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RESEARCH ARTICLE

Using remote, digital, multi-day testing to characterize long-term forgetting in cognitively unimpaired older adults

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Abstract

INTRODUCTION: Accelerated long-term forgetting (LTF) might be an early marker of subtle memory changes in older adults at risk for Alzheimer's disease (AD). We leveraged remote, multi-day digital testing to characterize LTF in older adults and investigated its association with initial learning and AD imaging biomarkers.

METHODS: One hundred four cognitively unimpaired older adults completed a face–name memory task for seven consecutive days and were asked to recognize face–name pairs 1 week later. LTF was computed as the number of correctly identified stimuli divided by a participant's maximum performance during learning.

RESULTS: Better learning was associated with less LTF ($\beta = 0.52$, 95% confidence interval [CI]:0.34–0.71, $p < 0.001$). Accelerated LTF was associated with cortical thinning in AD-signature regions ($\beta = 0.33$, 95% CI: 0.13–0.52, $p = 0.001$), but associations with regional tau were more subtle.

DISCUSSION: Remote, multi-day testing may facilitate the assessment of LTF as an early cognitive marker of preclinical AD, but further replication is needed.

KEYWORDS
Alzheimer's disease, cognition, digital assessment, long-term forgetting, tau

Highlights

- Using digital, remote assessments, we evaluated long-term forgetting in cognitively unimpaired older adults.
- We found a potential association between long-term forgetting and tau in Alzheimer's disease (AD)–related regions.
- Assessing long-term forgetting may facilitate early detection of AD-related cognitive decline.

1 | BACKGROUND

Episodic memory impairment, specifically an individual's ability to encode, store, and retrieve information, is a key clinical feature of Alzheimer's disease (AD). Successful episodic memory depends heavily on the medial temporal lobe and interactions with temporal neocortical regions.[1,2] These regions are also among the earliest regions that are vulnerable to AD-related tau pathology and structural brain changes.[3–5] These AD pathophysiological changes begin to occur many years before overt symptom onset, during which cognitive changes remain undetected using traditional in-clinic paper-and-pencil cognitive assessments.[6–9] To that end, there is a need for novel assessments that are sensitive to the earliest memory changes that occur at the preclinical AD stage.

As a result, more sensitive cognitive paradigms such as assessments of "long-term forgetting" (LTF) have recently garnered interest as a potentially early cognitive marker of preclinical AD.[10–12] Accelerated LTF reflects the phenomenon whereby individuals have unimpaired recall performance during standard in-clinic testing (with delays of 20–30 min) but show abnormally rapid forgetting of information after longer intervals (from 24 h to several weeks).[13,14] Accelerated LTF was originally studied in patients with temporal lobe epilepsy.[15] These studies have suggested that LTF measures may be useful for identifying subtle temporal lobe dysfunction.[14,16–18] Other studies have investigated LTF in the context of early symptomatic stages of AD and demonstrated that individuals with mild cognitive impairment (MCI) and mild AD dementia experience more accelerated forgetting of stimuli than unimpaired control groups.[19–21] More recently, researchers have shown that accelerated LTF could be detected even before the onset of MCI, that is, in asymptomatic individuals with autosomal dominant AD.[12] Others have also shown that accelerated LTF is more strongly present in apolipoprotein E (*APOE*) ε4 carriers than in non-carriers[10,11] and is associated with global amyloid beta (Aβ) burden.[22,23] However, the associations between LTF and tau deposition, and LTF and structural brain changes in AD signature areas, have not yet been studied.

Previous LTF studies have typically utilized paper-and-pencil assessments that include recall measures after extended delays using at-home or in-clinic paper-and-pencil administration.[13,24] However, assessing recall at home or in clinic days or weeks after initial learning assessments bears practical limitations that impact the flexibility of assessing LTF and the reliability of LTF scores. For example, additional in-clinic LTF assessments increase participant burden, and at-home LTF assessments require participants to be responsible for safekeeping the stimuli and following instructions to keep them concealed. Leveraging a digital cognitive assessment that can be administered remotely may provide a more feasible and adaptable way to assess LTF at multiple time points. The Boston Remote Assessment for Neurocognitive Health (BRANCH) is a digital cognitive assessment that has been validated previously for use in cognitively unimpaired (CU) older adults. BRANCH utilizes a multi-day learning paradigm that allows individuals to learn the material by exposing them to it for seven consecutive days.[25,26] In addition, the BRANCH paradigm allows for assessing participants' retention of previously learned material after longer delays and thereby facilitates a more feasible assessment of LTF than extant approaches.

RESEARCH-IN-CONTEXT

1. **Systematic Review**: The authors reviewed the literature for studies focusing on long-term forgetting (LTF), comparing paper-and-pencil cognitive assessments to digital cognitive assessments, and examining associations between Alzheimer's disease (AD)–related biomarkers and memory using databases such as PubMed.
2. **Interpretation**: This study provides complementary evidence to previous work showing that accelerated LTF may be an early marker of preclinical AD. Our finding that LTF was associated with medial temporal and neocortical tau deposition in cognitively unimpaired older adults indicates that assessing LTF may reveal early AD-related memory changes in this population.
3. **Future Directions**: Future work will seek to replicate these findings in a larger sample with more variability in parti CI pants' tau and amyloid values, explore LTF of a free-recall component, and try to determine the most optimal time interval to use for assessing LTF.

As such, we leveraged the BRANCH paradigm to investigate whether assessing LTF might aid in detecting subtle memory changes in preclinical AD. First we characterized LTF at 1 week after the multi-day learning phase in CU older adults and investigated the association between LTF and initial learning. Because a stronger multi-day learning curve is thought to reflect more efficient consolidation of learned material, which is in turn expected to result in better retrieval,[13,25] we hypothesized that stronger performance during the initial learning phase would be associated with less LTF. Subsequently, we investigated the relationship between LTF and AD biomarkers, including global Aβ and regional tau deposition in the medial temporal and neocortical regions.[27] Given that early tau deposition in the medial temporal and neocortical regions has emerged as a more significant predictor of memory impairment than Aβ positivity alone,[28,29] we hypothesized that accelerated LTF would be particularly associated with greater tau deposition in those regions. Finally, we examined the association between LTF and AD-signature cortical thickness,[30] and we hypothesized that lower LTF scores would be associated with greater AD signature cortical thinning.

2 | METHODS

2.1 | Study participants

A total of 104 CU older adults were recruited from three observational cohorts affiliated with Mass General Brigham: the Harvard

Aging Brain Study (HABS; 2P01AG036694-11-Sperling, Johnson), the Instrumental Activities of Daily Living study (IADL; R01AG053184 and R01AG067021-Marshall), and the Subjective Cognitive Decline study (SCD; 1R01AG058825-01A-Amariglio). All cohorts recruited community-dwelling adults aged 55 and older, who were deemed to be CU as defined by a Clinical Dementia Rating (CDR) global score = 0 or 0.5, Mini-Mental State Examination (MMSE) score >25, and Logical Memory Delayed Recall (LMDR) scores above education-adjusted cutoffs (≥9 for 16+ years of education; ≥5 for 8–15 years of education). Recruited participants with a global CDR ≥0.5 (n = 4 [4%], all global CDR = 0.5) were discussed in multidisciplinary clinical consensus and considered eligible for the current study because they were deemed CU based on standardized cognitive and functional test scores and medical history.[31] Finally, to be eligible for BRANCH, participants were required to have access to an electronic device with Wi-Fi or cellular service, such as a smartphone, tablet, or computer. Study-issued devices with Wi-Fi connectivity were available, if necessary, but all participants used personal devices in the current study. Study procedures were conducted in accordance with human subjects' protections, and the Massachusetts General Brigham Institutional Review Board (IRB) approved the study protocol. All participants provided written informed consent.

2.2 | Multi-Day BRANCH paradigm

The Multi-Day BRANCH assessment is a web-based battery that consists of three memory tasks that are repeated daily with identical stimuli for seven consecutive days.[25,26] The BRANCH Face-Name test is a modified version of the Face-Name Associative Memory Exam (FNAME).[25,32,33] In the current study, we focus on the Face-Name task, given that previous work has found associations between Face-Name performance and AD biomarkers.[30,31] The Face-Name test requires participants to remember a set of 20 face-name pairs. After a brief delay, participants are presented with each face and asked to select the first letter of the name that was paired with that face (first letter name recall). Next, participants are shown a previously learned face alongside three names (target name, a re-paired same-sex name, and a same-sex foil name) and are asked to identify the correct name that was paired with that face (face-name memory). The same test procedure is followed for seven consecutive days, with identical face-name pairs used each day. Our outcome measure of interest was daily accuracy performance on the face-name memory test, which is computed as the number of correctly identified face-name pairs. We focus only on the face-name memory task in the current work, as data collection on first letter name recall is still ongoing.

2.2.1 | Multi-day learning curve

A multi-day learning curve (MDLC) score is computed using daily accuracy scores to quantify a participant's learning performance on the face-name memory task over 7 days.[25,26] The MDLC is determined by calculating the area under the "learning" curve (AUC) using daily accuracy data to capture both the rapidity with which an individual learns and the total accumulation of content[25,26]. Here, the use of an AUC allows us to produce a summary metric for the overall proportion of information learned using a general formula from integral calculus. Furthermore, to account for an individual's starting point (Day 1 performance), we computed a scaled AUC that equals AUC/AUC_{max}, where AUC_{max} is the maximum value of the AUC obtained if the participant scored at the maximum value from the second through the final test administration.[25,26]

2.2.2 | Long-term forgetting (LTF) assessment

One week after their initial learning period, participants were asked to complete a recognition task where they were tested on the same face-name pairs from the initial multi-day learning period (see Figure 1 for an illustration of the study paradigm). LTF was computed by dividing the percentage of correctly recognized face-name pairs by the participant's maximum performance on the task during the 7-day learning phase. A lower percentage of retained material at 1-week recall indicates accelerated LTF. An LTF score greater than 1 indicates that the participant performed better at 1-week recall than on their day of maximum performance during the initial learning period. Given that participants are asked to complete Multi-Day BRANCH every 6 months, we implemented an additional LTF assessment using the same stimuli after 6 months to explore whether LTF after a longer interval would provide valuable information on an individual's cognition. They completed the same LTF tasks as described previously (see supplemental materials).

2.2.3 | Procedures

Participants completed Multi-Day BRANCH via their personal electronic device (e.g., a smartphone or computer) for 7 days in a row.[25,31] When being scheduled for their multiday BRANCH testing, participants were asked what time of day they would prefer to complete the assessment. They were informed that their notifications containing the test link would arrive at the same time each day. Participants were given the choice to receive these notifications either by text message or email. If participants did not complete the assessment within 2 h of their notification, they were sent one additional notification as a reminder to complete that day's assessment. At the start of each day's assessment, participants were required to attest to completing the tasks independently, without recording stimuli or responses, to mitigate the possibility of inflated performances from unauthorized memory aid use. The assessment battery takes ≈12 min to complete each day.[26]

One week after their 7-day "learning period," participants completed the 1-week long-term forgetting assessment. On average, it took parti CI pants 67.2 ± 11.5 s to complete the face-name memory LTF assessment. Parti CI pants were sent a notification for this test via

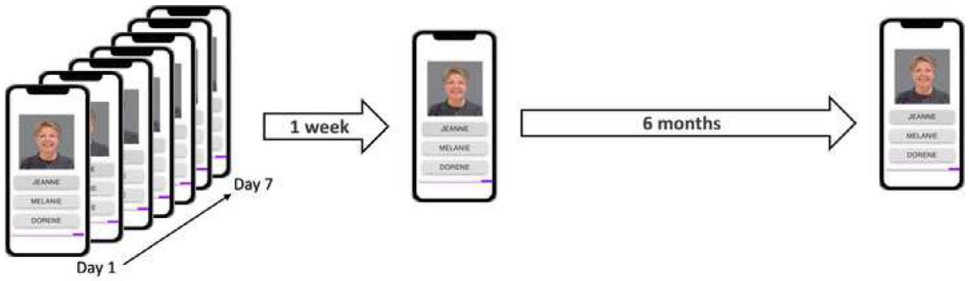

FIGURE 1 Multi-Day Boston Remote Assessment for Neurocognitive Health (BRANCH) and long-term forgetting paradigm.

the previously selected method and at the previously selected time of the day.

2.3 | In-clinic cognitive testing

Baseline global cognitive performance was characterized using the Preclinical Alzheimer's Cognitive Composite-5 (PACC-5). The PACC-5 score is a composite score computed as the average z-score of the MMSE, the LMDR, the Digit Symbol Coding Test (DSCT), the Free and Cued Selective Reminding Test (FCSRT) free and total recall, and the Category Fluency Test (CFT).[34,35]

2.4 | Amyloid and tau biomarkers

A subset of participants underwent positron emission tomography (PET) imaging that used 11C-Pittsburgh compound-B (PiB; n = 100, within a mean of 2.82 SD = 2.06 years of BRANCH) and 18F-flortaucipir (FTP; n = 97, within a mean of 1.97 SD = 1.71 years of BRANCH) to quantify amyloid burden and tau deposition, respectively. Images were acquired in accordance with established protocols.[36,37] Both PiB and FTP images were acquired on either a Siemens ECAT HR+ or GE Discovery PET scanner. PiB images were captured using a 60-min dynamic acquisition, whereas FTP images were captured using a 75- to 105-min post-injection acquisition. After these images were acquired, a mean PET image was created and co-registered with the corresponding T1 magnetic resonance images using FreeSurfer-based (Version 6) structural regions of interest mapped into native PET space using the SPM12 package (Wellcome Centre for Human Neuroimaging). PiB was represented using the distribution volume ratio (DVR) with cerebellum gray matter as the reference region. A global cortical aggregate was calculated for each participant for the frontal, lateral temporoparietal, and retrosplenial regions. Participants were categorized into low (Aβ–) versus high (Aβ+) global amyloid groups (DVR cutoff ≥1.185). FTP was represented as an average standardized uptake value ratio (SUVR) with cerebellum gray matter as the reference region and corrected for partial volume (PVC) effects. We used the SUVR PVC values from the entorhinal, amygdala, parahippocampal, inferior temporal, middle temporal, and fusiform regions.

2.4.1 | Tau composites

The medial temporal lobe and temporal neocortex have been shown to be regions of early tau accumulation in AD.[3,4] In the present study, we utilized a medial temporal composite, computed as an average of the entorhinal, amygdala, and parahippocampal SUVR PVC values, and a neocortical composite, computed as an average of the inferior temporal, middle temporal, and fusiform SUVR PVC values.[3,4]

2.5 | Cortical thickness in AD signature regions

All 104 participants had magnetic resonance imaging (MRI) that was acquired within 1.41 ± 1.76 years of BRANCH testing. MRI scans were performed on a 3T scanner (TIM Trio; Siemens) with a 12-channel phased-array head coil. A T1-weighted volumetric magnetization-prepared rapid-acquisition gradient echo (MPRAGE) image was acquired with following parameters: repetition time (TR) = 2300 ms, echo time (TE) = 2.95 ms, inversion time (TI) = 900 ms, flip angle = 9°, resolution = 1.1 × 1.1 × 1.2 mm. T1-weighted images were processed and quality-assessed using the automated reconstruction protocol in FreeSurfer (version 6.0). We used a FreeSurfer-derived AD-signature composite as our MRI measure of interest, composed of the surface-area weighted average of the mean cortical thickness in the following individual regions of interest (ROIs): bilateral entorhinal, parahippocampal, inferior-temporal, middle temporal, and fusiform.[30,38]

2.6 | Statistical analyses

Statistical analyses were conducted using R Version 4.2.1. Statistical significance was set at $p < 0.05$. To investigate the association between initial learning and LTF on the face-name memory task, we performed linear regression analyses using face-name memory MDLC scores as the predictor and 1-week face-name memory LTF scores as the outcome. To investigate the associations between LTF and AD biomarkers, we conducted a series of separate linear regression analyses with 1-week LTF scores as the outcome, and global amyloid burden (DVR, continuous), tau deposition (SUVRs, continuous) in the medial tem-

poral lobe and neocortical regions, and an AD meta-ROI composite of cortical thickness as predictors. All analyses were corrected for demographic variables (age, sex, and years of education) and the days between individuals' last day of learning and their LTF assessment. Models including tau or amyloid were adjusted accordingly for the time interval between BRANCH and the tau-PET scan or the time interval between BRANCH and the amyloid-PET scan. Similarly, analyses with cortical thickness were adjusted for the time interval between BRANCH and the MRI scan.

2.6.1 | Exploratory analyses

To explore LTF after an extended time interval, we used linear regression models in a sample that had LTF after 6 months to investigate the association between LTF performance after 6 months as the outcome and tau deposition in the medial temporal and neocortical regions as predictors of interest. These analyses corrected for demographic variables (age, sex, and years of education), the days between individuals' last day of learning and their LTF assessment, and the time interval between BRANCH and the tau-PET scan.

3 | RESULTS

3.1 | Participant characteristics

Table 1 shows the demographic and clinical characteristics of the 104 participants (mean age of 75.1, 16.3% Aβ+) who completed the 1-week recall assessment. The majority of our sample (84.6%) completed all 7 days of testing during the initial learning phase, whereas only 12.5% ($n = 12$) completed 6 of 7 days, 1.0% ($n = 1$) completed 5 of 7 days, and 2.9% ($n = 3$) completed 4 of 7 days. Table 1 also shows the same characteristics for the subset of individuals with a global CDR of 0 ($n = 93$). The demographic and clinical characteristics of the subset were not significantly different from those of the full sample (Table 1). (See Table S1 for the demographic and clinical characteristics of the participants who completed an LTF assessment after 6 months.)

3.2 | Characterizing LTF and its association with initial learning

Figure 2 shows the trajectories of face-name matching performance accuracy from the initial learning phase (Day 1 to Day 7) to 1-week LTF assessment. On average, participants correctly recognized 89 ± 14.6% of the learned face-name pairs after 1 week, based on their maximum performance during the initial learning phase. Linear regression analyses showed that higher face-name MDLC scores were associated with higher LTF scores ($\beta = 0.52$, 95% CI: 0.34–0.71, $p < 0.001$), indicating that greater initial learning is associated with better recognition of learned material after 1 week (Figure 3).

TABLE 1 Participant demographics for the full sample of individuals with 1-week LTF.

Characteristic	$N = 104$	CDR 0 subsample, $n = 93$	p-value[a]
Age, mean (SD)	75.1 (7.85)	75.0 (7.93)	0.954
Race, *n* (%)			0.952
White	92 (88.5%)	83 (89.2%)	
Black	9 (8.7%)	7 (7.5%)	
Asian	3 (3.9%)	3 (3.2%)	
Female, *n* (%)	77 (74.0%)	69 (74.2%)	1
Years of education, mean (SD)	16.1 (2.56)	16.1 (2.56)	0.944
PACC5, mean (SD)	0.299 (0.705)	0.443 (0.729)	0.461
MMSE, mean (SD)	29.0 (1.23)	29.1 (1.14)	0.642
AD Meta-ROI cortical thickness, mm, mean (SD)	2.83 (0.137)	2.82 (0.139)	0.950
Aβ+, *n* (%)	17 (16.3%) $n = 100$	17 (18.3%) $n = 89$	0.853
Global Aβ, DVR, mean (SD)	1.13 (0.169) $n = 100$	1.13 (0.178) $n = 89$	0.793
MTL tau, SUVR, PVC, mean (SD)	1.29 (0.245) $n = 97$	1.29 (0.249) $n = 87$	0.937
NEO tau, SUVR, PVC, mean (SD)	1.42 (0.196) $n = 97$	1.42 (0.198) $n = 87$	0.939

Abbreviations: LTF, long term forgetting; AD, Alzheimer's disease; ROI, region of interest; Aβ, amyloid beta; CDR, Clinical Dementia Rating; DVR, distribution volume ratio; MMSE, Mini-Mental Status Examination; MTL, medial temporal lobe; NEO, neocortical; PACC5, Preclinical Alzheimer Cognitive Composite; PVC, partial volume correction; SUVR, standardized uptake volume ratio.

[a]Group differences were tested using independent *t*-tests for continuous variables or chi-square for discrete variables.

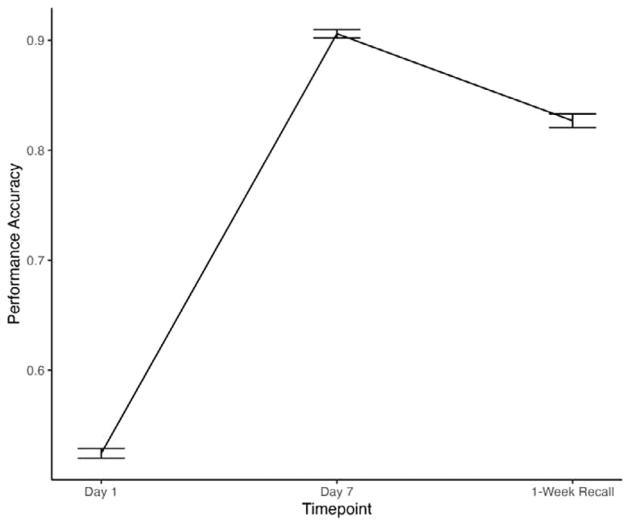

FIGURE 2 Group average performances on the face-name memory task over time. *Note*: Error bars represent 95% confidence intervals.

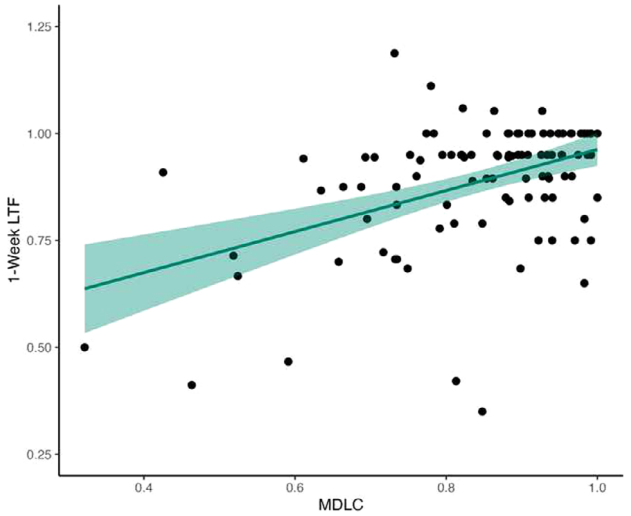

FIGURE 3 Correlation between face-name memory 1-week LTF and initial learning MDLCs.

3.3 | Associations between LTF and AD biomarkers

There was no association between 1-week LTF and global amyloid burden (β = −0.07, 95% CI: −0.23 to 0.09, p = 0.418) (Figure 4). However, linear regression analyses showed that accelerated LTF of face-name pairs after 1 week was associated with greater tau deposition in the medial temporal lobe (β = −0.18, 95% CI: −0.29 to −0.07, p = 0.001) (Table 2, Figure 4) and neocortex (β = −0.16, 95% CI: −0.31 to −0.01, p = 0.032) (Table 2, Figure 4). In addition, linear regression analyses demonstrated an association between greater cortical thickness in the AD meta-ROI and 1-week LTF scores (β = 0.33, 95% CI: 0.13–0.52, p = 0.001) (Table 3, Figure 4). Of note, we found no significant associations between any of the AD biomarkers and LTF after 6 months (see Table S2, Figure S1).

3.4 | Sensitivity analyses

In a sensitivity analysis in a subsample of participants with CDR = 0 (n = 93, Table 1), the associations between 1-week LTF and tau in the medial temporal and neocortical regions did not change (β = −0.20, 95% CI: −0.30 to −0.09, p = 0.001; β = -0.20, 95% CI: −0.34 to −0.05, p = 0.009); nor did the association between initial MDLCs and 1-week LTF (β = 0.48, 95% CI: 0.28–0.68, $p < 0.001$). However, a sensitivity analysis excluding the one participant with the highest tau value showed that associations between 1-week LTF and tau in the medial temporal and neocortical regions were no longer significant (β = −0.06, 95% CI: − 0.20 to 0.09, p = 0.436; β = 0.10, 95% CI: −0.10 to 0.30, p = 0.305).

4 | DISCUSSION

In the current study, we leveraged a remote, digital cognitive assessment to characterize multi-day learning and LTF in a sample of CU older adults. We examined the association between multi-day learning performance and LTF and investigated the association between LTF performance and AD biomarkers. We found that greater initial learning was associated with less LTF after 1 week, suggesting that assessing learning across several days provides participants with a comprehensive learning opportunity that promotes the successful retrieval of that same information a week later. We also found that more accelerated LTF after 1 week was associated with greater tau deposition in both the medial temporal and neocortical regions, which seemed particularly driven by participants with higher tau in both of those regions. Similarly, we found that lower LTF scores were associated with greater cortical thinning in AD-signature regions. Altogether, these initial findings suggest that assessing LTF after a multi-day learning phase may provide a useful marker of subtle memory changes associated with tau deposition in preclinical AD.

4.1 | Multi-day learning and LTF

Our study provides novel insights into the phenomenon of LTF, as it leverages a paradigm where individuals have the opportunity to learn and consolidate material over repeated exposures before the assessment of LTF. Implementing a study paradigm where the "baseline" assessment involves learning material over the course of 7 days is fundamentally different from using a single timepoint assessment, such that there are more opportunities for the material to be consolidated into long-term memory.[39] Providing an opportunity to encode information through multiple exposures in the individuals' environment may also be a more ecologically valid method to assess learning. In everyday life, we are typically given multiple chances to learn something before being asked or required to freely recall it. For example, when we meet someone for a brief, singular instance, and they tell us their name, it may be difficult to remember it the next time we see them. However, if we see them a few more times, the multiple exposures to the face-name pair allow us to learn and have a greater opportunity to remember it. Our finding that greater learning over 7 days was associated with less LTF suggests that our multi-day learning paradigm indeed promotes memory consolidation, which, in turn, is associated with better memory retrieval.

4.2 | LTF and AD biomarkers

We did not find an association between LTF and global amyloid burden, which is consistent with a previous study that found an amyloid effect on learning performance but not for long-term recall performance at 1-week follow-up.[22] However, another study by Lu et al.[40] (2024)[40] did find an association between accelerated LTF on a Complex Figure Drawing task and elevated amyloid. A potential explanation for the contrasting findings between our study and that of Lu et al. is that the association between LTF and amyloid may depend on the type of memory assessment that is used in the study paradigm. That is, their study used an LTF assessment of visual memory, namely the Complex Figure Drawing task, whereas the face-name memory task used in BRANCH is

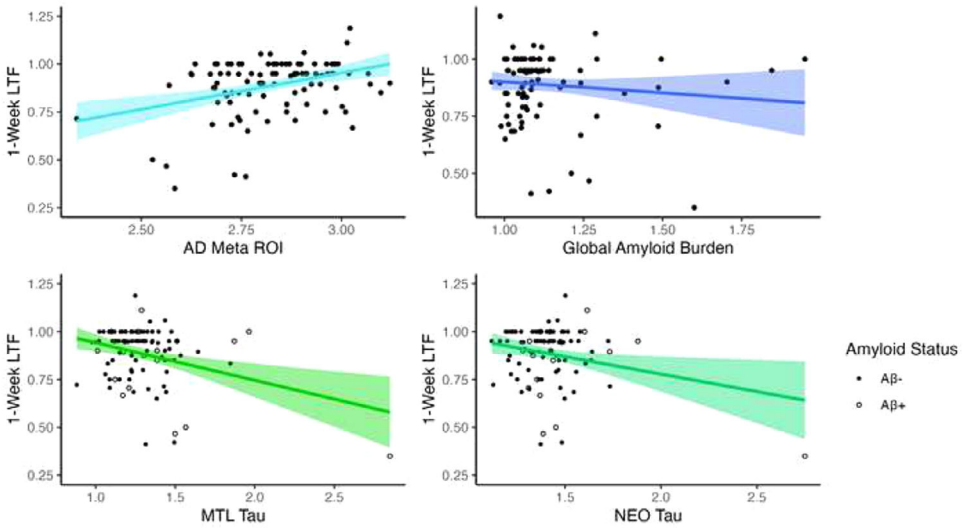

FIGURE 4 Correlations between face-name memory 1-week LTF and AD biomarkers (AD-signature cortical thickness, global amyloid burden, MTL tau, and NEO tau). *Note*: LTF scores greater than 1 indicate that the participant performed better on the 1-week recall test than on their maximum performance day during the learning period. Plots with MTL and NEO tau indicate amyloid status.

TABLE 2 Output from linear regression model investigating the association between 1-week LTF on the face-name memory task and the medial temporal (MTL) and neocortical (NEO) tau composites.

	MTL tau			NEO tau		
Predictors	*Estimates*	*95% CI*	*p*	*Estimates*	*95% CI*	*p*
(Intercept)	1.27	0.98 to 1.57	**<0.001**	1.30	0.98 to 1.62	**<0.001**
Tau-PET, SUVR (PVC)	−0.18	−0.29 to −0.07	**0.001**	−0.16	−0.31 to −0.01	**0.032**
Age	0	−0.01 to 0.00	0.067	0	−0.01 to 0.00	0.060
Sex, M	−0.05	−0.11 to 0.02	0.141	−0.05	−0.11 to 0.02	0.146
Years of education	0.01	0.00 to 0.02	0.058	0.01	0.00 to 0.02	0.081
Time b/w tau-PET and BRANCH	0	−0.01 to 0.02	0.815	0	−0.02 to 0.01	0.822
Time b/w learning and recall	0	−0.01 to 0.00	**<0.001**	0	−0.01 to 0.00	**<0.001**

Note: Bold *p* values should be considered significant if they are less than 0.05.
Abbreviations: b/w, between; M, male; MTL, medial temporal lobe; NEO, neocortical; tau-PET, positron emission tomography targeting tau; PVC, partial volume correction; SUVR, standardized uptake value ratio.

TABLE 3 Output from linear regression model investigating the association between 1-week LTF on the face-name memory task and the AD meta-ROI cortical thickness composite.

	Face-name memory 1-week LTF		
Predictors	*Estimates*	*95% CI*	*p*
(Intercept)	−0.08	−0.62 to 0.78	0.823
AD Meta-ROI cortical thickness (mm)	0.33	0.13 to 0.52	**0.001**
Age	0	−0.01 to 0.00	0.188
Sex, M	−0.05	−0.10 to 0.01	0.113
Years of education	0.01	0.00 to 0.02	0.096
Time b/w MRI and BRANCH	0	−0.02 to 0.01	0.661
Time b/w learning and recall	0	−0.01 to 0.00	**<0.001**

Note: Bold *p* values should be considered significant if they are less than 0.05. Abbreviations: AD, Alzheimer's disease; b/w, between; M, Male; MRI, magnetic resonance imaging; ROI, region of interest.

a paired-associative memory task.[40] In addition, it should be noted that our proportion of the Aβ+ individuals (16.3%) was lower than expected in a sample of older adults, and that the limited variability in global amyloid deposition may have prevented us from finding a significant association between LTF and level of amyloid.

Our associations between LTF and tau deposition were in the expected direction; however, they were driven primarily by one participant with higher tau. Previous studies examining cognition in CU older adults using single timepoint testing have shown subtle associations between worse episodic memory recall and tau deposition in the medial temporal lobe independent of amyloid status.[41,28,42–45] However, these studies did not find associations between episodic memory recall and tau-PET deposition in neocortical regions, or Braak stages III/IV, where tau is known to later progress in the context of elevated amyloid.[3,6] Whereas tau deposition in the medial temporal lobe may sometimes be attributed to age-related changes, tau that has advanced

to the neocortical regions is thought to be more indicative of AD progression and considered an intermediate stage of preclinical AD.[27,46] Our finding that accelerated LTF was associated with tau deposition in regions associated with both early and intermediate Braak stages suggests that assessing LTF may reveal early AD-related memory changes beyond "age-related" cognitive decline. This is further supported by the fact that our results seemed driven by individuals with higher tau and, thus, greater disease progression. Our finding that accelerated LTF was associated with AD-signature cortical thinning provides complementary evidence for the notion that accelerated LTF may be an early sign of subtle memory changes in individuals at risk for AD.[9–12] This finding that cortical thickness is associated with cognition in CU older adults is consistent with the previous literature[30] and is more convincing than our tau findings given that our complete sample had available MRI data.

4.3 | Implications

Our findings may help us better understand the nature of learning and forgetting processes over more frequent, short-term time intervals, which were previously challenging to assess with single timepoint assessments. Furthermore, leveraging remote digital testing allowed us to administer recall assessments at multiple timepoints and measure LTF performance with very little burden to participants or interference with their everyday life. In addition, our results support the conclusion from previous work that long-term forgetting measures can provide valuable information on the cognition of older adults that may aid early detection of AD-related cognitive decline. Thereby, the results of this study provide another example of how digital tools can be beneficial for advancing preclinical AD research.[47–49] Assessments of multi-day learning and subsequent LTF may be particularly useful in clinical trials, as they improve our ability to capture very early nuances of memory change in participants without adding extra burden.

4.4 | Limitations and future directions

Only 11.5% of our sample was from underrepresented minority groups, and most participants were highly educated women. This demographic breakdown is not representative of the greater U.S. population at risk for AD.[50,51] In addition, although we do our best to control for the remote aspect of the assessment by providing clear instructions to complete the assessment independently, we cannot be completely certain that participants are following instructions while unsupervised. A similar concern is that participants may try to use memory aides to remember the stimuli before their 1-week recall assessment; however, we proactively made efforts to counter this challenge by informing participants that they would be asked to complete an extra assessment 1 week after their initial 7 days of testing, but not revealing that this would be a recall assessment. Administering cognitive assessments remotely does inherently have some limitations, in that the control we have over participants' adherence to study guidelines is limited; however, using a remote study paradigm provides unique opportunities to collect more data at multiple, more frequent time intervals with very little burden to participants.

Data collection for this study is still ongoing. Therefore, there is an opportunity to address some of our outstanding questions. First, given the feasibility of administering additional recall assessments after various time intervals, future work will make efforts to narrow down the most optimal time interval for capturing accelerated LTF. Although our results demonstrate that assessing recall after 1 week is associated with the accumulation of tau, and that recall after 6 months does not have a significant relationship with AD biomarkers, further exploration is needed to determine whether there is a better time interval to use, perhaps somewhere in between 1 week and 6 months. In additional next steps, Elliot et al. (2014)[13] recommends including both a recognition and a recall measure when assessing LTF. We have now introduced a first letter name recall measure to our LTF assessment, which will allow us to address this important question in the future.

In addition, the current study sample unfortunately has a limited range of tau values. However, given the lower-than-expected proportion of Aβ+ individuals (16.3%), it was not surprising that only a few individuals appeared to have high tau in AD-related regions. We acknowledge that the participant with high tau has driven the associations between LTF and tau deposition, and future work will seek to replicate these findings with a larger sample and a more continuous spectrum of tau deposition. Future work will explore these analyses in a sample that is more akin to a preclinical AD clinical trial sample, with a higher proportion of AB+ individuals and a more heterogeneous range in tau values. Finally, to further characterize LTF and understand how LTF may change over time, future studies may analyze longitudinal measures of LTF. Evaluating LTF longitudinally may determine whether LTF has any predictive utility for cognitive decline. For instance, we could explore an LTF measure's ability to predict participants' progression from CU to MCI. Our sample is currently undergoing longitudinal assessments. Therefore, we hope to be able to address this question over the next few years.

5 | CONCLUSIONS

Overall, we demonstrated that in a sample of CU older adults that utilizing a remote, digital, multi-day learning assessment followed by a recall assessment of learned material after 1-week can reveal accelerated LTF that is associated with early-to-intermediate AD-related tau deposition and AD-related cortical thinning. These findings are valuable in continuing to advance assessment methods for the early detection of preclinical AD.

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CONFLICT OF INTEREST STATEMENT

G.A.M. has received consulting fees from Ono Pharma USA Inc., and has received research salary support for serving as site principal investigator for clinical trials funded by Eisai Inc. and Eli Lilly and Company. The remaining authors declare that they have no commercial or financial relationships that could be construed as a potential conflict of interest relevant to the current study. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

The MassGeneral Brigham Institutional Review Board, which oversees research conducted at Massachusetts General Hospital and Brigham and Women's Hospital, approved this study. 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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