across multiple samples are needed to more thoroughly evaluate cognitive changes in the potentially critical range of Aβ-PET burden. There was also a high proportion of *APOE* ε4 carriers in the CL20 to CL40 range (n = 7 of 10), and while the small number precluded statistical analysis, future analyses in large or combined samples may help to determine the importance of the *APOE* ε4 allele to cognitive decline as Aβ emerges.

PiB longitudinal measures were optimized after many years of work and growing consensus in the field about how to reliably measure Aβ longitudinally.[32,33] However, because tau tracers are newer, the optimal longitudinal modifications to FTP processing have not yet been established, and tau change may be comparatively underestimated. While concurrent assessment of the contributions of Aβ and tau on cognitive decline after the introduction of FTP PET involves equivalent numbers of FTP and PiB scans, estimates of the prior effects of Aβ and tau rely on only 1 FTP scan but 2 to 3 PiB scans. Delayed effects of tau proliferation on cognitive decline may therefore be underestimated by the current models. Continuing longitudinal FTP and PiB data collection in HABS will help to more fully evaluate early effects of tau pathology.

By evaluating the longitudinal changes in Aβ, tau, and cognition in individuals with initially lower Aβ burden, we were able to detect evidence of an early, Aβ-mediated cognitive slowing and declining memory retrieval related to accumulation of both Aβ and tau. A composite of these measures may be an optimal method to assess the cognitive consequences of emerging AD pathology in research and clinical trials aimed at the earliest possible intervention. However, because there were a small number of individuals in the study with intermediate Aβ and given the health of the HABS sample relative to the older adult population, replication and further elucidation of these preliminary findings of early Aβ- and tau-associated cognitive changes are needed.

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Disclosure

M.E. Farrell has no disclosures. K.V. Papp has served as an advisor to Biogen Idec and Digital Cognition Technologies. R.F. Buckley and H.I.L. Jacobs have no disclosures. A.P. Schultz has been a paid consultant for Janssen Pharmaceuticals and Biogen. M.J. Properzi, P. Vannini, and B.J. Hanseeuw have no disclosures. D.M. Rentz has served as a consultant for Eli Lilly, Biogen Idec, and Digital Cognition Technologies and serves as a member of the Scientific Advisory Board for Neurotrack. K.A. Johnson has served as paid consultant for Bayer, GE Healthcare, Janssen Alzheimer's Immunotherapy, Siemens Medical Solutions, Genzyme, Novartis, Biogen, Roche, ISIS Pharma, AZTherapy, GEHC, Lundberg, and Abbvie. He is a site coinvestigator for Eli Lilly/Avid, Pfizer, Janssen Immunotherapy, and Navidea. He has spoken at symposia sponsored by Janssen Alzheimer's Immunotherapy, and Pfizer. R.A. Sperling has served as a paid consultant for AC Immune, Alynlam, Cytox, Genentech, Janssen, Neurocentria, Prothena, and Roche. She has received research support as an investigator for Eli Lilly, Janssen, and Eisai AD clinical trials. These relationships are not related to the content in the manuscript. Go to Neurology.org/N for full disclosures.

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Appendix *(continued)*

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