

RESEARCH ARTICLE

Diminished Learning Over Repeated Exposures (LORE) in preclinical Alzheimer's disease

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Abstract

Introduction: We determine whether diminished Learning Over Repeated Exposures (LORE) identifies subtle memory decrements in cognitively unimpaired (CU) older adults with Alzheimer's disease (AD) biomarker burden.

Methods: Ninety-four CU participants (mean age = 77.6 ± 5.02) completed a challenging associative memory test, at home, monthly, for up to 1 year (mean = 9.97 months) on a study-issued iPad. Learning curves for face-name memory were computed for two versions completed monthly: same face-name pairs (A-A-A) and alternate face-name pairs (B-C-D). Positron emission tomography (PET) imaging characterized global amyloid (Pittsburgh Compound-B (PiB); amyloid beta ($A\beta$)+/-) and regional tau burden (flortaucipir).

Results: Diminished LORE for same (but not alternate) face-name pairs was associated with greater amyloid and tau burden. $A\beta$ +/- group differences for same face-name pairs emerged by the fourth exposure and was of medium-to-large magnitude (Cohen's $d = 0.66$; 95% confidence interval [CI] = 0.25-1.08).

Discussion: Subtle decrements in learning related to AD pathological burden in CU are detectable over short time-intervals (ie, months). Implications for prevention trial design are discussed.

KEYWORDS

amyloid PET, computerized testing, digital biomarkers, learning curves, practice effects, preclinical Alzheimer's disease, tau PET

1 | BACKGROUND

Decline in memory is an early and prototypical sign in the Alzheimer's disease (AD) continuum.¹ However, cognitive decline is challenging to detect and efficiently track at the preclinical stage of disease, that is, in individuals who are clinically unimpaired (CU), but who have abnormal AD biomarkers.² Longitudinal studies suggest that AD-related cognitive decrements in CU are subtle (<0.25 standard deviations/year³)

and primarily detectable over multiple annual assessments.⁴ Despite this, the preclinical period remains an ideal interval of 10+ years in which to intervene to slow or prevent progression of cognitive decline.

Previous research indicates that a lack of the characteristic improvement in performance on re-testing (ie, a diminished practice effect) may be a subtle indicator of cognitive decrements prior to overt cognitive decline. Diminished practice effects have been observed in mild cognitive impairment (MCI), where patients do not improve on

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re-testing at the same rate as their CU peers.^{5,6} Similarly, a diminished practice effect has been shown to predict incident MCI and/or dementia among CU older adults.^{7,8}

However, the specific cognitive mechanisms underlying the practice effect have not been well-specified. Two types of practice effects exist, with the latter being, in our view, most relevant to AD: (1) general practice effects associated with task familiarity (eg, development of test-taking strategies, reduced test anxiety) and (2) memory for the specific test items previously encountered, which we term “learning over repeated exposures” or LORE to distinguish from general practice effects.⁹

Previous work from the Harvard Aging Brain Study (HABS) showed that CU older adults with elevated amyloid beta ($A\beta+$) initially recalled as many details on a story memory task as $A\beta-$, but subsequently failed to recall further details at rate of $A\beta-$ on annual re-testing,¹⁰ which aligns with other studies exhibiting diminished practice effects among CU $A\beta+$.¹¹ Functional imaging studies have suggested that successful acquisition of new information involves different medial temporal lobe responses for novel versus previously encountered stimuli.¹² However, individuals on the AD spectrum have an equivalent neural response to new versus repeated stimuli.¹³ Thus assessing LORE, particularly over shorter re-test intervals, may be particularly relevant in AD. Reducing the time interval^{14,15} over which diminished LORE can be observed (months rather years) is now feasible with independent at-home tablet-based testing among older adults who are increasingly comfortable with technology.¹⁶

As such, we examined whether more frequently and remotely administered memory testing among CU older adults could identify differences in learning curves associated with AD biomarkers (ie, $A\beta$ and tau on positron emission tomography [PET] imaging). Participants completed two versions of a challenging cross-modal associative memory task monthly for up to 1 year: (1) learning of alternate face-name pairs (B-C-D...) to assess general practice effects and (2) learning of the same face-name pairs (A-A-A...) to assess LORE. We hypothesized that greater $A\beta$ and tau burden would be associated with diminished LORE.

2 | METHODS

2.1 | Standard protocol approvals, registrations, and patient consents

This study was approved to use human subjects by the institutional review board of the Partners Healthcare System. Participants provided written consent to participate in the HABS and the At-Home Digital Cognition Sub-Study.

2.2 | Participants

Participants were recruited from HABS, an ongoing longitudinal observational study of CU older adults.¹⁵ Participants were

RESEARCH IN CONTEXT

1. Systematic review: The authors searched the literature (PubMed) for “practice effects” and “learning curves” in Alzheimer’s disease (AD). Diminished practice/learning effects have been associated with a diagnosis of mild cognitive impairment and risk for dementia but comparatively understudied in preclinical AD.
2. Interpretation: Our findings indicate that diminished learning curves are not only associated with greater amyloid and tau burden in cognitively unimpaired older adults but observable over a short test-retest interval of months and collectable remotely. Furthermore, we refine the type of learning curve affected in AD by comparing different version schedules.
3. Future directions: Future studies are needed to determine whether diminished learning curves can be captured over even shorter time intervals (ie, days vs months) and in larger and more diverse populations to ultimately determine the utility of this sensitive paradigm to more rapidly and efficiently identifying and tracking subtle AD-related cognitive decrements.

deemed CU at the start of their participation in the At-Home Digital Cognition Sub-Study by clinician consensus,¹⁶ which included review of cognitive and functional measures and medical history.

2.3 | Cognitive outcome: Face-name associative memory exam with monthly at-home administration

Participants completed the Computerized Cognitive Composite (C3) on the Cogstate platform using a study-issued iPad. The C3, described elsewhere,^{17,18} includes the Face Name Associative Memory Exam-FNAME.^{19–21} An adapted C3 was used where participants completed two FNAME versions¹⁸ monthly: (1) learning of the same face-name pairs (A-A-A...) to assess LORE followed by (2) learning of alternate face-name pairs (B-C-D...) to assess general practice effects. For each version, participants are shown 12 face-name pairs presented serially and asked whether the name “fits” or “doesn’t fit” each face to ensure adequate attentiveness to the stimuli.¹⁸ Following an approximate 10-minute active delay, participants are asked to identify the previously learned faces, presented alongside two distractor faces of matching age, race, and sex (face recognition). The target face is subsequently presented with a touchscreen keyboard and the participant selects the first letter of the name paired with that face (first letter name recall). Finally, the target face is presented with three names (target name, a re-paired same-sex name, and an age- and sex-matched foil name) and the participant must select the correct name (face-name memory).

TABLE 1 Demographic, clinical, neuropsychological, and neuroimaging characteristics

	Total	A β +	A β -	t/X ²	P
N	94	25	69		
Timepoints	9.97 (4.52)	10.50 (4.01)	9.71 (4.7)	0.80	0.376
Age	77.6 (5.02)	78.3 (4.78)	77.3 (5.11)	-0.88	0.379
Sex (% female)	60.6%	48%	36.2%	0.63	0.428
Race (% White)	88.2%	90.3%	87.1%		
Education (y)	16.4 (2.78)	15.8 (3.18)	16.7 (2.60)	-1.43	0.157
MMSE	29.1 (1.33)	28.5 (1.69)	29.30 (1.12)	2.63	0.010
CDR (0, 0.5)	87.7	22.3	65.4	0.32	0.570
A β PiB-PET (DVR)	1.20 (0.23)	1.54 (0.21)	1.08(0.44)	-16.86	<0.001
Time between PiB-PET scan and initial assessment (y)	1.52 (1.26)	1.34(.92)	1.58(1.35)	1.01	0.315
N	84	24	60		
Time between FTP-PET scan and initial assessment (y)	1.15 (0.88)	1.04 (0.69)	1.19 (0.94)	0.83	0.410
FTP-PET ET Tau (SUVR)	1.38 (0.27)	1.51 (0.32)	1.31 (0.23)	-2.96	0.004
FTP-PET IT Tau (SUVR)	1.47 (0.16)	1.55 (0.20)	1.44 (0.13)	-2.92	0.004
FTP-PET Mean ET & IT Tau (SUVR)	1.41 (0.19)	1.53 (0.25)	1.37 (0.16)	-3.31	<0.001

Abbreviations: CDR, Clinical Dementia Rating Scale (Global, Sum of Boxes); ET, entorhinal; FTP, flortaucipir; IT, inferior temporal; MMSE, Mini-Mental Status Exam; PET, positron emission tomography; PiB = Pittsburgh compound B; SUVR, standardized uptake value.

Accuracy for each component is scored /12. Here we focus on the last outcome, face-name memory, as this aspect of the paradigm captures the integrity of associative memory.²²

2.4 | At-home digital cognition study administration protocol

Baseline and conclusion of the At-Home Digital Cognition Study coincided with participants' annual HAB visit where they received or returned the iPad, respectively (Supplementary Figure 1). At baseline, participants completed an iPad and Cogstate one-on-one training session.¹⁴ The first test was taken in-clinic and the first At-Home C3 taken 1 week later. Participants completed the monthly C3 thereafter for 12 At-Home sessions. The final C3 administration occurred in-clinic (total of 14 sessions). Participants received reminder calls prior to their scheduled test date and were encouraged to complete the C3 at the same time monthly (eg, morning).

2.5 | Neuropsychological assessment

The HABS annual visit neuropsychological battery has been described previously.^{15,23} Briefly, each participant is administered the Preclinical Alzheimer Cognitive Composite (PACC-5^{10,24}) which, among other measures, includes the Free and Cued Selective Reminding Test (FCSRT)²⁵ and the Mini Mental Status Exam (MMSE).

2.6 | AD biomarkers of amyloid and tau: PET data acquisition and analysis

Participants underwent PET⁷ with ¹¹C-Pittsburg Compound-B (PiB; n = 94) and ¹⁸F-Flortaucipir (FTP; n = 84) using previously published procedures.²⁶ FTP images were acquired from 75-105 minutes and PiB images were acquired using a 60-minute dynamic acquisition on a Siemens ECAT HR+ PET scanner. PET images were co-registered to corresponding T1 images using Freesurfer-based (v6) structural regions of interest (ROIs) mapped into native PET space using SPM12. FTP was expressed as a standard uptake volume ratios (SUVRs) and PiB as the distribution volume ratio (DVR). The reference region was cerebellar gray using an MRI-based method; FTP-PET data were corrected for partial volume effects. For PiB, a global cortical aggregate was calculated for each participant, and participants were dichotomized into low (A β -) versus high (A β +) groups (cut-off-1.185).²⁷ Bilateral entorhinal cortex and inferior temporal lobe were used as ROIs in FTP analyses. A composite of entorhinal and inferior temporal lobe was calculated after similar results were observed for these regions independently (Table 1).

2.7 | Statistical analyses

Statistical analyses were completed using Rv3.6. Demographic differences between A β +/- groups were examined with *t* tests and X² tests (two-sided, *P* < 0.05). Linear mixed models (LMMs) were used to determine whether change in face-name memory for either same versus alternate versions was observed over time (in months), and

subsequently to separately assess the association between $A\beta$ (both continuous and by group) and continuous tau deposition and change in face-name memory for same versus alternate versions. Age (centered at mean), sex (female), and education (centered at mean), as well as their interactions with time were modeled as covariates. The magnitude of the $A\beta$ group effect was quantified using a Cohen's d effect size for learning slopes between groups. To determine at which monthly administration performance differed between $A\beta+/-$, we completed mixed models of repeated measures (MMRMs) using baseline performance and age as covariates, with a compound symmetric correlation structure and heterogeneous variance.²⁸ The MMRM analysis treats time as an ordinal variable, allowing examination of differences at each time point without assuming a linear trajectory.

Finally, to explore comparisons between the sensitivity of diminished LORE to standard paper and pencil measures, we examined 1-year difference scores between study baseline and conclusion on face-name memory and standard measures among current At-Home Digital Cognition Study-completers.

3 | RESULTS

3.1 | Participant recruitment and at-home testing

Of those recruited from HABS, 86% consented to participate. Documented refusals included lack of comfort with technology, no WiFi at home, and lack of interest/time. Because the study is ongoing, participants were included in analyses if they had progressed through at least the first two at-home assessments. Ninety-four individuals have completed a mean of 9.97 (range 2-14) assessments. Currently, 44 individuals have progressed through the entirety of the 1-year study and 47 remain actively enrolled. Three individuals who discontinued are included in analyses because they completed two or more at-home assessments pre-discontinuation. A total of 92% of C3 administrations were completed within 1 week of the target date. Most participants were able to complete the tests independently, but about 30% sought technical assistance. Data validity checks were excellent (Supplementary Results 1)

3.2 | Demographic characteristics

Demographic characteristics are described in Table 1. There were no $A\beta$ group differences in age, sex, education, or global CDR. $A\beta+$ participants performed slightly worse on the MMSE and exhibited higher levels regional tau deposition (Table 1).

3.3 | LORE versus general practice effects on monthly computerized testing

Positive learning slopes were observed for both same and alternate versions of face-name memory regardless of amyloid status, with

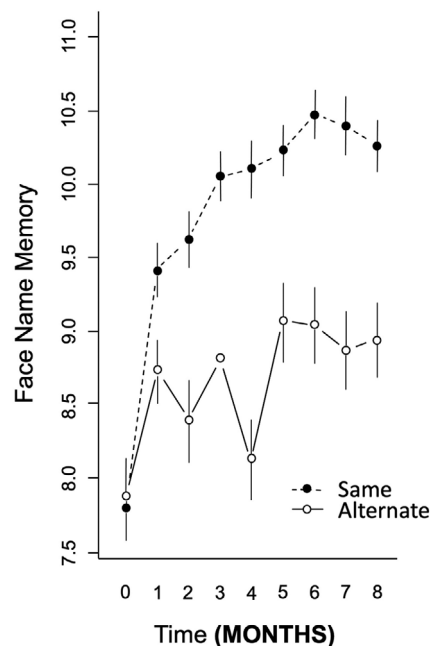


FIGURE 1 Learning Over Repeated Exposures (LORE) (Same Version) for Face Name Memory versus general practice effects (Alternate Version) over months. NOTE. The y-axis represents the mean and standard deviation of the number of correct responses on face-name memory out of 12. Same = Same Version (A-A-A) is a measure of LORE and Altern = Alternate Version (B-C-D) is a measure of general practice effects. The time between visit 0 and 1 is 1 week; all other testing is monthly

all participants remembering more face-name pairs over time (Figure 1). However, the magnitude of improvement was nearly twice as large for the same version (increase of 0.15 points/administration) versus the alternate version (increase of 0.09 points/administration). As expected, most participants ($n = 56$, 59.5%) eventually reached ceiling of 12/12 on same version face-name memory. However, ceiling was not reached until an average of 5.7 assessments. There were no differences between males and females in likelihood to reach ceiling ($\chi^2 = 0.53$, $P = 0.466$); however, there was a statistical trend for $A\beta-$ to be more likely to reach ceiling compared with $A\beta+$ ($\chi^2 = 2.79$, $P = 0.095$). On alternate face-name memory, a smaller proportion reached ceiling on any given version ($n = 39$, 41%).

3.4 | Diminished LORE and amyloid burden

At baseline, there were no group differences in face-name memory by $A\beta$ group (Table 2). However, over time, $A\beta+$ participants showed less steep learning slopes for face-name memory when the same version was administered monthly. For example, the $A\beta+$ only increased their performance on FNMA by 0.07 points/administration in contrast with $A\beta-$ who improved 0.14 points/administration. The magnitude of the $A\beta+/-$ effect on learning slopes was statistically moderate to large (Cohen's $d = 0.66$; 95% CI = 0.25-1.08). In contrast, there was no

TABLE 2 Regression coefficients from linear mixed models for accuracy of face-name memory for same versus alternate versions over months and in relation to PET A β +/- status and tau deposition

	Face name memory accuracy (Same Version-LORE)		Face name memory accuracy (Alternate Version-general practice effect)	
	β (SE)	P-value	β (SE)	P-value
Intercept	9.55 (0.18)	<0.001	8.90 (0.22)	<0.001
A β + Group	0.26 (0.28)	0.813	-0.56 (0.35)	0.109
Time (m)	0.14 (0.01)	<0.001	0.07 (0.02)	<0.001
Age	-0.04 (0.03)	0.110	-0.11 (0.03)	<0.001
Sex (male)	-0.52 (0.27)	0.056	-0.57 (0.33)	0.090
Education	0.02 (0.05)	0.727	-0.00 (0.06)	0.968
Time \times Age	0.00 (0.00)	0.778	0.00 (0.00)	0.903
Time \times Sex	0.04 (0.02)	0.040	0.00 (0.03)	0.980
Time \times Educ.	0.00 (0.00)	0.264	0.01 (0.004)	0.231
Time \times A β + Group	-0.06 (0.02)	<0.001 ^a	0.03 (0.03)	0.348
# of observations	951			
	Mean Slopes (SD)			
A β + Group (n = 25)	0.07 (0.10)			
A β - Group (n = 69)	0.14 (0.11)			
Cohen's d (95% CI)	0.66 (0.25-1.08)			
	Face name memory accuracy (Same Version-LORE)		Face name memory accuracy (Alternate version- general practice effect)	
	β (SE)	P-value	β (SE)	P-value
Intercept	8.61(1.07)	0.000	8.78(1.37)	0.000
FTP- Mean ET & IT Tau	0.73(0.77)	0.336	0.09(0.98)	0.925
Time (months)	0.36(0.08)	0.000	0.16(0.11)	0.143
Age	-0.03(0.03)	0.294	-0.09(0.03)	0.006
Sex (male)	-1.08 (0.28)	0.000	-0.95(0.34)	0.008
Education	0.01(0.05)	0.846	-0.03(0.06)	0.593
Time \times Age	-0.00(0.00)	0.507	-0.00(0.00)	0.910
Time \times Sex	0.06(0.02)	0.001	0.00(0.03)	0.901
Time \times Educ.	0.01(0.00)	0.108	0.00(0.00)	0.582
Time \times FTP- Mean ET & IT Tau	-0.16(0.06)	0.004^a	-0.06(0.08)	0.468
# of observations	856			

Abbreviations: ET, entorhinal; FTP, flortaucipir; IT, inferior temporal; PET, positron emission tomography; LORE, Learning Over Repeated Exposures; education was centered at 16 and age was centered at 77;.

^aremains significant with a multiple comparison Bonferroni-corrected P-value of 0.0125.

difference in learning slopes by A β +/- for alternate versions (Table 2). Females exhibited non-significant trends toward better baseline face-name memory but exhibited flatter learning curves on the same but not alternate versions compared with males. All results were comparable when excluding 10 participants with CDR = 0.5 (Supplementary Table 1) and when treating A β continuously (Supplementary Table 2).

3.5 | Time intervals required to detect amyloid-related diminished LORE

A β - began outperforming A β + on the same version of face-name memory at the fourth timepoint (Figure 2) and thereafter. In contrast, no A β +/- differences were observed at any timepoint for alternate versions.

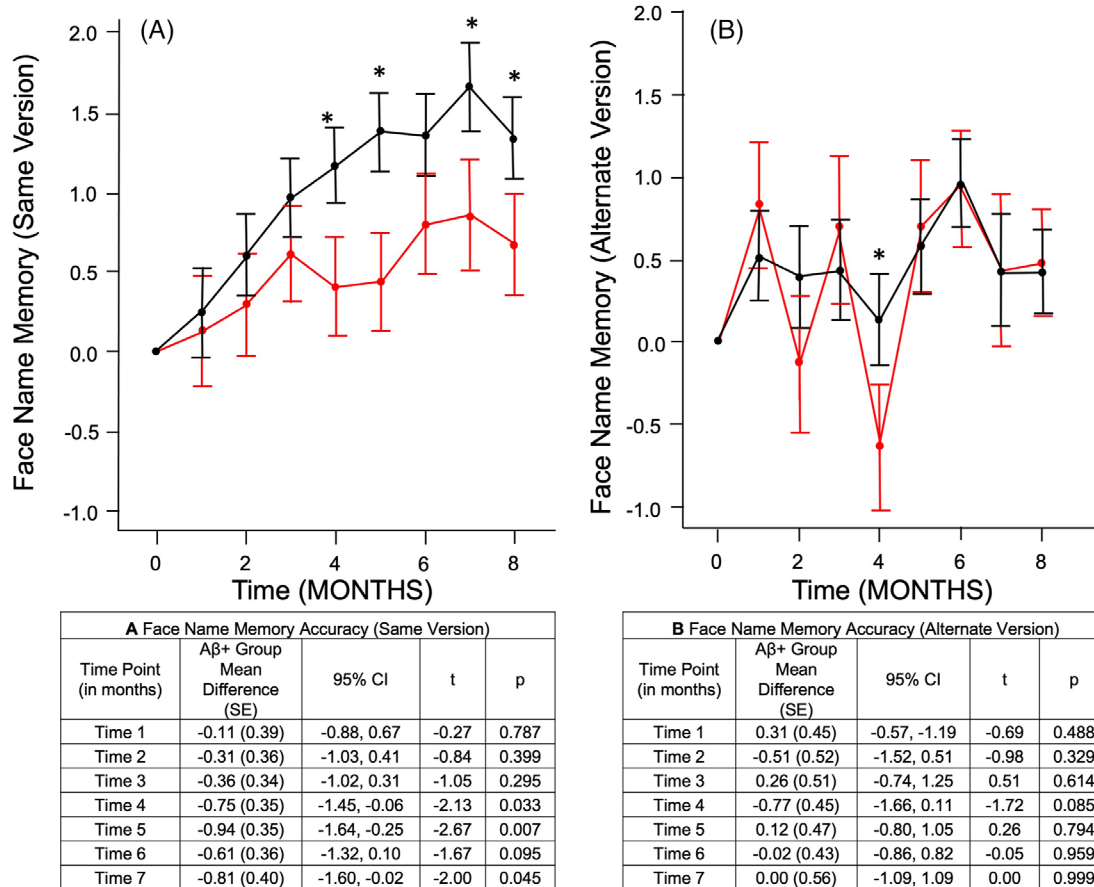


FIGURE 2 Mixed model for repeated measures (MMRM) analysis shows diminished Learning Over Repeated Exposures (LORE) for Aβ+ versus Aβ- groups for face-name memory accuracy (A; same version) but no difference between groups for general practice effects (B; alternate version). NOTE: The y-axis represents change in the number of items answered correctly (/12) for face name memory. Diminished LORE for Aβ+ group versus the Aβ- group was observed on monthly same-version memory testing at time 4 (mean difference in words recalled = -0.75, $P = 0.033$). There was no difference in general practice effects between Aβ+ versus Aβ- groups for alternate face-name memory versions. Analyses, by definition, control for baseline performance. Analyses are controlled for age

3.6 | Diminished LORE and tau burden

At study baseline, there was no association between face-name memory and tau burden (Table 2). However, individuals with higher levels of tau exhibited less steep learning slopes for face-name memory when the same version was administered monthly (Supplementary Figure 2; $r = -0.22$, $P = 0.045$). In contrast, there was no relationship between level of tau deposition and learning slope for alternate versions. When including both amyloid and tau in a model predicting FNMA slopes (Same version), both were significant independent predictors (Supplementary Table 3, Supplementary Figure 2).

3.7 | LORE versus annual testing

Among study completers, no 1-year change was observed differentially by Aβ+/- on standard cognitive measures (MMSE, PACC, FCSRT; Table 3) or on face-name memory (Alternate). In contrast, the Aβ+/- difference in face-name memory (Same) was observable between study baseline and 1 year (Table 3).

4 | DISCUSSION

Early detection and tracking of subtle cognitive changes in preclinical AD is critical to advancing treatments. Here we observed that diminished learning over repeated exposures (LORE), but not a diminishment in general practice effects, was associated with elevated global Aβ and entorhinal/inferior temporal tau among CU older adults. Most importantly, Aβ+/- differences in LORE were identified after only four self-administered digital assessments occurring within a 3-month period. In contrast, subtle cognitive decrements have been historically undetectable for at least 2 to 3 years on annual cognitive assessments.^{29,30} Likewise, in contrast to the observed AD biomarker-related diminished LORE over months, traditional cognitive measures (eg, PACC, MMSE) were insensitive to 1-year cognitive change. Taken together, these findings suggest that diminished LORE has the potential to serve as a more sensitive and rapid means of tracking subtle cognitive decrements associated with the earliest cognitive manifestations of AD.

What distinguishes the current findings from previous studies examining learning curves and AD risk^{6,31,32} is (1) a CU population with AD biomarkers of both amyloid and tau and (2) the ability to define

TABLE 3 Comparison of 1-year change in performance for face name memory accuracy versus standard neuropsychological measures

	MMSE		PACC5		Face-name memory accuracy (Same)		Face-name memory accuracy (Alternate)		FCSRT FR	
	β (SE)	P	β (SE)	P	β (SE)	P	β (SE)	P	β (SE)	P
A β Group	-0.37(0.29)	0.205	-0.28(0.17)	0.119	0.80 (0.52)	0.129	-0.09(0.63)	0.883	-2.99 (1.68)	0.083
Time (y)	-0.24 (0.22)	0.281	-0.02 (0.07)	0.813	2.85 (0.49)	0.000	1.53 (0.49)	0.003	-0.93 (1.17)	0.431
Time \times A β Group	-0.03 (0.33)	0.928	0.07 (0.11)	0.481	-1.61 (0.71)	0.028	-0.27 (0.72)	0.699	2.82 (1.68)	0.102

NOTE: All models included age, sex, and education as covariates; n = 44. Abbreviations: FCSRT FR, Free and Cued Selective Reminding Test-Free Recall MMSE, Mini-Mental Status Exam; PACC5, Preclinical Alzheimer's Cognitive Composite-5.

the LORE cognitive signature by comparing same versus alternate version schedules on a challenging associative memory task. In addition, we contribute to recent studies highlighting the utility of shorter test-retest intervals (eg, days and months vs years).³³

4.1 | Diminished LORE in biomarker-defined preclinical AD

Our results align with other studies showing an association between diminished practice effects and signs of brain vulnerability in CU older adults (A β +, MRI, FDG-PET).^{7,8} We also show a relationship between diminished LORE and greater tau PET deposition in entorhinal and inferior temporal lobes, which are both early sites of deposition in AD³⁴ and regions (particularly entorhinal cortex layer II neurons) implicated in successful associative memory formation.^{35,36} The FNAME may be particularly suited to capture subtle memory decrements arising from early regional tau accumulation given that it is a cross-modal, paired associative memory task. However, other paired associate memory tasks may be equally sensitive when administered in a LORE format. For example, a recent study examined learning of Chinese character translations (Online Repeatable Cognitive Assessment [ORCA]), finding that A β + CU exhibited diminished learning relative to A β - over six daily assessments.³³ Although they did not examine medial temporal lobe tau deposition, diminished learning was associated with smaller hippocampal volumes. Both amyloid and tau provided explanatory variance regarding diminished LORE in the current study, highlighting the relevance of this cognitive signature to AD. Of note, the A β +/- effect size for ORCA was very large (d = 2.2) compared with the medium effect size observed here (d = 0.6). This may be attributable to sample differences including a much higher proportion of A β + participants (48% A β + compared with 27% here) but also, in part, because of the greater complexity and challenge of the ORCA task (eg, 50 vs 12 memory targets).

4.2 | Diminished LORE versus general practice effects in preclinical AD

The lack of a relationship between AD biomarkers and general practice effects (ie, memory for alternate face-name pairs) suggests that more general performance improvements on retesting are not impacted by

AD biomarker burden among CU. The differential relationship between same versus alternate face-name memory and AD biomarkers highlights that a core AD cognitive profile is characterized by failures in learning despite repeated exposure to the same stimuli over discrete testing sessions. Practically, these results suggest that the critical element of "diminished practice effect" as a measure of prognosis or risk likely rests in failure of memory for repeated items.⁹ Furthermore, practice effect paradigms that do not incorporate repeated items will likely be insensitive to prognosis/risk.

4.3 | Demographic factors

Similar to results from previous studies,¹⁸ females generally outperformed males on FNAME. However, in the LORE paradigm, in contrast with the practice effect version, females exhibited flatter learning curves compared with males. Interpretation of these sex effects are confounded by females' trend toward higher baseline performance, which attenuated their learning curves such that they reached maximal (ie, ceiling) performance more rapidly. This sex effect was not observed on alternate versions where learning curves were less steep. Although this ceiling effect is a limitation that must be addressed in future iterations, the persistent association between diminished LORE and AD biomarkers highlights its robustness.

4.4 | Short-term versus long-term learning curves

The majority of studies assessing practice effects in preclinical AD have leveraged longitudinal cohorts, examining learning on annual assessments.^{7,8,31} In these cases, diminished LORE may partly reflect disease progression given the years-long retest intervals. In contrast, diminished LORE over months is unlikely to capture disease progression among CU. However, it will be important to understand the consistency of an individual's short-term learning curve, sampled over longer time intervals to help determine whether measuring LORE solely improves sensitivity to subtle cognitive decrements at a static timepoint or whether these learning curves are dynamic.

In addition, the observed A β +/- group difference in learning at the fourth administration suggests that the current year-long study is not necessary to observe the LORE effect. Furthermore, diminished AD-related learning curves were recently shown to be observable over

six daily assessments among CU.³³ Further refinement of FNAME (eg, increasing the number of stimuli and/or decreasing the test-retest interval from months to days) will be necessary to practically apply the tasks to different uses (eg, screening vs tracking).

4.5 | Future uses of short-term learning curves in clinical trials

The assessment of learning curves over short time intervals may improve AD clinical trial design, particularly in prevention trials, which require many individuals to be screened and many years to assess therapeutic effects. Pre-screening with a short-term LORE paradigm may help enrich samples for A β +. For example, among MCI patients, diminished 1-week practice effects was associated with 14 times higher odds for A β +.⁶ Such large effects are unlikely to be observed in CU populations, but recent results suggest that very challenging and complex learning paradigms among CU may improve predictive risk for A β positivity.³³

LORE could serve as a paradigm for exploring the psychopharmacokinetic profiles of medications to assess for either efficacy of cognitive enhancement or cognitive safety. In this case, short-term learning curves would be captured at multiple intervals over the course of a study. Recent clinical trials of BACE inhibitors (β -site amyloid precursor protein cleaving enzyme) were halted in the context of a worsening of cognition^{38,39} at 6 months. Capturing learning curves over days and remotely may provide a more rapid means of assessing cognitive safety of novel agents. In these cases as well as if using diminished LORE as an outcome, learning paradigms would need to continue to be feasible as individuals may become impaired as they progress along the pre-clinical trajectory. Additional applications for short-term LORE are in identifying individuals at greatest risk for cognitive decline^{7,8} (a population of interest in secondary prevention), or alternatively, individuals most likely to benefit from a specific intervention.³⁷ These applications require further work to quantify the clinical meaningfulness of diminished LORE to risk for disease progression.

4.6 | Limitations

An important limitation to consider is the currently limited generalizability of our results to larger more ethnically, racially, and socioeconomically diverse populations. Our sample was primarily Caucasian, well-educated, and tech-literate (eg, those with home WiFi). As such, we are developing a more accessible web/smartphone version of this memory paradigm with the hope of capturing a much larger and more diverse sample.⁴⁰

Another challenge for remote assessments is the fidelity of data from an uncontrolled testing environment. Study-issued iPads, as opposed to an individual's own device, enhanced standardization because the same software and operating systems were used. iPads were also configured to be minimally distracting (applications disabled, no access to notifications, and so on) and participants were instructed

on best practices to complete the task (eg, environment, consistency of time of day). High performance validity checks, low within-testing session discontinuation rates, high rates of on-time completion each month and positive feedback were reassuring for data integrity. Finally, there are purposeful actions that may affect data integrity (eg, cheating, having someone else complete the task), which we were not able to monitor with the current technology/study design. However, we would not expect cheating to be differentially observed in those with abnormal AD biomarkers.

Finally, we were unable to determine whether diminished LORE was a consequence of memory encoding versus consolidation deficits. We hypothesize that memory consolidation is differentially impacted over memory encoding, given that diminished learning over multiple trials within a single testing session has proven insensitive to biomarker burden in preclinical AD.^{41,42} However, further refining the LORE paradigm (eg, assessing memory for previously learned items prior to re-learning) will allow us to better understand the specific memory processes underlying diminished LORE.

5 | CONCLUSION

CU individuals with elevated AD biomarkers exhibit quantifiable alterations in memory for information presented repeatedly each month. These findings add to a literature suggesting that diminished learning curves may be inherently meaningful and possibly a prognostic marker for future clinical progression³¹ in preclinical AD. We have outlined how the LORE cognitive signature is sensitive to AD biomarker burden among CU, in contrast with general practice effect paradigms, and have described how this type of paradigm may contribute to secondary prevention trials through enhanced screening, rapid assessment of cognitive benefits or safety concerns, or use as a sensitive outcome. Future work is required to assess the generalizability of AD biomarker-related LORE to larger, more diverse populations and to optimize the paradigm for specific uses (eg, preclinical disease stage, screening vs outcome).

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CONFLICT OF INTEREST

A. Samaroo, R. Amariglio, S. Burnham, P. Sparks, M. Properzi, A. Schultz, and R. Buckley have no disclosures to report. D. Rentz has served as a consultant for Eli Lilly, Biogen Idec, and Lundbeck Pharmaceuticals, and serves as a member of the Scientific Advisory Board for Neurotrack. R.A. Sperling has received research funding from the NIH, Alzheimer's Association, and Eli Lilly for this research. She has served as a consultant for AC Immune, Biogen, Eisai, Janssen, Neurocentria, and Roche. K. Johnson has served as a consultant to Biogen, Janssen, and Novartis. K. Papp has served as a consultant for Biogen Idec and Digital Cognition Technologies.

AUTHOR CONTRIBUTIONS

Aubryn Samaroo, Research Coordinator, data collection, writing, data analysis, data interpretation. Rebecca Amariglio, Co-Investigator, data collection, writing, data analysis, data interpretation. Samantha Burnham, Collaborator, data analysis. Paige Sparks, Research Coordinator, data collection. Michael Properzi, Co-Investigator, data analysis, data interpretation. Aaron Schultz, Co-Investigator, data analysis, data interpretation. Rachel Buckley, Co-Investigator, data analysis, data interpretation. Keith Johnson, Principal Investigator, study supervision, study concept, and design. Reisa Sperling, Principal Investigator, study supervision, study concept and design. Dorene Rentz, Co-Investigator, study supervision, study concept and design. Kathryn Papp, Co-Investigator, data collection, writing, data analysis, data interpretation, study concept and design, study supervision.

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SUPPORTING INFORMATION

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

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