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RESEARCH ARTICLE

Delayed primacy recall performance predicts *post mortem* Alzheimer's disease pathology from unimpaired *ante mortem* cognitive baseline

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Abstract

We propose a novel method to assess delayed primacy in the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) memory test. We then examine whether this measure predicts *post mortem* Alzheimer's disease (AD) neuropathology in individuals who were clinically unimpaired at baseline. A total of 1096 individuals were selected from the Rush Alzheimer's Disease Center database registry. All participants were clinically unimpaired at baseline, and had subsequently undergone brain autopsy. Average age at baseline was 78.8 (6.92). A Bayesian regression analysis was carried out with global pathology as an outcome; demographic, clinical, and apolipoprotein E (*APOE*) data as covariates; and cognitive predictors, including delayed primacy. Global AD pathology was best predicted by delayed primacy. Secondary analyses showed that delayed primacy was mostly associated with neuritic plaques, whereas total delayed recall was associated with neurofibrillary tangles. Sex differential associations were observed. We conclude that CERAD-derived delayed primacy is a useful metric for early detection and diagnosis of AD in unimpaired individuals.

KEYWORDS
Alzheimer's disease, CERAD, memory, neuropathology, serial position

Highlights

- We propose a novel method to analyse serial position in the CERAD memory test.
- We analyse data from 1096 individuals who were cognitively unimpaired at baseline.
- Delayed primacy predicts *post mortem* pathology better than traditional metrics.

1 | BACKGROUND

Promoting early detection and diagnosis of Alzheimer's disease (AD) is one of the critical components of the global response to the growing dementia crisis.[1] A timely diagnosis of AD can promote patients' safety, help avoid preventable hospitalizations, aid identification of caregivers, and support financial planning.[2–4] In addition, early detection of AD can facilitate the selection of individuals for clinical trials.[5]

Research into the use of biomarkers for early detection and diagnosis of AD has seen substantial progress in recent years, including the introduction of promising blood-based biomarkers (see e.g.,[6]). Despite this, many studies still rely in great part on assessments based upon positron-emission tomography (PET) imaging and/or lumbar puncture. These tests can be intimidating, and require access to highly specialized clinical settings.[7] As the burden of dementia worldwide is affecting especially low- and middle-income countries,[8] early detection frameworks should focus on accurate, but also affordable and accessible technologies.

Testing neuropsychological functions is noninvasive, requires relatively minimal training, and is inexpensive. Of relevance to AD is especially the assessment of episodic memory ability.[9–12] However, neuropsychological test metrics were designed primarily for diagnostic purposes, that is, the identification of well-defined changes in performance, and not for the detection of subtle shifts in neuropsychological function due to emergent underlying pathology.[13] An alternative to the examination of standard clinical metrics is process analysis of neuropsychological test performance (or the Boston process approach[14,15]). Analysis of process scores is based upon the principle that different cognitive processes underlie overall test performance, and that unearthing these processes may be more informative than simply evaluating typical composite scores.

Examples of effective process scores applied to verbal memory testing derive from the analysis of serial position performance. The serial position curve is a common pattern in tests of human memory, where performance tends to be better for stimuli learned at the beginning (primacy) and/or at the end (recency) of a list, as compared to those in the middle (hence, the curve shape; e.g., Murdock[16]). This recall pattern has been reproduced countless times. Primacy effects have been ascribed to extra opportunities for rehearsal,[17] edge effects,[18] and increased attention,[19] among other things, whereas recency effects have been associated primarily with working memory processing.[20] Importantly, participants with AD diagnoses present with specific patterns of serial position performance, and these patterns can be examined for the purposes of early detection and diagnosis. In particular, a reduction of the primacy effect has been reported frequently in immediate recall tests in conjunction with AD risk and pathology (e.g.,[21,22]). Gicas et al.,[23] for example, have shown that higher immediate primacy performance is associated with less risk of AD neuropathology, including hippocampal sclerosis; and increased pathology predicted greater longitudinal decline in primacy performance.[24]

Gicas et al.[23,24] measured serial position performance using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) memory test. In this memory test, participants are presented with a list of 10 words three times, in different presentation orders. Immediately after each presentation, participants are asked to free recall the words in any order (immediate recall). Subsequently, they are also asked to free recall the words after a delay (delayed recall). So far, analysis of serial position effects in the CERAD memory test has focused exclusively on immediate word-list recall from the first list, as the presentation order of the words changes in each learning trial. However, past analyses of word-list learning performance with tests other than CERAD have shown delayed primacy to be a better longitudinal predictor of global cognitive decline,[25] and mild cognitive impairment (MCI[26]) compared to immediate primacy. A reason for this may be that delayed primacy is sensitive to synaptic consolidation, as also suggested by its association with hippocampal gray matter volume[27] and increased functional connectivity between left and right hippocampus.[28] Therefore, the aim of the present study was to determine whether delayed primacy in CERAD was more effective at predicting AD neuropathology than immediate primacy.

In order to extract delayed primacy information from CERAD, we propose that each time the word list (A, B, and C) is presented, one item will be shown *first*. The three items shown first (i.e., A1, B1, and C1) should all benefit from primacy exposure (e.g., extra opportunity for rehearsal, edge effects, etc.). Hence, when examining delayed recall performance, memory for items A1, B1, and C1 will give an account of delayed primacy. Using this method, we carried out secondary data analyses on Rush Alzheimer's Disease Center cohort data. We hypothesized that a measure of delayed primacy, extracted from the CERAD memory test, would be effective in predicting *post mortem* AD-related pathology from a cognitively unimpaired baseline. Additionally, as women account for a greater proportion of AD cases than men,[29] while, perhaps paradoxically, maintaining a life-long advantage in verbal memory,[30] we set out to evaluate also sex-related differences in the association between memory performance and *post mortem* pathology.

RESEARCH IN CONTEXT

1. **Systematic review**: We searched articles through online databases such as Pubmed, PsychInfo, and Google Scholar. We focused on papers regarding early detection and diagnosis of Alzheimer's disease (AD).
2. **Interpretation**: We propose a method to compute delayed primacy in the CERAD memory test, and show that this measure is better at predicting *post mortem* neuropathology from a cognitively unimpaired baseline than standard CERAD metrics.
3. **Future directions**: More work should elucidate the neurocognitive mechanisms underlying the association between serial position performance and neurodegenerative AD pathology.

The R code used in JASP for the analyses is reported in the Supplementary Materials.

2 | METHODS

2.1 | Participants

A total of 5158 unique participants' data were available from the Rush Alzheimer's Disease Center (RADC) database registry. From this total, we selected individuals who (a) were diagnosed as having no cognitive impairment at baseline (see below for diagnostic criteria); (b) had received a *post mortem* examination; (c) were diagnosed as being cognitively unimpaired, or having MCI or Alzheimer's disease at death (i.e., mixed cases were excluded; see below for diagnostic criteria); (d) had the necessary CERAD data at baseline; and (e) had apolipoprotein E (*APOE)* genotype data. Once these criteria were applied, the overall sample size was reduced to 1096. These participants came from four different RADC cohort studies: The Religious Order Study (ROS; $n = 486$); the Memory and Aging Project (MAP; $n = 577$); the Minority Aging Research Study (MARS; $n = 32$); and the Latino Core Study (LATC; $n = 1$). ROS[31] started in 1994 and comprises 65 year and older Catholic nuns, priests, and brothers from across the United States. All were without known dementia at enrollment and agreed to yearly evaluation and brain donation after death. MAP started in 1997 and comprises 65 year and older adults from retirement communities and subsidized senior housing in the Chicago area, and north–eastern Illinois. All were without known dementia at enrollment and agreed to yearly evaluation and brain donation after death. MARS[32] started in 2004 and is made up of 65 year and older adults identifying as African American and living in the Chicago area and suburbs. All were without known dementia at enrollment and agreed to yearly evaluations, in addition to optional brain donation after death. LATC[33] started in 2015 and also includes 65 year and older adults from the Chicago area, who identify as Latino/Hispanic. All were without known dementia at enrollment and agreed to yearly evaluations, in addition to optional brain donation after death. Overall, average age at baseline was 78.8 (6.93), average time between baseline and death was 10.56 (5.90) years, and average years of education were 16.29 (3.72). In total, 776 (71%) were female, and the *APOE* genotype was distributed as follows: 4 had $\varepsilon2\varepsilon2$; 151 had $\varepsilon2\varepsilon3$; 26 had $\varepsilon2\varepsilon4$; 711 had $\varepsilon3\varepsilon3$; 191 had $\varepsilon3\varepsilon4$; and 13 had $\varepsilon4\varepsilon4$. All participants signed a Repository Consent to allow their data to be shared. Ethics approvals for the studies included in these analyses were obtained from an Institutional Review Board of Rush University Medical Center. This research was completed in accordance with the Helsinki Declaration.

2.2 | Baseline diagnosis

Baseline diagnosis[34,35] was based on a three-stage process including: computer scoring of a cognitive battery of 19 cognitive tests, clinical judgment by a neuropsychologist blinded to participants demographics, and a final diagnostic classification by a clinician (neurologist, geriatrician, or geriatric nurse practitioner). Clinical diagnosis of Alzheimer's dementia is based on criteria of the joint working group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA). The diagnosis of Alzheimer's disease requires evidence of a meaningful decline in cognitive function relative to a previous level of performance with impairment in memory and at least one other area of cognition. Diagnosis of MCI is rendered for persons who are judged to have cognitive impairment by the neuropsychologist but are judged not to meet criteria for dementia by the clinician. Finally, persons without dementia or MCI are categorized as having no cognitive impairment.

2.3 | Diagnosis at death

Diagnosis at death was based on assessment of all available clinical data, which was reviewed by a neurologist with expertise in dementia, leading to a summary diagnostic opinion rendered regarding the most likely clinical diagnosis at the time of death. Summary diagnoses were blind to all *post mortem* data. Case conferences including one or more neurologists and a neuropsychologist were used for consensus on selected cases.

2.4 | Cognitive assessment

Participants completed a 19-test neuropsychological evaluation in a standardized format to assess functioning in the domains of episodic memory (with three delayed recall tests), semantic memory, working memory, visuospatial ability, and perceptual speed.[36] The raw scores from these tests were then converted to z-scores and averaged to create a global cognitive function index. The CERAD Word List Memory test[37] was part of this battery, and was the basis for the serial position scores. This test is composed of a list of 10 semantically unrelated words that are repeated across three trials (A, B, and C) with varying word order. Participants are asked to recall as many words as possible immediately after presentation of each word list. Performance over the three trials is combined to give a total recall score. Later, after a delay of several minutes, participants are asked to recall as many words from the initial list as possible in any order, providing a total delayed recall score. Following Gicas et al.[23,24] we defined *immediate primacy* as the ability to recall the first three words presented in the first three trials (i.e., A1-A3, B1-B3, and C1-C3), immediately after presentation of that list, and then divided that sum by the total number of possible items (i.e., nine). For comparison, we also computed an alternative measure of immediate primacy which included only the first three words presented in the first trial (i.e., A1-A3; one list immediate primacy). *Delayed primacy* was defined as the ability to recall the first word presented in the first trial, the first words presented in the second trial, and the first word presented in the third trial (i.e., A1, B1, and C1), in the delayed recall task.

2.5 | Post mortem evaluation

All participants in these analyses underwent brain autopsy at death.[35] The standard protocol involved removal of the brainstem and cerebellum, followed by cutting one hemisphere into 1 cm coronal slabs that were immediately frozen. The other hemisphere was fixed in 4% paraformaldehyde for 3–21 days and subsequently cut into 1 cm coronal slabs. Regional blocks of tissue were embedded in paraffin, sliced into 6 μm sections, and mounted to glass slides for microscopic evaluation by a neuropathologist blinded to all clinical information.

A global AD pathology burden score was then extracted as a quantitative summary of AD pathology. This score derived from the average of three AD pathologies: neuritic plaques, diffuse plaques, and neurofibrillary tangles, as determined by microscopic examination of silver-stained slides from five regions: midfrontal cortex, midtemporal cortex, inferior parietal cortex, entorhinal cortex, and hippocampus.

2.6 | APOE genotyping

DNA was extracted from PBMCs or brain. Participants were genotyped for APOE alleles by Polymorphic DNA Technologies (http://www.polymorphicdna.com/).

2.7 | Data analysis

Bayesian regression analyses were carried out. A Bayesian framework was employed to allow for comparison across different models (including one or more predictors) to identify the most plausible, that is, to identify which combination of variables may best predict the outcomes. In these analyses, all combinations of predictors were tested for data fit, including models with only one predictor, against the null model. The primary analysis had global AD pathology as outcome; *APOE* genotype, baseline age, sex, years of education, final diagnosis, and time from baseline to death as control variables (null model); and cognitive scores as predictors: total recall, total delayed recall, immediate primacy (either the three- or one-list immediate type in separate analyses), and delayed primacy were derived from CERAD, while the global cognitive function index was obtained from the test battery (see the Cognitive Assessment section). Credible intervals (CIs) were set to 95%. The prior was set to JZS, and the model prior was set to Uniform. One thousand Markov chain Monte–Carlo simulations were conducted to determine parameters. Secondary analyses were carried out with neuritic plaques, diffuse plaques, and neurofibrillary tangles as outcomes, both globally and in the hippocampus specifically, while otherwise maintaining the same parameters as in the primary analysis. Analyses split by reported sex at birth were then carried out post hoc to examine sex-differential associations. Analyses were carried out in JASP 0.17.3.

TABLE 1 Neuropathological and memory data

	Mean	SD
Global pathology	0.667	0.576
Neuritic plaques	0.762	0.773
Diffuse plaques	0.683	0.722
Neurofibrillary tangles	0.554	0.683
Global cognitive index	0.110	0.572
Immediate recall	18.376	4.456
Delayed recall	5.928	2.171
Three-list Immediate primacy	0.669	0.211
One-list Immediate primacy	1.687	1.017
Delayed primacy	2.048	0.871

Note: SD = standard deviation.

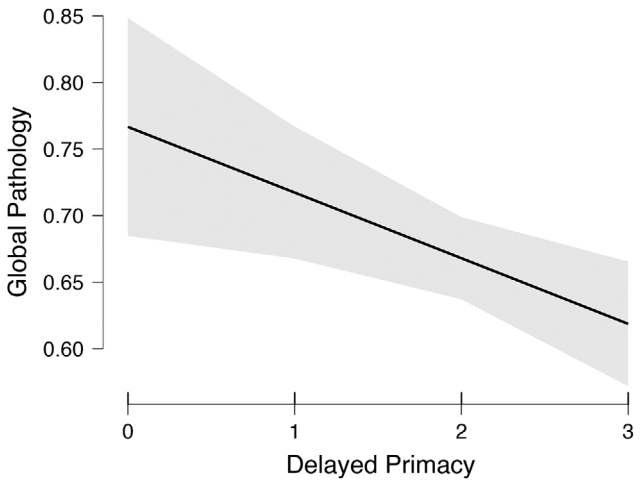

FIGURE 1 Marginal effects plot. Global Alzheimer's disease pathology (y-axis) by delayed primacy (x-axis), and 95% confidence intervals

3 | RESULTS

Table 1 reports means and standard deviations for the neuropathological and memory scores.

Global AD pathology was best predicted by delayed primacy, $BF_{10} = 5.577$, with moderate evidence. This model was roughly twice as effective as the second best model ($BF_{10} = 2.681$) including total delayed recall only. The mean coefficient for delayed primacy was −0.028 (0.028; 95% credible intervals from −0.077 to 0), indicating that more global AD pathology was associated with poorer delayed primacy at baseline (Figure 1). These numbers suggest that, comparing cross-sectionally, one *less* unit of primacy corresponded to ~ 4.2% *more* global AD pathology (based on the mean overall level of global AD pathology; Table 1): hence, comparing a person with 0 delayed primacy to a person with full delayed primacy (i.e., three units), the former will have upward of 12% more global AD pathology. $BF_{inclusion}$ for delayed primacy was 1.467, suggesting that adding delayed primacy to the model improved its fit to the data by 47%. Tables 2 and 3 recap this analysis.

TABLE 2 Model fits in primary analysis with global pathology as outcome

Models	P(M)	P(M|data)	BF_M	BF_{10}	R^2
Null model (including: age at baseline, *APOE* genotype, years of education, sex, elapsed time, and diagnosis)	0.033	0.051	1.564	1.000	0.186
Delayed primacy	0.033	0.285	11.579	5.577	0.192
Delayed recall	0.033	0.137	4.609	2.681	0.191
Immediate recall + Delayed primacy	0.033	0.070	2.176	1.364	0.193
Immediate recall	0.033	0.066	2.044	1.287	0.190
Global composite + Delayed primacy	0.033	0.057	1.754	1.115	0.193
Delayed recall + Delayed primacy	0.033	0.055	1.690	1.076	0.193
Immediate primacy + Delayed primacy	0.033	0.052	1.595	1.019	0.193
Immediate primacy	0.033	0.030	0.892	0.584	0.189
Global composite + Delayed recall	0.033	0.027	0.807	0.529	0.192

Note. All models include age at baseline, *APOE* genotype, years of education, sex, elapsed time, and diagnosis. Only the top 10 models are reported. P(M) denotes prior probability; P(M|data) denotes posterior probability; BFM reports model odds; BF10 reports model odds relative to the null model; and R^2 denotes variance explained. Immediate primacy is here three-list immediate primacy, which performed analogously to, albeit slightly better than, one-list primacy.

Secondary analyses with neuritic plaques presented the same pattern of results, as this AD-related pathology was best predicted by delayed primacy, $BF_{10} = 4.163$, with moderate evidence. This model was over twice as strong as the second best model ($BF_{10} = 1.560$), again including only total delayed recall. The mean coefficient for delayed primacy was −0.041 (0.038; 95% credible intervals from −0.109 to <0.001), indicating that more neuritic plaque pathology was associated to poorer delayed primacy at baseline. $BF_{inclusion}$ was 1.879, suggesting that adding delayed primacy to the model improved its fit to the data by 88%.

None of the models predicted diffuse plaques better than the null models including the covariates (best $BF_{10} < 1$). However, total delayed recall was an extremely strong predictor of neurofibrillary tangles ($BF_{10} = 2891.180$), narrowly beating out the model combining delayed primacy and three-list immediate primacy ($BF_{10} = 2592.755$). The mean coefficient for total delayed recall was −0.022 (0.019; 95% credible intervals from −0.053 to 0), indicating that more neurofibrillary tangle pathology was associated to poorer delayed recall at baseline. $BF_{inclusion}$ was 1.969, suggesting that adding delayed primacy to the model improved its fit to the data by 97%.

When we isolated the hippocampus as region of interest, however, none of the memory predictors provided a better fit compared to the null models.

Finally, sex-differential analyses (with delayed primacy and delayed recall as predictors, and all covariates as in the main analyses) presented a significantly different picture of the overall results. First of all, the best predictive model of global global AD pathology became the interaction between delayed primacy and sex ($BF_{10} = 79.42$). Consistently, when conducting separate analyses by sex, delayed primacy was a moderate predictor of global AD pathology (beating out delayed recall) in females ($n = 776$), $BF_{10} = 8.47$, with a mean coefficient of −0.058 (0.029; 95% credible intervals from −0.103 to 0), but neither predictor successfully fit the data in males ($BF_{10} < 0.300$; $n = 322$). Analogously, we found the same pattern with neuritic plaques: delayed primacy predicted the outcome in females, $BF_{10} = 3.06$, −0.058 (0.029), −0.127–0. While memory scores again were not predictive with diffuse plaques, as in the whole sample, delayed recall was only predictive of neurofibrillary tangles in females ($BF_{10} = 2238.67$; −0.051, 0.012, −0.074 to −0.029) but not males ($BF_{10} = 0.33$).

4 | DISCUSSION

In this secondary data analysis of over 1000 decedents who had participated in an RADC cohort study, we tested the hypothesis that a measure of delayed primacy, extracted from the CERAD memory test, would be effective in predicting *post mortem* AD-related pathology from a cognitively unimpaired baseline. These efforts are in line with the general goal of providing affordable, accessible, and accurate tools to aid early detection and diagnosis of dementia of the Alzheimer's type. We propose a way to estimate delayed primacy in CERAD despite the fact that the word list order is changed over three consecutive learning trials: we suggest taking into account delayed recall performance for the words presented *first* in each of the three learning trials, that is, the A1, B1, and C1 words. Our primary analysis showed that delayed primacy was the best predictor of global AD pathology, outperforming both total and delayed recall. In secondary analyses, delayed primacy was again the best predictor of neuritic plaques, while delayed recall was better for neurofibrillary tangles, although this pattern of results was not confirmed when isolating specifically the hippocampus. Neither three-list nor one-list immediate primacy scores were better predictors than delayed primacy in any analysis. Finally, our results were qualified by a sex-differential effect whereby these associations were present only in women.

One observation from these results is that delayed recall measures, whether specifically for the primacy words or for the whole list, associated better with neuropathological outcomes than immediate recall measures. This finding is not surprising given the reported links between delayed recall and consolidation – as consolidation of new information requires time and biochemical changes in the central nervous system, delayed responses are more likely to be able to assess overall health of this mechanism than immediate responses.[25–27,38]

However, primacy versus whole list recall appeared to associate better with different types of *post mortem* pathology. Neuritic plaques, which are the consequence of amyloid-β protein aggregation, and neurofibrillary tangles, which derive from the accumulation of tau proteins,

TABLE 3 Mean coefficients, standard deviations and 95% credible intervals in primary analysis

Coefficient	P(incl|data)	P(excl|data)	$BF_{inclusion}$	Mean	SD	95% CILower	95% CIUpper
Age at baseline	1.000	0.000	1.000	0.006	0.003	<0.001	0.011
APOE genotype	1.000	0.000	1.000	0.024	0.004	0.017	0.032
Years of education	1.000	0.000	1.000	0.003	0.004	-0.005	0.012
Sex	1.000	0.000	1.000	-0.117	0.035	-0.181	-0.050
Elapsed time	1.000	0.000	1.000	0.008	0.003	0.003	0.014
Diagnosis	1.000	0.000	1.000	0.203	0.021	0.164	0.241
Global composite	0.167	0.833	0.200	0.004	0.014	-0.005	0.051
Delayed recall	0.308	0.692	0.509	-0.005	0.009	-0.030	0.000
Immediate recall	0.230	0.770	0.341	-0.001	0.003	-0.011	<0.001
Immediate primacy	0.165	0.835	0.198	-0.011	0.048	-0.162	0.022
Delayed primacy	0.595	0.405	1.467	-0.028	0.028	-0.077	0.000

Note: P(incl|data) denotes the probability of including a predictor after considering the data; P(excl|data) denotes the probability of excluding a predictor after considering the data; BFinclusion reports how much a predictor increases model odds. Immediate primacy is three-list immediate primacy.

are the hallmarks of Alzheimer's disease.[39–41] Delayed primacy was most sensitive to the former, while delayed recall was most sensitive to the latter. The association of delayed primacy with neuritic plaques is somewhat consistent with a previous report in a different dataset, showing that poor delayed primacy (and primacy forgetting) in story recall was associated with increased amyloid load, as measured with Pittsburgh compound-B PET imaging.[42] While the exact neurobiological mechanism linking delayed primacy recall to amyloid deposition is not clear, we have previously suggested that this association may be mediated by a failure to consolidate effectively the temporal information paired with the items, thus leading to poorer information clustering and, eventually, retention. This hypothesis, which requires further testing, is tentatively consistent with the observation that amyloid deposition in the brain begins in the neocortex,[43] where associative memory function may be expressed.[44] An alternative, but not mutually exclusive, possibility is also that delayed primacy may be more sensitive to neuritic plaques because they will begin to accumulate years before neurofibrillary tangles, as per the amyloid cascade hypothesis[40]; therefore, delayed primacy may be sensitive to early subtle changes that total delayed recall is unable to detect.

With regard to delayed recall and its preferential association with neurofibrillary tangles, we similarly do not have a specific mechanism to propose, except for highlighting how tangles have been observed to appear initially in the medial temporal region, first in the entorhinal cortex and then the hippocampus, which are areas strongly associated with memory consolidation.[45] To determine whether delayed recall performance broadly, as opposed to nonprimacy delayed recall specifically, was preferentially associated with neurofibrillary tangles, we carried out a posthoc analysis analogous to the main analyses. Outcome was *post mortem* neurofibrillary tangles; control variables were unchanged; and predictors were delayed recall, and the unstandardized residuals of regressing delayed primacy out of delayed recall (i.e., a measure of delayed recall independent of delayed primacy). This new analysis did not show primacy-independent delayed recall to be a good predictor of tangles, $BF_{10} = 1.363$, thus confirming the original conclusion that it was delayed recall *overall* that best associated with neurofibrillary tangles.

Another note is that clinical composite scores, such as the global cognitive function index we employed in our analyses (which, however, to note, was not norm-corrected), are more likely to be used in clinical settings than raw scores. Although composite scores have shown reduced variability and stronger associations with amyloid burden compared to raw scores in some instances,[46,47] they have also been criticized for missing out on subtle cognitive changes.[48] In particular, in our analyses, the global cognitive function index, which included performance over 19 standardized neuropsychological tests, was not predictive of *post mortem* neuropathology in our analyses, and therefore underperformed when compared to the delayed primacy and delayed recall raw scores.

Importantly, *post hoc* sex-differential secondary analyses showed that these associations were only confirmed in women, and not in men. We know that women tend to maintain a life-long advantage in verbal memory over men,[30] but in our sample, women did not perform better than men in either delayed primacy (Bayesian t-test, $BF_{10} = 0.431$) or CERAD delayed recall ($BF_{10} = 0.158$). In contrast, women were older ($BF_{10} = 1749.31$) and less educated ($BF_{10} > 20$ million) than men, while also carrying more global pathology ($BF_{10} = 87.67$), which is consistent with the observation whereby AD pathology is more common in women than in men.[29] Despite the fact that demographic characteristics were controlled for in our *post hoc* analyses, it is nevertheless possible that the sex-differential association we observed in our data depended upon the more advanced state of pathology in our women compared to men. These findings require further inspection in future investigations.

A clear limitation of this study is that the exact mechanisms underlying the link between delayed primacy, delayed recall, and other portions of the serial position, and AD-related pathology remain speculative at this stage. While a modest number of studies have examined the association between serial position performance and cognitive impairment, few have tackled the neurocognitive bases of this

association. Further research, possibly involving functional neuroimaging and connectivity, should be considered toward this goal. Additionally, the effect sizes of the associations we reported here are relatively modest. For instance, an increase of one point of delayed primacy corresponds to approximately 2% less global pathology in the whole sample. However, this effect size was doubled when examining females specifically - on average, a woman remembering all three delayed primacy items would be expected to have ~ 12% less pathology than a woman remembering no delayed primacy items. Another possible limitation is the fact that our sample was, on the whole, quite well educated; it is therefore possible that we may not see the same associations when examining individuals whose level of education is lower. While we do not find a different patterns of results when isolating people from our sample with 12 or fewer years of education (n = 224), we are unable to test our models on the least educated individuals in our data due to low sample size.

Finally, it may be argued that *delayed primacy* is a misnomer for the metric we have calculated. While the three words that we used for delayed primacy all appear as the first word once, and are the only words that do so, these words also appear in nonprimacy positions. As such, it is arguable that our proposed measure of delayed primacy is not truthfully a measure of primacy, but of something else entirely. In response to this compelling point, a – perhaps somewhat circular – argument can be made as follows to justify the use of the "delayed primacy" label: first, as noted, only these three words are the very first word in each list, and thus should accrue the most primacy exposure overall; second, as examining recall for these words specifically gives us better prediction of pathology than the alternatives, such as immediate primacy, we can appeal to previous literature where delayed primacy, as measured less ambiguously with other word-list tests, outperformed immediate primacy.[25–27] Based on these points, we draw the circumstantial conclusion that the effect we observed may indeed be a primacy effect. However, we admit this conclusion is questionable. Nevertheless, we currently lack a better explanation as to why these three specific words are providing us with the best fit in our analysis, and suggest this point may warrant further inquiry.

To conclude, both CERAD-derived delayed primacy and delayed recall predicted *post mortem* AD pathology in individuals who were classed as unimpaired at baseline, above and beyond demographics. These measures displayed different associations – delayed primacy correlated with global pathology and neuritic plaques, while delayed recall correlated with neurofibrillary tangles – and both performed better than the overall composite score. All in all, both the traditional recall scores and their process approach counterparts should be considered in research and clinical settings where the CERAD memory test is employed.

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CONFLICT OF INTEREST STATEMENT

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

DATA AVAILBILITY STATMENT

Data can be requested at: https://www.radc.rush.edu/requests.htm.

CONSENT STATEMENT

All participants provided informed consent.

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REFERENCES

1. Olivari BS, French ME, McGuire LC. The public health road map to respond to the growing dementia crisis. *Innov Aging*. 2020;4(1):1-11. doi:10.1093/geroni/igz043
2. Bradford A, Kunik ME, Schulz P, Williams SP, Singh H. Missed and delayed diagnosis of dementia in primary care: prevalence and contributing factors. *Alzheimer Dis Assoc Disord*. 2009;23(4):306-314. doi:10.1097/wad.0b013e3181a6bebc
3. Chodosh J, Petitti DB, Elliott M, et al. Physician recognition of cognitive impairment: evaluating the need for improvement. *J Am Geriatr Soc*. 2004;52(7):1051-1059. doi:10.1111/j.1532-5415.2004.52301.x
4. Werner P, Karnieli-Miller O, Eidelman C. Current knowledge and future directions about the disclosure of dementia: a systematic review of the first decade of the 21st century. *Alzheimers Dement*. 2013;9(2):e74-88. doi:10.1016/j.jalz.2012.02.006
5. Mattsson N, Carrillo MC, Dean RA, et al. Revolutionizing Alzheimer's disease and clinical trials through biomarkers. *Alzheimers Dement* . 2015;1(4):412-419. doi:10.1016/j.dadm.2015.09.001
6. Cullen NC, Leuzy A, Janelidze S, et al. Plasma biomarkers of Alzheimer's disease improve prediction of cognitive decline in cognitively unimpaired elderly populations. *Nat Commun*. 2021;12(1):3555. doi:10.1038/s41467-021-23746-0
7. Manera V, Rovini E, Wais P. Early detection of neurodegenerative disorders using behavioral markers and new technologies: new methods and perspectives. *Front Aging Neurosci*. 2023;15:1-3. doi:10.3389/fnagi.2023.1149886
8. Walker R, Paddick SM. Dementia prevention in low-income and middle-income countries: a cautious step forward. *Lancet Glob Health*. 2019;7(5):e538-539. doi:10.1016/s2214-109x(19)30169-x
9. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* . 2011;7(3):270-279. doi:10.1016/j.jalz.2011.03.008
10. De Simone MS, Perri R, Fadda L, Caltagirone C, Carlesimo GA. Predicting progression to Alzheimer's disease in subjects with amnestic mild cognitive impairment using performance on recall and recognition tests. *J Neurol*. 2019;266:102-111. doi:10.1007/s00415-018-9108-0
11. De Tollis M, De Simone MS, Perri R, Fadda L, Caltagirone C, Carlesimo GA. Verbal and spatial memory spans in mild cognitive impairment. *Acta Neurol Scand*. 2021;144(4):383-393. doi:10.1111/ane.13470
12. Dubois B, Feldman HH, Jacova C, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS–ADRDA criteria. *Lancet Neurol*. 2007;6(8):734-746. doi:10.1016/s1474-4422(07)70178-3

13. Mueller KD, Du L, Bruno D, et al. Item-level story recall predictors of amyloid-beta in late middle-aged adults at increased risk for Alzheimer's disease. *Front Psychol*. 2022;3553. doi:10.3389/fpsyg.2022.908651
14. Libon DJ, Swenson R, Ashendorf L, Bauer RM, Bowers D. Edith Kaplan and the Boston process approach. *Clin Neuropsychol*. 2013;27(8):1223-1233. doi:10.1080/13854046.2013.833295
15. Milberg WP, Hebben N, Kaplan E, (2009). The Boston Process Approach to neuropsychological assessment. In I. Grant & K. M. Adams (Eds.), *Neuropsychological assessment of neuropsychiatric and neuromedical disorders* (pp. 42–65). Oxford University Press. doi:10.1093/arclin/act087
16. Murdock Jr BB. The serial position effect of free recall. *J Exp Psychol*. 1962;64(5):482. doi:10.1037/h0045106
17. Kelly MO, Risko EF, Offloading memory: serial position effects. *Psychon Bull Rev* . 2019;26:1347-1353. doi:10.3758/s13423-019-01615-8
18. Neath I. Evidence for similar principles in episodic and semantic memory: the presidential serial position function. *Mem Cognit*. 2010;38(5):659-666. doi:10.3758/mc.38.5.659
19. Azizian A, Polich J. Evidence for attentional gradient in the serial position memory curve from event-related potentials. *J Cogn Neurosci*. 2007;19(12):2071-2081. doi:10.1162/jocn.2007.19.12.2071
20. Rosen VM, Bergeson JL, Putnam K, Harwell A, Sunderland T. Working memory and apolipoprotein E: what's the connection? *Neuropsychologia*. 2002;40(13):2226-2233. doi:10.1016/s0028-3932(02)00132-x
21. La Rue A, Hermann B, Jones JE, Johnson S, Asthana S, Sager MA. Effect of parental family history of Alzheimer's disease on serial position profiles. *Alzheimers Dement* . 2008;4(4):285-290. doi:10.1016/j.jalz.2008.03.009
22. Kloth N, Lemke J, Wiendl H, Meuth SG, Duning T, Johnen A. Serial position effects rapidly distinguish Alzheimer's from frontotemporal dementia. *J Neurol*. 2020;267:975-983. doi:10.1007/s00415-019-09662-w
23. Gicas KM, Honer WG, Wilson RS, et al. Association of serial position scores on memory tests and hippocampal-related neuropathologic outcomes. *Neurology*. 2020;95(24):e3303-3312. doi:10.1212/wnl.0000000000010952
24. Gicas KM, Honer WG, Leurgans SE, et al. Longitudinal change in serial position scores in older adults with entorhinal and hippocampal neuropathologies. *J Int Neuropsychol Soc*. 2023;29(6):561-571. doi:10.1017/s1355617722000595
25. Bruno D, Reiss PT, Petkova E, Sidtis JJ, Pomara N. Decreased recall of primacy words predicts cognitive decline. *Arch Clin Neuropsychol*. 2013;28(2):95-103. doi:10.1093/arclin/acs116
26. Talamonti D, Koscik R, Johnson S, Bruno D. Predicting early mild cognitive impairment with free recall: the primacy of primacy. *Arch Clin Neuropsychol*. 2020;35(2):133-142. doi:10.1093/arclin/acz013
27. Bruno D, Grothe MJ, Nierenberg J, et al. A study on the specificity of the association between hippocampal volume and delayed primacy performance in cognitively intact elderly individuals. *Neuropsychologia*. 2015;69:1-8. doi:10.1016/j.neuropsychologia.2015.01.025
28. Brueggen K, Kasper E, Dyrba M, et al. The primacy effect in amnestic mild cognitive impairment: associations with hippocampal functional connectivity. *Front Aging Neurosci*. 2016;8:244. doi:10.3389/fnagi.2016.00244
29. Nichols E, Steinmetz JD, Vollset SE, et al. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *Lancet Public*. 2022;7(2):e105-e125.
30. Sundermann EE, Maki PM, Rubin LH, Lipton RB, Landau S, Biegon A. Alzheimer's Disease Neuroimaging Initiative. Female advantage in verbal memory: evidence of sex-specific cognitive reserve. *Neurology*. 2016;87(18):1916-1924. doi:10.1212/WNL.0000000000003288. Epub 2016 Oct 5. PMID: 27708128; PMCID: PMC5100712.
31. Bennett DA, Buchman AS, Boyle PA, Barnes LL, Wilson RS, Schneider JA. Religious orders study and rush memory and aging project. *J Alzheimers Dis*. 2018;64(s1):S161-189. doi:10.3233/jad-179939
32. Barnes LL, Shah RC, Aggarwal NT, Bennett DA, Schneider JA. The Minority Aging Research Study: ongoing efforts to obtain brain donation in African Americans without dementia. *Curr Alzheimer Res*. 2012;9(6):734-745. doi:10.2174/156720512801322627
33. Marquez DX, Glover CM, Lamar M, et al. Representation of older Latinxs in cohort studies at the Rush Alzheimer's Disease Center. *Neuroepidemiology*. 2020;54(5):404-418. doi:10.1159/000509626
34. Bennett DA, Wilson RS, Schneider JA, et al. Natural history of mild cognitive impairment in older persons. *Neurology*. 2002;59(2):198-205. doi:10.1212/wnl.59.2.198
35. Bennett DA, Schneider JA, Aggarwal NT, et al. Decision rules guiding the clinical diagnosis of Alzheimer's disease in two community-based cohort studies compared to standard practice in a clinic-based cohort study. *Neuroepidemiology*. 2006;27(3):169-176. doi:10.1159/000096129
36. Wilson RS, Boyle PA, Yu L, et al. Temporal course and pathologic basis of unawareness of memory loss in dementia. *Neurology*. 2015;85(11):984-991. doi:10.1212/wnl.0000000000001935
37. Morris JC, Mohs RC, Rogers H. Consortium to establish a registry for Alzheimer's Disease (CERAD) clinical and neuropsychological. *Psychopharmacol Bull*. 1989;24(3-4):641.
38. Gomar JJ, Bobes-Bascaran MT, Conejero-Goldberg C, Davies P, Goldberg TE. Alzheimer's Disease Neuroimaging Initiative. Utility of combinations of biomarkers, cognitive markers, and risk factors to predict conversion from mild cognitive impairment to Alzheimer disease in patients in the Alzheimer's disease neuroimaging initiative. *Arch Gen Psychiatry*. 2011;68(9):961-969. doi:10.1001/archgenpsychiatry.2011.96
39. Hampel H, Hardy J, Blennow K, et al. The amyloid-β pathway in Alzheimer's disease. *Mol Psychiatry*. 2021;26(10):5481-5503. doi:10.1038/s41380-021-01249-0
40. Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. *Science*. 1992;256(5054):184-185. doi:10.1126/science.1566067
41. Tiraboschi P, Hansen LA, Thal LJ, Corey-Bloom J. The importance of neuritic plaques and tangles to the development and evolution of AD. *Neurology*. 2004;62(11):1984-1989. doi:10.1212/01.wnl.0000129697.01779.0a
42. Bruno D, Mueller KD, Betthauser T, et al. Serial position effects in the Logical Memory Test: loss of primacy predicts amyloid positivity. *J Neuropsychol*. 2021;15(3):448-461. doi:10.1111/jnp.12235
43. Thal DR, Rüb U, Orantes M, Braak H. Phases of Aβ-deposition in the human brain and its relevance for the development of AD. *Neurology*. 2002;58(12):1791-1800. doi:10.1212/wnl.58.12.1791
44. Aschauer D, Rumpel S. The sensory neocortex and associative memory. *Curr Top Behav Neurosci* . 2018:37:177-211. doi:10.1007/7854_2016_453
45. Metaxas A, Kempf SJ. Neurofibrillary tangles in Alzheimer's disease: elucidation of the molecular mechanism by immunohistochemistry and tau protein phospho-proteomics. *Neural Regen Res*. 2016;11(10):1579. doi:10.4103/1673-5374.193234
46. Bransby L, Lim YY, Ames D, et al. Sensitivity of a Preclinical Alzheimer's Cognitive Composite (PACC) to amyloid β load in preclinical Alzheimer's disease. *J Clin Exp Neuropsychol*. 2019;41(6):591-600. doi:10.1080/13803395.2019.1593949
47. Jonaitis EM, Koscik RL, Clark LR, et al. Measuring longitudinal cognition: individual tests versus composites. *Alzheimers Dement (Amst)* . 2019;11:74-84. doi:10.1016/j.dadm.2018.11.006
48. Bock JR, Russell J, Hara J, Fortier D. Optimizing cognitive assessment outcome measures for Alzheimer's disease by matching wordlist memory test features to scoring methodology. *Front Digit Health*. 2021:161. doi:10.3389/fdgth.2021.750549

SUPPORTING INFORMATION

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

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