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RESEARCH ARTICLE

Identifying cognitive test scores associated with early tau burden in Alzheimer's disease

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Abstract

INTRODUCTION: This study aimed to identify cognitive tests that optimally relate to tau positron emission tomography (PET) signal in the inferior temporal cortex (ITC), a neocortical region associated with early tau accumulation in Alzheimer's disease (AD).

METHODS: We analyzed cross-sectional data from the harvard aging brain study (HABS) (n = 128) and the Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) study (n = 393). We used elastic net regression to identify the most robust cognitive correlates of tau PET signal in the ITC. Secondary analyses examined whether the cognitive correlates remained significantly associated with tau after adjusting for structural brain measures.

RESULTS: Episodic memory measures, including both total and "process" scores, were the most robust correlates of ITC tau across both cohorts. These cognitive test scores remained significant after accounting for structural brain measures.

DISCUSSION: These findings highlight the potential of specific episodic memory test scores to detect and monitor neuropathological changes associated with early AD.

KEYWORDS
Alzheimer's pathology, elastic net regression, machine learning, neuropsychology, tau PET

Highlights

- Machine learning identified cognitive correlates of early Alzheimer's disease tau burden.
- Both traditional and process scores predicted early tau burden.
- Episodic memory scores were among the strongest correlates.
- Cognitive scores remained significant after accounting for structural brain measures.

1 | BACKGROUND

Alzheimer's disease (AD) is the most common cause of dementia, accounting for up to 80% of all cases.[1] AD is characterized by two hallmark pathologies: amyloid beta (Aβ) plaques and tau neurofibrillary tangles, which begin accumulating in the brain decades before clinical symptoms appear.[2,3] Clinical trials are increasingly recruiting cognitively intact individuals who have AD pathology,[4–6] with the aim of administering disease-modifying therapies before widespread brain changes occur.[6] The success of these trials relies heavily on the ability to detect subtle cognitive changes that may be indicative of early AD pathology. Therefore, sensitive cognitive tests are crucial for both identifying suitable participants and tracking the effectiveness of disease-modifying therapies.

Advancements in Aβ and tau positron emission tomography (PET) tracers now allow for the quantification of AD pathology in the living brain. Cross-sectional studies show weak and inconsistent associations between Aβ burden and cognition in cognitively unimpaired individuals.[7] In contrast, tau pathology has demonstrated more robust associations with cognitive performance[8,9] and is a strong predictor of future AD progression.[10–12]

The U.S. food and drug administration (FDA) has emphasized the importance of identifying appropriate cognitive endpoints for clinical trials in preclinical AD.[13] There are two main approaches for selecting these types of endpoints. One approach is theoretically driven, where tests are selected a priori based on cognitive domains known to be affected early in AD, such as episodic memory.[14] Another approach is data driven, whereby endpoints are selected based on their ability to predict AD pathology or clinical progression in real-world data.[15–17]

The aim of the present study was to use a data-driven approach to identify cognitive test scores that optimally relate to tau PET signal in the inferior temporal cortex (ITC). The ITC is one of the earliest neocortical regions to exhibit tau pathology in AD and is a strong predictor of disease progression.[10,11,18] A secondary objective was to investigate whether the identified cognitive tests maintained their associations with ITC tau after accounting for structural magnetic resonance imaging (MRI) measures. This approach allowed us to identify cognitive test scores that are sensitive to early tau accumulation and provide unique information beyond what is captured by brain MRI measures. We used data from two independent cohorts: the harvard aging brain study (HABS)[19] and the Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) Study.[20,21] Given the distinct characteristics of each cohort—HABS representing a general aging cohort and A4 focusing on Aβ positive individuals at high risk for AD—identifying similar cognitive test scores across both cohorts would provide greater confidence in the result. We included both: (1) conventional cognitive test scores, such as accuracy; and (2) "process" scores,[22] which capture behaviors and errors during test completion (i.e., perseverations, intrusions, and trial-by-trial learning), as these scores have been shown to be sensitive to early AD progression.[23–25]

2 | METHODS

2.1 | Participants

2.1.1 | HABS

HABS is an ongoing longitudinal study of aging and preclinical AD. The study design has been described previously.[19] Briefly, participants are required to be cognitively unimpaired at baseline (Year 1) based on the following criteria: Clinical dementia rating (CDR)[26] global score = 0, Mini-mental status examination (MMSE)[27] $\geq$ 27, and performance above the education-adjusted cutoff score on Logical Memory delayed recall[28] ($\geq$16 years of education, $\geq$9; 8–15 years, $\geq$ 5; 0–7 years, $\geq$3). The present study included data from the Year 4 follow-up visit, as this was when most participants underwent their first tau PET scan. Only participants who completed a tau PET scan, cognitive testing, and a structural MRI scan at Year 4 were included.

2.1.2 | A4 Study

The A4 Study is a secondary prevention trial that enrolled cognitively unimpaired participants 65–85 years of age with elevated Aβ burden.[21] To be considered cognitively unimpaired, participants had to have a CDR[26] global score = 0, MMSE[27] score $\geq$25, and a Logical Memory delayed recall[28] score between 6 and 18. The present study included participants with publicly available tau PET and neuropsychological test data. In secondary analyses, we restricted the sample to

RESEARCH IN CONTEXT

1. **Systematic review**: We conducted a literature review using established databases, such as PubMed. Although studies demonstrate associations between tau pathology and cognitive outcomes across the Alzheimer's disease (AD) spectrum, the optimal set of cognitive test scores linked to tau pathology in AD remains unclear. Identifying these tests is crucial for detecting and monitoring treatment-related neuropathological changes in the early stages of AD.
2. **Interpretation**: We identified a set of episodic memory test scores that were associated with tau pathology in a neocortical region known to be affected early in AD. These included both conventional cognitive test scores (e.g., accuracy) and "process" measures (e.g., perseverations, intrusions, and trial-by-trial learning).
3. **Future directions**: Future research is needed to validate the clinical utility of the identified set of cognitive predictors in independent data sets, with an emphasis on including more diverse populations and stratifying by sex.

participants who also had available structural MRI scans. Demographic and clinical data for both cohorts are presented in Table 1.

TABLE 1 Participant characteristics.

Cohort	HABS	A4 Study (Full analytic sample)	A4 Study (MRI subset)
N	128	393	341
Age, years	76.8 (6.4)	71.5 (4.6)	71.8 (4.6)
Education, years	16.0 (3.2)	16.3 (2.8)	16.3 (2.8)
Females, *N* (%)	71 (55%)	237 (60%)	206 (60%)
Race			
White	113 (88%)	375 (95%)	325 (95%)
Black	13 (10%)	10 (3%)	10 (3%)
Other	2 (2%)	8 (2%)	7 (2%)
Aβ positive, *N* (%)	41 (32%)	393 (100%)	341 (100%)
Tau, SUVR	1.2 (0.1)	1.5 (0.3)	1.5 (0.3)
APOE ε4 carrier[a], *N* (%)	40 (31%)	210 (53%)	197 (58%)

Abbreviations: A4, Anti-Amyloid Treatment in Asymptomatic Alzheimer's; HABS, Harvard Aging Brain Study. SUVR, standardized uptake value ratio.
[a]At least one *APOE* ε4 allele

2.2 | Tau PET scans

2.2.1 | HABS

The tau PET protocol in HABS has been described previously.[8] Tau burden was measured with [^{18}F]flortaucipir. Standardized uptake value ratios (SUVRs) were computed in FreeSurfer-defined regions of interest (ROIs) with bilateral cerebellar gray matter serving as the reference region. PET data were not corrected for partial volume effects, as these data were not publicly available. We focused our analysis on tau PET signal in the ITC, averaged across the left and right hemispheres, as this is one of the earliest neocortical regions to exhibit tau pathology in AD and is a strong predictor of disease progression.[10,11,18]

2.2.2 | A4 Study

The tau PET protocol in the A4 Study has been described previously.[29] A subset of Aβ-positive participants in the A4 Study underwent tau PET scanning at their baseline visit before treatment randomization. As in HABS, tau burden was measured with [^{18}F]flortaucipir. SUVRs were calculated for FreeSurfer-defined ROIs using bilateral cerebellar gray matter as the reference region.[29] PET data were corrected for partial volume effects, as this significantly improves the measurement of flortaucipir in cross-sectional studies among cognitively unimpaired individuals.[30] As mentioned in 2.2.1, we focused our analysis on tau PET signal in bilateral ITC.

2.3 | Cognition

2.3.1 | HABS

We used all available Year 4 cognitive test scores in our analyses (Table 2), with a few exceptions. We excluded omission errors from the trail making test (TMT) Parts A and B due to extremely low error rates, and item-level data from the MMSE due to low variability. To address missing cognitive test scores ($n = 22$), we employed a single imputation method,[31] where the missing data points were filled by calculating the average of each participant's scores from Year 3 and Year 5.

2.3.2 | A4 Study

We used all available cognitive test scores in our analyses (Table 2). However, we excluded item-level data from the MMSE due to low variability.

2.4 | Neuroimaging

2.4.1 | HABS

We used available data from MRI scans collected at Year 4. The MRI protocol has been described previously.[18] T1-weighted images were

TABLE 2 Cognitive test scores included in each cohort.

HABS	A4
Digit Symbol Substitution Test	Digit Symbol Substitution Test
Total score	Total score
Logical Memory Task	**Logical Memory Task**
Immediate recall	Immediate recall
Delayed recall	Delayed recall
Percent retained	Percent retained
Free and cued selective reminding test (FCSRT)	**Free and cued selective reminding test (FCSRT)**
Free recall	Free recall
Free recall trial 1	Free recall trial 1
Free recall trial 2	Free recall trial 2
Free recall trial 3	Free recall trial 3
Total recall	Total recall
Total recall trial 1	Total recall trial 1
Total recall trial 2	Total recall trial 2
Total recall trial 3	Total recall trial 3
FCSRT 96 (free + total recall)	FCSRT 96 (free + total recall)
Mini-mental state examination (MMSE)	**Mini-mental state examination (MMSE)**
Total score	Total score
Structured Telephone Interview for Dementia Assessment, Self-report	**Memory complaint questionnaire (MACQ) Self-report**
Total score	Total score
Boston naming test (BNT)	**Cognitive function index (CFI) Self-report**
Total score	Total score
Category Fluency	**Behavioral pattern separation object test (BPSO)**
Total score	Total errors
Total intrusions	Total correct
Total perseverations	Accuracy
Total score for animals	Percentage correct
Total score for vegetables	Bias (Similar|Similar—Similar|New)
Total score for fruit	**Detection test (DET)**
Digit Span	Total errors
Total score forward	Total correct
Total score backward	Accuracy
Phonemic fluency (FAS)	**One card learning test (OCL)**
Total score	Total errors
Total intrusions	Total correct
Total perseverations	Accuracy
Total score for F	**One back test (ONB)**
Total score for A	Total errors
Total score for S	Total correct
Selective reminding test (SRT)	Accuracy
Delayed recall	**Identification test (IDN)**
Continuous long-term retrieval	Total errors
Continuous retrieval	Total correct
Long term retrieval	Accuracy
Long term storage	**Face name associative memory exam (FNAME)**
Recognition recall	First Letter Name Recall
Short term retrieval	Total errors
Total recall	Total correct
Trail making test (TMT)	Accuracy
Time to complete A	Face Recognition
Commission errors on A	Total errors
Sequencing errors on A	Total correct
Time to complete B	Accuracy
Commission errors on B	Face Name Matching
Sequencing errors on B	Total errors
Set-shifting errors on B	Total correct
Visual form discrimination test (VFDT)	Accuracy
Total score	–
Letter-Number Sequencing	-
Total score	–

Abbreviations: A4, Anti-Amyloid Treatment in Asymptomatic Alzheimer's; HABS, Harvard Aging Brain Study; percent retained, delayed recall/immediate learning.

processed with FreeSurfer version 6.0 to generate regional volume estimates.[32,33]

2.4.2 | A4 Study

MRI scans were available for a subset of Aβ positive participants in A4. T1-weighted images were processed using NeuroQuant (Cortechs.ai), a fully automated segmentation pipeline that generates an age- and sex-specific atlas for each participant. These atlases were then used to generate regional volume estimates.

For the analyses, we used ROIs from the frontal, temporal, and parietal lobes that were available in both cohorts (Table 3). Regions were averaged across the left and right hemispheres.

2.5 | Analyses

We used elastic net regression[34] (glmnet[35] package in R[36]) to identify cognitive test scores that were optimally related to tau PET signal in the ITC. Elastic net regression is a machine-learning regularization

TABLE 3 Structural neuroimaging variables included in both cohorts.

ROIs
Amygdala
Entorhinal cortex
Parahippocampal gyrus
Hippocampus
Fusiform gyrus
Inferior temporal gyrus
Middle temporal gyrus
Superior temporal gyrus
Temporal pole
Inferior parietal lobule
Superior parietal lobule
Superior frontal gyrus
Globus pallidus

Note: All volumetric regions were entered as bilateral variables and corrected for intracranial volume.
Abbreviation: ROIs, regions of interest.

technique that combines ridge and least absolute shrinkage and selection operator (LASSO) regression to create a final sparse model.[34] In an elastic net regression, α controls the penalty, and can vary between $\alpha = 1$ (LASSO regression) and $\alpha = 0$ (ridge regression), whereas λ tunes the strength of the penalty applied to the predictor variables. As in LASSO regression, coefficients for nonsignificant predictors are reduced to zero. However, in contrast to LASSO regression, elastic net regressions are better equipped to handle highly correlated predictor variables,[34] which is often the case with cognitive test scores. The penalty applied to the predictor variables is tuned to be sufficiently stringent such that the resulting models are sparse with only nonredundant predictors remaining as non-zero predictors. Within this modeling approach, all non-zero predictors are interpreted as significantly and uniquely contributing to the outcome.

In each cohort, separate elastic net models were used to identify the cognitive test scores that optimally relate to tau PET signal in the ITC. Hyperparameter tuning involved 10-fold cross-validation repeated 10 times to identify the optimal α and λ that minimized model mean square error. Potential α values included 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, and 1. The elastic net model was then retrained on the entire data set using these identified hyperparameters to estimate the final model. All model predictors were included as linear predictors, as we found no evidence that nonlinear predictor relationships requiring nonlinear smoothers were present. We repeated this process for each model presented.

The goal of this study was to identify cognitive test scores that optimally correlate with ITC tau. Thus, in the first elastic net model, cognitive test scores (Table 2) were entered as predictors and ITC tau was entered as the outcome variable. Before entering these variables into the models, we regressed out age, sex, and years of education. A secondary goal was to investigate whether these cognitive test scores (Table 2) maintained their associations with ITC tau after including regional MRI measures (Table 3) in the model. Age, sex, years of education, and total intracranial volume were regressed out of the MRI measures before entering them into the models. All variables were standardized to enable direct comparison of model coefficients within the study.[34] The value of each model coefficient represents the relative weight of each predictor within the model, with the sign of the coefficients indicating whether the relationship between the cognitive predictor and ITC tau is positive or negative.

3 | RESULTS

3.1 | HABS

Demographic and clinical data for the HABS cohort are presented in Table 1. As mentioned above, we included data from participants at their Year 4 follow-up visit, as this was when most participants underwent their first tau PET scan. A total of 261 participants had cognitive data available in Year 4; however, only 135 participants had tau PET imaging data available. Altogether, 131 participants had cognitive, structural MRI, and tau PET data in Year 4. Participants were excluded if they had missing cognitive tests scores at Years 3, 4, and 5 ($n = 2$), or if their scores were extreme outliers on any cognitive tests (defined as mean $\pm$ 4 standard deviations [SD], $n = 1$ excluded for the TMT A). The final HABS sample consisted of 128 participants (55% female, 88% White) with a mean age of 76.9 years (SD = 6.5). Twelve participants (9%) had a CDR global score of 0.5 at their Year 4 follow-up visit. All participants with imputed cognitive test scores ($n = 22$) had a CDR global score of 0 at Year 5. A sensitivity analysis excluding participants with a CDR global score of 0.5 ($n = 12$) had no significant effect on the results, and, therefore, the full sample is reported. Another sensitivity analysis, which involved rerunning the analyses after excluding participants with imputed cognitive test scores ($n = 22$), showed no significant impact on the results.

In the elastic net model (Model 1), where only cognitive test scores were entered as predictor variables, a 10-fold cross-validation repeated 10 times resulted in the model hyperparameters of $\alpha = 0.8$ and $\lambda = 0.013$. Statistically significant, nonredundant predictors of ITC tau are summarized in Table 4. All nonsignificant variables had β coefficients that were not significantly different from zero. The model fit statistics were $R^2 = 0.19$ and root mean squared error (RMSE) = 0.08.

Next, we added structural MRI measures to the model (Model 2). A 10-fold cross-validation repeated 10 times resulted in the final model hyperparameters of $\alpha = 0.4$ and $\lambda = 0.026$. As summarized in Table 4, all cognitive test scores identified as significant in Model 1 retained significance in Model 2, with the addition of worse performance on the Free and Cued Selective Reminding Test (FCSRT) 96. Furthermore, we observed significant associations between smaller entorhinal, inferior temporal, and parahippocampal volumes with greater ITC tau burden. All nonsignificant variables had β coefficients that were not significantly different from zero. The model fit statistics were $R^2 = 0.20$ and RMSE = 0.05.

TABLE 4 HABS Models 1 and 2: Cognitive and MRI correlates of tau.

Variable	Model 1: β Coefficients (e-03)	Model 2: β Coefficients (e-03)
FCSRT Free Recall Trial 3	−7.28	−5.77
FCSRT Total Recall Trial 2	−6.76	−4.43
VFDT	−4.43	−3.75
SRT Recognition Recall	−4.37	−4.40
TMT A Commission Errors	1.90	1.95
Category Fluency Perseverations	1.83	1.42
TMT A Sequencing	0.89	1.90
FAS Perseverations	0.84	0.83
FCSRT Total Recall	−0.31	−1.19
FCSRT 96 (free+total recall)	–	−0.09
Entorhinal Volume	–	−0.01
Parahippocampal Volume	–	< −0.01
Inferior temporal Volume	–	< −0.01

Notes: For Model 1, variables are presented in order of their absolute weights or importance in the model.
Abbreviations: FCSRT, Free And Cued Selective Reminding Test; HABS, Harvard Aging Brain Study; SRT, Selective Reminding Test; TMT, Trail Making Test; VFDT, Visual Form Discrimination Test.

TABLE 5 A4 Models 1 and 2: Cognitive and neuroimaging predictors of tau.

Variable	Model 1: β Coefficients (e-03)	Model 2: β Coefficients (e-03)
FCSRT 96	−17.35	−17.27
CFI	15.56	12.33
IDN Accuracy	−8.36	–
Logical Memory Delayed Recall	−7.98	−8.77
Face Name Matching Errors	5.59	2.80
FCSRT Cued Recall Trial 2	5.49[a]	3.05[a]
MMSE	−4.95	−4.29
BPSO Errors	3.16	2.27
Face Recognition Accuracy	−2.03	−23.24
OCL Total Correct	−1.91	−0.96
Face Name Matching Total Correct	−0.95	−1.65
BPSO Total Correct	−0.53	−1.42
Amygdala Volume	–	−251.09
Inferior Parietal Volume	–	−8.95
Middle Temporal Volume	–	−7.90
Fusiform Volume	–	−7.46
Inferior Temporal Volume	–	−6.55
Superior Temporal Volume	–	−0.03

Notes: For Model 1, variables are presented in order of their absolute weights or importance in the model.
Abbreviations: A4, Anti-Amyloid Treatment in Asymptomatic Alzheimer's; BPSO, Behavioral Pattern Separation Object Test; CFI, Cognitive Function Index; FCSRT, Free and Cued Selective Reminding Test; MMSE, Mini-Mental State Examination; OCL, One Card Learning.
[a]That lower performance on FCSRT Cued Recall Trial 2 correlated with greater tau burden may seem counterintuitive; however, Cued Recall on Trial 2 was inversely correlated with Free Recall on Trial 2. That is, as participants remembered more words during free recall, they required fewer cues to recall the words they missed.

3.1.1 | A4

Demographic and clinical data for the A4 cohort are presented in Table 1. A total of 393 participants in the A4 sample had cognitive test and tau PET data. Participants were excluded if they had missing cognitive test scores ($n = 3$) or if their scores were extreme outliers on any cognitive tests (mean ± 4 SD, $n = 1$ excluded for the Identification test or IDN). As summarized in Table 1, the final A4 sample consisted of 393 participants (60% female, 95% White), with a mean age of 71.5 (SD = 4.6) years. All participants included in the final sample had a CDR global score of 0.

For the secondary analyses, we included individuals who met the above criteria and had available structural MRI data, resulting in a final sample size of $N = 341$. The demographic characteristics for these participants were very similar to those included in the main analytic sample and are presented in Table 1.

In the primary elastic net model (Model 1), where only cognitive test scores were entered as predictor variables, a 10-fold cross-validation repeated 10 times resulted in hyperparameters of $\alpha = 0.9$ and $\lambda = 0.014$. The significant cognitive test scores that optimally correlated with ITC tau are summarized in Table 5. The model fit statistics were $R^2 = 0.13$ and RMSE = 0.24.

When structural MRI variables were added as predictor variables (Model 2), a 10-fold cross-validation repeated 10 times resulted in hyperparameters of $\alpha = 0.8$ and $\lambda = 0.018$. In this model, IDN accuracy was no longer significant. As summarized in Table 5, all other cognitive test scores from the primary model remained significant. We also found that smaller amygdala, middle temporal, inferior parietal, inferior temporal, fusiform, and superior temporal volumes were significantly associated with greater ITC tau. The model fit was $R^2 = 0.20$ and RMSE = 0.24.

4 | DISCUSSION

We applied a machine-learning regularization approach to two independent cohorts to identify cognitive test scores that optimally relate to tau burden in the ITC, a region associated with early AD. Across both cohorts, episodic memory measures—including both conventional and "process" scores—emerged as the strongest correlates of tau burden. These cognitive test scores remained significant after adjusting for structural MRI measures. Together, these findings underscore the utility of conventional and "process" cognitive test scores, particularly

those related to episodic memory, in detecting and monitoring early AD-related changes.

Consistent with previous research in preclinical AD,[9,37] episodic memory test scores were the strongest correlates of ITC tau burden. In addition to conventional episodic memory scores, such as free recall and recognition performance, episodic memory "process" scores were also significant, including trial-by-trial learning and error scores. These findings align with prior studies demonstrating that "process" scores can aid in detecting cognitive inefficiencies early in the course of AD.[38,39]

Unlike theory-driven approaches, our data-driven method provided the opportunity to identify cognitive test scores that we might not have expected to correlate with AD pathology., Nevertheless, this approach still identified episodic memory scores to be significantly related to ITC tau. This convergence demonstrates the robustness of episodic memory test scores as a sensitive marker of early AD pathology.

Across both cohorts, test scores from the FCSRT were the strongest correlates of ITC tau. Unlike other list-learning memory tests, the FCSRT offers the unique advantage of using semantic categories to facilitate effective encoding.[40] At retrieval, the same category cues are used for items not recalled freely. This controlled encoding and retrieval paradigm helps ensure that any observed difficulties are due to genuine memory difficulties rather than impairments in other cognitive domains (e.g., attention or executive function) that may impact test performance.[41]

The cognitive function index (CFI),[42] a self-report measure of subjective cognitive decline, emerged as one of the strongest correlates of ITC tau burden in the A4 Study. This measure was not available in Year 4 of HABS. Previous research has demonstrated associations between subjective cognitive decline and AD biomarkers, including elevated Aβ and tau burden.[43,44] In this study, the CFI outperformed many objective cognitive scores, underscoring its potential to complement objective cognitive tests in predicting tau burden. Importantly, the CFI has demonstrated measurement invariance (i.e., equivalence) across several ethnoracial groups,[45] unlike many standard tests.[46]

Executive function "process" scores also emerged as significant correlates of ITC tau burden in HABS. These included commission errors on Trails A (i.e., deviating from the correct sequence) and repetition errors on both category and phonemic fluency. These cognitive tests were not administered in A4. These executive "process" scores may reflect subtle difficulties with self-monitoring, which may not be captured by standard executive function test scores. providing a more sensitive approach to detecting cognitive inefficiencies in the earliest stage of the disease.

Several other non-episodic memory measures were significantly associated with ITC tau. In HABS, a test of visuoperceptual discrimination (i.e., Visual Form Discrimination Test) was among the strongest correlates of ITC tau. This association likely reflects the involvement of the ITC in visual object recognition/discrimination.[47] Indeed, prior work has shown that these processes are impaired early in the course of AD.[48,49] A similar visuoperceptual measure was not available in A4. Within A4, accuracy on a reaction time task (i.e., IDN) was significantly correlated with ITC tau but was no longer significant when structural MRI measures were added to the model.

Across both HABS and A4, several cognitive test scores remained significant even after adjusting for structural MRI measures, highlighting their sensitivity to early neocortical tau. In HABS, cognitive test scores showed stronger associations with ITC tau compared to structural MRI measures, emphasizing their relevance in detecting early tau accumulation. In A4, smaller amygdala volume emerged as the strongest correlate of ITC tau. This discrepancy may be due to differences in the cohorts: all participants in the A4 study were Aβ positive, whereas only a third of participants in HABS were Aβ positive. This difference may contribute to greater variability in structural MRI measures within A4, potentially influencing the associations between the cognitive test scores and ITC tau.

In both cohorts, reduced volumes in medial and lateral temporal regions emerged as significant correlates of ITC burden. These associations likely reflect the close correlation between tau burden and regional atrophy,[18] and align with Braak staging of tau pathology in AD.[50] Medial temporal structures, including the entorhinal cortex and parahippocampal gyrus, are among the earliest sites affected by tau. In early AD, tau pathology later extends to lateral temporal regions, including the ITC.[50] Therefore, the significant volumetric correlates are likely the result of reduced volume caused by tau spreading.

In HABS and A4, the elastic net models with cognitive predictors alone explained 19% and 13% of the variance in ITC tau, respectively. When structural MRI measures were incorporated into the models, there was a modest improvement in model fit in both HABS and A4, resulting in a 0.5% and 7.3% increase in explained variance, respectively. These findings underscore the potential for further model refinement and suggest that more sensitive cognitive tests—specifically those targeting functions supported by the ITC—could capture additional variance in ITC tau.

Several important limitations should be considered when interpreting the results of this study. First, cross-cohort validation was not feasible due to limited overlapping cognitive test scores between the two cohorts. Second, the relatively small sample sizes in both cohorts precluded the possibility of a test-train split. As a result, the models presented here were trained and tested within the same data set, emphasizing the need for validation in independent data sets. Third, the small sample size of the cohorts also prevented us from examining whether the correlates of ITC tau differed by sex. Fourth, the structural MRI measures in HABS and A4 were derived using different pipelines, which could have contributed to different results across the two cohorts. Finally, both HABS and A4 cohorts are predominately White and highly educated, and therefore future work should aim to replicate the study findings in more diverse samples.

In conclusion, our application of a machine-learning regularization approach revealed that episodic memory measures, including both total and "process" scores, are robust correlates of tau burden in the ITC, a neocortical region associated with early AD. These cognitive test scores remained strong correlates of tau, even when structural MRI measures were accounted for. Together, these findings underscore the

potential of specific episodic memory test scores to detect and monitor early cognitive changes associated with AD.

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CONFLICTS OF INTEREST STATEMENT

S.E.B. has served as a paid consultant for Roche, Biogen, and NovoNordisk. S.E.B. serves on the advisory board for the Conference Board of Canada, World Dementia Council, National Institute of Neurological Disorders and Stroke, and the University of Rochester Contribution to the Mission and Scientific Leadership of the Small Vessel VCID Biomarker Validation Consortium. R.A.S. has received grants or contracts from the National Institute on Aging, Eli Lilly (public–private partnership trial funding), Eisai (public–private partnership trial funding), Alzheimer's Association, and GHR Foundation. R.A.S. has received consulting fees from Abbvie, AC Immune, Acumen, Alector, Biohaven, Bristol-Myers Squibb, Ionis, Janssen, Oligomerix, Prothena, Roche, Shionogi, and Vaxxinity. J.S.R. was supported by the Temerty-Tanz-TDRA Seed Fund. K.V.P. was supported by a grant from the National Institutes of Health (R01AG084017-01A1). C.M.T., M.W.A., R.P.C., S.Z.B., and J.P. have no conflicts of interest or funding sources to declare. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

HABS protocols were approved by the Partners HealthCare Institutional Review Board, and all participants provided informed consent. A4 protocols were approved by relevant research ethics committees at each institution and all participants provided informed consent.

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SUPPORTING INFORMATION

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

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