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RESEARCH ARTICLE

Digital cognitive assessments as low-burden markers for predicting future cognitive decline and tau accumulation across the Alzheimer's spectrum

Casey R. Vanderlip | **Craig E. L. Stark** | **for the Alzheimer's Disease Neuroimaging Initiative**

Department of Neurobiology and Behavior, 1424 Biological Sciences III Irvine, University of California Irvine, Irvine, California, USA

Correspondence
Craig E. L. Stark, Department of Neurobiology and Behavior, 1424 Biological Sciences III Irvine, University of California Irvine, Irvine, CA, 92697 USA.
Email: cestark@uci.edu

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Abstract

BACKGROUND: Digital cognitive assessments, particularly those that can be done at home, present as low-burden biomarkers for participants and patients alike, but their effectiveness in the diagnosis of Alzheimer's disease (AD) or predicting its trajectory is still unclear. Here, we assessed what utility or added value these digital cognitive assessments provide for identifying those at high risk of cognitive decline.

METHODS: We analyzed >500 Alzheimer's Disease Neuroimaging Initiative participants who underwent a brief digital cognitive assessment and amyloid beta (Aβ)/tau positron emission tomography scans, examining their ability to distinguish cognitive status and predict cognitive decline.

RESULTS: Performance on the digital cognitive assessment was superior to both cortical Aβ and entorhinal tau in detecting mild cognitive impairment and future cognitive decline, with mnemonic discrimination deficits emerging as the most critical measure for predicting decline and future tau accumulation.

DISCUSSION: Digital assessments are effective at identifying at-risk individuals, supporting their utility as low-burden tools for early AD detection and monitoring.

KEYWORDS
Alzheimer's disease, digital cognitive assessments, early detection, mnemonic discrimination

Highlights

- Performance on digital cognitive assessments predicts progression to mild cognitive impairment at a higher proficiency compared to amyloid beta and tau.
- Deficits in mnemonic discrimination are indicative of future cognitive decline.
- Impaired mnemonic discrimination predicts future entorhinal and inferior temporal tau.

1 | INTRODUCTION

Alzheimer's disease (AD) pathologies, such as amyloid beta (Aβ) and tau tangles, develop up to 20 years before overt cognitive decline.[1,2] Therefore, identifying individuals before cognitive decline is essential for the treatment of this disease. While there has been substantial progress in techniques for treating these pathologies prior to cognitive decline, the development of sensitive cognitive tasks has lagged behind. Many of the common tasks currently used to assess cognitive function, such as the Mini-Mental State Examination (MMSE) or Clinical Dementia Rating (CDR) score, are relatively unaffected until late in disease progression,[2,3] with impairments on these tasks lagging years behind AD biomarkers.[4–6] Therefore, it is now common to believe that cognitive decline occurs well after the buildup of pathology. While this may be the case for tests designed to measure overt cognitive impairment, there is little reason to assume that this must necessarily be the case and that pathological load could not be read out in subtle changes in cognition. If digital biomarkers can be developed and validated to reflect some aspect of AD pathology, they offer a non-invasive, low-burden way to predict AD risk or monitor disease or treatment progression.

Recent work has demonstrated that digital cognitive batteries that tax circuits related to AD can accurately distinguish between individuals with cognitive impairment and cognitively healthy controls.[7–9] Further, longitudinal performance on these batteries is related to AD biomarkers prior to cognitive decline and is predictive of future decline on standardized cognitive tasks.[10,11] However, the tasks in these batteries are not equivalent in predicting AD biomarker status and future cognitive impairment. Tasks that tax circuits most vulnerable to AD are the best predictors of future decline. Hippocampus-dependent tasks, such as the Mnemonic Similarity Task (MST) or list-learning paradigms, decline early in AD.[10,12,13] Conversely, motor speed and executive function decline later in disease progression.[5,14] Further, work has shown that within cognitive batteries, memory-based tasks are able to better predict amyloid and tau status in cognitively normal (CN) older adults.[10,15] For example, one study that administered a series of cognitive tasks that included tasks of memory, attention, and psychomotor function found the strongest relationships between amyloid and memory function compared to attention and psychomotor function.[16]

Substantial progress has been made in understanding the neural circuits that contribute to differing cognitive functions and which circuits are particularly susceptible to AD pathologies.[17–19] Specifically, the hippocampus, a region critical for memory formation, is affected (directly and indirectly) early in the disease progression.[19,20] This vulnerability makes tasks that tax hippocampal integrity ideal candidates for detecting early cognitive changes in AD. A primary mechanism carried out in the hippocampus is pattern separation, which is used to overcome competing interference between similar representations.[21–23] To this end, it is unsurprising that one of the earliest cognitive changes in AD is the ability to differentiate between similar events.[24,25]

RESEARCH IN CONTEXT

1. **Systematic review**: Using traditional sources, such as PubMed, the authors identified studies connecting digital cognitive assessments to Alzheimer's disease (AD) risk. Prior studies demonstrated that performance on digital cognitive assessments decreases in individuals with cognitive impairment, yet the ability of these assessments to identify older adults with increased risk of future impairment remains underexplored.
2. **Interpretation**: If digital cognitive assessments can predict future cognitive decline and AD pathology, they can serve as low-burden biomarkers with prognostic value. We demonstrate that digital cognitive assessments identify individuals at risk of future cognitive decline as well as, and often reliably better than, Aβ and tau deposition. We find that deficits in mnemonic discrimination is particularly indicative of future decline.
3. **Future directions**: We encourage future researchers to utilize digital cognitive assessments, which include tasks that tax mnemonic discrimination, in their investigations of early pathological changes in AD.

Mnemonic discrimination tasks have been developed to tax hippocampal pattern separation, and they show promise in identifying individuals at high risk of AD.[26,27] Indeed, work has found that performance on these tasks is impaired in individuals with mild cognitive impairment (MCI) compared to CN older adults.[28,29] Further, these tasks can identify individuals with elevated Aβ and tau prior to cognitive decline.[15,30] However, it is not yet fully known if mnemonic discrimination deficits are predictive of future AD pathology and cognitive decline.

In this study, we investigated whether subtle cognitive changes could outperform Aβ and tau at predicting future cognitive decline. We used the Cogstate Brief Battery data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) as a testbed to assess the validity of digital biomarkers and demonstrated that performance on the cognitive battery better predicted conversion to MCI compared to Aβ and tau deposition. Further, we demonstrated that deficits in mnemonic discrimination drive this, suggesting that mnemonic discrimination deficits are an early marker of AD.

2 | METHODS

The data used here come from the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public–private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging

TABLE 1 Demographics.

	CN	MCI	AD
N	338	185	7
Age	71.59 (7.07)	72.45 (8.01)	70.71 (8.64)
Years of education	16.78 (2.24)	15.15 (2.52)	15.14 (3.24)
Percentage female (%)	60.01	40.00	28.57
Race			
White	282 (83.43%)	164 (88.65%)	5 (71.43%)
Asian	12 (3.55%)	3 (1.62%)	
African American	33 (9.76%)	14 (7.57%)	2 (28.57%)
More than one	7 (2.07%)	2 (1.08%)	n/a
Other	4 (1.18%)	2 (1.08%)	n/a
Ethnicity			
Hispanic or Latino	20 (5.92%)	12 (6.49%)	n/a
Not Hispanic or Latino	316 (93.49%)	172 (92.97%)	7 (100%)
Unknown	2 (0.59%)	n/a	n/a

Abbreviations: AD, Alzheimer's disease; CN, cognitively normal; MCI, mild cognitive impairment

(MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. For up-to-date information, see www.adni-info.org.

2.1 | Participants

Five hundred and thirty older adults who took the Cogstate Brief Battery (CBB) and underwent Aβ and tau PET imaging were included in ADNI3 (Table 1). Participants who underwent the CBB and the two PET scans within 90 days were included in the study to enable direct comparisons between the cognitive assessment and imaging biomarkers. No participants had a history of major neurological or psychiatric disorders, head trauma, or history of drug abuse or dependency. Diagnosis as CN, MCI, or AD was provided by ADNI.

2.2 | Digital cognitive battery

The CBB is a brief digital cognitive battery that includes four cognitive tasks, each designed to probe separate cognitive domains.[31,32] Subjects completed the battery in one sitting on a computer. All tasks involve playing cards and require yes or no responses. The four tasks include a detection task (DET), an identification task (IDN), one-back task (OBT), and the One Card Learning (OCL) task. Participants had to complete 75% of trials to be included in the study.

Descriptions of the tasks have been outlined in detail elsewhere.[31,33] Briefly, DET is a task that measures psychomotor speed where subjects click "Yes" when a playing card turns over. Psychomotor speed is calculated as the average reaction time over 35 valid trials. Invalid trials (anticipatory responses of less than 250 ms) were not included in the calculations, and a replacement trial was added to total 35 valid trials. IDN is a visual attention task in which either a red or black joker card flips over, and the subject responds yes if the card is red and no if it is black. The performance outcome of this task is an average reaction time over 30 valid trials. For the OBT, individuals are shown a series of playing cards and asked if the card is the same as the previous card. This task taxes working memory and performance is quantified as average reaction time over 31 trials. OCL is a task that taxes hippocampal pattern separation, which is critical for episodic memory. In this task, participants are shown a series of playing cards and are asked if they have seen the playing card previously during the task. Four cards are randomly selected to repeat eight times throughout the task. Critically, to perform this task, individuals must remember details of each playing card (ie, the conjunction of suit and number) to accurately identify these cards later in the task in the face of interference from other similar cards. For example, even though they have seen many clubs and several jacks, it is only the Jack of Clubs that are repeating. The task consists of 80 trials, and the performance outcome is accuracy.

To develop a composite score reflecting overall cognitive performance, we standardized the scores from all four tasks using *z*-scores and inverted DET, IDN, and OBT so that more negative *z*-scores corresponded to poorer performance. Then we calculated the average of these adjusted scores across all tasks to obtain the composite measure.

2.3 | PET imaging

All individuals underwent Aβ PET imaging and tau PET imaging within 90 days of administration of the CBB. Individuals either underwent flobetapir (FBP) (n = 295) or florbetaben (FBB) (n = 235) imaging to quantify Aβ standard uptake value ratio (SUVR) and flortaucepir (FTP) to quantify tau SUVR. Preprocessing of the data was handled by the ADNI PET core. Comprehensive information regarding the PET processing and acquisition techniques is available on the ADNI website at https://adni.loni.usc.edu/wp-content/uploads/2012/10/ADNI3_PET-Tech-Manual_V2.0_20161206.pdf.

Amyloid and tau PET quantification was provided by ADNI. For amyloid, a cortical composite SUVR was calculated that included the frontal, anterior/posterior cingulate, lateral parietal, and lateral temporal regions. Individuals who had a SUVR greater than two standard deviations above young controls (FBP: > 1.11, FBB: > 1.08) were considered Aβ+.[34] For continuous measures, SUVR was converted to Centiloids to enable comparisons across tracers.[35]

For assessing longitudinal Aβ and tau deposition, individuals with a follow-up PET scan after the initial scan were included. Both Aβ and tau SUVR annual percentage change (APC) was calculated by taking the difference in uptake (Centiloids for Aβ, SUVR for tau) between the initial scan and the most recent scan divided by the years between scans.

2.4 | Statistical analyses

All analyses were done in Python and RStudio. Logistic regressions were run using statsmodels[36] to predict cognitive status and conversion status. Area under the curve (AUC) measures were derived from receiver operating characteristic (ROC) curves of the logistic regressions. Random permutation tests with 1000 permutations were used to compare AUCs between models. Commonality analyses were performed using the yhat package in RStudio. To identify how each variable acted in relation to the others, we performed a 6-choose-3 combinatorial analysis and quantified the number of times each metric appeared in the top third of AUCs. Pearson correlations were used to assess the associations between two continuous variables. One-way ANOVAs with Tukey's honestly significance difference (HSD) post hoc tests were used to identify within-factor differences. For all analyses, $p < 0.05$ was considered reliable.

3 | RESULTS

3.1 | Digital cognitive biomarkers perform as well as and often better than Aβ and EC tau at distinguishing between CN, MCI, and AD

Significant research has shown that Aβ and tau levels are elevated in MCI and AD compared to CN older adults. Consequently, we investigated whether digital biomarkers could also differentiate between CN, MCI, and AD statuses. As expected, our findings indicate an increase in Aβ in individuals with MCI or AD compared to CN older adults with a marginal increase between MCI and AD (Figure 1A; one-way ANOVA: $F(2) = 12.04$, $p < 0.0001$, Tukey's HSD: CN vs MCI: $p < 0.0001$, CN vs AD: $p < 0.0001$, MCI vs AD: $p = 0.09$). Similarly, EC tau was increased in MCI and further increased in AD (Figure 1B; one-way ANOVA: $F(2) = 39.39$, $p < 0.0001$, Tukey's HSD: CN vs MCI: $p < 0.0001$, CN vs AD: $p < 0.0001$, MCI vs AD: $p < 0.01$). Additionally, performance on the digital cognitive battery was related to cognitive status, with CN individuals outperforming those with MCI, who in turn outperformed those with AD (Figure 1C; one-way ANOVA: $F(2) = 40.15$, $p < 0.0001$, Tukey's HSD: CN vs MCI: $p < 0.0001$, CN vs AD: $p < 0.0001$, MCI vs AD: $p = 0.03$).

Given that all measures could differentiate individuals based on cognitive tasks, we explored whether the degree of differences between groups varied when considering Aβ, tau, or cognitive performance. To assess this, we computed effect sizes for the differences categorized by cognitive status. We observed that cognitive performance and EC tau had roughly equivalent effect sizes for CN versus MCI and for MCI versus AD (Figure 1D) with cortical Aβ having a smaller effect size (CN vs MCI: cortical Aβ d = 0.37, confidence interval [CI] = [0.19 0.56], EC tau d = 0.72, CI = [0.53 0.90], digital cognitive battery d = 0.74, CI = [0.56 0.93]; MCI vs AD: cortical Aβ d = 0.66, CI = [−0.10 1.43], EC tau d = 0.89, CI = [0.13 1.66], digital cognitive battery d = 0.92, CI = [0.16 1.69]). Conversely, EC tau had the largest effect size for separating AD from CN (cortical Aβ d = 1.36, CI = [0.60 2.12], EC tau d = 2.64, CI = [1.86 3.41], digital cognitive battery d = 1.80, CI = [1.04 2.57]).

To better understand the sensitivity and specificity of these various markers, we next performed a set of logistic regression and ROC analyses using cortical Aβ, EC tau, and cognitive performance as variables to predict cognitive status (Figure 1G-I). Our analysis confirmed that each of the three measures could effectively differentiate between CN and MCI (Figure 1G). However, performance on the digital cognitive battery reached a higher AUC compared to either Aβ or tau measures (cortical Aβ AUC = 0.55, $p < 0.0001$, EC tau AUC = 0.65, $p < 0.0001$, digital cognitive battery AUC = 0.70, $p < 0.0001$).

We used a permutation test (1000 permutations) to determine whether any of these AUCs reliably differed. We found that performance on the digital cognitive battery and EC tau proved to be more predictive of diagnostic status than Aβ and performance on the digital cognitive battery was qualitatively better compared to tau, and this approached significance (digital cognitive battery vs cortical Aβ $p < 0.0001$, EC tau vs cortical Aβ $p < 0.01$, digital cognitive battery vs EC tau $p = 0.07$). Further, all three measures could differentiate CN versus AD (Figure 1I; cortical Aβ AUC = 0.66, $p < 0.001$, EC tau AUC = 0.80, $p < 0.0001$, digital cognitive battery AUC = 0.87, $p < 0.0001$), with cognitive performance reaching a qualitatively higher AUC compared to both Aβ and tau, but a random permutation test ($n = 1000$) found no reliable differences between AUCs (all ps > 0.15). Conversely, only EC tau and cognitive performance could reliably distinguish MCI and AD, with both measures reaching similar AUCs (Figure 1H; cortical Aβ AUC = 0.64, $p = 0.10$, EC tau AUC = 0.69, $p = 0.04$, digital cognitive battery AUC = 0.70, $p = 0.02$), with a random permutation test ($n = 1000$) finding no reliable differences between models (all ps > 0.5). Thus, performance on the digital cognitive battery was at least as good as, and often reliably better than, amyloid and tau at differentiating individuals based on cognitive status.

3.2 | Deficits in mnemonic discrimination is the best predictor of MCI and AD

Given the high performance of the digital cognitive battery in detecting cognitive impairment, we next asked which cognitive domains were particularly informative by assessing performance on each of the four tasks separately. We found that performance on DET differed as a function of cognitive status with decreased psychomotor speed in MCI and AD compared to CN (Figure 2A). However, performance was not reliably different in individuals with AD compared to MCI (one-way ANOVA: $F(2) = 13.99$, $p < 0.0001$, Tukey's HSD: CN vs MCI: $p < 0.0001$, CN vs AD: $p < 0.01$, MCI vs AD: $p = 0.14$). Similarly, we found that visual attention, measured via IDN, was compromised in MCI and AD compared to CN, but there was no reliable difference on IDN between MCI and AD (Figure 2B; one-way ANOVA: $F(2) = 19.68$, $p < 0.0001$, Tukey's HSD: CN vs MCI: $p < 0.0001$, CN vs AD: $p < 0.01$, MCI vs AD: $p = 0.21$). Next, we found that performance on the OBT, which assesses working memory, declined in MCI and AD compared to CN, but was not

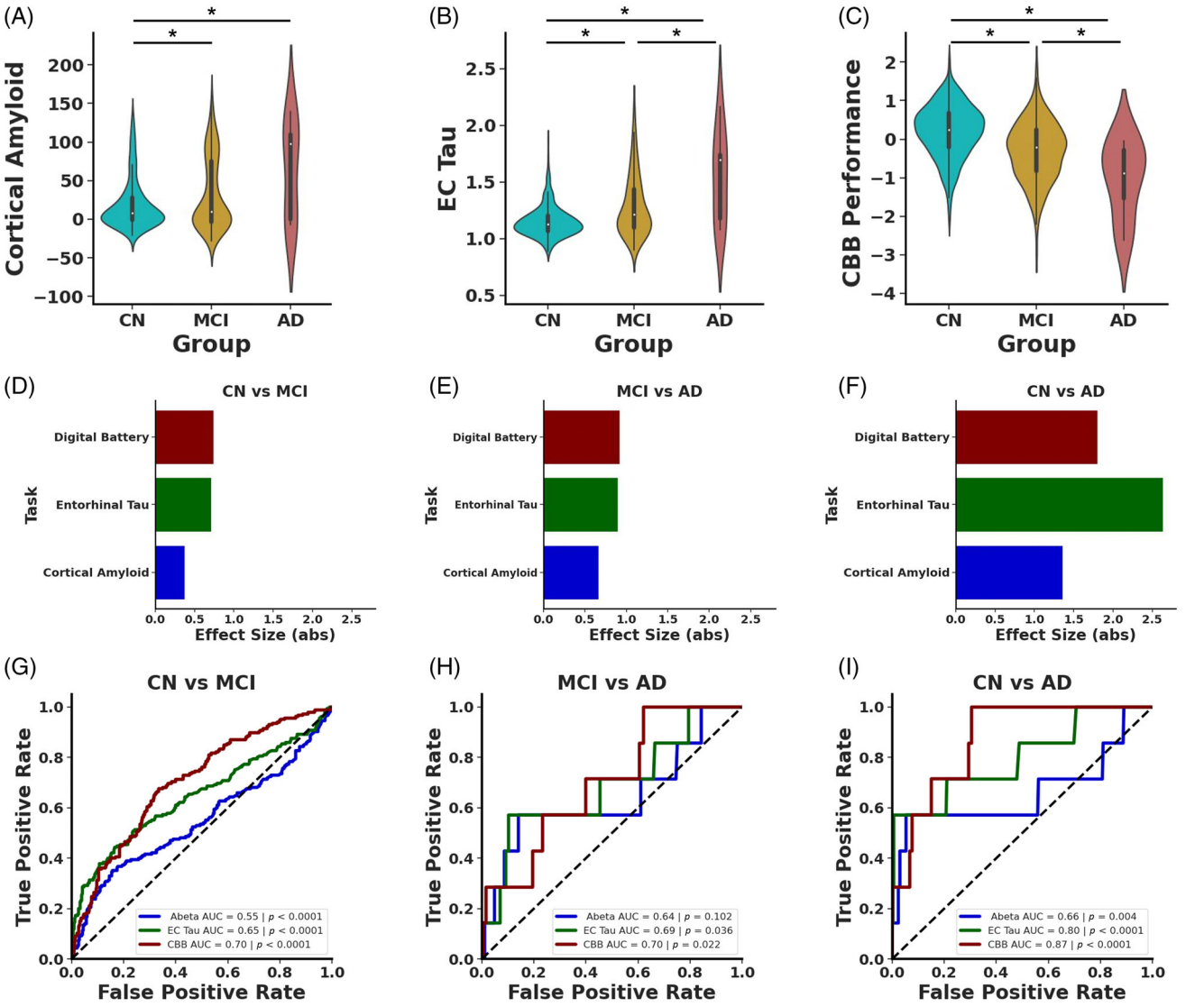

FIGURE 1 AD pathologies and digital cognitive assessments differentiate by diagnosis. (A) Cortical Aβ is increased in MCI (yellow) and AD (red) compared to CN (blue) older adults. (B) EC tau SUVR is increased in MCI compared to CN and further increased in AD compared to MCI. (C) Performance on digital cognitive battery declines in MCI with further impairment in AD. Effect sizes for cortical Aβ (blue), EC tau (green), and performance on digital cognitive assessment (maroon) between (D) CN and MCI, (E) MCI and AD, and (F) CN and AD. (G) ROC curves show that AD pathologies and performance on digital cognitive assessment can each differentiate CN and MCI, but the digital cognitive assessment was reliably better than the other two measures. (H) ROC curves demonstrating that only the digital cognitive assessment and EC tau can differentiate MCI and AD. (I) Each measure reliably differentiates CN from AD.

reliably different between AD and MCI (Figure 2C; one-way ANOVA: $F(2) = 17.92$, $p < 0.0001$, Tukey's HSD: CN vs MCI: $p < 0.0001$, CN vs AD: $p < 0.01$, MCI vs AD: $p = 0.21$). Finally, we assessed whether OCL, which measures mnemonic discrimination, declined as a function of cognitive status. We observed that performance on OCL declined in MCI compared to CN, and this was exacerbated in AD (Figure 2D; one-way ANOVA: $F(2) = 40.65$, $p < 0.0001$, Tukey's HSD: CN vs MCI: $p < 0.0001$, CN vs AD: $p < 0.0001$, MCI vs AD: $p = 0.048$), indicating that only OCL was sensitive to the additional decline in AD.

These findings collectively imply that MCI and AD are associated with widespread cognitive deficits. However, OCL showed the greatest difference between individuals who were CN compared to those with MCI (Figure 2E) or AD (Figure 2G) based on the magnitude of effect sizes calculated for each cognitive task (CN vs MCI: DET d = 0.42, CI = [0.24 0.60], IDN d = 0.53, CI = [0.35 0.71], OBT d = 0.50, CI = [0.31 0.68], OCL d = 0.75, CI = [0.56 0.94], CN vs AD: DET d = 1.21, CI = [0.45 1.97], IDN d = 1.35, CI = [0.59 2.11], OBT d = 1.21, CI = [0.45 1.97], OCL d = 1.64, CI = [0.88 2.40]). However, OCL and DET were roughly equivalent in their effect sizes between MCI and AD (Figure 2F; DET d = 0.67, CI = [−0.09 1.43], IDN d = 0.52, CI = [−0.24 1.29], OBT d = 0.59, CI = [−0.17 1.35], OCL d = 0.95, CI = [0.19 1.72]).

To further investigate how well these tasks separate individuals based on cognitive status, we conducted separate logistic regressions

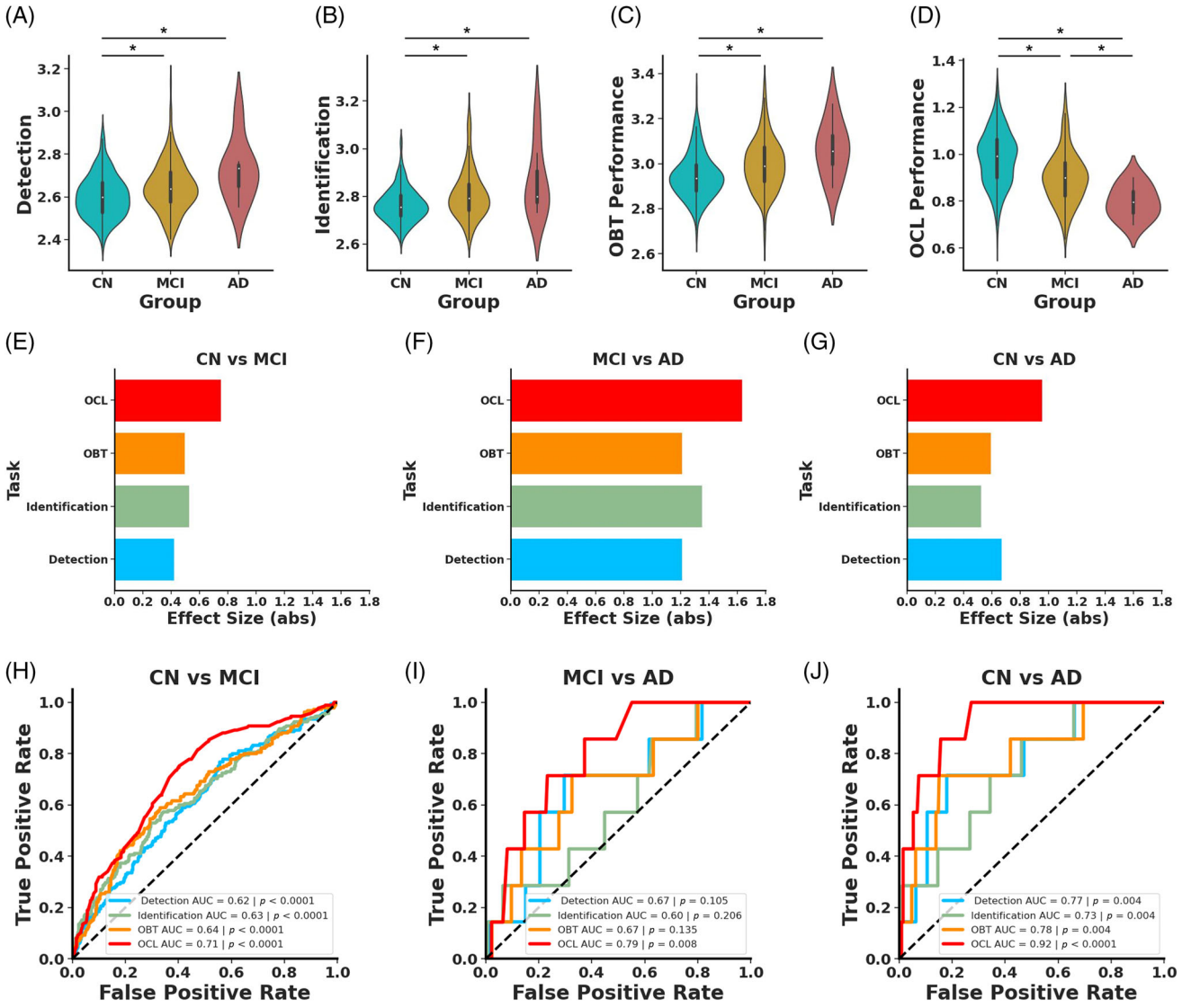

FIGURE 2 OCL is superior to other tasks for differentiating individuals by diagnosis. Violin plots depicting performance differences on (A) DET, (B) IDN, (C) OBT, and (D) OCL tasks as a function of cognitive status. Individuals with MCI (yellow) or AD (red) are impaired on all four tasks compared to CN (blue) and individuals with AD are reliably worse on OCL compared to MCI. Effect sizes for IDN (light green), DET (light blue), OBT (orange) OCL (red) between (E) CN and MCI, (F) MCI and AD, and (G) CN and AD. (H) ROC curves show that each task can reliably differentiate CN and MCI with OCL performing reliably better than the other measures. (I) Only OCL performance can differentiate MCI and AD. (J) Performance on each task reliably differentiates CN from AD with OCL performance reaching the highest AUC.

using performance on each of the cognitive tasks to predict cognitive status. The results demonstrated that all tasks could differentiate CN from MCI, with OCL reaching the highest AUC (Figure 2H; DET AUC = 0.62, $p < 0.0001$, IDN AUC = 0.63, $p < 0.0001$, OBT AUC = 0.64, $p < 0.0001$, OCL AUC = 0.71, $p < 0.0001$). We next asked which cognitive task was the most predictive of MCI by conducting a random permutation test and found that OCL better predicted cognitive status compared to the other three tasks (OCL vs DET $p < 0.01$, OCL vs IDN $p = 0.01$, OCL vs OBT $p = 0.03$). Further, the other tasks did not vary in their predictive power (all ps > 0.28). This pattern held true when predicting CN versus AD, where again all tasks were effective (Figure 2J; DET AUC = 0.77, $p < 0.01$, IDN AUC = 0.73, $p < 0.01$, OBT AUC = 0.78, $p < 0.01$, OCL AUC = 0.92, $p < 0.0001$), and the models did not differ in their predictive value (all ps > 0.15). However, when differentiating MCI from AD, only the OCL task showed reliable predictive capability, unlike the other tasks (Figure 2I; DET AUC = 0.67, $p = 0.11$, IDN AUC = 0.60, $p = 0.21$, OBT AUC = 0.67, $p = 0.14$, OCL AUC = 0.79, $p < 0.01$). However, a random permutation test found no reliable differences between models (all ps > 0.16). Given that OCL better differentiated CN and MCI compared to the other tasks, we compared the predictive capacity of OCL compared to Aβ and tau. A random permutation test ($n = 1000$) found that OCL was superior at differentiating CN and MCI compared to both cortical Aβ and EC tau (OCL vs cortical Aβ $p < 0.0001$, OCL vs EC tau $p = 0.049$). This suggests that OCL, which taxes hippocampal pattern separation, is particularly vulnerable to MCI and AD.

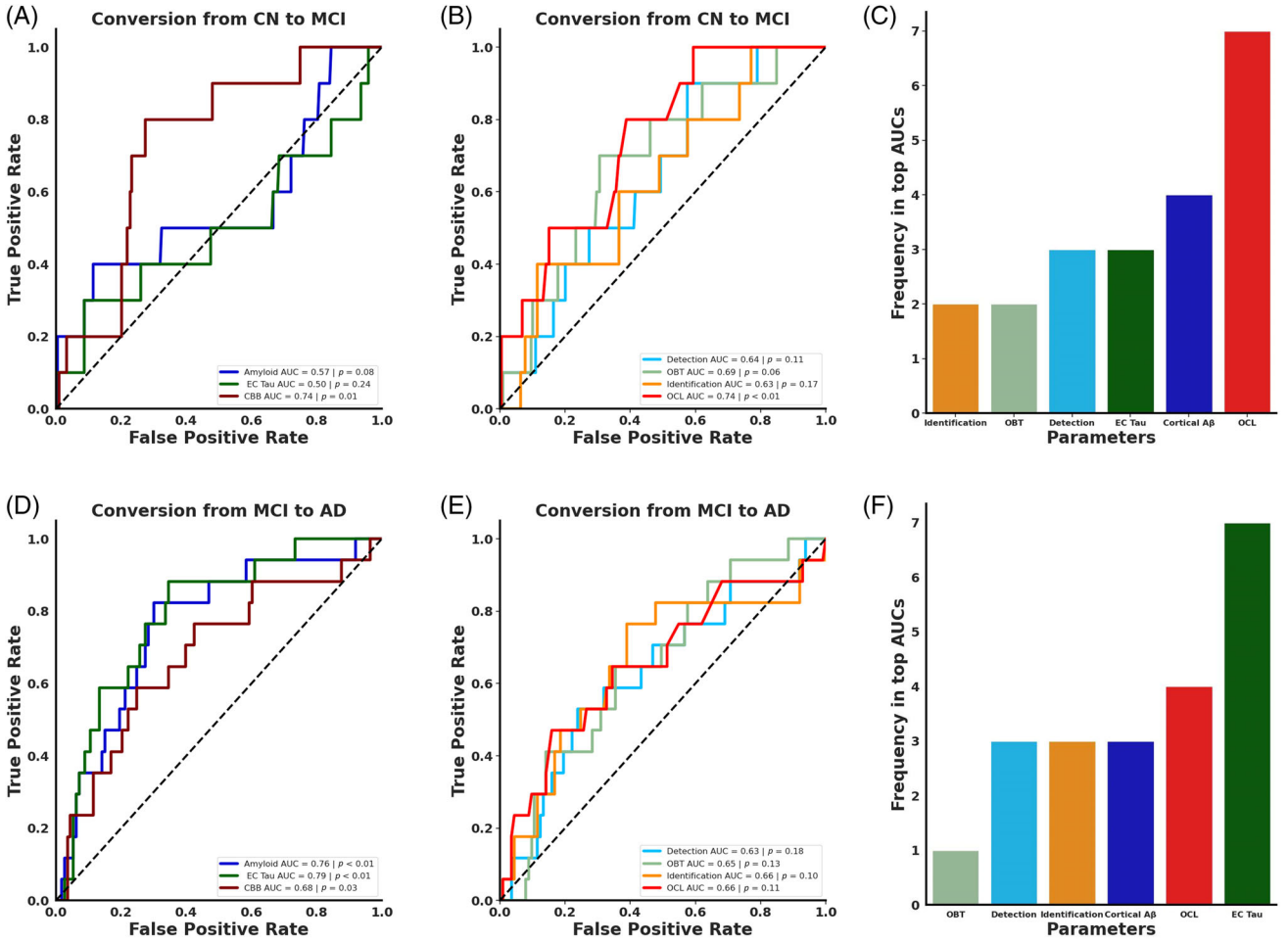

FIGURE 3 Predicting cognitive decline over 2 years. (A) ROC curves demonstrating that performance on the digital cognitive battery (maroon) reliably predicts future cognitive decline while cortical Aβ (blue) and EC tau (green) do not. (B) OCL performance reliably predicts future cognitive decline while IDN (light green), DET (light blue), and OBT (orange) do not. (C) OCL appears nearly twice as often in top third of models from a permutation analysis, suggesting that OCL performance is most influential in predicting future cognitive decline. (D) ROC curves demonstrate that cortical Aβ, EC tau, and the digital cognitive assessment could each predict conversion from MCI to AD. (E) None of the cognitive tasks could reliably predict conversion from MCI to AD. (F) A permutation analysis found that EC tau was the most common metric in the top third of models suggesting that this measure is important for predicting progression from MCI to AD.

3.3 | Deficits in mnemonic discrimination are the best predictor of progression to MCI, while all measures predict progression to AD

We next asked whether performance on the digital cognitive assessment could better predict conversion from CN to MCI compared to Aβ and tau. To explore this, we identified individuals who had a follow-up visit 2 years after undergoing the digital cognitive assessment and Aβ and tau PET imaging. All individuals who had a study visit within 1 to 3 years of their digital cognitive assessment were included in this analysis. For individuals with multiple visits in this timeframe, we selected the visit closest to 2 years after the assessment. Individuals who were CN at baseline and remained CN 2 years later were called non-converters ($n = 219$, age = 72.37 [7.09], 130F, 16.82 [2.31] years of education), while individuals who progressed to MCI within 2 years of baseline were called converters ($n = 10$, age = 72.00 [6.91], 3F, 16.10 [2.47] years of education). We next conducted logistic regressions using either baseline digital cognitive assessment scores, cortical Aβ, or EC tau to differentiate converters and non-converters. We found that performance on the digital cognitive assessment predicted conversion over 2 years while Aβ and tau could not (Figure 3A; cortical Aβ AUC = 0.57, $p = 0.08$, EC tau AUC = 0.50, $p = 0.24$, digital cognitive battery AUC = 0.74, $p = 0.01$). A random permutation test demonstrated that the digital cognitive battery was superior to EC tau, with no reliable difference between the digital cognitive battery and cortical Aβ (digital cognitive battery vs EC tau $p = 0.04$, digital cognitive battery vs cortical Aβ $p = 0.17$, EC tau vs cortical Aβ $p = 0.54$).

To further assess whether the digital cognitive battery was superior to cortical Aβ and EC tau, we conducted a multiple logistic regression with all three measures predicting conversion status. The combined model was able to reliably predict conversion status ($R^2 = 0.10$, BIC = 95.55, $p = 0.04$), but performance on the digital cognitive battery was the only predictor that was statistically reliable after controlling

for the other variables (digital cognitive battery z = -2.25, $p = 0.03$, EC tau z = 0.45, $p = 0.66$, cortical Aβ z = 1.15, $p = 0.25$). Further, we conducted a commonality analysis to identify which measure contributes the most to predicting conversion to MCI. We found that performance on the digital cognitive battery contributed the most to the model, explaining 56.2% of the variance. Conversely, cortical Aβ explained 18.7% and EC tau explained 1.5% of the variance (Table 2). These results suggest that the digital cognitive measures were superior to Cortical Aβ and EC tau in predicting short-term conversion to MCI.

To investigate which cognitive domains were the best indicators of conversion from CN to MCI, we conducted separate logistic regressions for each task. We found that only OCL could predict conversion to MCI over 2 years while the other tasks did not reliably predict converters (Figure 3B; Detection AUC = 0.64, $p = 0.11$, Identification AUC = 0.69, $p = 0.06$, OBT AUC = 0.63, $p = 0.17$, OCL AUC = 0.74, $p < 0.01$). A random permutation test did not find any reliable differences between models (all ps > 0.32). Notably, the predictive strength of OCL was comparable to the composite score of the entire digital cognitive battery.

In a post-hoc analysis using a multiple logistic regression, we found that the overall model was modestly able to predict conversion status ($R^2 = 0.11$, Bayesian information criterion (BIC) = 100.25, $p = 0.06$). Within the model, OCL was the only statistically reliable predictor (OCL Z = −2.18, $p = 0.03$, OBT Z = 0.08, $p = 0.94$, DET Z = 0.29, $p = 0.77$, IDN Z = 0.42, $p = 0.67$), demonstrating that mnemonic discrimination was still a reliable predictor even when controlling for the other cognitive domains assessed. A commonality analysis found that OCL explained 54.3% of the variance, far more than any other task, with no other task explaining more than 5% of the variance. Importantly, only 11% of the variance was shared across all tasks, suggesting that while the tasks are somewhat related, they each individually contribute to assessing the risk of progressing from CN to MCI (Table 2). To further verify that OCL was the superior measure for predicting conversion to MCI, we performed a 6-choose-3 combinatorial analysis and quantified how often each measure occurred in the top third of resulting AUCs. We found that OCL appeared in all the top models and appeared nearly twice as much as any other measure (Figure 3C). These results collectively suggest that deficits in mnemonic discrimination are predictive of conversion to MCI.

We next investigated whether these measures could predict progression from MCI to AD over 2 years. To address this, we first identified individuals who were initially diagnosed with MCI and divided them into two groups: non-converters, who remained stable with MCI ($n = 113$, age = 73.08 [8.36], 40F, 16.06 [2.69] years of education), and converters, who progressed to AD ($n = 17$, age = 74.82 [7.61], 8F, 16.76 [2.25] years of education). Employing logistic regressions for each measure, we found that EC tau, cortical Aβ, and the digital cognitive assessment were all effective predictors of progression (Figure 3D; cortical Aβ AUC = 0.76, $p < 0.01$, EC tau AUC = 0.79, $p < 0.01$, digital cognitive battery AUC = 0.68, $p = 0.03$). Further, we did not find any differences between the measures for predicting conversion to AD (all ps > 0.28).

TABLE 2 Commonality analysis predicting conversion from cognitively normal to mild cognitive impairment.

AD biomarkers versus digital biomarkers: cognitively normal to mild cognitive impairment		
Measure	**Coefficient**	**Percentage variance explained (%)**
Cortical Aβ	0.00765	18.75
EC tau	0.00063	1.55
Digital cognitive battery	0.02295	56.25
Cortical Aβ and EC tau	0.00289	7.08
Cortical Aβ and digital cognitive battery	0.00330	8.09
EC tau and digital cognitive battery	0.00093	2.27
Cortical Aβ and EC tau and digital cognitive battery	0.00245	6.01
Digital cognitive tasks: cognitively normal to mild cognitive impairment		
Measure	**Coefficient**	**Percentage variance explained (%)**
OCL	0.02195	54.34
OBT	0.00001	0.02
Identification	0.00214	5.30
Detection	0.00008	0.20
OCL and OBT	0.00003	0.08
OCL and Identification	0.00163	4.03
OBT and Identification	0.00082	2.04
OCL and Detection	0.00061	1.52
OBT and Detection	0.00001	0.01
Identification and Detection	0.00179	4.43
OCL and OBT and Identification	0.00190	4.71
OCL and OBT and Detection	−0.00003	−0.07
OCL and Identification and Detection	0.00355	8.80
OBT and Identification and Detection	0.00147	3.64
OCL and OBT and Identification and Detection	0.00442	10.95

Abbreviations: Aβ, amyloid beta; OBT, one-back task; OCL, One Card Learning.

Interestingly, in a post hoc multiple logistic regression, we found that while the overall model was significant ($R^2 = 0.17$, BIC = 102.94, $p < 0.001$), none of the measures could reliably predict conversion from MCI to AD (digital cognitive battery Z = −1.09, $p = 0.28$, cortical Aβ Z = 1.48, $p = 0.14$, EC tau Z = 2.53, $p = 0.11$). This suggests that the measures likely share variance and therefore are not individually significant

after controlling for the other measures. To this end, we conducted a commonality analysis and found that nearly half the variance (49.18%) was shared between cortical Aβ and EC tau and 12.18% of the variance was explained by EC tau alone. Conversely, cortical Aβ and the digital cognitive battery each explained less than 10% of the variance (Table 3).

We next asked which cognitive domains predicted conversion from MCI to AD. We conducted separate logistic regressions and found that none of the cognitive tasks could predict progression from MCI to AD (Figure 3E; DET AUC = 0.63, $p = 0.18$, IDN AUC = 0.65, $p = 0.13$, OBT AUC = 0.66, $p = 0.10$, OCL AUC = 0.66, $p = 0.11$). These measures also did not statistically differ in predicting conversion status (all ps > 0.70). A post hoc multiple logistic regression was not able to differentiate converters and non-converters ($R^2 = 0.06$, BIC = 119.36, $p = 0.21$), and none of the individual metrics were able to reliably predict converters (all ps > 0.12). In a commonality analysis, 39.20% of the variance was unique to OCL, with no more than 6% of the variance being unique to any of the other tasks (Table 3). When conducting a 6-choose-3 combinatorial analysis with all the measures, we observed that EC tau was the most represented in the top third of models, with OCL as a distant second (Figure 3F). This underscores that while multiple measures predict progression to AD, EC tau may be particularly indicative of future decline.

In a subset of individuals, we investigated whether OCL performance could predict converters as well as standard neuropsychological tasks. For predicting those who transitioned from CN to MCI, we found that OCL performance did as well as performance on the RAVLT, a gold-standard episodic memory task that also taxes mnemonic discrimination. Further, OCL did qualitatively better than the trail-making task (difference in seconds between trails A and B) and the clock drawing task (Figure S1A; clock-drawing AUC = 0.64, $p = 0.24$, trail-making AUC = 0.67, $p = 0.01$, RAVLT AUC = 0.75, $p = 0.02$, OCL AUC = 0.76, $p < 0.01$). For predicting those who progressed from MCI to AD, we found the OCL performance did as well as RAVLT performance and performance on both trail making and clock drawing were not reliable predictors (Figure S1B; clock-drawing AUC = 0.61, $p = 0.26$, trail-making AUC = 0.67, $p = 0.44$, RAVLT AUC = 0.76, $p < 0.01$, OCL AUC = 0.70, $p = 0.04$).

3.4 | Mnemonic discrimination deficits predict future impairment on MMSE in CN older adults

Given that OCL was the most important measure for predicting conversion to MCI, we next asked whether performance on this task predicted cognitive changes in CN older adults. To assess this, we asked whether OCL performance, EC tau, or cortical Aβ predicted decline on the MMSE, a standard task used to quantify global cognitive ability. We calculated MMSE APC as the difference between the most recent MMSE score and the MMSE score at baseline divided by the difference in years. We found that baseline cortical Aβ and EC tau were not associated with longitudinal change on the MMSE (Figure 4A; cortical Aβ: $r_p = -0.07$. $p = 0.30$, Figure 4B; EC tau: $r_p = 0.02$, $p = 0.76$). Conversely, we found a reliable positive association between baseline OCL performance and MMSE APC (Figure 4C; $r_p = 0.25$, $p < 0.0001$), suggesting that impairments on OCL were related to longitudinal cognitive decline. Further, we found that there was no relationship between baseline MMSE and longitudinal changes in cortical Aβ, EC tau, or OCL

TABLE 3 Commonality analysis predicting conversion from mild cognitive impairment to Alzheimer's disease.

AD biomarkers versus digital biomarkers: mild cognitive impairment to Alzheimer's disease		
Measure	**Coefficient**	**Percentage variance explained (%)**
Cortical Aβ	0.01313	9.04
EC tau	0.02456	16.90
Digital cognitive battery	0.01164	8.01
Cortical amyloid and EC tau	0.07165	49.31
Cortical Aβ and digital cognitive battery	0.00157	1.08
EC tau and digital cognitive battery	0.00506	3.48
Cortical Aβ and EC tau and digital cognitive battery	0.01770	12.18
Digital Cognitive tasks: mild cognitive impairment to Alzheimer's disease		
Measure	**Coefficient**	**Percentage variance explained (%)**
OCL	0.01662	39.30
OBT	0.00279	6.59
Identification	0.00259	6.12
Detection	0.00067	1.59
OCL and OBT	0.00220	5.20
OCL and Identification	−0.00091	−2.15
OBT and Identification	0.00371	8.77
OCL and Detection	−0.00001	-0.03
OBT and Detection	0.00050	1.19
Identification and Detection	0.00361	8.55
OCL and OBT and Identification	0.00036	0.86
OCL and OBT and Detection	0.00019	0.46
OCL and Identification and Detection	−0.00083	−1.97
OBT and Identification and Detection	0.01011	23.91
OCL and OBT and Identification and Detection	0.00068	1.61

Abbreviations: Aβ, amyloid beta; OBT, one-back task; OCL, One Card Learning

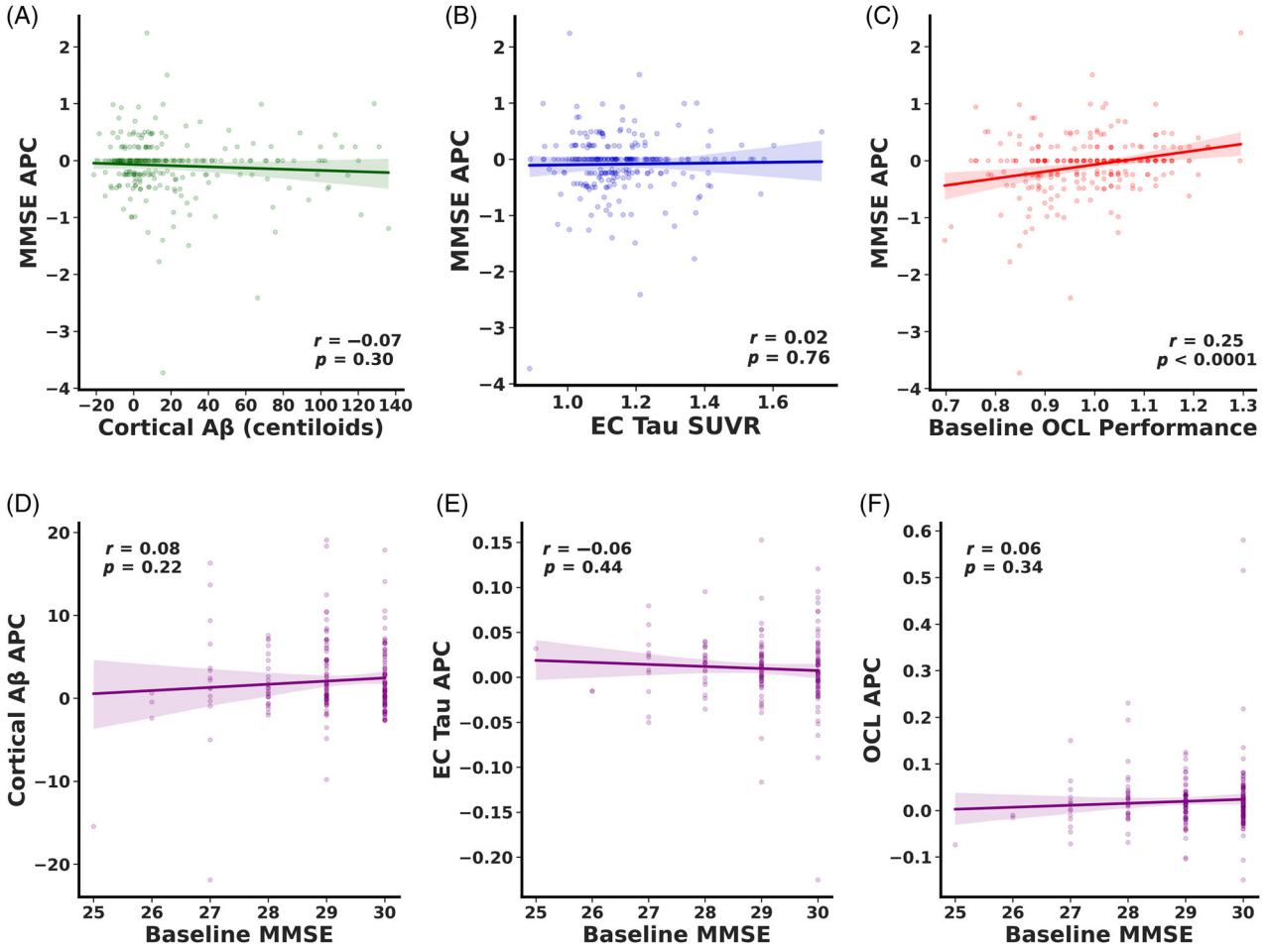

FIGURE 4 Only OCL performance predicts cognitive decline in CN older adults. No relationship was observed between baseline (A) cortical Aβ or (B) EC tau and longitudinal change on MMSE. (C) Positive correlation with OCL performance and annual change on MMSE suggesting that lower OCL performance is associated with longitudinal decline on MMSE. No relationship was established between baseline MMSE and longitudinal change in (D) cortical Aβ (E) EC tau or (F) OCL performance.

performance (Figure 4D; cortical Aβ: $r_p = 0.08$, $p = 0.22$, Figure 4E; EC tau: $r_p = -0.06$, $p = 0.44$, Figure 4F; OCL: $r_p = 0.06$, $p = 0.34$). This suggests that OCL performance predicts future cognitive decline in CN older adults.

3.5 | Mnemonic discrimination performance predicts future tau accumulation in entorhinal cortex and inferior temporal cortex

Given the significance of OCL performance as an indicator of future cognitive decline, we proceeded to explore whether performance could serve as a predictor of future tau accumulation in EC and Inferior Temporal (IT) cortex. To do this, we correlated baseline performance on the OCL task with tau SUVR APC in A$\beta-$ and A$\beta+$ individuals. Our findings revealed a significant negative correlation between baseline OCL performance and EC tau accumulation among A$\beta+$ but not A$\beta-$ CN older adults (Figure 5A; A$\beta+$: $r_p = -0.26$, $p = 0.03$, A$\beta-$: $r_p = -0.06$, $p = 0.55$). Conversely, there was no association between baseline OCL and EC tau SUVR APC in subjects with MCI, regardless of Aβ status (Figure 5B; A$\beta+$: $r_p = -0.04$, $p = 0.82$, A$\beta-$: $r_p = 0.17$, $p = 0.33$). When investigating whether OCL related to future tau deposition in IT cortex, we found a modest relationship between baseline OCL and IT tau SUVR APC in A$\beta+$, but not A$\beta-$ CN individuals (Figure 5C; A$\beta+$: $r_p = -0.23$, $p = 0.07$, A$\beta-$: $r_p = -0.03$, $p = 0.76$). However, we did observe a significant negative association between OCL performance and IT tau SUVR APC in A$\beta+$ subjects with MCI, but not A$\beta-$ MCI individuals (Figure 5D; A$\beta+$: $r_p = -0.43$, $p = 0.01$, A$\beta-$: $r_p = 0.19$, $p = 0.30$).

4 | DISCUSSION

There is a critical need for the development and validation of low-burden biomarkers that identify individuals at high risk of future cognitive decline. While great strides have been made with biofluid and imaging biomarkers, less work has identified cognitive biomarkers that predict future cognitive decline. Here we used the CBB as a testbed to demonstrate that digital cognitive assessments can predict future cognitive decline. We found that the digital cognitive battery identified

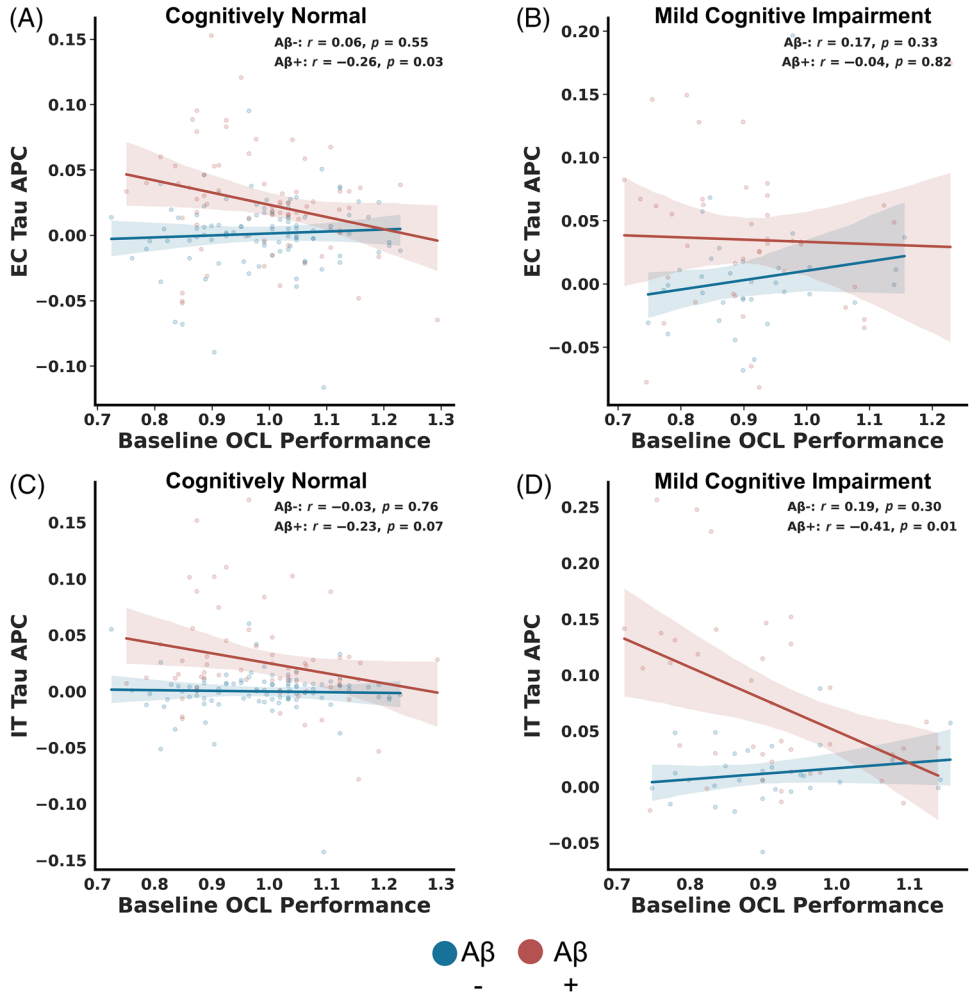

FIGURE 5 OCL is related to future tau accumulation. (A) Lower OCL performance is associated with future EC tau in Aβ+ (red), but not Aβ− (blue) CN older adults. (B) No reliable relationship was observed between OCL performance and EC tau regardless of Aβ status in MCI. (C) No reliable correlation was observed between baseline OCL and IT tau accumulation in either Aβ+ or Aβ− CN older adults. (D) Lower baseline OCL performance is associated with increased future IT tau accumulation in Aβ+ but not Aβ− (red) MCI older adults.

individuals with MCI and predicted future cognitive decline at a higher proficiency compared to Aβ and tau levels. Further, mnemonic discrimination deficits were most predictive of future cognitive decline and are also related to future tau accumulation in Aβ+ older adults. This work highlights the value of digital cognitive biomarkers for identifying those at high risk of AD.

4.1 | Utility of digital cognitive batteries in identifying individuals with cognitive decline

Prior work demonstrated the ability of digital cognitive batteries to identify individuals with cognitive impairment.[8,9] Specifically, the CBB can accurately distinguish between CN and MCI states at high proficiency, with each of the four tasks differentiating between unimpaired and impaired older adults.[37] We replicated this in a different cohort demonstrating that all tasks can distinguish between CN and MCI. In addition, other cognitive batteries have shown promise in distinguishing between CN and MCI at high proficiency.[9,25] Specifically, a battery including multiple mnemonic discrimination tasks could identify those with increased AD biomarkers and was informative of future cognitive decline.[38] However, less has been done to assess how digital cognitive assessments compare to Aβ and tau pathology in distinguishing CN and MCI. We demonstrated that the digital cognitive battery was superior to both cortical Aβ and EC tau in differentiating CN from MCI, reaffirming the benefits of digital cognitive batteries. While our work suggests that digital cognitive assessments can accurately predict diagnosis, future work is needed to understand whether these assessments can aid the diagnosis process in the clinical setting.

Identifying individuals at high risk of future cognitive decline can increase the therapeutic window for currently approved therapies and can aid in clinical trial recruitment. Prior work found that Aβ and tau pathologies were predictive of future cognitive decline.[39] However, the lack of specificity and sensitivity of these AD biomarkers suggests

that other biomarkers are also needed. We demonstrated that digital cognitive biomarkers were superior to Aβ and tau in predicting future cognitive decline. However, one limitation is the relatively short (2 years) follow-up time between the battery and future diagnosis, resulting in a limited number of individuals who converted. The digital cognitive battery was added to ADNI recently, precluding longer follow-up visits, but future work will need to address how early deficits emerge on digital cognitive assessments in preclinical AD.

4.2 | All biomarkers were predictive of progression to dementia

The digital cognitive battery was superior to Aβ and tau for predicting progression to MCI, but we did not see the same pattern in individuals progressing from MCI to AD. In these individuals, performance on the digital cognitive assessment did predict progression, but entorhinal tau was more indicative of future decline. This aligns with prior work suggesting that tau accumulation is most rapid during MCI and relates to neurodegeneration and cognitive decline in MCI.[40,41] Importantly, in a commonality analysis, we found that nearly half of the variance was shared by cortical Aβ and entorhinal tau, which suggests that these pathologies are critical for progression to dementia. However, these biomarkers were not reliably better than the digital cognitive assessments at differentiating MCI from AD or predicting conversion to AD. Together, these results indicate that cognitive changes are often superior to AD biomarkers for predicting progression to MCI, but once individuals exhibit overt cognitive impairment, AD pathologies and digital assessments are both able to predict progression to dementia.

4.3 | Selective vulnerability of mnemonic discrimination in AD

The digital cognitive battery included tasks across multiple domains that tap into different neural circuits, so we asked whether one task was superior to the others in differentiating cognitive impairment and predicting future decline. We found that performance on the OCL task was most informative of cognitive status, reaching higher AUCs compared to the other tasks. Of note, MCI and AD were diagnosed cognitively, so it is not completely unsurprising that OCL performance decreased in MCI and AD. Critically, however, we compared this with other cognitive domains and Aβ and tau. Further, performance on the digital unsupervised tasks was not used in the diagnosis of MCI or AD. Rather, a comprehensive in-person gold-standard neuropsychological testing session was used for diagnosis. The OCL task requires individuals to remember details of playing cards despite accumulating interference hindering one from accurately identifying cards later in the task while rejecting similar playing cards; therefore, prima facie, it taxes hippocampal pattern separation. This design is similar to common mnemonic discrimination tasks, such as the MST, which require individuals to remember the details of everyday objects in order to identify these objects later in the task and reject similar, but not identical, lures. Both these tasks are designed based on the complementary learning systems framework, where it is proposed that the hippocampus uses pattern separation to rapidly learn details.[42] However, future work will need to investigate whether OCL deficits correlate with deficits on common mnemonic discrimination tasks such as the MST and whether OCL performance is impaired in individuals with compromised hippocampal integrity. Therefore, our work suggests that deficits in mnemonic discrimination were able to reliably predict impairment across the entire neuropsychological battery and at a higher proficiency than the other cognitive domains and AD biomarkers. Further, we demonstrate that OCL performance reliably predicted progression to MCI over 2 years even when controlling for performance on the other tasks. Additionally, when comparing OCL performance to performance on standard neuropsychological assessments, we found that this task did as well as RAVLT performance and was qualitatively better than the clock-drawing and trail-making tasks in identifying converters. The RAVLT is a gold-standard episodic memory task that taxes mnemonic discrimination by not only leveraging a traditional list-learning paradigm (requiring quickly learning the association between the items and the context of being on the study list) but also leveraging the need to overcome interference. However, this task is administered by a trained psychometrist in a clinic. Therefore, not only was OCL task performance capable of predicting those at risk for future cognitive decline, but it could also match the ability of traditional in-person assessments.

We hypothesize that hippocampal pattern separation, which reduces interference between similar representations, is particularly vulnerable to AD pathology.[27,28] Indeed, performance on tasks that tax hippocampal pattern separation, such as the MST, declines in MCI and preclinical AD.[13,26,43,44] This is likely because the hippocampus is one of the earliest areas affected (both directly and indirectly) by AD pathologies.[19] Specifically, previous work identified age and AD-related changes in this circuit, such as perforant path degradation and CA3 hyperexcitability.[28,45–47] However, these pathologies have not been directly linked to performance on the OCL task. Future work needs to investigate whether the same hippocampal pathologies give rise to impairments on the OCL task.

4.4 | Hippocampal hyperexcitability as a predictor of future tau

Recent work has suggested that increasing tau deposition is a critical predictor of future cognitive decline.[48,49] Specifically, it has been proposed that amyloid deposition is not pathological without tau tangles; however, amyloid can drive accumulation of tau.[50–53] While the mechanism by which this happens is not fully understood, it has been suggested that hippocampal hyperexcitability may be the mediating factor.[54,55] Increased hippocampal activity is negatively associated with performance on mnemonic discrimination tasks, and pharmacologically reducing this hyperexcitability increases performance.[28,46] Therefore, we propose that tasks that tax hippocampal pattern separation could serve as an indirect proxy for hippocampal dysfunction and,

in particular, hippocampal hyperactivity. This would suggest that performance on the OCL may be predictive of future tau accumulation. We found a negative relationship between OCL performance and future EC tau accumulation in Aβ+ CN older adults. Conversely, we found that OCL was related to future IT tau accumulation in Aβ+ MCI individuals. Some research has revealed that this aligns with prior work finding that hippocampal hyperactivity was related to future tau accumulation in both regions,[55] but tau accumulates in EC prior to IT.[6,17] Further, the finding that this is selective to Aβ+ individuals aligns with work finding that Aβ potentiates tau accumulation. While promising, future work will be needed to understand the direct connection between OCL performance and hippocampal hyperexcitability.

5 | CONCLUSION

In this study, we asked whether digital cognitive assessments could serve as low-burden biomarkers in AD. We demonstrated that performance on these assessments exceeded Aβ and entorhinal tau in distinguishing between CN and MCI and predicting progression to MCI. Further, we demonstrated that deficits in mnemonic discrimination, which relies on hippocampal pattern separation, were informative of future cognitive decline and tau deposition. Our work suggests that digital cognitive assessments are important tools for predicting cognitive decline, and these assessments should include tasks that tax hippocampal pattern separation.

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CONFLICT OF INTEREST STATEMENT

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

CONSENT STATEMENT

All human subjects 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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