HHS Public Access

Author manuscript

Alzheimers Dement. Author manuscript; available in PMC 2024 November 01.

Published in final edited form as:

Alzheimers Dement. 2023 November ; 19(Suppl 9): S19–S28. doi:10.1002/alz.13159.

Learning slopes in early-onset Alzheimer's disease

Dustin B. Hammers[1], **Sára Nemes**[1], **Taylor Diedrich**[1], **Ani Eloyan**[2], **Kala Kirby**[1], **Paul Aisen**[3], **Joel Kramer**[4], **Kelly Nudelman**[5], **Tatiana Foroud**[5], **Malia Rumbaugh**[5], **Alireza Atri**[6], **Gregory S. Day**[7], **Ranjan Duara**[8], **Neill R. Graff-Radford**[7], **Lawrence S. Honig**[9], **David T. Jones**[10,11], **Joseph C. Masdeu**[12], **Mario F. Mendez**[13], **Erik Musiek**[14], **Chiadi U. Onyike**[15], **Meghan Riddle**[16], **Emily Rogalski**[17], **Steve Salloway**[16], **Sharon J. Sha**[18], **Raymond Scott Turner**[19], **Sandra Weintraub**[17], **Thomas S. Wingo**[20], **David A. Wolk**[21], **Bonnie Wong**[22], **Maria C. Carrillo**[23], **Bradford C. Dickerson**[22], **Gil D. Rabinovici**[4], **Liana G. Apostolova**[1,5,24], **LEADS Consortium**

[1]Department of Neurology, Indiana University School of Medicine, Indianapolis, Indiana, USA

[2]Department of Biostatistics, Center for Statistical Sciences, Brown University, Providence, Rhode Island, USA

[3]Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego, California, USA

[4]Department of Neurology, University of California, San Francisco, California, USA

[5]Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, Indiana, USA

[6]Banner Sun Health Research Institute, Sun City, Arizona, USA

[7]Department of Neurology, Mayo Clinic, Jacksonville, Florida, USA

[8]Wien Center for Alzheimer's Disease and Memory Disorders, Mount Sinai Medical Center, Miami, Florida, USA

[9]Taub Institute and Department of Neurology, Columbia University Irving Medical Center, New York, New York, USA

[10]Department of Radiology, Mayo Clinic, Rochester, Minnesota, USA

[11]Department of Neurology, Mayo Clinic, Rochester, Minnesota, USA

[12]Nantz National Alzheimer Center, Houston Methodist and Weill Cornell Medicine, Houston, Texas, USA

Correspondence Dustin B. Hammers, Department of Neurology, Indiana University School of Medicine, Department of Neurology, 355 West 16th, Street (GH4027), Indianapolis, IN 46202, USA. HammersD@iu.edu.

CONFLICT OF INTEREST STATEMENT

No authors associated with this project have reported conflicts of interest that would impact these results. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All authors have read and provided consent to be associated with this manuscript.

SUPPORTING INFORMATION

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

[13]Department of Neurology, David Geffen School of Medicine at UCLA, Los Angeles, California, USA

[14]Department of Neurology, Washington University in St. Louis, St. Louis, Missouri, USA

[15]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

[16]Department of Neurology, Alpert Medical School, Brown University, Providence, Rhode Island, USA

[17]Department of Psychiatry and Behavioral Sciences, Mesulam Center for Cognitive Neurology and Alzheimer's Disease, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA

[18]Department of Neurology & Neurological Sciences, Stanford University, Palo Alto, California, USA

[19]Department of Neurology, Georgetown University, Washington D.C., USA

[20]Department of Neurology and Human Genetics, Emory University School of Medicine, Atlanta, Georgia, USA

[21]Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

[22]Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA

[23]Medical & Scientific Relations Division, Alzheimer's Association, Chicago, Illinois, USA

[24]Department of Radiology and Imaging Sciences, Center for Neuroimaging, Indiana University School of Medicine Indianapolis, Indianapolis, Indiana, USA

Abstract

OBJECTIVE: Investigation of learning slopes in early-onset dementias has been limited. The current study aimed to highlight the sensitivity of learning slopes to discriminate disease severity in cognitively normal participants and those diagnosed with early-onset dementia with and without β-amyloid positivity

METHOD: Data from 310 participants in the Longitudinal Early-Onset Alzheimer's Disease Study (aged 41 to 65) were used to calculate learning slope metrics. Learning slopes among diagnostic groups were compared, and the relationships of slopes with standard memory measures were determined

RESULTS: Worse learning slopes were associated with more severe disease states, even after controlling for demographics, total learning, and cognitive severity. A particular metric—the learning ratio (LR)—outperformed other learning slope calculations across analyses

CONCLUSIONS: Learning slopes appear to be sensitive to early-onset dementias, even when controlling for the effect of total learning and cognitive severity. The LR may be the learning measure of choice for such analyses.

Keywords

early-onset Alzheimer's disease; learning slopes; memory

1 | INTRODUCTION

While an estimated 6.5 million Americans over the 65 are living with Alzheimer's disease (AD) in 2022,[1] only 4% to 6% of those with AD manifest clinical symptoms and are diagnosed with early-onset AD (EOAD) before the age of 65.[2] Early studies suggest that patients with EOAD experience a steeper rate of cognitive decline[3] and greater burden of cognitive impairments[4] than the traditional late-onset AD (LOAD). Greater involvement of non-memory cognitive domains as the predominant presenting symptom are observed,[5] with EOAD being associated with atypical dementia phenotypes (e.g., logopenic primary progressive aphasia, posterior cortical atrophy).[4] Research on memory functioning in EOAD has been somewhat equivocal, with some studies suggesting a relative sparing of memory in EOAD,[6,7] whereas others have noted memory impairments.[8,9] More specific investigation into the influence of EOAD on unique aspects of memory has been limited, and to date examination of other factors like learning slopes have yet to been considered.

Learning slopes represent an individual's capacity to acquire information across repeated trials of a learning task. They have been associated with encoding abilities, as well as enhanced retention of incoming information.[10] They tap into both episodic memory-related and working memory/attention-related aspects of cognition,[11] with impairments in learning slopes associated with hippocampal,[12] ventrolateral prefrontal,[11] and dorsolateral prefrontal atrophy.[13] These regions coincide with the diffuse network involvement of EOAD—greater overall cortical atrophy and white matter degeneration relative to prominent temporal lobe changes in LOAD[14,15]—suggesting that patients with EOAD may be particularly susceptible to deficiencies in learning slope. Several methods of calculating learning slopes exist, including the simple difference between first-trial and final/best trial performance (raw learning score, or RLS), reflecting the simple gain in acquired knowledge after trial 1 of a multi-trial learning task.[16–18] Learning over trials (LOT) represents incremental learning after factoring out trial 1 performance of a task,[19,20] by subtracting the first trial value from each subsequent trial. Finally, the learning ratio (LR) builds on the RLS by dividing the difference between the first and final/best trial by the number of items yet to be learned after trial 1,[21] and therefore reflects the proportion of information learned after trial 1 relative to the amount of information left to learn. The reader is referred to the Methods for detailed equations for each learning slope.

The purpose of this research is twofold. The first aim of the study is to examine whether individuals with EOAD possess deficiencies in learning slope, as this represents a gap in the literature at the present time. Given the necessary incorporation of several cognitive demands in the acquisition of information, it is hypothesized that patients with EOAD will have greater difficulty with learning slope performance on the Rey Auditory Verbal Learning Test (RAVLT)[22] than cognitively-intact same-aged peers. As learning slopes have also been shown to be sensitive to AD pathology,[12] EOAD participants are also anticipated to possess

weaker learning slopes than a cohort of same-aged peers with cognitive deficits related to non-AD pathology (early-onset non-AD; EOnonAD).

Second, we aim to investigate differences in sensitivity between learning slope metrics in EOAD populations. Previous research has suggested that LR tends to be (1) more closely associated with traditional measures of learning and memory[21,23] and AD biomarkers of hippocampal volumes and β-amyloid (Aβ) burden,[23,24] and (2) better at discriminating between those along the LOAD continuum[25] than other learning slopes. Additionally, preliminary evidence suggests that LR may be a stronger predictor of memory retention in cognitively healthy older adults.[26] Correspondingly, declines in LR may identify patients with clinically meaningful cognitive decline, early in the symptomatic course. The proposed mechanism for this outperformance by LR is that in other learning slope metrics, acquisition of information is constrained by performance at trial 1.[21] In essence, learning more information at trial 1 means less information is available to learn on successive trials. However, LR controls for the competition between trial 1 and subsequent trial performance by dividing by the yet-to-be-learned information, therefore it appears to be free of this confound. It is therefore hypothesized that LR will better discriminate diagnostic classification status than the other learning slopes examined.

Overall, should our hypotheses be correct, our results would provide documentation that learning slopes are sensitive to decline in EOAD. This has applications to diagnosis and decision-making in the clinic (and research studies), and for tracking response for patients with EOAD following interventions (eg, clinical trials). In particular, use of learning slopes in EOAD may enable greater consideration of trial-by-trial learning capacity than total recall scores, and may permit more personalized treatment recommendations for some patients. Additionally, it would expand findings of the superiority of the LR metric over other learning slopes into younger stages of the AD continuum. Together, these results would represent an important step forward in advancing our knowledge of this understudied neurodegenerative condition.

2 | METHODS

Participant data were obtained from the multi-center Longitudinal Early-Onset AD Study (LEADS).[27] The LEADS was launched in 2018. Please see the LEADS website (https://leads-study.medicine.iu.edu/) for a detailed explanation of the study leadership, resources, and data sharing policies. Institutional Review Board approval is provided through a central IRB overseen by Indiana University. Written informed consent was obtained from study participants or their authorized representatives.

As of July 2021, finalized baseline cognitive data were available for 310 LEADS participants, including 166 participants classified as EOAD, 62 participants classified as EOnonAD, and 82 participants classified as being cognitively normal (CN). Inclusion criteria for the LEADS involved being within the age range of 40 to 64 at the time of consent; fluent in English; and having a knowledgeable informant. Relevant exclusion criteria included magnetic resonance imaging (MRI) evidence of significant vascular disease or other central nervous system disorder; known pathogenic variants in *APP*, *PSEN1*,

PSEN2, *GRN*, *MAPT*, or pathogenic repeat expansions in *C9ORF72*; having participated in therapeutic trials targeting Aβ and/or tau; moderate or severe substance abuse; severe medical or psychiatric disorders, suicidal ideation, or another neurological disorder.[27]

EOAD and EOnonAD participants met National Institute on Aging and Alzheimer's Association (NIA-AA) criteria for dementia or mild cognitive impairment (MCI) via diagnostic consensus criteria with neurologists, neuropsychologists, and/or psychiatrists,[27] and had a global Clinical Dementia Rating (CDR) scale[28] score of ≤1.0 at the time of enrollment. The key feature separating EOAD from EOnonAD participants was the presence of positive Aβ deposition on amyloid-PET scan for EOAD participants on visual read. CN participants possessed a global CDR = 0 and a Mini-Mental State Examination (MMSE)[29] score of ≥24, and had cognitive scores consistently within the normal range on neuropsychological testing (National Alzheimer's Coordinating Center's Uniform Data Set [NACC UDS])[30]; participants meeting the threshold for MCI or dementia were classified as either EOAD or EOnonAD. Of note, while RAVLT recall scores—from which the learning slopes were derived—informed diagnosis, they represented a fraction of the clinical, cognitive, and imaging data utilized for diagnostic consideration.

2.1 | Procedure

All participants underwent an extensive clinical and neuropsychological battery at a baseline visit. For the current study, the following neuropsychological and clinical measures were of relevance:

1. The RAVLT[22] is a verbal list-learning task containing 15 words presented over five trials. The Total Recall score is the total number of words correctly recalled across all trials (range = 0 to 75), and the Delayed Recall score is the number of words correctly recalled following a 20- to 30-min delay (range = 0 to 15). Learning slope performances were evaluated by raw data from individual trials. Higher raw values indicate better performance.
2. The Craft Story 21 Memory Test[31] is a verbal paragraph recall task requiring acquisition of a short story both immediately (Recall Immediate) and after a 20-min delay (Recall Delayed). Consistent with usage in the NACC UDS 3.0 battery,[30] the Immediate and Delayed Recall paraphrase scores (range = 0 to 25) were used as independent variables in the current study. Higher raw values indicate better performance.
3. The Benson Delayed Recall Test[32] measures nonverbal memory and requires recall of details of the previously-copied Benson Delayed Recall after a 15-min delay. The Benson Delayed Recall score is the number of details correctly recalled (range = 0 to 17), with higher raw values indicating better performance.
4. The Word Recall subtest from the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)[33] is a verbal list-learning task with 10 words presented over three trials. For the current study, Total Score reflects the number of words correctly recalled across trials (range = 0 to 30), and Delayed Recall score is the number of correctly recalled words after a 10-min delay (range = 0 to

10).[26] While this scoring deviates from test developer's protocols, it permits higher raw values to indicate better performance—consistent with all other memory measures in the study. Of note, the Total Score from the ADAS-Cog was also included in the current study, with a range of 0 to 85 and lower scores indicating better performance.

5. The Barona Index[34] is a regression-based estimate of premorbid intellect using age, education, race, occupational attainment, geographic region, and sex. Recent findings suggest that the Barona Index—after adjustment for the Flynn Effect[35]—predicts intelligence comparably to other performance-based premorbid intellect estimates.[36] The Barona Index with Flynn Effect adjustment results in an intelligence estimate in standard scores (M = 100, SD = 15), with higher values indicating greater baseline intellectual functioning.

6. The 15-item Geriatric Depression Scale (GDS)[37] was used to assess self-reported depression. Higher scores indicate greater self-reported depression.

7. Additional neuropsychological tests were incorporated related to supplemental analyses. As these tests are common to most dementia clinicians and researchers, they will not be described here. They included the Montreal Cognitive Assessment (MoCA),[38] Trail Making Test Parts A and B (TMT-A and TMT-B),[39] Animal (Semantic) Fluency,[40] and the Multilingual Naming Test (MINT).[41]

Finally, advanced brain imaging was undertaken using positron emission tomography (PET) for Aβ (^{18}F-Florbetaben) for supplemental analyses, as per the LEADS protocol.[27]

2.2 | Calculation of learning slopes

As indicated previously, learning slopes were derived from performance on learning trials of the RAVLT. Please see the formulas for the RLS, LOT, and LR below for a mathematical description of the calculation for each metric. The RLS scores were computed as the highest number of items learned on trials 2 through 5, relative to trial 1.[17,18] The LOT scores were calculated as the sum of trials 1 through 5 minus the value of trial 1 multiplied by 5.[19] The LR scores reflect the following proportion: the difference in performance between the highest trial score (of trials 2 through 5) and trial 1 in the numerator, and the difference between the maximum possible trial score and trial 1 performance in the denominator.[21]

$$\text{RLS} = (\text{Highest Trial Score [of Trials 2 through 5]} - \text{Trial 1})$$

$$\text{LOT} = (\text{Sum of Trials 1 through 5} - (\text{Trial 1} * 5))$$

$$\text{LR} = \frac{(\text{Highest Trial Score [of Trials 2 through 5]} - \text{Trial 1})}{(\text{Number of items possible to be learned} - \text{Trial 1})}$$

2.3 | Data analysis

For the primary criterion analyses, analyses of covariance (ANCOVA) were conducted comparing diagnostic classification (NC, EOnonAD, and EOAD) on the RAVLT learning slope performances (LR, RLS, LOT, and trial 1) after controlling for appropriate demographic covariates. For significant ANCOVA analyses, Bonferroni post hoc corrections were implemented among diagnostic group performances. To determine the appropriateness of covariates in these ANCOVA analyses, analyses of variance were conducted between continuous demographic variables (eg, age, education) and diagnostic group, and chi-square analyses were conducted between categorical demographic variables (eg, sex, and ethnicity) and diagnostic group. Supplemental analyses included RAVLT Total Recall and MoCA performances as additional covariates to examine if group differences were present in learning slopes above and beyond total learning and global cognitive severity; relatedly, hierarchical regression was additionally included with demographic variables and RAVLT Total Recall in Model 1 and RAVLT LR in Model 2 to assess RAVLT LR's incremental variability accounted for when predicting Diagnostic Group membership.

For the convergent analyses, partial correlation coefficients were calculated comparing learning slope performances to standard immediate and delayed memory measures. Supplementary analyses included partial correlation comparing RAVLT LR performance to non-memory cognitive measures (TMT-B, Animal Fluency, and MINT), as well as to Aβ deposition standardized uptake value ratio (SUVR) using ^{18}F-Florbetaben amyloid-PET. To determine appropriateness of covariates for the partial correlation analyses, bivariate correlation coefficients were calculated between demographic variables and learning slope scores.

Measures of effect size were expressed as Cohen's d (ANCOVA) and r^2 values (partial correlations). Comparisons between Cohen's d values were investigated by examining the overlap in 95% compatibility intervals (CIs), as described by Cumming & Finch.[42] Comparisons between correlations were examined using Fisher r to z transformations. To protect against multiple comparisons, a Holm-Bonferroni method of adjustment of the two-tailed alpha level was undertaken for all primary analyses.

3 | RESULTS

3.1 | Demographics

This study included 310 participants, classified as CN (n = 82), amyloid-positive EOAD (n = 166), or amyloid-negative EOnonAD (n = 62) participants (Table 1). The mean age was 57.70 (SD = 5.2) years old, with the total sample having an average of 15.82 (SD = 2.5) years of education. Age was different between the three groups (P < 0.001, d = 0.54), with the CN group being younger than the EOAD group (P < 0.001). Similarly, education differences existed between groups (P < 0.001, d = 0.53), with the CN group having higher levels of education than either the EOAD or EOnonAD groups (P = 0.001 to 0.01). No differences existed in age and education when comparing the EOAD and EOnonAD cohorts (P = 0.21 to 0.99). Please see the Supplement for expanded results of demographic analyses.

Additionally, differences existed between groups for sex ($P = 0.004$, $\varphi = 0.18$) and ethnicity ($P < 0.001$, $\varphi = 0.22$). Specifically, the EOnonAD group had a greater percentage of men than the CN or EOAD groups, and the CN group had a higher number of Hispanic/non-Caucasian participants than the EOAD or EOnonAD cohorts. While self-reported depression was generally low across the total sample, group differences were observed ($P < 0.001$, $d = 0.55$). Specifically, both EOAD and EOnonAD groups endorsed higher levels of depression than the CN group (all $P < 0.001$), though there was no difference between EOnonAD and EOAD groups ($P = 0.33$). The sample had a high level of estimated baseline intelligence, with no differences between groups ($P = 0.19$, $d = 0.21$).

Differences were observed between groups for global cognitive status, based on the MoCA ($P < 0.001$, $d = 1.88$). The EOAD group performed worse than the EOnonAD group ($P < 0.001$), who performed worse than the CN group ($P < 0.001$). Differences were additionally observed between groups for the RAVLT Total Recall, RAVLT Delayed Recall, CRAFT Immediate Recall, CRAFT Delayed Recall, Benson Delayed Recall, ADAS-Cog Word Recall Immediate Recall, ADAS-Cog Word Recall Delayed Recall, and ADAS-Cog Total Score (all $P < 0.001$; $d = 1.54$ to 2.41). In each case, the EOAD group performed worse than the EOnonAD group (all $P < 0.001$), which performed worse than the CN group (all $P < 0.001$).

3.2 | Criterion analyses

Based on the aforementioned demographic results, age, education, sex, and ethnicity were used as covariates in the subsequent ANCOVA analyses. As seen in Table 2, differences were observed between groups for all learning scores when controlling for covariates: LR ($F(2,301) = 141.00$, $P < 0.001$, $d = 1.94$), RLS ($F(2,301) = 71.99$, $P < 0.001$, $d = 1.38$), LOT ($F(2,301) = 75.28$, $P < 0.001$, $d = 1.41$), and trial 1 ($F(2,301) = 62.35$, $P < 0.001$, $d = 1.29$). For LR, RLS, and LOT, EOAD participants performed worse than EOnonAD participants, who performed worse than CN participants (all $P < 0.001$). For trial 1, EOAD participants performed worse than both EOnonAD and CN participants (all $P < 0.001$), but only a trend existed between EOnonAD and CN participants ($P = 0.03$). Upon direct comparison in Table 2, the magnitude of the omnibus effect for LR was stronger than for RLS, LOT, and trial 1. Specifically, the lack of overlap in the 95% CIs between LR's midpoint and the upper bound of the other learning slopes indicates distinct magnitudes of effect. As indicated above, supplemental analyses were additionally conducted with RAVLT Total Recall and MoCA performances as further covariates (in addition to demographic variables) to examine if group differences were present in learning slopes above and beyond severity of total learning and global cognitive severity. Similar to the primary analyses, group differences persisted following adjustment for both RAVLT Total Recall (LR: $P < 0.001$, $d = 0.49$; RLS: $P < 0.001$, $d = 0.43$; LOT: $P < 0.001$, $d = 0.45$; and trial 1: $P < 0.001$, $d = 0.45$) and MoCA (LR: $P < 0.001$, $d = 1.03$; RLS: $P < 0.001$, $d = 0.73$; LOT: $P < 0.001$, $d = 0.78$; and trial 1: $P < 0.001$, $d = 0.51$). For all four learning slopes, EOAD participants performed worse than CN participants for both sets of analyses ($P = 0.001$ to 0.002, $d = 0.40$ to 0.54 for RAVLT Total Recall; $P = 0.001$ to 0.007, $d = 0.37$ to 1.34 for MoCA). EOAD participants performed worse than EOnonAD participants for LR and trial 1 performances (all $P < 0.001$, $d = 0.49$ to 0.52) after MoCA covariation, but for not the other comparisons (all P

> 0.05). Further, hierarchical regression indicated that when RAVLT LR was added to a model that already contained demographic variables (age, education, sex, and ethnicity) and RAVLT Total Recall, RAVLT LR explained an additional 16.4% of variation in Diagnostic Group; this change in r^2 was significant ($P < 0.001$). When factoring out the contribution of demographic variables, RAVLT LR explained an additional 23.3% of variation in Diagnostic Group beyond RAVLT Total Recall alone.

3.3 | Convergent analyses

Bivariate correlation coefficients between LR and age, education, and ethnicity were significant ($r = -0.23$, $P < 0.001$, $r^2 = 0.05$ for age, $r = 0.24$, $P < 0.001$, $r^2 = 0.06$ for education, and $r = -0.16$, $P = 0.004$, $r^2 = 0.03$ for ethnicity). While LR and sex were not associated, $r = -0.09$, $P = 0.11$, $r^2 = 0.01$, RAVLT Total Recall and sex were, $r = -0.11$, $P = 0.05$, $r^2 = 0.01$. Consequently, age, education, ethnicity, and sex were used as covariates in the subsequent learning slope comparisons.

After controlling for covariates, all four learning slopes were significantly and positively related to immediate and delayed memory performances (all $P < 0.001$; see Table 3) across the total sample. When comparing across learning slopes, LR score correlations were consistently larger than those for RLS, LOT, and trial 1. Specifically, Fisher r to z transformations indicated that partial correlations were greater for LR than all other learning slope calculations (eg, RLS, LOT, and trial 1) for RAVLT Delayed Recall ($z = 5.32$ to 7.84, all $P < 0.001$) and ADAS-Cog Word Recall Delayed Recall ($z = 2.75$ to 5.15, $P = 0.001$ to 0.005). Additionally, partial correlations were greater for LR than RLS and LOT for RAVLT Total Recall ($z = 5.99$ to 6.67, all $P < 0.001$) and ADAS-Cog Word Recall Immediate Recall ($z = 2.89$ to 3.21, all $P < 0.01$). Partial correlations were additionally greater for LR versus trial 1 for Craft Delayed Recall ($z = 3.25$, $P = 0.001$) and Benson Delayed Recall ($z = 4.10$, $P < 0.001$). Comparable results across tests can be observed when examining the analyses within diagnostic groups.

Finally, further consideration of convergent validity was undertaken by conducting supplemental partial correlations between RAVLT LR and (1) non-memory-related neuropsychological measures, and (2) Aβ SUVR values across the total sample. As seen in Table 3, after controlling for covariates LR was significantly related to language and executive functioning performances (all $P < 0.001$) across the total sample. Lower LR scores corresponded with lower semantic fluency, confrontation naming, and mental flexibility performances, with Fisher r to z transformation indicating that the correlations between LR and both semantic fluency and mental flexibility were significantly larger than that with confrontation naming ($z = 3.78$, $P < 0.001$). Additionally, RAVLT LR was significantly and negatively related to Aβ deposition in the total sample of participants after controlling for covariates ($r = -0.54$, $P < 0.001$), such that higher Aβ deposition was associated with lower RAVLT LR performance.

4 | DISCUSSION

Learning slopes derived from the RAVLT were significantly worse for more severe early-onset disease states in this study, such that CN participants outperformed

EOnonAD participants, who outperformed EOAD participants. As this represents the first documentation of learning slope performance differences in EOAD, these results should be replicated in future research. This finding is consistent with previous work suggesting that learning slopes are sensitive to disease severity along the LOAD continuum,[11,25] including that participants with MCI outperform those with dementia due to AD. Additionally, our work coincides with observations of cognitive impairment in patients with EOAD for both memory[8,9] and non-memory domains[5] (attention), which makes conceptual sense as learning slopes are thought to incorporate aspects of both memory and working memory/attention (as will be described below).[11] As the presence of Aβ pathology represented a key distinction between the EOAD and EOnonAD groups, our results suggest that learning slope performance is particularly sensitive to AD pathology. This suggestion is reinforced by the moderate ($r^2 = 0.29$) and inverse relationship we observed between LR and Aβ deposition, which corresponds to other recent research suggesting that learning slope performance is associated with Aβ deposition and hippocampal atrophy.[11,12] While initial research is promising,[43] future research into learning slopes as a function of tau pathology may shed further light on its sensitivity toward AD pathology.

When considering group performances on individual markers of learning slope, our results suggest that the LR metric was more sensitive to group differences than other metrics (Table 2). This is based on the magnitude of the effect across CN to EOAD groups being larger for LR than other metrics. These findings are consistent with previous results that LR is more sensitive to neurodegeneration[23] and AD pathology[12] than traditional learning slope metrics. More recent work has also shown that LR is also more sensitive to cognitive deficit than LOT in older adults.[44]

Additionally, supplemental analyses suggested that these group differences in learning slope remained even after total learning and cognitive severity were added as covariates to the learning slope ANCOVA analyses. Also, hierarchical regression was conducted to better understand the degree of incremental utility of LR over RAVLT Total Recall, which showed that RAVLT LR explained an additional 16.4% to 23.3% of the variance in Diagnostic Group membership—above and beyond demographics and RAVLT Total Recall ($P < 0.001$). These results suggest that learning slopes in general—and LR in particular—appear to enhance our ability to predict group membership along the EOAD continuum—more so than summary scores or measures of global cognition alone. This is consistent with previous research suggesting that learning slopes explained more variance with neuroimaging markers in AD after accounting for other common memory indices, such as total learning.[11] Use of process scores like LR in the diagnosis or clinical-decision making of EOAD may enable greater consideration of trial-by-trial learning capacity than total learning, delayed recall, or global screening scores—or the currently used raw learning calculations. This may therefore enhance a provider's clinical decision-making for an individual, and allow for more personalized treatment recommendations for some patients in clinical settings. Consequently, the use of LR or other learning slopes is not intended to replace Total or Delayed Recall scores, but to supplement them.

Further, although all learning slope performances were positively and significantly correlated with traditional learning and memory measures after accounting for covariates

(Table 3), the associations for LR were consistently larger than other learning metrics (following Fisher r to z transformation). This was observed not only with the RAVLT Total Recall and Delayed Recall, but also with learning and memory tasks that were not related to the learning slope calculation (eg, Craft 21 Story Memory Test, Benson Delayed Recall, and ADAS-Cog Word Recall). The magnitude of the correlations for LR were consistent with—if not slightly larger than—previous LR research derived from the Hopkins Verbal Learning Test–Revised[18] (HVLT-R) across a mixed AD continuum sample. Specifically, association of LR with Total Recall aspects of the same measure (eg, HVLT-R LR with HVLT-R Total Recall) have been observed at $r = 0.71$,[45] relative to $r = 0.87$ in the current study. Current association of LR and both another word-list-learning task ($r = 0.70$) and a story memory task ($r = 0.57$) were also either stronger than or comparable with previous findings ($r = 0.58$ and $r = 0.54$, respectively).[45] These slight differences in the magnitude of association between studies may be accounted for by differences used in the calculation of RLS and subsequently LR. Whereas Spencer's original calculation included "Final Trial − Trial 1" for the RLS (and for the numerator of LR), we used "Highest Trial Score (of Trials 2 through 5)" − Trial 1″[17] because for 1/3 of our sample the final trial was not the highest trial score—likely a result of the greater number of trials in the RAVLT relative to other measures used in LR research.[18,46] This led to slightly larger ranges of performance than would have resulted using Spencer's original calculation, and subsequently enhanced the correlation coefficients observed.[47]

Convergent validity analyses additionally indicated that lower LR scores corresponded with lower semantic fluency ($r = 0.58$), confrontation naming ($r = 0.33$), and mental flexibility performances ($r = 0.59$). This represents the first documentation of convergence between LR and non-memory cognitive measures. Analyzing the data more closely, Fisher r to z transformation indicated that the correlations between LR and both semantic fluency and mental flexibility were significantly larger than that with confrontation naming ($z = 3.78$, $P < 0.001$). As recent findings have suggested that (animal) semantic fluency is impacted by both language and executive functioning in AD,[48] these results raise the possibility that LR is highly influenced by executive processes—almost to the level though quite not as highly as memory processes (eg, $r = 0.70$ to 0.78 with Word Recall from ADAS-Cog). This corresponds with past work implicating the dorsolateral prefrontal cortex in learning slope performance,[13] and suggests that future research to more thoroughly examine the impact of executive functioning on LR should be encouraged.

Together, this work supports previous assertions that LR should be the preferred learning slope metric for use with individuals either with or without cognitive impairment.[21] This is true even for the LOT calculation that has been used in a variety of prediction studies —like predicting Aβ deposition and neurodegeneration[20] or performance on computerized cognitive testing.[19] Thomas and colleagues[49] previously considered LOT to be a sensitive enough process measure to predict progression to MCI; however, our findings suggest that prediction accuracy may have been even stronger if LR were selected as their measure of choice.

The current study is not without limitations. First, the demographic make-up of our sample (mostly Caucasian and highly educated) restricts the generalizability of these findings.

Although the CN participants reflected a broader racial/ethnic representation of the US population (25% being Hispanic/non-Caucasian individuals), only 7% to 11% of the clinical groups were Hispanic/non-Caucasian participants. Future work should consider replication of these findings in more diverse populations. Second, these results are unique to the RAVLT in samples under the age of 65 and cannot necessarily be generalized to participants with later-onset forms of dementia. Future investigation is encouraged to consider if learning slopes possess sensitivity at discerning EOAD from LOAD. Finally, while LR has shown to be both sensitive to early manifestation of AD and more consistent with trajectories observed in aging than other learning slopes,[21,45] it may overlook some patterns of performance across trial-based learning tasks. Future research to identify different performance patterns of learning—which have not yet been fully idealized—is recommended.

Despite these limitations, our results suggest that learning slopes appear sensitive to early-onset dementias, with LR being the learning measure of choice for such analyses. These findings advance our knowledge of EOAD, and suggest that LR may serve as a valuable tool for diagnosis, decision-making, and tracking of EOAD in the clinic and clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

We would like to thank all members of the LEADS Consortium, as well as the LEADS Clinical Outcomes group, and Constantine Gatsonis, PhD, for his statistical guidance. This study is generously supported by Alzheimer's Association AARG-22–926940, Alzheimer's Association LDRFP-21–818464, R56 AG057195, NIA U01AG6057195, NIA U24AG021886, Alzheimer's Association LEADS GENETICS-19–639372, NIA U01 AG016976, NIA P30 AG010133, NIA P50 AG008702, NIA P50 AG025688, NIA P50 AG005146, NIA P30 AG062421, NIA P30 AG062422, NIA P50 AG023501, NIA P30 AG010124, NIA P30AG066506, NIA P30 AG013854, NIA P50 AG005681, NIA P50AG047366, and NIA U24AG021886.

REFERENCES

1. Alzheimer's Association. 2021 Alzheimer's disease facts and figures. Alzheimers Dementia. 2021;17:327–406.
2. Zhu XC, Tan L, Wang HF, et al. Rate of early onset Alzheimer's disease: a systematic review and meta-analysis. Ann Transl Med. 2015;3:38. [PubMed: 25815299]
3. Wattmo C, Wallin AK. Early- versus late-onset Alzheimer's disease in clinical practice: cognitive and global outcomes over 3 years. Alzheimers Res Ther. 2017;9:70. [PubMed: 28859660]
4. Mendez MF. Early-onset Alzheimer disease. Neurol Clin. 2017;35:263–281. [PubMed: 28410659]
5. Palasi A, Gutierrez-Iglesias B, Alegret M, et al. Differentiated clinical presentation of early and late-onset Alzheimer's disease: is 65 years of age providing a reliable threshold? J Neurol. 2015;262:1238–1246. [PubMed: 25791224]
6. Binetti G, Magni E, Padovani A, Cappa SF, Bianchetti A, Trabucchi M. Executive dysfunction in early Alzheimer's disease. J Neurol Neurosurg Psychiatry. 1996;60:91–93. [PubMed: 8558161]
7. Smits LL, Pijnenburg YA, Koedam EL, et al. Early onset Alzheimer's disease is associated with a distinct neuropsychological profile. J Alzheimers Dis. 2012;30:101–108. [PubMed: 22366769]
8. Joubert S, Gour N, Guedj E, et al. Early-onset and late-onset Alzheimer's disease are associated with distinct patterns of memory impairment. Cortex. 2016;74:217–232. [PubMed: 26694580]

9. Koedam EL, Lauffer V, van der Vlies AE, van der Flier WM, Scheltens P, Pijnenburg YA. Early-versus late-onset Alzheimer's disease: more than age alone. J Alzheimers Dis. 2010;19:1401–1408. [PubMed: 20061618]
10. Hammers DB, Spencer RJ, Apostolova LG. Validation of and demographically adjusted normative data for the learning ratio derived from the RAVLT in robustly intact older adults. Arch Clin Neuropsychol. 2022;37(5):981–993. [PubMed: 35175287]
11. Gifford KA, Phillips JS, Samuels LR, et al. Associations between verbal learning slope and neuroimaging markers across the cognitive aging spectrum. J Int Neuropsychol Soc. 2015;21:455–467. [PubMed: 26219209]
12. Hammers DB, Suhrie KR, Dixon A, et al. Relationship between a novel learning slope metric and Alzheimer's disease biomarkers. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2022;29(5):799–819. [PubMed: 33952156]
13. D'Esposito M, Postle BR, Ballard D, Lease J. Maintenance versus manipulation of information held in working memory: an event-related fMRI study. Brain Cogn. 1999;41:66–86. [PubMed: 10536086]
14. Caso F, Agosta F, Mattavelli D, et al. White matter degeneration in atypical Alzheimer disease. Radiology. 2015;277:162–172. [PubMed: 26018810]
15. Migliaccio R, Agosta F, Possin KL, et al. Mapping the Progression of Atrophy in early- and late-onset Alzheimer's disease. J Alzheimers Dis. 2015;46:351–364. [PubMed: 25737041]
16. Wehling E, Lundervold AJ, Standnes B, Gjerstad L, Reinvang I. APOE status and its association to learning and memory performance in middle aged and older Norwegians seeking assessment for memory deficits. Behav Brain Funct. 2007;3:57. [PubMed: 17974013]
17. Benedict R Brief Visuospatial Memory Test-Revised. Psychological Assessment Resources, Inc.; 1997.
18. Brandt J, Benedict R. Hopkins Verbal Learning Test-Revised. Psychological Assessment Resources, Inc.; 1997.
19. Morrison RL, Pei H, Novak G, et al. A computerized, self-administered test of verbal episodic memory in elderly patients with mild cognitive impairment and healthy participants: a randomized, crossover, validation study. Alzheimers Dement (Amst). 2018;10:647–656. [PubMed: 30456291]
20. Thomas KR, Bangen KJ, Weigand AJ, et al. Objective subtle cognitive difficulties predict future amyloid accumulation and neurodegeneration. Neurology. 2020;94:e397–e406. [PubMed: 31888974]
21. Spencer RJ, Gradwohl BD, Williams TF, Kordovski VM, Hammers DB. Developing learning slope scores for the repeatable battery for the assessment of neuropsychological status. Appl Neuropsychol Adult. 2022;29(4):584–590. [PubMed: 32654521]
22. Schmidt M The Rey Auditory Verbal Learning Test. Western Psychological Services; 1996.
23. Hammers DB, Gradwohl BD, Kucera A, Abildskov T, Wilde EA, Spencer RJ. Preliminary validation of a measure for learning slope for the HVLT-R and BVMT-R in older adults. Cogn Behav Neurol. 2021;34(3):170–181. [PubMed: 34473668]
24. Hammers DB, Suhrie KR, Dixon A, et al. Relationship between a novel learning slope metric and Alzheimer's disease biomarkers. Neuropsychology, and Cognition. 2021; 29(5):799–819.
25. Hammers DB, Suhrie KR, Dixon A, Gradwohl BD, Duff K, Spencer RJ. Validation of HVLT-R, BVMT-R, and RBANS learning slope scores along the Alzheimer's continuum. Arch Clin Neuropsychol. 2021;37(1):78–90.
26. Hammers DB, Spencer RJ, Apostolova LG. Alzheimer's disease neuroimaging I. Validation of and demographically adjusted normative data for the learning ratio derived from the RAVLT in robustly intact older adults. Arch Clin Neuropsychol. 2022;37:981–993. [PubMed: 35175287]
27. Apostolova LG, Aisen P, Eloyan A, et al. The Longitudinal Early-onset Alzheimer's Disease Study (LEADS): framework and methodology. Alzheimers Dement. 2021;17(12):2043–2055. [PubMed: 34018654]
28. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology. 1993;43:2412–2414.
29. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189–198. [PubMed: 1202204]

30. Weintraub S, Besser L, Dodge HH, et al. Version 3 of the Alzheimer Disease Centers' Neuropsychological Test Battery in the Uniform Data Set (UDS). Alzheimer Dis Assoc Disord. 2018;32:10–17. [PubMed: 29240561]
31. Craft S, Newcomer J, Kanne S, et al. Memory improvement following induced hyperinsulinemia in Alzheimer's disease. Neurobiol Aging. 1996;17:123–130. [PubMed: 8786794]
32. Possin KL, Laluz VR, Alcantar OZ, Miller BL, Kramer JH. Distinct neuroanatomical substrates and cognitive mechanisms of figure copy performance in Alzheimer's disease and behavioral variant frontotemporal dementia. Neuropsychologia. 2011;49:43–48. [PubMed: 21029744]
33. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry. 1984;141:1356–1364. [PubMed: 6496779]
34. Barona A, Reynolds C, Chastain R. A demographically based index of premorbid intelligence for the WAIS—R. J Consult Clin Psychol. 1984;52:885–887.
35. Norton K, Watt S, Gow B, Crowe SF. Are tests of premorbid functioning subject to the Flynn effect? Aust Psychol. 2016;51:374–379.
36. Kirton JW, Soble JR, Marceaux JC, et al. Comparison of models of premorbid IQ estimation using the TOPF, OPIE-3, and Barona equation, with corrections for the Flynn effect. Neuropsychology. 2020;34:43–52. [PubMed: 31414828]
37. Sheikh JI, Yesavage J. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. Clin Gerontol. 1986;5:165–172.
38. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53:695–699. [PubMed: 15817019]
39. Reitan R Trail Making Test: Manual for Administration and Scoring. Reitan Neuropsychology Laboratory; 1992.
40. Morris JC, Heyman A, Mohs RC, et al. The consortium to establish a registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. Neurology. 1989;39:1159–1165. [PubMed: 2771064]
41. Gollan TH, Weissberger GH, Runnqvist E, Montoya RI, Cera CM. Self-ratings of spoken language dominance: a Multilingual Naming Test (MINT) and preliminary norms for young and aging Spanish–English bilinguals. Biling: Lang Cogn. 2012;15:594–615.
42. Cumming G, Finch S. Inference by eye: confidence intervals and how to read pictures of data. Am Psychol. 2005;60:170–180. [PubMed: 15740449]
43. Hammers DB, Kostadinova RV, Spencer RJ, et al. Sensitivity of memory subtests and learning slopes from the ADAS-Cog to distinguish along the continuum of the NIA-AA Research Framework for Alzheimer's Disease. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2022:1–19.
44. Hammers DB, Spencer RJ, Apostolova LG. Validation of and demographically-corrected normative data for the Learning Ratio derived from the RAVLT in robustly intact older adults. Arch Clin Neuropsychol. 2022;37(5):981–993. [PubMed: 35175287]
45. Hammers DB, Suhrie K, Dixon A, Gradwohl BD, Duff K, Spencer RJ. Validation of HVLT-R, BVMT-R, and RBANS learning slope scores along the Alzheimer's Continuum. Arch Clin Neuropsychol. 2022;37(1):78–90. 2021. [PubMed: 33899087]
46. Randolph C Repeatable Battery for the Assessment of Neuropsychological Status. The Psychological Corporation; 2012.
47. Bland JM, Altman DG. Correlation in restricted ranges of data. BMJ. 2011;342:d556. [PubMed: 21398359]
48. Rofes A, de Aguiar V, Jonkers R, Oh SJ, DeDe G, Sung JE. What drives task performance during animal fluency in people with Alzheimer's disease? Front Psychol. 2020;11:1485. [PubMed: 32774312]
49. Thomas KR, Edmonds EC, Eppig J, Salmon DP, Bondi MW. Alzheimer's disease neuroimaging I. Using neuropsychological process scores to identify subtle cognitive decline and predict progression to mild cognitive impairment. J Alzheimers Dis. 2018;64:195–204. [PubMed: 29865077]

RESEARCH IN CONTEXT

Systematic review:

The authors reviewed the literature using traditional sources (eg, PubMed) and the expertise of the LEADS Consortium. While early evidence suggests that early-onset Alzheimer's disease (EOAD) may present cognitively in a unique fashion to late-onset Alzheimer's disease (LOAD), the literature on learning in EOAD is limited.

Interpretation:

In a sample of 310 participants aged ≤65 across a range of diagnostic groups (cognitively normal, EOAD, and early-onset non-Alzheimer's disease), results showed that learning slopes—the ability to improve acquisition after the initial trial of a multi-trial memory task—are sensitive to early-onset dementias, above and beyond the impact of total learning and cognitive severity. This finding is consistent with preliminary evidence that patients with EOAD commonly experience non-amnestic cognitive changes.

Future direction:

This manuscript supports future work into understanding biological differences between EOAD and LOAD, which inform variances in performance patterns in learning.

Highlights

- Learning is impaired in amyloid-positive EOAD, beyond cognitive severity scores alone.
- Amyloid-positive EOAD participants perform worse on learning slopes than amyloid-negative participants.
- Learning ratio appears to be the learning metric of choice for EOAD participants.

TABLE 1

Demographic, neuropsychological, and behavioral variables for the diagnostic groups and total sample.

Variable	CN	EOAD	EOnonAD	Total sample
N	82	166	62	310
Age (years)[a]	55.63 (6.0)	58.82 (3.9)	57.45 (6.2)	57.70(5.2)
Education (years)[a,b]	16.84 (2.1)	15.36(2.4)	15.69 (2.6)	15.82 (2.5)
Sex(%female)[b,c]	61.0%	54.8%	35.5%	52.6%
Race (% Caucasian)[a,b]	68.5%	92.3%	89.2%	85.1%
Geriatric Depression Scale[a,b]	1.35 (1.8)	2.49 (2.3)	3.03 (2.6)	2.28 (2.3)
Barona estimate of verbal intelligence	107.36 (5.3)	105.85 (6.4)	106.07 (6.7)	106.31 (6.2)
MoCA[a,b,c]	27.12(2.5)	16.53(5.5)	21.54 (5.0)	20.35 (6.6)
RAVLTTotal Recall[a,b,c]	48.44 (8.3)	22.08 (9.4)	34.71 (11.8)	31.58(14.8)
RAVLT Delayed Recall[a,b,c]	9.90 (3.2)	1.64 (2.3)	4.90 (4.0)	4.47 (4.5)
Craft Story 21 Recall[a,b,c]	15.17(5.4)	6.86 (4.3)	11.32 (4.8)	10.06 (5.9)
Craft Story 21 Recall Delaye[a,b,c]	14.73 (5.2)	4.42 (4.4)	9.60 (5.4)	8.36 (6.6)
Benson Delayed Recal[a,b,c]	12.16(2.6)	3.64 (3.7)	9.09 (4.0)	7.21 (5.2)
ADAS-Cog Total Scor[a,b,c]	17.97 (3.6)	34.68 (8.5)	26.65 (7.3)	28.67(10.1)
ADAS-Cog Word Recall Immediate Recal[a,b,c]	22.36 (3.5)	10.88 (4.7)	16.34 (4.5)	15.00(6.6)
ADAS-Cog Word Recall Delayed Recal[a,b,c]	7.70 (1.7)	1.95(2.1)	4.64 (2.4)	4.03 (3.2)

Note: Barona Estimate ofVerbal Intelligence score is listed as a standard score. All other scores are rawscores. All values are mean (standard deviation) unless listed otherwise.

Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; CN, cognitively normal; EOAD, early-onset Alzheimer's disease; EOnonAD, early-onset non-Alzheimer's disease; MoCA, Montreal Cognitive Assessment; RAVLT, Rey Auditory Verbal Learning Test.

[a]Denotes significant difference between CN and EOAD groups.

[b]Denotes significant difference between CN and EOnonAD groups.

[c]Denotes significant difference between EOAD and EOnonAD groups.

TABLE 2

RAVLT learning slope and process scores for the diagnostic groups and total sample.

Variable	CN	EOAD	EOnonAD	Total sample	Omnibus effect size (with 95% CI)
N	82	166	62	310	
RAVLT LR[a,b,c]	0.75 (0.2; 0.38–1.00)	0.27 (0.2; 0.00–1.00)	0.46 (0.3; 0.08–1.00)	0.44 (0.3; 0.00–1.00)	1.94(1.67–2.21)
RAVLT RLS[a,b,c]	7.10(1.9; 3.00–11.00)	3.27 (1.8; 0.00–11.00)	4.65 (2.5; 1.00–11.00)	4.55 (2.6; 0.00–11.00)	1.38(1.14–1.63)
RAVLT LO[a,b,c]	20.88 (6.7; 8.00–37.00)	8.26 (5.9; −4.00–33.00)	11.97(7.8; −1.00–33.00)	12.34 (8.4; −4.00–37.00)	1.41(1.17–1.66)
RAVLT trial 1[a,c]	5.51(1.7; 2.00–10.00)	2.77 (1.7; 0.00–8.00)	4.55(2.0; 1.00–11.00)	3.85 (2.1; 0.00–11.00)	1.29(1.04–1.53)

Note: All values are mean (standard deviation; range) unless listed otherwise. Omnibus effect size is the effect size of omnibus multivariate analyses of covariances expressed as Cohen's *d*.

Abbreviations: CI, compatibility interval; CN, cognitively normal; EOAD, early-onset Alzheimer's disease; EOnonAD, early-onset non-Alzheimer's disease; LR, learning ratio; RAVLT, Rey Auditory Verbal Learning Test; RLS, raw learning score; LOT, learning over trials.

[a]Denotes significant difference between CN and EOAD groups.

[b]Denotes significant difference between CN and EOnonAD groups.

[c]Denotes significant difference between EOAD and EOnonAD groups.

TABLE 3

Partial correlation coefficients between Rey Auditory Verbal Learning Test learning slope/process scores and neuropsychological test scores across diagnostic groups and the total sample, after controlling for age, education, sex, and ethnicity.

Variable	Correlated with	CN	EOAD	EOnonAD	Total sample
N		82	168	64	314
RAVLT LR	RAVLTTotal Recall	0.73, $P < 0.001$	0.69, $P < 0.001$	0.82, $P < 0.001$	0.87, $P < 0.001$
	RAVLT Delayed Recall	0.64, $P < 0.001$	0.66, $P < 0.001$	0.90, $P < 0.001$	0.87, $P < 0.001$
	ADAS-Cog Word Recall Immediate Recall	0.25, $P = 0.03$	0.44, $P < 0.001$	0.50, $P < 0.001$	0.70, $P < 0.001$
	ADAS-Cog Word Recall Delayed Recall	0.34, $P = 0.003$	0.57, $P < 0.001$	0.67, $P < 0.001$	0.78, $P < 0.001$
	CraftStory 21 Recall Immediate	0.10, $P = 0.39$	0.33, $P < 0.001$	0.56, $P < 0.001$	0.57, $P < 0.001$
	CraftStory 21 Recall Delayed	0.11, $P = 0.37$	0.42, $P < 0.001$	0.66, $P < 0.001$	0.66, $P < 0.001$
	Benson Delayed Recall	0.08, $P = 0.50$	0.52, $P < 0.001$	0.47, $P < 0.001$	0.69, $P < 0.001$
	Semantic Fluency	0.02, $P = 0.87$	0.31, $P < 0.001$	0.59, $P < 0.001$	0.58, $P < 0.001$
	Multilingual Naming Test	−0.02, $P = 0.90$	0.17, $P < 0.001$	0.35, $P < 0.001$	0.33, $P < 0.001$
	Trail Making Test, Part B	−0.11, $P = 0.36$	−0.26, $P < 0.001$	−0.45, $P < 0.001$	−0.59, $P < 0.001$
RAVLT RLS	RAVLTTotal Recall	0.22, $P = 0.06$	0.49, $P < 0.001$	0.51, $P < 0.001$	0.65, $P < 0.001$
	RAVLT Delayed Recall	0.31, $P = 0.007$	0.53, $P < 0.001$	0.72, $P < 0.001$	0.71, $P < 0.001$
	ADAS-Cog Word Recall Immediate Recall	−0.04, $P = 0.72$	0.33, $P < 0.001$	0.33, $P = 0.01$	0.54, $P < 0.001$
	ADAS-Cog Word Recall Delayed Recall	0.13, $P = 0.27$	0.49, $P < 0.001$	0.56, $P < 0.001$	0.65, $P < 0.001$
	CraftStory 21 Recall Immediate	−0.09, $P = 0.43$	0.26, $P = 0.002$	0.45, $P < 0.001$	0.45, $P < 0.001$
	CraftStory 21 Recall Delayed	−0.13, $P = 0.25$	0.36, $P < 0.001$	0.58, $P < 0.001$	0.54, $P < 0.001$
	Benson Delayed Recall	−0.04, $P = 0.75$	0.47, $P < 0.001$	0.46, $P < 0.001$	0.60, $P < 0.001$
RAVLT LOT	RAVLTTotal Recall	0.39, $P < 0.001$	0.48, $P < 0.001$	0.57, $P < 0.001$	0.68, $P < 0.001$
	RAVLT Delayed Recall	0.40, $P < 0.001$	0.52, $P < 0.001$	0.69, $P < 0.001$	0.72, $P < 0.001$
	ADAS-Cog Word Recall Immediate Recall	0.05, $P = 0.64$	0.35, $P < 0.001$	0.31, $P = 0.02$	0.56, $P < 0.001$
	ADAS-Cog Word Recall Delayed Recall	0.27, $P = 0.02$	0.48, $P < 0.001$	0.56, $P < 0.001$	0.67, $P < 0.001$
	CraftStory 21 Recall Immediate	−0.01, $P = 0.94$	0.29, $P < 0.001$	0.43, $P = 0.001$	0.46, $P < 0.001$
	CraftStory 21 Recall Delayed	−0.05, $P = 0.65$	0.36, $P < 0.001$	0.58, $P < 0.001$	0.54, $P < 0.001$
	Benson Delayed Recall	0.00, $P = 0.99$	0.42, $P < 0.001$	0.49, $P < 0.001$	0.58, $P < 0.001$
RAVLT trial 1	RAVLTTotal Recall	0.63, $P < 0.001$	0.78, $P < 0.001$	0.74, $P < 0.001$	0.82, $P < 0.001$
	RAVLT Delayed Recall	0.37, $P < 0.001$	0.35, $P < 0.001$	0.43, $P < 0.001$	0.60, $P < 0.001$
	ADAS-Cog Word Recall Immediate Recall	0.40, $P < 0.001$	0.50, $P < 0.001$	0.43, $P < 0.001$	0.65, $P < 0.001$

Variable	Correlated with	CN	EOAD	EOnonAD	Total sample
	ADAS-Cog Word Recall Delayed Recall	0.24, $P = 0.04$	0.30, $P < 0.001$	0.29, $P = 0.03$	0.55, $P < 0.001$
	CraftStory 21 Recall Immediate	0.26, $P = 0.02$	0.32, $P < 0.001$	0.30, $P = 0.03$	0.48, $P < 0.001$
	CraftStory 21 Recall Delayed	0.32, $P = 0.005$	0.26, $P = 0.002$	0.21, $P = 0.12$	0.49, $P < 0.001$
	Benson Delayed Recall	0.15, $P = 0.20$	0.19, $P = 0.03$	0.14, $P = 0.35$	0.47, $P < 0.001$

Note: Values reflect partial correlation coefficients and resultant *P*-value.

Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; CN, cognitively normal; EOAD, early-onset Alzheimer's disease; EOnonAD, early-onset non-Alzheimer's disease; LOT, learning over trials; LR, learning ratio; RAVLT, Rey Auditory Verbal Learning Test; RLS, raw learning score.