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RESEARCH ARTICLE

Integrating plasma p-tau217 and digital cognitive assessments for early detection in Alzheimer's disease

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Abstract

INTRODUCTION: Plasma phosphorylated tau (p-tau)217 is an early Alzheimer's disease (AD) biomarker, but the timing of pathological changes and cognitive decline varies substantially. Digital cognitive assessments can detect subtle cognitive changes, suggesting they may complement p-tau217 for early detection. Here, we evaluate whether combining these tools improves the detection of individuals at risk for future decline.

METHODS: We analyzed 954 amyloid-positive cognitively unimpaired individuals who completed a digital cognitive assessment and a blood test for p-tau217, assessing their ability to predict future decline on the Preclinical Alzheimer Cognitive Composite (PACC) and Mini-Mental State Examination (MMSE).

RESULTS: Combining performance on a digital cognitive assessment with p-tau217 improved identification of individuals who declined on the PACC and MMSE in the next 5 years. The predictive value was stronger in apolipoprotein E ε4 noncarriers but did not differ by sex.

DISCUSSION: This approach offers a sensitive method for identifying individuals at high risk for AD-related cognitive decline.

KEYWORDS
Alzheimer's disease, digital cognitive assessments, early detection, low-burden measures, memory, phosphorylated tau 217

Highlights

- Combining plasma phosphorylated tau 217 with baseline digital cognitive assessment improved the prediction of cognitive decline on gold-standard neuropsychological tests over the next 5 years, achieving greater accuracy than either measure alone.
- This combination also predicted a decline in a global cognitive screening test.
- Pairing a blood test with a digital cognitive assessment offers a scalable and feasible approach for Alzheimer's disease screening.

1 | INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia worldwide. It is characterized by the accumulation of amyloid beta (Aβ) plaques and neurofibrillary tangles composed of hyperphosphorylated tau, developing years before clinical symptoms emerge.[1–3] The earliest phase, known as the preclinical stage, involves subtle biological and cognitive changes that often go unnoticed in standard clinical assessments.[4–6] While early detection of individuals with elevated AD pathologies is crucial for timely intervention, not everyone with AD pathology follows the same cognitive trajectory. Some individuals remain cognitively stable for years despite pathological changes, making it difficult to determine when intervention is necessary.[7] This variability in disease progression poses a significant challenge in predicting who will develop AD-related impairment and when cognitive decline will occur.

Recent advances in fluid biomarkers have significantly improved the ability to detect AD pathology before cognitive symptoms appear.[8–10] Among these, plasma phosphorylated tau (p-tau) 217 has emerged as a highly specific and sensitive marker of amyloid pathology and disease progression. Studies have shown that elevated plasma p-tau217 levels strongly correlate with amyloid burden in the brain, making it a powerful tool for early detection.[11,12] Notably, recent guidelines suggest that p-tau217 is the only plasma biomarker recommended for AD diagnosis.[1] However, while p-tau217 reliably indicates underlying pathology, it does not directly measure cognitive function, creating uncertainty about its ability to predict when an individual will experience cognitive decline.

Cognitive assessments, particularly digital cognitive tests, offer a complementary approach to biomarker-driven detection by capturing subtle functional changes that may signal early AD-related cognitive decline.[13–17] In particular, digital cognitive tests that tax hippocampal memory have proven to be highly sensitive to early AD-related changes, including detecting amyloid and tau pathology and predicting future clinical symptoms.[18–20] Some evidence even suggests that these assessments may outperform biological biomarkers in identifying individuals at high risk for future cognitive decline.[21] However, the specificity of these cognitive measures in distinguishing AD-related cognitive changes from normal aging or other conditions remains unclear.

Given the distinct strengths of fluid biomarkers and cognitive assessments, an integrated approach combining plasma p-tau217 with a digital cognitive battery may enhance the ability to identify cognitively unimpaired individuals at high risk for future decline. By leveraging both biological markers of AD pathology and sensitive cognitive performance metrics, this approach has the potential to improve early detection and risk stratification.

In this study, we examined whether combining plasma p-tau217 with a brief digital cognitive battery consisting of three hippocampal-based memory tasks could reliably identify cognitively unimpaired individuals at high risk for future cognitive decline. Specifically, we hypothesized that combining p-tau217 levels with digital cognitive performance would improve the accuracy and reliability of identifying individuals at risk for cognitive decline over the next 5 years. We analyzed data from 954 cognitively unimpaired individuals in the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) clinical trial who underwent both a blood test for p-tau217 and a digital cognitive assessment at baseline. We assessed the predictive ability of these measures individually and in combination to predict future decline on established cognitive assessments, including the Preclinical Alzheimer Cognitive Composite (PACC) and the Mini-Mental State Examination (MMSE). Additionally, we examined whether their predictive value differed by sex or apolipoprotein E (*APOE*) genotype, well-established AD-related risk factors.

By assessing both biological and cognitive markers, this study aims to refine early detection strategies for AD, providing a more reliable and sensitive method for identifying-risk individuals. If successful, this approach could enhance clinical decision making, inform early interventions, and improve trial recruitment for disease-modifying therapies.

RESEARCH IN CONTEXT

1. **Systematic review**: Using traditional sources such as PubMed, we identified studies linking plasma phosphorylated tau (p-tau) 217 and digital cognitive assessments to the risk of Alzheimer's disease (AD)-related cognitive decline. Prior research has shown that both plasma p-tau217 and digital cognitive assessments can identify older adults at increased risk of future impairment. However, whether integrating these measures improves accuracy and reliability remains unknown.
2. **Interpretation**: If blood tests complemented by digital cognitive assessments can predict future cognitive decline, they could serve as low-burden biomarkers with prognostic value. We demonstrate that combining plasma p-tau217 with digital cognitive assessments enhances the identification of individuals at risk for future cognitive decline. Those with both elevated p-tau217 and subtle memory deficits exhibit the most rapid cognitive decline.
3. **Future directions**: Future research should explore whether additional plasma biomarkers or digital cognitive tasks could further improve detection. Additionally, more work is needed to determine how well combining these measures can differentiate between different causes of dementia.

2 | METHODS

2.1 | Participants

All data were obtained from the A4 clinical trial, a study whose design and aims have been described in detail previously.[22–24] Briefly, A4 was

TABLE 1 Demographics.

	APOE ε4 carrier	*APOE ε4* non-carrier
n	594	360
Age	71.30 (4.51)	73.26 (5.03)
Sex (% female)	42.10%	38.30%
Education	16.64 (2.71)	16.54 (2.95)
Baseline PACC	0.02 (2.73)	−0.02 (2.63)
Group (% in treatment)	49.30%	51.10%
Race		
White	576	337
Black or African American	11	10
American Indian or Alaskan Native	2	0
Asian	0	6
More than one race	3	5
Unknown or not reported	2	2
Ethnicity		
Not Hispanic or Latino	575	344
Hispanic or Latino	14	13
Unknown or not reported	5	3

Abbreviations: *APOE*, apolipoprotein E; PACC, Preclinical Alzheimer Cognitive Composite.

a double-blind, placebo-controlled, 240-week phase 3 trial evaluating an anti-Aβ monoclonal antibody in older adults with preclinical AD. Participants were eligible if they were 65 to 85 years old, Aβ+, cognitively unimpaired (Clinical Dementia Rating = 0, MMSE 25–30), and living independently. Elevated brain amyloid was confirmed using 18F-florbetapir positron emission tomography (PET) imaging, based on a combination of standardized uptake value threshold (≥ 1.15) and central visual read. Participants were randomized 1:1 to solanezumab or placebo, with stratification by *APOE ε4* status, education, and trial site. Additionally, each participant completed a brief digital cognitive battery at screening and underwent a blood test at baseline. We included all 954 subjects who underwent their baseline visit along with the digital cognitive battery and a blood test, regardless of the treatment group (Table 1). However, we regressed out effects of treatment for all analyses.

2.2 | Digital cognitive battery

The Computerized Cognitive Composite (C3) is a brief digital cognitive battery completed by all A4 participants. This composite has been previously described in detail.[19,20] Briefly, it includes three hippocampal memory tasks, the Behavioral Pattern Separation Task (BPST), Face-Name Task (FNAME), and One Card Learning Task (OCL), along with three control tasks: a detection psychomotor speed task, an identification visual attention task, and a one-back working memory task. Prior research has shown that hippocampal memory-based tasks are more sensitive to AD-related changes. Therefore, we focused our analyses on the three hippocampal memory tasks.

The BPST, now known as the Mnemonic Similarity Task (MST), is a hippocampal memory task designed to assess pattern separation.[25,26] In this study, a shortened version of the MST was used. Briefly, during the encoding phase, participants viewed 40 images of everyday objects on a white background, making indoor/outdoor judgments via button press (5 seconds per image, 0.5 seconds inter-stimulus interval [ISI]). Immediately afterward, they received instructions for a recognition memory test, in which they classified objects as "old" (identical to a previously seen image), "similar" (a slightly altered version of a studied item, such as a different exemplar or rotation), or "new." During this phase, participants viewed 60 images (5 seconds per image, 0.5 seconds ISI), consisting of 20 exact repeats from encoding (targets), 20 completely novel images (foils), and 20 similar but non-identical images (lures). The primary measure of interest was the lure discrimination index (LDI), calculated as the proportion of "similar" responses to lures minus the proportion of "similar" responses to foils, adjusting for response bias.

For the FNAME, participants viewed 12 face–name pairs presented sequentially and judged whether each name "fit" the face to maintain attentiveness. They had 5 seconds to respond and were instructed to remember the pairings. After a 12 to 15 minute delay filled with other cognitive tasks, memory was assessed through three tasks: face recognition (FSBT), first-letter name recall (FNLT), and face-name matching (FNMT). In FSBT, participants identified previously learned faces from a set of three, including two distractors matched for age, race, and sex. In FNLT, they selected the first letter of the paired name using an on-screen keyboard. In FNMT, they chose the correct name from three options: the target name, a re-paired name, and a matched foil. Each task was scored out of 12, with FNMT accuracy serving as the primary outcome measure.

OCL is modeled off the MST and is a task that taxes hippocampal pattern separation, which is critical for episodic memory.[19,27–29] In this task, four target cards (one from each suit) are each repeated eight times across 80 total trials, interspersed with visually similar and novel playing cards. On each trial, a single card is displayed for 2 seconds, followed by an ISI that varies randomly between 0.5 and 1.5 seconds. Participants respond "yes" if they believe they have seen the card earlier in the task and "no" if they have not. Accuracy is emphasized over speed. The task consists of 80 trials and the performance outcome is accuracy.

The C3 consisted of one primary outcome from each of the three memory tasks and is calculated as the average of these *z* scored outcomes, standardized based on screening data.

2.3 | Neuropsychological assessments

All participants completed in-person, traditional neuropsychological testing, including the PACC.[30,31] The PACC comprises four components: the total score on the Free and Cued Selective Reminding Test (FCSRT), delayed paragraph recall from the Logical Memory IIa test

(Wechsler Memory Scale), the Digit Symbol Substitution Test (Wechsler Adult Intelligence Scale–Revised), and the MMSE total score.[30,32] To minimize practice effects, alternate versions of these tests were used at each session. To control for baseline performance, each component score was converted to a *z* score by subtracting the baseline mean and dividing by the baseline standard deviation (SD). The PACC score was calculated as the sum of these *z* scores, with negative values indicating cognitive decline.

2.4 | Plasma p-tau217

Plasma samples were provided to Lilly to aid in developing a p-tau217 assay for cognitively impaired individuals. The Lilly Clinical Diagnostics Laboratory measured p-tau217 levels using an electrochemiluminescent immunoassay, with sample preparation automated by the Tecan Fluent workstation and detection conducted on the MSD Sector S Imager 600 MM.

2.5 | Statistical analyses

All analyses were conducted in RStudio. For baseline comparisons, low performers were defined as individuals scoring > 1.5 SDs below the group average. To predict future cognitive decline, participants were categorized as progressors or non-progressors based on changes in the PACC or MMSE. We selected timepoints based on the follow-up schedule in the A4 trial. Specifically, the timepoints were baseline, 1.8 years (Week 96 study visit), and 4.6 years (Week 240 study visit). At each timepoint, progressors on the PACC were defined as those who declined > 1.5 SDs below their baseline performance relative to the group average. For MMSE analyses, a score < 25 was used as the cutoff for cognitive impairment, a commonly accepted clinical threshold.[33–35] We identified decliners at the 2.8 year (Week 144), 3.7 year (Week 192), and 4.6 year (Week 240) study visits, as only a few participants reached this threshold before the 2 year mark.

Logistic regression models were used to predict which individuals would exhibit cognitive decline on either the PACC or MMSE. For all models, we used p-tau217 at baseline and C3 scores from screening, and both measures were *z* scored to standardize values. To prevent overfitting and improve generalizability, all models were evaluated using leave-one-out (LOO) cross-validation. Model performance was assessed using area under the curve (AUC) values derived from receiver operating characteristic (ROC) curves. Confidence intervals (CIs) were generated via bootstrapping with 1000 permutations. To assess model sensitivity, true positive rates were calculated at a predefined false positive rate of 20% using the 1000 bootstrap samples.

For odds ratio analyses, we examined the likelihood of future cognitive decline in individuals with either (1) p-tau217 levels 1 SD above the group mean, (2) a C3 composite score 1 SD below the mean, or (3) both risk factors. *Z* tests were used to compare the differences in log odds across these conditions. Linear mixed-effects models were used to investigate longitudinal changes in the PACC and MMSE. Additionally, one-way analysis of variance (ANOVA) with Tukey honestly significant difference (HSD) post hoc tests were performed to identify within-factor differences. For all analyses, P values < 0.05 were considered statistically reliable.

3 | RESULTS

3.1 | Only C3 scores differentiate high and low PACC performers at baseline

To assess whether combining plasma p-tau217 and C3 scores enhances clinical utility, we began by initially examining their ability to predict PACC performance at baseline before turning to their ability to predict cognitive decline from baseline after either ≈ 2 or 5 years. To investigate baseline performance, individuals were categorized as high or low performers on the PACC, with low performers defined as those scoring > 1.5 SDs below the group average. We then trained four separate logistic regression models to predict high versus low performers (Figure 1A, top).

The base model, which included demographic variables (age, sex, treatment group, and education), reliably distinguished between high and low performers (LOO AUC: 0.716, CI: 0.651–0.778). Notably, adding p-tau217 to the demographic model did not improve predictive accuracy, suggesting that p-tau217 does not contribute additional explanatory power (LOO AUC: 0.741, CI: 0.679–0.796). In contrast, incorporating C3 performance into the demographic model significantly enhanced its predictive value for distinguishing low and high performers suggesting that C3 and PACC performance are correlated (LOO AUC: 0.811, CI: 0.755–0.861). Finally, a model combining demographics, C3 performance, and p-tau217 performed similarly to the model including only C3 performance, significantly outperforming the baseline demographic model but not adding substantial predictive benefit over C3 alone (LOO AUC: 0.822, CI: 0.776–0.863).

To further evaluate model sensitivity, we set an a priori false positive rate of 20% and calculated sensitivity across all bootstrapped models. Sensitivity values were compared across models, revealing significant differences. The C3 composite model outperformed all others, followed by the combined model, which performed better than the p-tau217 and base demographic models (Figure 1A, middle, two-way ANOVAs, $F[3, 3996] = 11{,}981$, $P < 0.0001$, Tukey HSD: all Ps < 0.001). Additionally, the p-tau217 model demonstrated greater sensitivity than the base model ($P < 0.001$). Last, we calculated the odds of low PACC performance based on elevated p-tau217 (≥ 1 SD above the group mean), low C3 composite scores (≥ 1 SD below the mean), or both. Elevated p-tau217 was associated with a 36% increased likelihood of being in the low-performance group (Figure 1A, bottom odds ratio [OR] = 1.360, CI = 2.085–3.815). In contrast, low C3 memory performance was linked to a significantly higher 182% increased risk (OR = 2.820, CI = 2.085–3.815) while having both elevated p-tau217 and low memory was associated with a 284% increased risk (OR = 3.835, CI = 2.639–5.575).

Z tests confirmed that both low memory and the combined condition were significantly associated with greater odds of low

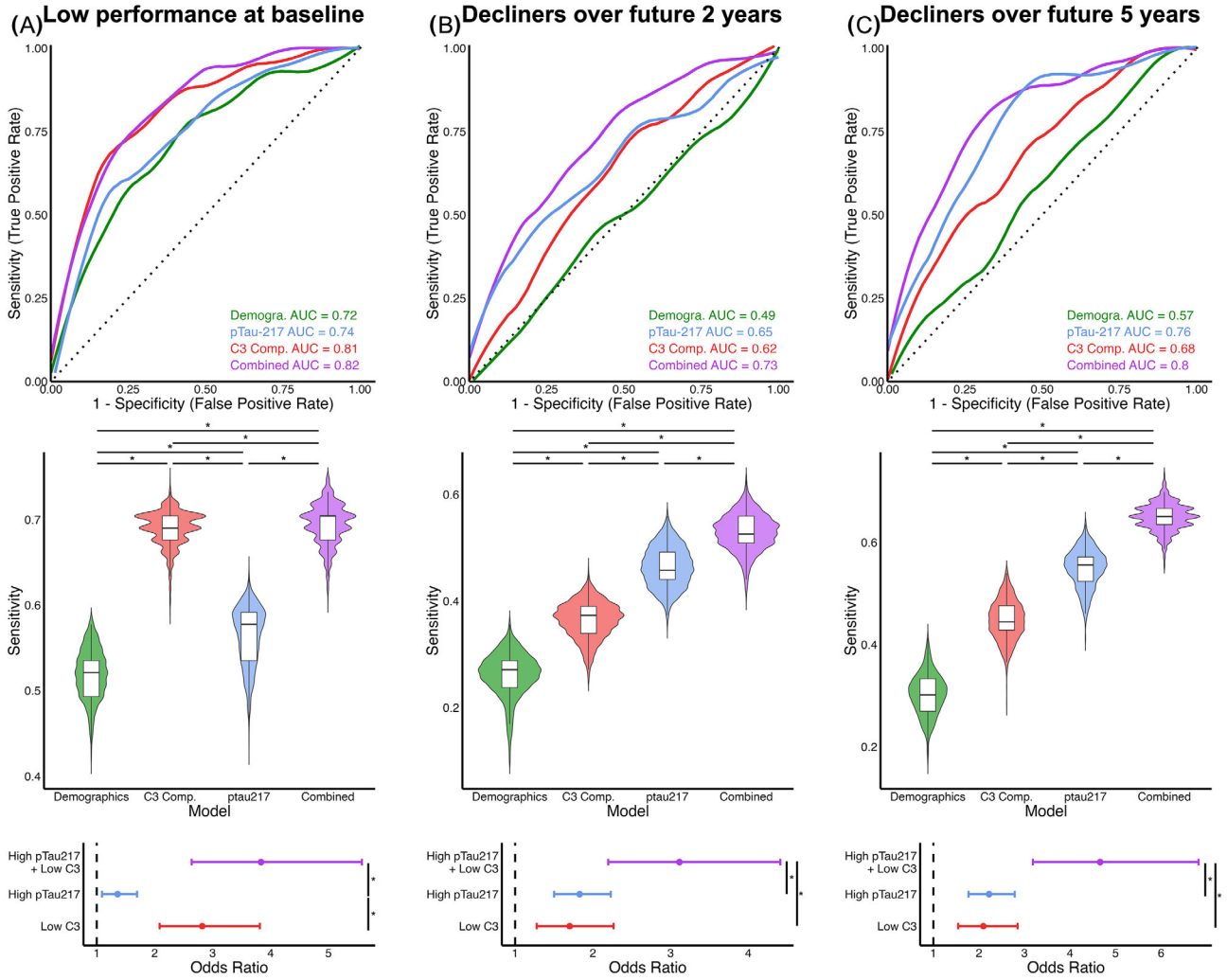

FIGURE 1 Integrating plasma p-tau217 and the C3 enhances prediction of future decline on the Preclinical Alzheimer Cognitive Composite (PACC). Comparison of models using demographics alone (green), demographics plus p-tau217 (blue), C3 composite (red), or both p-tau217 and C3 (purple) for predicting low performers and future cognitive decline. Top, ROC curves illustrating the predictive value of each model. Middle, Violin plots depicting model sensitivity at a false positive rate of 20%. Bottom, Odds ratios for future decline based on low memory (red), high p-tau217 (blue), or both (purple). A, At baseline, the C3 composite was the strongest predictor of high and low performers, showing the highest sensitivity and odds ratios. Over 2 (B) and 5 (C) years, the combined model (p-tau217 + C3) was the most predictive of future decline, achieving the highest AUCs and sensitivity. Critically, individuals with both high baseline p-tau217 and low baseline C3 performance had significantly higher odds of cognitive decline compared to those with only one of these risk factors. AUC, area under the curve; p-tau, phosphorylated tau; C3, Computerized Cognitive Composite; ROC, receiver operating characteristic

performance, while the combined condition did not differ significantly from low memory alone (high p-tau217 vs. low memory: $Z = -3.822$, $P < 0.001$; both vs. high p-tau217: $Z = 4.679$, $P < 0.001$; both vs. low memory: $Z = 1.253$, $P = 0.210$). These findings suggest that, unsurprisingly, baseline cognitive performance is more strongly predicted by a digital cognitive test performance than by plasma p-tau217 levels.

3.2 | Combining plasma p-tau217 and C3 scores enhance prediction of future cognitive decline

It is unsurprising that C3 performance was a stronger predictor of high and low PACC performers compared to p-tau217, as both the C3 and PACC are cognitive measures designed to assess early stages of dementia. However, the true test of its utility lies in its ability at baseline or screening to predict future decline in the PACC. Thus, we examined whether these measures could predict individuals who experienced the greatest cognitive decline over 96 weeks (≈ 1.9 years). Decline was calculated as the difference between PACC scores at the 96-week visit and baseline; thus, we controlled for baseline performance. Demographics alone were not sufficient to identify those who exhibited the most decline (Figure 1B, top LOO AUC: 0.490, CI: 0.472–0.588). However, adding either p-tau217 or C3 performance individually improved predictive accuracy above chance, with both models reaching similar AUCs (p-tau217: LOO AUC: 0.654, CI: 0.571–0.733, C3: LOO AUC: 0.622, CI: 0.557–0.695). Notably, the best

predictive model included both p-tau217 and C3 performance alongside demographics, suggesting that each measure provides complementary explanatory power (LOO AUC: 0.725, CI: 0.650–0.795). Furthermore, at the predefined false positive rate of 20%, the combined model demonstrated the highest sensitivity, outperforming all other models (Figure 1B, middle, two-way ANOVA, F[3, 3996] = 10,475, $P < 0.0001$, Tukey HSD: all Ps < 0.001).

Examining ORs for cognitive decline over 2 years, we found that elevated baseline p-tau217 and low baseline memory performance were associated with an 83% and 70% increased risk of decline, respectively (Figure 1B, bottom p-tau217: OR = 1.830, CI = 1.501–2.230; low memory: OR = 1.702, CI = 1.278–2.267). These odds did not significantly differ ($Z = 0.408$, $P = 0.683$). However, individuals with both high p-tau217 and low memory performance at baseline had a 211% increased risk of 2 year decline (OR = 3.114, CI = 2.198–4.411). Importantly, the combined condition conferred a significantly greater risk of decline than either measure alone (combined vs. p-tau217: $Z = 2.601$, $P = 0.009$; combined vs. low memory: $Z = 2.626$, $P = 0.009$). Together, these findings support the value of combining hippocampal memory performance and plasma p-tau217 to improve the prediction of future cognitive decline.

Next, we extended this analysis to examine whether baseline measures could predict cognitive decline over 240 weeks (≈ 4.6 years) and observed similar results. Once again, the most accurate model included both p-tau217 and C3 performance, reinforcing that these measures together improve the prediction of cognitive decline for up to 5 years (Figure 1C, top demographics: LOO AUC: 0.570, CI: 0.485–0.645, p-tau217: LOO AUC: 0.762, CI: 0.705–0.821, C3: LOO AUC: 0.679, CI: 0.612–0.745, combined: LOO AUC: 0.799, CI: 0.742–0.855). At the predefined false positive rate, the combined model demonstrated the highest sensitivity, followed by the plasma p-tau217 model (Figure 1C, middle, $F[3, 3996] = 17{,}171$, $P < 0.0001$, Tukey HSD: all Ps < 0.001). Examining ORs, we found that elevated p-tau217 was associated with a 122% increased risk of decline (Figure 1C, bottom OR = 2.222, CI = 1.772–2.786), while low memory performance was associated with a 110% increased risk (OR = 2.097, CI = 1.544–2.850). These risks did not significantly differ ($Z = 0.297$, $P = 0.767$). However, individuals with both high p-tau217 and low memory performance at baseline had a 366% increased risk of decline (OR = 4.661, CI = 3.185–6.821), which was significantly greater than either measure alone (combined vs. p-tau217: $Z = 3.278$, $P = 0.001$; combined vs. low memory: $Z = 3.201$, $P = 0.001$). These findings further support the utility of combining plasma p-tau217 and a brief cognitive battery to identify individuals at risk for future cognitive decline.

3.3 | Hippocampal memory tasks are more sensitive than non-memory tasks for predicting future cognitive decline

Here, we focused on a composite of three hippocampal memory tasks, given that deficits in hippocampal memory are among the earliest cognitive changes in AD. However, it is possible that integrating non-memory tasks could provide comparable or even greater predictive value for identifying individuals at risk for future cognitive decline. To test this, we created a composite of non-memory tasks, including a detection task (motor speed), identification task (attention), and one-back task (working memory), and evaluated its predictive utility alongside demographics and plasma p-tau217. We then compared this model to the previously described C3 composite, which includes hippocampal memory tasks (AUC values for the memory composite are recapitulated from earlier in the article). The non-memory model showed lower predictive accuracy at all timepoints (baseline: AUC = 0.785, CI: 0.728–0.829; 96 weeks: AUC = 0.652, CI: 0.562–0.729; 240 weeks: AUC = 0.756, CI: 0.692–0.813), compared to the memory composite (baseline: AUC = 0.822, CI: 0.776–0.863; 96 weeks: AUC = 0.725, CI: 0.650–0.795; 240 weeks: AUC = 0.799, CI: 0.742–0.855). These findings suggest that hippocampal memory tasks integrate more effectively with plasma p-tau217 than non-memory tasks for predicting future cognitive decline.

To evaluate whether one of the three hippocampal memory tasks from the C3 was particularly sensitive or better integrated with plasma p-tau217, we ran separate models in which each task was paired individually with demographics and plasma p-tau217. This approach allowed us to compare the predictive performance of each task when modeled on its own, rather than as part of the full C3 composite. Each model included the same covariates: age, sex, education, and p-tau217, with one hippocampal task entered as the cognitive variable. Overall, we found that, across timepoints, each of the three hippocampal memory tasks showed comparable predictive accuracy. At baseline, MST had the highest AUC (0.801, CI: 0.752–0.845), followed by OCL (0.777, CI: 0.726–0.828) and FNAME (0.768, CI: 0.710–0.823). At 96 weeks, OCL performed slightly better (AUC: 0.701, CI: 0.626–0.771) than FNAME (AUC: 0.690, CI: 0.613–0.763) and MST (AUC: 0.666, CI: 0.582–0.749). At 240 weeks, FNAME had the highest AUC (0.811, CI: 0.753–0.864), with OCL (0.769, CI: 0.715–0.820) and MST (0.761, CI: 0.702–0.814) performing similarly. Overall, there was no consistent pattern of superiority across timepoints, and confidence intervals showed substantial overlap. These results suggest that all three hippocampal tasks contribute similarly when paired with plasma p-tau217 for predicting future cognitive decline.

3.4 | Clinical utility of combining plasma p-tau217 and a remote cognitive battery differs by *APOE* ε4 genotype but not by sex

AD risk differs by sex and *APOE* genotype, and the efficacy of currently approved treatments varies based on these risk factors.[36–38] Therefore, it is critical to determine whether the clinical utility of plasma p-tau217 and cognitive measures differs across subgroups. To investigate this, we conducted post hoc analyses, evaluating the ability of the combined model derived above (demographics, p-tau217, and C3 composite scores) to predict low versus high performers at baseline and cognitive decline over 96 and 240 weeks, stratified by sex and *APOE* genotype.

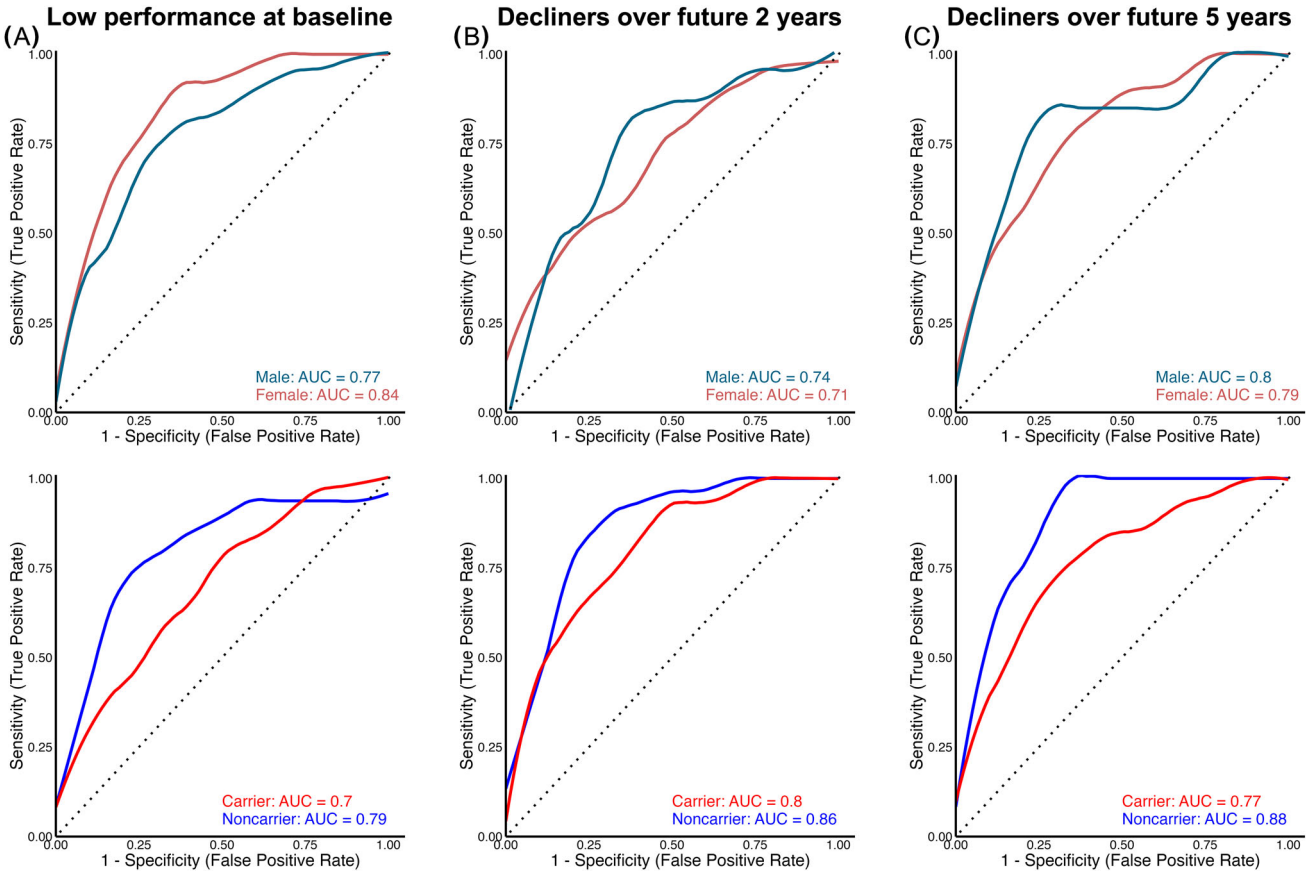

FIGURE 2 Predictive capacity of the combined model (demographics, plasma p-tau217, and C3) differs by *APOE* ε4 carrier status but not sex. Top, ROC curves illustrating the predictive value of the combined model in males (blue) and females (red). Bottom, ROC curves illustrate the predictive value of the combined model in *APOE* ε4 non-carriers (blue) and *APOE* ε4 carriers (red). A, At baseline, the model performed similarly in males and females, with a slight advantage in females (top). Additionally, no significant difference was observed between *APOE* ε4 carriers and non-carriers in baseline performance. B, C, When predicting future cognitive decline, the models performed equally well in males and females at both 2 (B) and 5 (C) years. However, the predictive capacity was stronger in *APOE* ε4 non-carriers compared to carriers at both time points. *APOE*, apolipoprotein E; AUC, area under the curve; C3, Computerized Cognitive Composite; p-tau, phosphorylated tau; ROC, receiver operating characteristic

At baseline, model performance was similar for distinguishing low versus high performers across sexes, though it performed slightly better in females (Figure 2A, top, males: LOO AUC: 0.773, CI: 0.700–0.841, females: LOO AUC: 0.839, CI: 0.767–0.905). Likewise, we did not observe substantial differences in predictive accuracy by *APOE* ε4 carriership (Figure 2A, bottom, non-carriers: LOO AUC: 0.856, CI: 0.793–0.912, carriers: LOO AUC: 0.801, CI: 0.738–0.860), suggesting that differentiating low and high performers does not differ by these risk factors.

Examining the prediction of cognitive decline over 96 and 240 weeks, we found no significant sex differences, indicating that the clinical utility of p-tau217 and the cognitive battery did not vary substantially by sex (Figure 2B, top, 2 years: males: LOO AUC: 0.744, CI: 0.637–0.837, females: LOO AUC: 0.712, CI: 0.615–0.799, Figure 2C, top, 5 years: males: LOO AUC: 0.804, CI: 0.681–0.903, females: LOO AUC: 0.788, CI: 0.719–0.856). However, the models performed significantly better at predicting a decline in *APOE* ε4 non-carriers compared to carriers (Figure 2B, bottom, 2 years: non-carriers: LOO AUC: 0.794, CI: 0.654–0.906, carriers: LOO AUC: 0.696, CI: 0.621–0.769, Figure 2C, bottom, 5 years: non-carriers: LOO AUC: 0.885, CI: 0.821–0.937, carriers: LOO AUC: 0.772, CI: 0.692–0.836), suggesting that *APOE* ε4 carriership may moderate the predictive value of these measures and *APOE* ε4 carriers may require different predictive markers or more tailored risk models to optimize early detection strategies.

3.5 | Plasma p-tau217 and the C3 composite predict future impairment on the MMSE

The PACC is a well-established neuropsychological battery, but it is not commonly used in clinical settings, where global screening tools such as the MMSE are more prevalent. Although all study participants initially scored within the normal range on the MMSE, for a subset of individuals, performance declined over the 5 year study period. We investigated whether baseline p-tau217, initial C3 performance,

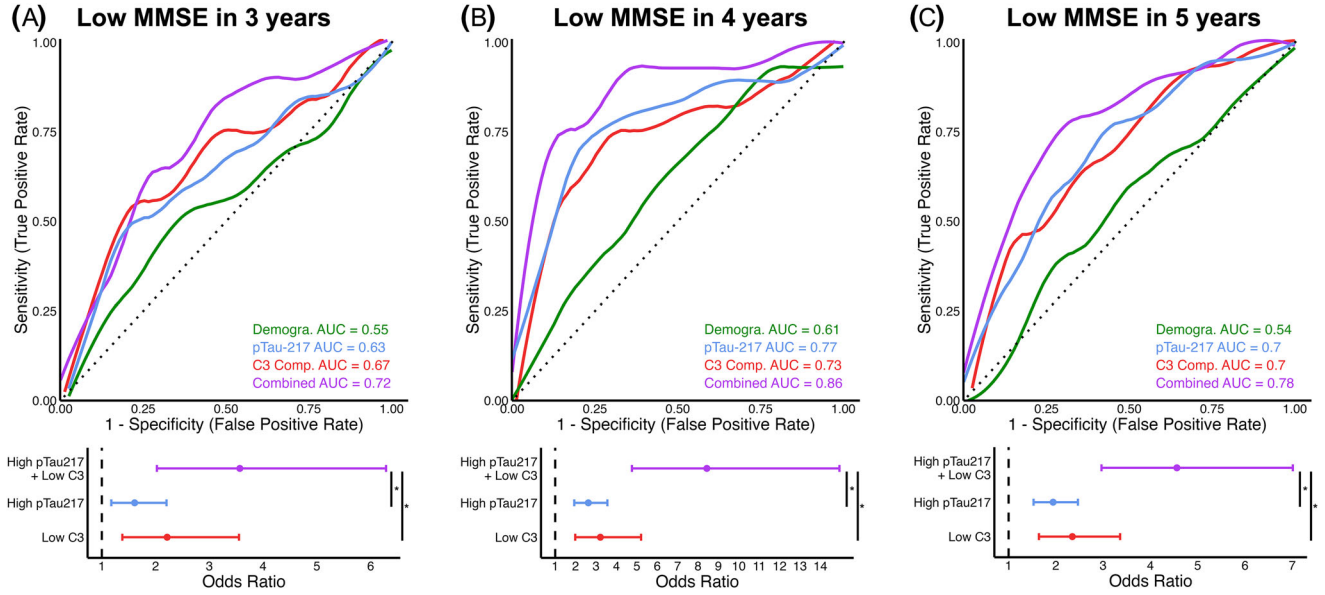

FIGURE 3 Integrating plasma p-tau217 and C3 enhances the prediction of individuals who progress to clinical impairment on the MMSE. Comparison of models using demographics alone (green), demographics plus p-tau217 (blue), C3 composite (red), or both p-tau217, and C3 (purple) for predicting low performers and future cognitive decline. Top, ROC curves illustrate the predictive value of each model. Bottom, Odds ratios for future impairment on the MMSE based on low memory (red), high p-tau217 (blue), or both (purple). The combined model incorporating both measures was the strongest predictor of individuals who would progress to clinical impairment on the MMSE over the next (A) 3, (B) 4, or (C) 5 years, achieving the highest AUCs (top) and demonstrating that individuals with both high p-tau217 and low C3 performance at baseline had the highest odds ratio for progressing to an impaired MMSE (bottom). AUC, area under the curve; C3, Computerized Cognitive Composite; MMSE, Mini-Mental State Examination; p-tau, phosphorylated tau; ROC, receiver operating characteristic

or a combination of both could predict which individuals would decline on the MMSE. Because most participants remained above the MMSE impairment threshold initially, we began predictions after 3 years. Demographics alone or with p-tau217 could not predict which individuals (n = 22) would progress to an MMSE score < 25 (demographics: LOO AUC: 0.545, CI: 0.466–0.696, p-tau217: LOO AUC: 0.631, CI: 0.490–0.772). However, the model with C3 scores significantly improved predictive accuracy (Figure 3A, top, LOO AUC: 0.668, CI: 0.532–0.797). Notably, the model that included both p-tau217 and C3 scores demonstrated the highest predictive value for identifying decliners (LOO AUC: 0.720, CI: 0.601–0.798).

This pattern remained consistent when predicting those who would fall below the critical MMSE threshold of 25 over 4 years (n = 34; Figure 3B, top, demographics: LOO AUC: 0.607, CI: 0.481–0.711, p-tau217: LOO AUC: 0.769, CI: 0.659–0.874, C3: LOO AUC: 0.733, CI: 0.619–0.840, combined: LOO AUC: 0.859, CI: 0.772–0.928 or 5 years (n = 51; Figure 3C, top, demographics: LOO AUC: 0.536, CI: 0.476–0.625, p-tau217: LOO AUC: 0.704, CI: 0.621–0.780, C3: LOO AUC: 0.698, CI: 0.620–0.777, Combined: LOO AUC: 0.780, CI: 0.702–0.851). Together, these findings further support the utility of combining p-tau217 and C3 scores to identify individuals at high risk for cognitive decline.

Next, we examined the odds of MMSE progression based on whether individuals had elevated p-tau217, low C3 scores, or both risk factors at baseline. At 144 weeks (≈ 2.8 years), elevated p-tau217 was associated with a 61% increased risk of progression (Figure 3A, bottom, OR = 1.610, CI = 1.177–2.204), while low memory performance was associated with a 122% increased risk (OR = 2.220, CI = 1.402–3.517). These two risk factors did not differ statistically ($Z = -1.103$, $P = 0.270$). However, individuals with both high p-tau217 and low memory had a 257% increased risk of progression (OR = 3.568, CI = 2.024–6.288), which was significantly higher than p-tau217 alone (combined vs. p-tau217: $Z = 2.241$, $P = 0.016$) but not significantly different from low memory alone (combined vs. low memory: $Z = 1.266$, $P = 0.205$). This suggests that individuals with both elevated p-tau217 and subtle memory deficits are at the highest risk of progression on the MMSE.

At 192 weeks (≈ 4 years), we observed a similar pattern. Elevated p-tau217 was associated with a 162% increased risk of progression (Figure 3B, bottom, OR = 2.625, CI = 1.934–3.561), while low memory was associated with a 221% increased risk (OR = 3.214, CI = 1.983–5.211). Having both risk factors dramatically increased the odds of progression, with an 8.44-fold higher risk (OR = 8.436, CI = 4.764–14.938), which was significantly greater than having either high p-tau217 ($Z = 3.532$, $P = 0.0004$) or low memory alone ($Z = 2.528$, $P = 0.011$). No significant difference was found between p-tau217 and low memory alone ($Z = -0.695$, $P = 0.487$). Again, this suggests that those with subtle memory deficits along with elevated p-tau217 are particularly at risk for future cognitive decline.

Last, we evaluated the predictive value of p-tau217 and memory performance for MMSE decline over 240 weeks (≈ 4.6 years). Again, having both high p-tau217 and low memory was associated with the highest risk of progression, with a 356% increased risk (Figure 3C, bottom, OR = 4.559, CI = 2.965–7.011), significantly greater than either

risk factor alone (p-tau217: OR = 1.942, CI = 1.529–2.466; low memory: OR = 2.348, CI = 1.642–3.359). Pairwise comparisons showed that the combined model was significantly more predictive than p-tau217 alone ($Z = 3.399$, $P = 0.0007$) or low memory alone ($Z = 2.323$, $P = 0.020$), with no significant difference between p-tau217 and low memory alone ($Z = -0.866$, $P = 0.387$). Together, these results further support that combining p-tau217 and memory performance improves the prediction of future decline on the MMSE.

3.6 | Accelerated cognitive decline in individuals with both high p-tau217 and low memory performance

The findings above suggest that individuals with both elevated p-tau217 and low performance on the digital cognitive battery at baseline experienced more rapid cognitive decline. To directly investigate this, we categorized participants into four groups based on baseline p-tau217 levels and memory performance. Because, by definition, all participants had elevated p-tau217, we distinguished those with p-tau217 levels > 1 SD above the group mean (p-tau217*) from those with p-tau217 levels ≤ 1 SD above the mean (p-tau217_o). Memory performance was classified as either normal (Mem_o) or subtly impaired (Mem*) based on whether an individual's memory score was > 1 SD below the group mean. This resulted in four groups: p-tau$217_o$$Mem_o$ (p-tau217 within group average, no memory deficits), p-tau217*Mem_o (p-tau217 > 1 SD above the group mean, no memory deficits), p-tau217_oMem* (p-tau217 within group average, subtle memory deficits), and p-tau217*Mem* (p-tau217 > 1 SD above the group mean, subtle memory deficits). To determine whether one of these groups declined faster, we first regressed out the effects of age, sex, and education on PACC and MMSE performance. We then examined longitudinal changes in these cognitive measures across the four groups.

We first examined PACC performance over 5 years across the four groups. Using linear mixed effects modeling, we found that relative to the p-tau$217_o$$Mem_o$ group, all other groups showed significantly greater rates of decline (Figure 4A, linear mixed-effect model: p-tau217*Mem*: $\beta = -0.00698$, standard error [SE] = 0.00049, $t = -14.153$, $P < 0.001$; p-tau217*Mem_o: $\beta = -0.00415$, SE = 0.00028, $t = -14.812$, $P < 0.001$; p-tau217_oMem*: $\beta = -0.00251$, SE = 0.00022, $t = -11.594$, $P < 0.001$). Specifically, individuals classified as p-tau217*Mem* exhibited the most rapid cognitive decline compared to all other groups (vs. p-tau$217_o$$Mem_o$: $z = 6.278$, $P < 0.001$; vs. p-tau217_oMem*: $z = 4.410$, $P < 0.001$; vs. p-tau217*Mem_o: $z = 2.486$, $P = 0.0129$). Additionally, p-tau217*Mem_o declined significantly faster than p-tau$217_o$$Mem_o$ ($z = 5.736$, $P < 0.001$) and p-tau217_oMem* ($z = 2.657$, $P = 0.0079$). Together, these findings suggest that individuals with both elevated p-tau217 and low memory performance at baseline are at the highest risk for accelerated cognitive decline, while either factor alone is associated with a moderate but significant increase in risk.

We next examined MMSE performance over 5 years across the four groups to determine whether baseline p-tau217 and memory performance predicted differential rates of cognitive decline. As with PACC, individuals in the p-tau217*Mem* group exhibited the most rapid decline, followed by p-tau217*Mem_o and p-tau217_oMem*, while the p-tau$217_o$$Mem_o$ group demonstrated the slowest decline. Specifically, a linear mixed-effects model revealed significant interactions between time and group, indicating distinct rates of decline among the four groups (Figure 4B, p-tau217*Mem*: $\beta = -0.00525$, SE = 0.00054, $t = -9.806$, $P < 0.001$; p-tau217*Mem_o: $\beta = -0.00201$, SE = 0.00031, $t = -6.527$, $P < 0.001$; p-tau217_oMem*: $\beta = -0.00160$, SE = 0.00024, $t = -6.711$, $P < 0.001$). Pairwise comparisons confirmed that p-tau217*Mem* declined significantly faster than all other groups (vs. p-tau$217_o$$Mem_o$: $z = 8.767$, $P < 0.001$; vs. p-tau217_oMem*: $z = 5.483$, $P < 0.001$; vs. p-tau217*Mem_o: $z = 5.911$, $P < 0.001$). Additionally, p-tau217*Mem_o showed a significantly steeper decline than p-tau$217_o$$Mem_o$ ($z = 3.398$, $P = 0.0007$), while p-tau217_oMem* also declined more rapidly than p-tau$217_o$$Mem_o$ ($z = 6.182$, $P < 0.001$). However, no significant difference was observed between p-tau217*Mem_o and p-tau217_oMem* ($z = -1.179$, $P = 0.2384$), suggesting that either high p-tau217 or low memory performance alone leads to similar rates of decline, but having both greatly accelerates progression. These findings align with PACC results, further supporting that individuals with both elevated p-tau217 and poor memory performance at baseline experience the most rapid cognitive decline, whereas either factor alone confers a moderate but significant risk.

4 | DISCUSSION

Advances in plasma biomarkers have significantly improved our ability to readily detect AD pathology, including amyloid and tau, before the onset of cognitive symptoms. However, the presence of these pathologies does not guarantee imminent cognitive decline; in many cases, amyloid and tau accumulate for years before symptoms emerge, and some individuals with elevated AD biomarkers never experience measurable cognitive decline.[7,39] This uncertainty complicates decisions about when and how to intervene. To address this, we need additional low-burden, scalable tools that can refine risk stratification and provide a clearer timeline for cognitive decline. Digital cognitive assessments have emerged as a promising solution, yet their utility in complementing plasma biomarkers to identify those at the highest risk remains underexplored. Here, we combined plasma p-tau217 with a composite of hippocampal memory tasks from a digital cognitive assessment in 954 cognitively unimpaired, amyloid-positive older adults. Our findings demonstrate that integrating p-tau217 with a brief memory battery significantly enhances the ability to predict cognitive decline over the next 5 years. Specifically, individuals with both elevated p-tau217 and lower memory scores were at the greatest risk for future decline on both the PACC and MMSE. These results underscore the importance of incorporating both biological markers of AD pathology and hippocampal memory assessments as a more precise screening approach for identifying individuals most vulnerable to cognitive decline.

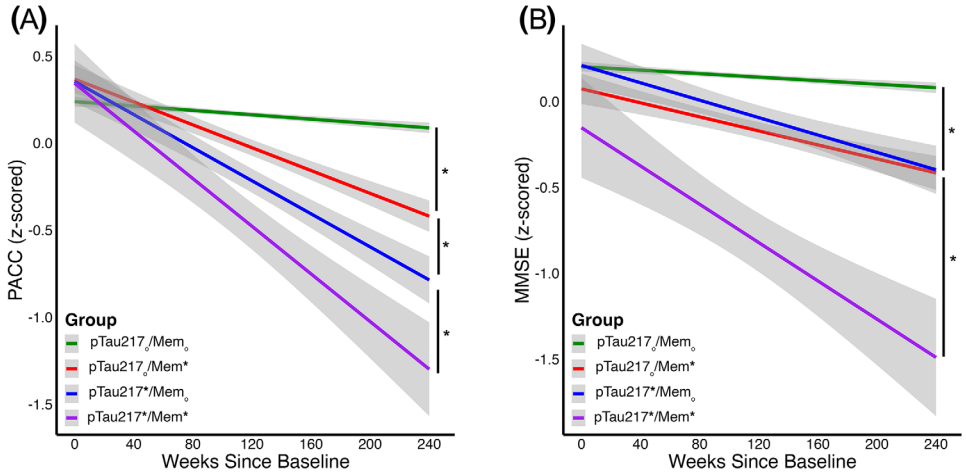

FIGURE 4 Longitudinal trajectories over 240 weeks on the Preclinical Alzheimer Cognitive Composite (PACC) and Mini-Mental State Examination (MMSE). A, Individuals in the p-tau217*Mem* group exhibited the most rapid decline in the PACC compared to the other three groups. p-tau217*Mem_o showed the second fastest decline, followed by p-tau217_oMem*, which declined more rapidly than p-tau$217_o$$Mem_o$. B, On the MMSE, p-tau217*Mem* individuals again exhibited the steepest decline. p-tau217*Mem_o and p-tau217_oMem* declined at similar rates, with both declining faster than p-tau$217_o$$Mem_o$. p-tau, phosphorylated tau

4.1 | Integrating p-tau217 and the C3 composite for identifying individuals at risk for cognitive decline

A critical question in AD research is whether integrating plasma and cognitive biomarkers improves the prediction of future cognitive decline. Identifying individuals at high risk for decline is essential for expanding the therapeutic window for currently approved treatments and optimizing clinical trial recruitment. While prior research has established that AD biomarkers, such as amyloid, are predictive of future decline, it remains unclear whether incorporating cognitive assessments can enhance predictive sensitivity and specificity.[40,41]

Consistent with previous findings, we demonstrated that both plasma p-tau217 and memory performance were individually predictive of future decline in the PACC, with each measure contributing a unique value to the models.[20,21,42,43] Further, the combined models with both measures had increased sensitivity compared to models with only one of the measures. Importantly, all analyses controlled for baseline PACC performance, ensuring that our findings were not merely driven by lower baseline cognitive scores. Our results strongly support the integration of both plasma and cognitive measures for AD detection and screening, demonstrating that a combined approach improves the prediction of cognitive decline and enhances risk stratification for clinical and therapeutic interventions.

4.2 | Predicting decliners differs by *APOE ε4* carrier status

Not all individuals are at equal risk for AD, with both sex and *APOE ε4* carriership being well-established risk factors.[37,44–46] Specifically, females and *APOE ε4* carriers face a higher likelihood of developing AD. Therefore, it is essential to validate screening tools across different populations to determine whether they perform equivalently or require adjustment based on demographic or genetic risk factors. We found that combining p-tau217 and memory performance provided comparable predictive value in males and females, both at baseline and for predicting decline over 2 and 5 years. However, while these measures were equally effective at differentiating high and low PACC performers at baseline regardless of *APOE ε4* status, their ability to predict future decline varied. Our models performed significantly better in *APOE ε4* non-carriers, where combining p-tau217 and memory scores achieved an AUC of nearly 0.90. In contrast, the models performed less effectively in *APOE ε4* carriers, suggesting that *APOE ε4* status influences the predictive utility of these measures.

APOE ε4 carriers are at higher risk for AD yet do not benefit as much from current treatments.[47,48] Additionally, their cognitive trajectories differ from non-carriers, with more rapid and severe hippocampal memory deficits that emerge earlier in the disease process.[49–51] In line with this, we observed reduced predictive accuracy for cognitive decline in *APOE ε4* carriers, suggesting fundamental differences in disease pathophysiology and progression.[44] This highlights the need for further investigation into whether distinct biomarkers or cognitive measures may be required to improve risk stratification and prediction in *APOE ε4* carriers.

4.3 | Hippocampal memory tasks as valuable digital cognitive assessments

The use of digital cognitive tasks to identify individuals at high risk for future cognitive decline has gained increasing attention. Notably, studies have shown that remote cognitive assessments can reliably predict progression on standardized clinical measures.[13,20,52] However, not

all cognitive tasks are equally effective in this regard. A consistent finding across studies is that tasks targeting hippocampal integrity are the most promising, likely due to the hippocampus being one of the earliest regions affected by AD.[18,21,53]

Our work reaffirms this, demonstrating that a composite measure incorporating three hippocampal-dependent memory tasks can reliably identify individuals at high risk for future cognitive decline, outperforming non-memory tasks. Notably, all three tasks were designed to tax pattern separation, a critical computation of the hippocampus.[54–56] The BPST, now widely known as the MST, was explicitly designed to assess pattern separation by requiring individuals to distinguish highly similar but not identical stimuli.[25] The OCL, adapted from the MST, requires participants to remember details about playing cards while managing competing interference from similar cards with overlapping features, thereby taxing hippocampal pattern separation mechanisms.[21,27] Last, the FNAME task assesses face–name associations, and given that participants must learn 12 unique pairs, successful performance likely relies on hippocampal pattern separation to differentiate and encode these associations.[57–59] These findings align with growing evidence that tasks taxing hippocampal pattern separation are early indicators of AD pathology and strong predictors of future cognitive decline.[20,21,53,60] Interestingly, when modeled individually, each task performed similarly, with none demonstrating clear superiority. This may reflect the fact that all three rely on the same underlying hippocampal circuitry. Further research is needed to determine whether specific memory tasks are more sensitive to the earliest signs of disease. Nonetheless, our results reinforce the importance of integrating hippocampal-dependent memory assessments into digital cognitive screening tools to improve early detection of at-risk individuals.

4.4 | Clinical utility of integrating blood biomarkers and digital cognitive testing

There is an urgent need for accessible, scalable tools to screen for AD in clinical settings, particularly in primary care, where early intervention could have the greatest impact. Blood biomarkers and digital cognitive testing are strong candidates for this purpose, as plasma collection is minimally invasive and widely available, and digital cognitive assessments can be administered remotely and autonomously at scale.[12,61,62] Our findings demonstrate the potential of these measures for identifying individuals at risk for future cognitive decline. However, critical steps remain to establish how they can be effectively implemented in real-world clinical practice. Specifically, all individuals in this study were amyloid positive at baseline. Therefore, additional research is needed to determine how well plasma p-tau217 and digital memory assessments perform in individuals who have not yet reached amyloid positivity.

Further, it should be noted that plasma p-tau217 7 correlates strongly with global amyloid burden measured via PET.[11,63] Consistent with this, results were highly similar when the global amyloid burden was used in place of plasma p-tau217. However, PET imaging provides spatial information about amyloid deposition, which may offer additional predictive value beyond what is captured by blood-based biomarkers alone. This may be especially relevant in certain subgroups, such as *APOE* ε4 carriers, who tend to have greater and more regionally specific amyloid accumulation.

A key challenge is that primary care providers do not have access to traditional neuropsychological testing, such as the PACC, and instead rely on global screening tools like the MMSE.[33,34,64] Here, we show that incorporating plasma p-tau217 and digital memory assessments improves the ability to predict who will decline on the MMSE over time. This suggests that a combined biomarker and cognitive screening approach could be integrated into routine clinical workflows to help identify individuals at the highest risk for cognitive decline, guiding referrals for further evaluation or early therapeutic intervention. For this approach to be clinically actionable, future work must determine optimal cutoff points for risk classification, the most effective cognitive tasks for remote assessment, and whether additional plasma biomarkers, such as neurofilament light chain or glial fibrillary acidic protein, could further strengthen predictive accuracy. Additionally, longitudinal studies are needed to assess whether this screening strategy improves patient outcomes by enabling earlier intervention and better treatment allocation.

5 | CONCLUSION

In this study, we investigated whether integrating plasma p-tau217 with a digital cognitive assessment could improve the prediction of future cognitive decline in amyloid-positive, cognitively unimpaired older adults. Our findings demonstrate that these measures complement one another in identifying individuals at the highest risk for cognitive decline. Specifically, those with elevated p-tau217 and subtle memory deficits exhibited the most rapid cognitive decline over 5 years. These results highlight the potential of combining plasma biomarkers with digital cognitive assessments as low-burden, scalable tools for AD screening. We propose that this approach could be seamlessly integrated into clinical settings, enabling earlier and more precise risk stratification. By facilitating early detection, this framework has direct implications for clinical decision making, patient monitoring, and timely therapeutic intervention, ultimately improving outcomes for those at risk for AD.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

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REFERENCES

1. Jack CR, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimers Dement*. 2024;20(8):5143-5169. doi:10.1002/alz.13859
2. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):280-292. doi:10.1016/j.jalz.2011.03.003
3. Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement J Alzheimers Assoc*. 2018;14(4):535-562. doi:10.1016/j.jalz.2018.02.018
4. Jack CR. Advances in Alzheimer's disease research over the past two decades. *Lancet Neurol*. 2022;21(10):866-869. doi:10.1016/S1474-4422(22)00298-8
5. Sperling RA, Mormino EC, Schultz AP, et al. The impact of amyloid-beta and tau on prospective cognitive decline in older individuals. *Ann Neurol*. 2019;85(2):181-193. doi:10.1002/ana.25395
6. Nestor PJ, Scheltens P, Hodges JR. Advances in the early detection of Alzheimer's disease. *Nat Med*. 2004;10:S34-41.
7. Dubois B, Villain N, Schneider L, et al. Alzheimer Disease as a Clinical-Biological Construct – An International Working Group Recommendation. *JAMA Neurol*. 2024;81(12):1304-1311. doi:10.1001/jamaneurol.2024.3770
8. Janelidze S, Teunissen CE, Zetterberg H, et al. Head-to-head comparison of 8 plasma amyloid-β 42/40 assays in Alzheimer disease. *JAMA Neurol*. 2021;78(11):1375. doi:10.1001/jamaneurol.2021.3180
9. Rissman RA, Langford O, Raman R, et al. Plasma Aβ42/Aβ40 and phospho-tau217 concentration ratios increase the accuracy of amyloid PET classification in preclinical Alzheimer's disease. *Alzheimers Dement*. 2024;20(2):1214-1224. doi:10.1002/alz.13542
10. Angioni D, Delrieu J, Hansson O, et al. Blood biomarkers from research use to clinical practice: what must be done? A report from the EU/US CTAD task force. *J Prev Alzheimers Dis*. 2022;9(4):569-579. doi:10.14283/jpad.2022.85
11. Rissman RA, Donohue MC, Langford O, et al. Longitudinal phospho-tau217 predicts amyloid positron emission tomography in asymptomatic Alzheimer's disease. *J Prev Alzheimers Dis*. 2024;11(4):823-830. doi:10.14283/jpad.2024.134
12. Mielke MM, Dage JL, Frank RD, et al. Performance of plasma phosphorylated tau 181 and 217 in the community. *Nat Med*. 2022;28(7):1398-1405. doi:10.1038/s41591-022-01822-2
13. Papp KV, Jutten RJ, Soberanes D, et al. Early detection of amyloid-related changes in memory among cognitively unimpaired older adults with daily digital testing. *Ann Neurol*. 2024;95(3):507-517. doi:10.1002/ana.26833
14. Öhman F, Hassenstab J, Berron D, Schöll M, Papp KV. Current advances in digital cognitive assessment for preclinical Alzheimer's disease. *Alzheimers Dement Diagn Assess Dis Monit*. 2021;13(1):e12217. doi:10.1002/dad2.12217
15. Toniolo S, Zhao S, Scholcz A, et al. Relationship of plasma biomarkers to digital cognitive tests in Alzheimer's disease. *Alzheimers Dement Diagn Assess Dis Monit*. 2024;16(2):e12590. doi:10.1002/dad2.12590
16. Tsoy E, VandeVrede L, et al. Scalable plasma and digital cognitive markers for diagnosis and prognosis of Alzheimer's disease and related dementias. *Alzheimers Dement*. 2024;20(3):2089-2101. doi:10.1002/alz.13686
17. Papp KV, Maruff P, Rentz DM, et al. Change in digital cognitive test performance between Solanezumab and Placebo Groups in preclinical Alzheimer's disease: secondary analyses from the A4 study. *J Prev Alzheimers Dis*. 2024;11(4):846-856. doi:10.14283/jpad.2024.137
18. Vanderlip CR, Lee MD, Stark CEL. Cognitive modeling of the Mnemonic Similarity Task as a digital biomarker for Alzheimer's disease. *Alzheimers Dement*. 2024;20(10):6935-6947. doi:10.1002/alz.14163
19. Papp KV, Rentz DM, Maruff P, et al. The Computerized Cognitive Composite (C3) in A4, an Alzheimer's disease secondary prevention trial. *J Prev Alzheimers Dis*. 2021;8(1):59-67. doi:10.14283/jpad.2020.38
20. Jutten RJ, Rentz DM, Fu JF, et al. Monthly at-home computerized cognitive testing to detect diminished practice effects in preclinical Alzheimer's disease. *Front Aging Neurosci*. 2022;13:800126. doi:10.3389/fnagi.2021.800126
21. Vanderlip CR, Stark CEL, for the Alzheimer's Disease Neuroimaging Initiative. Digital cognitive assessments as low-burden markers for predicting future cognitive decline and tau accumulation across the Alzheimer's spectrum. *Alzheimers Dement*. 2024;20(10):6881-6895. doi:10.1002/alz.14154
22. Sperling RA, Rentz DM, Johnson KA, et al. The A4 Study: stopping AD before symptoms begin? *Sci Transl Med*. 2014;6(228):228fs13. doi:10.1126/scitranslmed.3007941
23. Sperling RA, Donohue MC, Raman R, et al. Trial of Solanezumab in Preclinical Alzheimer's disease. *N Engl J Med*. 2023;389(12):1096-1107. doi:10.1056/NEJMoa2305032
24. Insel PS, Donohue MC, Sperling R, Hansson O, Mattsson-Carlgren N. The A4 study: β-amyloid and cognition in 4432 cognitively unimpaired adults. *Ann Clin Transl Neurol*. 2020;7(5):776-785. doi:10.1002/acn3.51048
25. Stark SM, Kirwan CB, Stark CEL. Mnemonic similarity task: a tool for assessing hippocampal integrity. *Trends Cogn Sci*. 2019;23(11):938-951. doi:10.1016/j.tics.2019.08.003
26. Stark SM, Stark CEL. Age-related deficits in the mnemonic similarity task for objects and scenes. *Behav Brain Res*. 2017;333:109-117. doi:10.1016/j.bbr.2017.06.049
27. For the AIBL Research Group, Maruff P, Lim YY, et al, for the AIBL Research Group. Clinical utility of the cogstate brief battery in identifying cognitive impairment in mild cognitive impairment and Alzheimer's disease. *BMC Psychol*. 2013;1(1):30. doi:10.1186/2050-7283-1-30
28. Racine AM, Clark LR, Berman SE, et al. Associations between performance on an abbreviated CogState battery, other measures of cognitive function, and biomarkers in people at risk for Alzheimer's disease. *J Alzheimers Dis*. 2016;54(4):1395-1408. doi:10.3233/JAD-160528
29. White JP, Schembri A, Edgar CJ, Lim YY, Masters CL, Maruff P. A paradox in digital memory assessment: increased sensitivity with reduced difficulty. *Front Digit Health*. 2021;3:780303. doi:10.3389/fdgth.2021.780303
30. Donohue MC, Sperling RA, Salmon DP, et al. The preclinical Alzheimer cognitive composite: measuring amyloid-related decline. *JAMA Neurol*. 2014;71(8):961. doi:10.1001/jamaneurol.2014.803
31. Donohue MC, Sperling RA, Petersen R, et al. Association between elevated brain amyloid and subsequent cognitive decline among cognitively normal persons. *JAMA*. 2017;317(22):2305. doi:10.1001/jama.2017.6669
32. Mormino EC, Papp KV, Rentz DM, et al. Early and late change on the preclinical Alzheimer's cognitive composite in clinically normal older individuals with elevated amyloid β. *Alzheimers Dement*. 2017;13(9):1004-1012. doi:10.1016/j.jalz.2017.01.018
33. Creavin ST, Wisniewski S, Noel-Storr AH, et al. Mini-Mental State Examination (MMSE) for the detection of dementia in clinically unevaluated people aged 65 and over in community and primary care populations. Cochrane Dementia and Cognitive Improvement Group, ed. *Cochrane Database Syst Rev*. 2016;2016(1):CD011145. doi:10.1002/14651858.CD011145.pub2

34. Hunt HA, Van Kampen S, Takwoingi Y, Llewellyn DJ, Pearson M, Hyde CJ. The comparative diagnostic accuracy of the Mini Mental State Examination (MMSE) and the General Practitioner assessment of Cognition (GPCOG) for identifying dementia in primary care: a systematic review protocol. *Diagn Progn Res*. 2017;1(1):14. doi:10.1186/s41512-017-0014-1
35. Hoops S, Nazem S, Siderowf AD, et al. Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease. *Neurology*. 2009;73(21):1738-1745. doi:10.1212/WNL.0b013e3181c34b47
36. Buckley RF, Mormino EC, Amariglio RE, et al. Sex, amyloid, and *APOE ε4* and risk of cognitive decline in preclinical Alzheimer's disease: findings from three well-characterized cohorts. *Alzheimers Dement*. 2018;14(9):1193-1203. doi:10.1016/j.jalz.2018.04.010
37. Wang X, Zhou W, Ye T, Lin X, Zhang J. Sex difference in the association of APOE4 with memory decline in mild cognitive impairment. *J Alzheimers Dis*. 2019;69(4):1161-1169. doi:10.3233/JAD-181234
38. Nemes S, Logan PE, Manchella MK, et al. Sex and *APOE ε4* carrier effects on atrophy, amyloid PET, and tau PET burden in early-onset Alzheimer's disease. *Alzheimers Dement*. 2023;19(S9):S49-S63. doi:10.1002/alz.13403
39. Rentz DM, Rosenberg PB, Sperling RA, et al. Characterizing clinical progression in cognitively unimpaired older individuals with brain amyloid: results from the A4 Study. *J Prev Alzheimers Dis*. 2024;11(4):814-822. doi:10.14283/jpad.2024.123
40. Ossenkoppele R, Pichet Binette A, Groot C, et al. Amyloid and tau PET-positive cognitively unimpaired individuals are at high risk for future cognitive decline. *Nat Med*. 2022;28(11):2381-2387. doi:10.1038/s41591-022-02049-x
41. Jack CR, Wiste HJ, Therneau TM, et al. Associations of amyloid, tau, and neurodegeneration biomarker profiles with rates of memory decline among individuals without dementia. *JAMA*. 2019;321(23):2316. doi:10.1001/jama.2019.7437
42. Mattsson-Carlgren N, Salvadó G, Ashton NJ, et al. Prediction of longitudinal cognitive decline in preclinical Alzheimer disease using plasma biomarkers. *JAMA Neurol*. 2023;80(4):360. doi:10.1001/jamaneurol.2022.5272
43. Ossenkoppele R, Salvadó G, Janelidze S, et al. Prediction of future cognitive decline among cognitively unimpaired individuals using measures of soluble phosphorylated tau or tau tangle pathology. *bioRxiv*. Preprint posted online June 13, 2024. doi:10.1101/2024.06.12.24308824
44. Fortea J, Pegueroles J, Alcolea D, et al. APOE4 homozygosity represents a distinct genetic form of Alzheimer's disease. *Nat Med*. 2024;30(5):1284-1291. doi:10.1038/s41591-024-02931-w
45. Gharbi-Meliani A, Dugravot A, Sabia S, et al. The association of APOE *ε4* with cognitive function over the adult life course and incidence of dementia: 20 years follow-up of the Whitehall II study. *Alzheimers Res Ther*. 2021;13(1):5. doi:10.1186/s13195-020-00740-0
46. Rahman A, Jackson H, Hristov H, et al. Sex and gender driven modifiers of Alzheimer's: the role for estrogenic control across age, race, medical, and lifestyle risks. *Front Aging Neurosci*. 2019;11:315. doi:10.3389/fnagi.2019.00315
47. Van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. *N Engl J Med*. 2023;388(1):9-21. doi:10.1056/NEJMoa2212948
48. Mohs R, Bakker A, Rosenzweig-Lipson S, et al. The HOPE4MCI study: a randomized double-blind assessment of AGB101 for the treatment of MCI due to AD. *Alzheimers Dement Transl Res Clin Interv*. 2024;10(1):e12446. doi:10.1002/trc2.12446
49. Vanderlip CR, Stark CEL, the Alzheimer's Disease Neuroimaging Initiative. APOE4 increases susceptibility to amyloid, accelerating episodic memory decline. *bioRxiv*. Preprint posted online December 24, 2024. doi:10.1101/2024.12.23.630203
50. Bondi MW, Salmon DP, Monsch AU, et al. Episodic memory changes are associated with the APOE- epsilon 4 allele in nondemented older adults. *Neurology*. 1995;45(12):2203-2206. doi:10.1212/wnl.45.12.2203
51. Eich TS, Tsapanou A, Stern Y. When time's arrow doesn't bend: APOE-*ε4* influences episodic memory before old age. *Neuropsychologia*. 2019;133:107180. doi:10.1016/j.neuropsychologia.2019.107180
52. Bock JR, Hara J, Fortier D, Lee MD, Petersen RC, Shankle WR. Application of digital cognitive biomarkers for Alzheimer's disease: identifying cognitive process changes and impending cognitive decline. *J Prev Alzheimers Dis*. 2021;8(2):123-126. doi:10.14283/jpad.2020.63
53. Berron D, Olsson E, Andersson F, et al. Remote and unsupervised digital memory assessments can reliably detect cognitive impairment in Alzheimer's disease. *Alzheimers Dement*. 2024;20(7):4775-4791. doi:10.1002/alz.13919
54. Bakker A, Kirwan CB, Miller NI, Stark CEL. Pattern separation in the human hippocampal CA3 and dentate gyrus. *Science*. 2008;319:1640-1642.
55. Yassa MA, Stark CE. Pattern separation in the hippocampus. *Trends Neurosci*. 2011;34:515-525. doi:10.1016/j.tins.2011.06.006
56. Kirwan CB, Stark CEL. Overcoming interference: an fMRI investigation of pattern separation in the medial temporal lobe. *Learn Mem*. 2007;14:625-633.
57. Amariglio RE, Frishe K, Olson LE, et al. Validation of the Face Name Associative Memory Exam in cognitively normal older individuals. *J Clin Exp Neuropsychol*. 2012;34:580-587. doi:10.1080/13803395.2012.666230
58. Rentz DM, Amariglio RE, Becker JA, et al. Face-name associative memory performance is related to amyloid burden in normal elderly. *Neuropsychologia*. 2011;49(9):2776-2783. doi:10.1016/j.neuropsychologia.2011.06.006
59. Kirwan CB, Stark CEL. Medial temporal lobe activation during encoding and retrieval of novel face-name pairs. *Hippocampus*. 2004;14:910-930.
60. Vanderlip CR, Taylor L, Kim S, et al. Amyloid-*β* deposition in basal frontotemporal cortex is associated with selective disruption of temporal mnemonic discrimination. *J Neurosci*. 2025;45(10):e1605242025. doi:10.1523/JNEUROSCI.1605-24.2025
61. Mielke MM, Anderson M, Ashford JW, et al. Recommendations for clinical implementation of blood-based biomarkers for Alzheimer's disease. *Alzheimers Dement*. 2024;20(11):8216-8224. doi:10.1002/alz.14184
62. Young CB, Mormino EC, Poston KL, et al. Computerized cognitive practice effects in relation to amyloid and tau in preclinical Alzheimer's disease: results from a multi-site cohort. *Alzheimers Dement Diagn Assess Dis Monit*. 2023;15(1):e12414. doi:10.1002/dad2.12414
63. Warmenhoven N, Salvadó G, Janelidze S, et al. A comprehensive head-to-head comparison of key plasma phosphorylated tau 217 biomarker tests. *Brain*. 2025;148(2):416-431. doi:10.1093/brain/awae346
64. Milne A, Culverwell A, Guss R, Tuppen J, Whelton R. Screening for dementia in primary care: a review of the use, efficacy and quality of measures. *Int Psychogeriatr*. 2008;20(5):911-926. doi:10.1017/S1041610208007394

SUPPORTING INFORMATION

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

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