Journal of the International Neuropsychological Society (2023), **29**, 561–571
doi:10.1017/S1355617722000595

Research Article

Longitudinal change in serial position scores in older adults with entorhinal and hippocampal neuropathologies

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Abstract

Objective: Serial position scores on verbal memory tests are sensitive to early Alzheimer's disease (AD)-related neuropathological changes that occur in the entorhinal cortex and hippocampus. The current study examines longitudinal change in serial position scores as markers of subtle cognitive decline in older adults who may be in preclinical or at-risk states for AD. **Methods:** This study uses longitudinal data from the Religious Orders Study and the Rush Memory and Aging Project. Participants ($n = 141$) were included if they did not have dementia at enrollment, completed follow-up assessments, and died and were classified as Braak stage I or II. Memory tests were used to calculate serial position (primacy, recency), total recall, and episodic memory composite scores. A neuropathological evaluation quantified AD, vascular, and Lewy body pathologies. Mixed effects models were used to examine change in memory scores. Neuropathologies and covariates (age, sex, education, APOE e4) were examined as moderators. **Results:** Primacy scores declined ($\beta = -.032$, $p < .001$), whereas recency scores increased ($\beta = .021$, $p = .012$). No change was observed in standard memory measures. Greater neurofibrillary tangle density and atherosclerosis explained 10.4% of the variance in primacy decline. Neuropathologies were not associated with recency change. **Conclusions:** In older adults with hippocampal neuropathologies, primacy score decline may be a sensitive marker of early AD-related changes. Tangle density and atherosclerosis had additive effects on decline. Recency improvement may reflect a compensatory mechanism. Monitoring for changes in serial position scores may be a useful *in vivo* method of tracking incipient AD.

Keywords: Alzheimer's disease; dementia; memory; cognitive decline; aging; neuropathology

(Received 17 February 2022; final revision 8 June 2022; accepted 23 June 2022; First Published online 5 September 2022)

Introduction

Alzheimer's disease (AD) is defined pathologically by the presence of beta-amyloid and neurofibrillary tau tangles and is a major contributor to dementia (DeTure & Dickson, 2019; Matthews et al., 2009). Clinical dementia due to AD, however, is the endpoint manifestation of pathological progression that unfolds over decades (Dickerson et al., 2011; Villemagne et al., 2013). Advances in the detection of amyloid and tau biomarkers *in vivo* now provide further support for the presence of AD pathology years before cognitive impairment is detectable (Tanner & Rabinovici, 2021; Younes et al., 2019). Yet, it remains challenging to differentiate cognitively normal persons who are in a preclinical state of AD. It is increasingly recognized that AD pathologies may lie on a continuum where progression is associated with a multitude of factors including age, APOE e4 status, cognitive reserve, genetics, and comorbidities (Dubois et al., 2016).

The entorhinal cortex and hippocampus are among the earliest regions to be affected by AD pathology, followed by a predictable pattern of disease progression extending to the neocortical regions of the temporal lobe and then more diffusely to frontal cortical regions (Braak & Del Tredici, 2015, 2020). The emergence of cognitive impairments track with disease progression such that the medial temporal lobe-dependent memory functions are among the first to decline and remain one of the best predictors of a later dementia diagnosis (Mortamais et al., 2017). However, in the preclinical stage of AD, composite memory scores do not yet meet the threshold for clinical impairment, nor do they show any significant association with hippocampal structure (Toledo et al., 2015). The routine cognitive scores that are relied upon to diagnose mild cognitive impairment (MCI) or dementia therefore lack sensitivity to detect more subtle cognitive changes that may take place in the at-risk or preclinical states when AD pathology is limited to the entorhinal cortex and hippocampus.

Upon closer inspection, there is ample evidence to support subtle cognitive changes in preclinical AD. Meta-analytic work has revealed small neuropsychological differences by biomarker status in cognitively normal older adults, with successive memory decrements noted for amyloid positive persons and those who are

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Cite this article: Gicas K.M., Honer W.G., Leurgans S.E., Wilson R.S., Boyle P.A., Schneider J.A., & Bennett D.A. (2023) Longitudinal change in serial position scores in older adults with entorhinal and hippocampal neuropathologies. *Journal of the International Neuropsychological Society*, 561–571, https://doi.org/10.1017/S1355617722000595

amyloid positive with tau pathology or neurodegeneration (Han et al., 2017). Thomas et al. (2018) have operationalized *early subtle cognitive decline* to identify persons with impairment on process scores (emphasizing *how* information was processed) who are classified as "cognitively normal" based on their routine total or composite cognitive test scores. Persons who met criteria for subtle cognitive decline showed faster amyloid accumulation and entorhinal cortical thinning compared to cognitively normal persons, whereas the MCI group showed faster hippocampal atrophy (Thomas et al., 2020). These findings suggest that subtle cognitive changes may track with early neuropathological changes in preclinical AD.

In line with the process score approach, serial position scores in verbal memory may be particularly sensitive to early neuropathological changes in the medial temporal lobe region. Serial position effects refer to the tendency to better remember items at the beginning (primacy) and end (recency) of a supraspan wordlist (Murdock, 1962). It is proposed that primacy items benefit from a greater opportunity for rehearsal and therefore become hippocampal-dependent as they are transferred to and retrieved from long-term memory stores, whereas recency items are held in and retrieved directly from short-term working memory stores (Atkinson & Shiffrin, 1968; Malmberg et al., 2019). Anatomically, this explanation is supported by functional neuroimaging that shows differential activation of hippocampal and frontoparietal regions when recalling primacy *versus* recency items, respectively (Talmi et al., 2005), as well as structural studies linking poorer primacy recall to hippocampal lesions and volume reductions (Bruno et al., 2015; Chander et al., 2018; Hermann et al., 1996). Clinically, the serial position effect is altered in Alzheimer's dementia, characterized by a diminished primacy effect with a relatively more pronounced recency effect (Bayley et al., 2000; Cunha et al., 2012; Howieson et al., 2011). Primacy scores have predicted transition to MCI and to Alzheimer's dementia with intervals from 18 months up to 13 years (Egli et al., 2014; Talamonti et al., 2019). Another serial position-derived memory score, the recency ratio, has shown association with cerebrospinal fluid markers of amyloid beta in persons with MCI who were considered at risk for AD (Bruno et al., 2019). These findings extend to verbal material presented in a story format, whereby primacy scores, but not total recall scores, predicted PET global amyloid burden in individuals without cognitive impairment (Bruno et al., 2021).

Understanding how early and subtle memory changes track with AD pathologies could be critical to early detection of disease, with implications for clinical trials eligibility and behavioural interventions. We previously reported an association between primacy performance measured years before death and an increasing burden of hippocampal neuropathologies using gold-standard postmortem evaluations (Gicas et al., 2020). We also found that primacy performance discriminated between clinical diagnoses proximate to death, providing robust support for the sensitivity of serial position scores to AD-related changes in the brain. The current study extends our prior work in two important ways. First, we are examining serial position scores longitudinally to identify subtle decline in the absence of decline on routine total recall and composite memory scores in older adults who did not have dementia at study enrollment. Second, we are focusing on a subsample of older adults who may be in the preclinical stage of AD based on autopsy evidence of tau pathology circumscribed to the entorhinal cortex and hippocampus, consistent with Braak stages I and II (Braak et al., 2006). This approach intentionally excludes persons who may demonstrate more objective memory changes associated with MCI and dementia, which typically coincide with Braak stage III when neurofibrillary tangles expand to the neocortex (Nelson et al., 2012). It is hypothesized that a select decline in the primacy score, but not recency or total recall scores, will be observed. A secondary aim is to investigate the role of specific AD pathologies in serial position score change over time. It is hypothesized that tangle density, but not neuritic plaques, will be associated with a steeper rate of primacy score change. This follows from observations that tau tangles may be the primary drivers of cognitive changes in Alzheimer's dementia (Arnsten et al., 2021; Nelson et al., 2012). Given that age-related cognitive changes and dementia are typically the result of mixed brain pathologies, we also explored the role of commonly co-occurring vascular pathologies and Lewy bodies in relation to serial position trajectories.

Method

Participants

This study used data from two parallel longitudinal clinical-pathologic cohort studies; the Religious Orders Study (ROS) and the Rush Memory and Aging Project (MAP; see overview of studies in Bennett et al., 2018). Participants enrolled in ROS were older nuns, priests, and brothers recruited from multiple regions across the United States beginning in 1994. MAP participants included community-dwelling older adults who were recruited from retirement facilities, churches, and social service agencies in Northeastern Illinois beginning in 1997. Eligibility for enrollment in ROS or MAP included consent to participant in annual assessments and signing an Anatomical Gift Act for organ donation at death. All participants signed a Repository Consent to allow their data to be shared. Ethics approvals for ROS and MAP were obtained from an Institutional Review Board of Rush University Medical Center. This research was completed in accordance with the Helsinki Declaration.

A total of 3678 participants enrolled in ROS and MAP completed a baseline cognitive evaluation at the time of the database curation (March 3, 2021). Eligibility for these analyses include (1) no dementia at study enrollment; (2) at least one follow-up evaluation, a complete CERAD (Consortium to Establish a Registry for AD) Word List Memory test; (3) a full neuropathological evaluation; (4) Braak stage I or II; (5) TDP-43 Stage 0 or 1; (6) no hippocampal sclerosis; and (7) no or low likelihood of pathologic AD based on the modified National Institute of Aging (NIA)-Reagan criteria (Bennett et al., 2006a; The National Institute on Aging, and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease, 1997). We excluded cases classified as being in advanced TDP-43 stages (i.e., inclusions in the hippocampus and neocortical regions) and/or with hippocampal sclerosis as these neuropathologies are known to impact episodic memory (Brenowitz et al., 2015; Nag et al., 2017), and we wished to more clearly evaluate the specific impacts of early stage AD pathology circumscribed to the entorhinal cortex and hippocampus. The flow chart in Figure 1 delineates the sample composition based on these criteria. The final analytic sample consisted of 141 participants who were on average 76.7 years old ($SD = 6.7$; range = 64.5–95.7) at study entry, with a mean of 17.1 years of education ($SD = 3.6$; range = 10–28); 51.1% were female, 96.5% were white, and 12.9% had at least one APOE ϵ4 allele. Participants were followed for a mean of 8.2 years ($SD = 4.5$, range = 1.0–22.1) and died at a mean age of 84.9 ($SD = 6.7$; range = 69.7–101.0).

https://doi.org/10.1017/S1355617722000595 Published online by Cambridge University Press

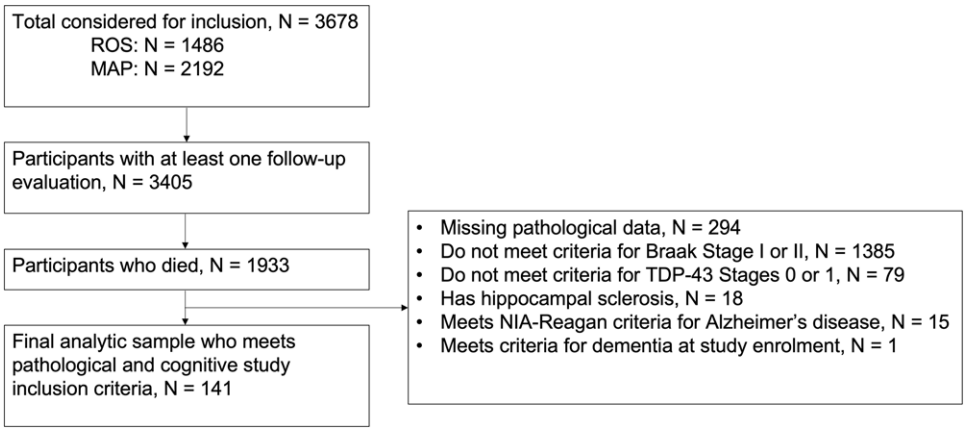

Figure 1. Flow chart delineating participant inclusion and exclusion.

Cognitive evaluation

Participants completed an annual neuropsychological evaluation in a standardized format involving a comprehensive test battery to assess functioning in the domains of episodic memory, semantic memory, working memory, visuospatial ability, and perceptual speed (Wilson et al., 2019). For the current study, serial position scores were computed for each annual evaluation using the CERAD Word List Memory test (Morris et al., 1989). This test is composed of a list of 10 semantically unrelated words that are repeated across three trials with varying word order. Participants are asked to immediately recall as many words as they can after each trial. Following a several minute delay, participants are asked to recall as many list words as they can (CERAD Word List Recall). Within each of the three immediate recall trials, the first three words comprise the primacy region and the last three words comprise the recency region. Serial position scores were computed as the proportion correctly recalled for each region (possible range = 0–1) by summing the total number of correct responses in a given region across the three trials divided by the total number of words presented in that region (i.e., primacy words = three per trial = nine total; (Moser et al., 2014)). An immediate recall total score was computed by summing the number of correctly recalled words across the three trials. A delayed recall total score was defined as the total number of words recalled on the delay trial. Raw scores were converted to *Z*-score units using the baseline mean and standard deviation of the full combined sample. To provide a broader index of episodic memory, a composite score was derived by averaging the *Z*-scores (using baseline mean and standard deviation) from the CERAD Word List Memory, Word List Recall, and Word List Recognition tests; Logical Memory A immediate and delayed recall (Wechsler, 1987); and the East Boston Story immediate and delayed recall (Albert et al., 1991). A composite score was only calculated if at least half of the individual scores were non-missing.

A clinical diagnosis was rendered for each annual visit classifying individuals as either having: (1) no cognitive impairment; (2) MCI; (3) Alzheimer's dementia; and/or (4) other dementia (no clinical evidence of Alzheimer's dementia). Classification was based on a three-stage system that involved computer scoring of the completed neuropsychological test battery, clinical judgment by a neuropsychologist blinded to participant demographics, and diagnostic classification by a clinician (neurologist, geriatrician, or geriatric nurse practitioner) after review of all available information. Details of the diagnostic procedures were previously reported (Bennett et al., 2002; Bennett et al., 2006a, 2006b). Diagnoses of MCI and dementia were based on criteria outlined by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA; McKhann et al., 1984).

Clinical diagnosis at the time of death was made by a neurologist using all available clinical data while blinded to postmortem data. Ambiguous cases were adjudicated. Classification of the most likely clinical cognitive diagnosis at death included MCI (one impaired domain) or dementia and the respective cause, as outlined above. Additionally, Alzheimer's dementia diagnoses were classified as possible or probable in accord with NINCDS/ADRDA criteria (McKhann et al., 1984). Individuals with no impaired domains were classified as having no cognitive impairment.

Neuropathological evaluation

Participants who died underwent brain autopsies, with full details reported elsewhere (Bennett et al., 2006a). The standard protocol involved removal of the brainstem and cerebellum, followed by cutting one hemisphere into 1cm coronal slabs that were immediately frozen. The other hemisphere was fixed in 4% paraformaldehyde for 3 to 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.

Bielschowsky silver stain was used to visualize neurofibrillary tangles and neuritic plaques in the frontal, temporal, parietal, entorhinal, and hippocampal regions. Braak staging was performed by assessing the distribution and severity of neurofibrillary tangles across the five regions. Relevant to the current study, Braak stages I and II were defined as having neurofibrillary tangles confined predominately to the entorhinal cortex, with some limited involvement of the hippocampal CA1/CA2 subfields (Braak et al., 2006). Quantitative measures of neurofibrillary tangle and neuritic plaque burden were each derived by a count of pathologies in five regions (midfrontal, midtemporal, inferior parietal, entorhinal, and hippocampus) divided by the corresponding standard deviation, and then averaged across regions to yield a summary measure. Data must be present for at least two of the five regions to compute a summary burden score.

Immunocytochemistry and image analysis were used to quantify the percentage of cortex occupied by amyloid beta within eight regions (superior frontal, anterior cingulate, calcarine, angular

https://doi.org/10.1017/S1355617722000595 Published online by Cambridge University Press

gyrus, inferior temporal, midfrontal, entorhinal, and hippocampus). A global amyloid level measure was derived by averaging values across the eight regions, with at least four or more regional measures required for calculation. Cerebral amyloid angiopathy (CAA) was assessed with immunostaining in four regions (midfrontal, midtemporal, parietal, and calcarine) and quantified using the protocol outlined by Love et al. (2014) based on amyloid deposition in meningeal and parenchymal vessels, scored from 0 to 4 and averaged across regions (Boyle et al., 2015). Additional immunocytochemistry using an antibody detecting abnormally phosphorylated tau protein was performed on the eight regions noted above to quantify neurofibrillary tangle density (mm^2) by stereology. The overall mean density was calculated by averaging across regions where data were presented for at least four of the regions. TDP-43 staging was performed via immunocytochemistry in eight brain regions (amygdala, entorhinal, hippocampus CA1, hippocampus dentate gyrus, anterior temporal pole, midtemporal, orbital frontal, and midfrontal). The presence of TDP-43 cytoplasmic inclusions in neurons and glia in each region were evaluated and successively classified as follows: stage 1 = none; stage 2 = amygdala; stage 3 = amygdala and limbic; stage 4 = amygdala, limbic, and neocortical (Nag et al., 2018). Cortical Lewy body disease was diagnosed using α-synuclein immunostaining to identify limbic-type and neocortical-type intracytoplasmic structures.

Cerebral atherosclerosis ratings of large vessels were made by visual inspection of the Circle of Willis. Severity was graded based on the number of arteries involved and the extent of each artery involvement, collapsed into four levels: 0 = none or possible; 1 = mild (typically less than 25% artery involvement, without significant occlusion); 2 = moderate (up to half of visualized arteries, less than 50% occlusion of any single artery); 3 = severe (more than half of visualized arteries and/or more than 75% occlusion of one or more arteries) (Arvanitakis et al., 2017). Arteriolosclerosis was rated based on histological changes to small vessels observed in the anterior basal ganglia using a semiquantitative rating system collapsed to four levels: 0 = none; 1 = mild; 2 = moderate; 3 = severe) (Buchman et al., 2011). Presence of one or more gross chronic cerebral infarcts and one or more chronic microinfarcts were identified via visual inspection by a neuropathologist blinded to clinical data (Arvanitakis et al., 2011). Hippocampal sclerosis was examined in a unilateral coronal section of the midhippocampus and deemed present if there was evidence of severe neuronal loss and gliosis in CA1 and/or the subiculum (Nag et al., 2015). Apolipoprotein (APOE) genotyping was completed using DNA from blood samples or postmortem brain tissue. For the current study, APOE ϵ4 positive status was defined as ϵ2/4, ϵ3/4 or ϵ4/4.

Statistical analysis

Data were examined for normality using visual inspection of histograms for continuous variables. Paired-samples *t*-tests were used to evaluate mean differences in serial position scores at the first and last available cognitive evaluations. Pearson correlations were used to examine linear relationships between continuous variables. To test the hypothesis that primacy scores would show select decline, a series of linear mixed effects models with random intercepts (for subjects) and slopes (for time) were conducted. Serial position scores (primacy, recency), as well as total scores (immediate, delayed) and the episodic memory composite score, were entered as repeated measures outcomes in separate models. Time was measured in years from the baseline evaluation. Covariates included age at baseline, sex (male, female), total years of education, and APOE ϵ4 status. All possible interactions between time and covariates were examined. A sex by education interaction was also examined to capture the intersection of these factors that contribute to gender identity. Only interactions that were significant at $p < .05$ were retained for inclusion in the final reported models. The assumptions of normality of residuals and random effects were evaluated.

A follow-up series of linear mixed effects models were conducted to screen for potential pathological moderators of primacy and recency trajectories. AD-related pathologies (each of neurofibrillary tangle density, neuritic plaques, beta-amyloid level), vascular pathologies (each of atherosclerosis, arteriolosclerosis, CAA, gross chronic infarcts, chronic microinfarcts), neocortical Lewy bodies, and early stage TDP-43 were examined independently in a total of 20 separate models (ten for each primacy and recency outcome), adjusted for the aforementioned covariates, including the age by sex interaction term for the recency model only. Square root transformations were applied to measures of neurofibrillary tangle density and beta-amyloid to correct for non-normality. All other neuropathologies were dichotomized to reflect presence or absence. Interaction terms (neuropathology*time) that were significant at $p < .10$ were retained for inclusion in the final moderation model. A more liberal alpha level was adopted at the screening step to ensure inclusion of the broadest range of pathologies in the final model, recognizing that some of these may exert effects in the presence of other pathologies.

A sensitivity analysis was conducted by re-running the main analyses after removing participants who met criteria for MCI across the first three visits. This was done to ensure that participants with MCI were not primarily accounting for any observed changes in memory. The Pseudo-R^2 was used to describe effect sizes of moderators by quantifying the proportion of variance explained in the random effects. Effect sizes are interpreted as small (0.02), medium (0.13), and large (0.26) based on Cohen's squared multiple correlation change. The alpha level was set to .05. Analyses were conducted in R (R Core Team, 2020) using the *lme*4 package (Bates et al., 2015).

Results

Participants were excluded from the analyses if they were missing data on neuropathological staging variables required for classification of early stage AD (see Figure 1). In the final sample ($n = 141$), one participant was missing data on APOE ϵ4 status and was excluded from the longitudinal analyses. At baseline, 83.7% ($n = 118$) of the sample included participants who were considered cognitively unimpaired and 16.3% ($n = 23$) of participants had MCI. Based on cognitive status most proximate to death, 61.7% ($n = 87$) of participants were cognitively unimpaired, 27.0% ($n = 38$) of participants had MCI, and 11.3% ($n = 16$) of participants had dementia. A descriptive summary of the distribution of the pathologies is provided in Table 1.

There was a weak correlation between primacy and recency scores at baseline ($r = .17$, $p = .041$) and a moderate correlation between scores at the last cognitive evaluation prior to death ($r = .27$, $p = .002$). The serial position profiles at baseline and at the last evaluation are depicted in Figure 2, stratified by clinical diagnosis (cognitive impairment [MCI or dementia] *vs.* no cognitive impairment [NCI]). Paired samples t-tests of baseline scores indicate that the middle score was lower compared to the primacy and recency scores in both the NCI (primacy: $t = 8.39$, $p < .001$;

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Table 1. Descriptive statistics of the distribution of neuropathologies

Variable	Mean (*SD*) or *n* (%)
Global beta-amyloid, square root transformed	.705 (.820)
Neurofibrillary tangle density (mm^3), square root transformed	.759 (.448)
Neuritic plaques, (present)	59/141 (41.8%)
Atherosclerosis (present)	110/141 (78.0%)
Arteriolosclerosis (present)	91/140 (65.0%)
Cerebral amyloid angiopathy (present)	75/137 (54.7%)
Gross chronic infarcts (present)	38/141 (27.0%)
Chronic microinfarcts (present)	32/141 (22.7%)
Neocortical Lewy bodies (present)	19/140 (13.6%)
TDP-43 – Stage 1 (present)	36/141 (25.5%)
Braak score	
Stage 1	66/141 (46.8%)
Stage 2	75/141 (53.2%)

recency: $t = -6.65$, $p < .001$) and MCI (primacy: $t = 3.10$, $p = .005$; recency: $t = -2.82$, $p = .010$) groups, whereas there was no difference between mean primacy and recency scores in either group (p-values > .280). When the serial position profiles were examined based on the last scores, the pattern for the NCI group was similar to baseline; the middle score was lower compared to the primacy ($t = 4.51$, $p < .001$) and recency ($t = -5.25$, $p < .001$) scores, with no difference between mean primacy and recency scores ($t = -0.87$, $p = .386$). By contrast, for the group with MCI or dementia, the pattern differed from baseline; the primacy score ($t = -2.19$, $p = .034$) and middle score ($t = -5.41$, $p < .001$) were both significantly lower compared to the recency score.

The results of the linear mixed effects models examining cognitive trajectories are reported in Table 2. After adjusting for the effects of demographics and APOE ϵ4 status, a decline in primacy scores was observed. By contrast, an increase in recency scores was observed over the same time period. None of the covariates significantly interacted with time and therefore these interaction terms were removed from the models. A sex by education interaction was evident only for the recency model whereby the association between higher years of education and better recency performance was stronger for females compared to males. No changes in immediate or delayed total recall, or episodic memory composite scores were observed.

In follow-up mixed effects models examining neuropathological moderators of primacy score trajectories, tangle density and atherosclerosis were retained for inclusion in the final model (see Table 3). Higher tangle density and the presence of atherosclerosis were independently associated with greater decline in primacy scores (see Figures 3 and 4). Probing of the interaction terms indicated that change in primacy scores was significant at the mean (0.78; $\beta = -.031$, $SE = .009$, $p < .001$) and one *SD* above the mean (1.24; $\beta = -.047$, $SE = .012$, $p < .001$) for tangle density. Change in primacy scores was also significant in the presence of atherosclerosis ($\beta = -.043$, $SE = .010$, $p <. 001$), but not in its absence. The addition of these neuropathologies to the model and their respective interactions with time explained 10.4% of the variance in primacy score change over time, corresponding to a small-to-medium effect size. A *post hoc* 3-way interaction between tangles, atherosclerosis, and time was conducted to determine if pathologies interacted to accelerate decline in primacy scores, but this was not statistically significant and therefore excluded from the final model. Recency score trajectories were not moderated by any of the neuropathologies (see Supplementary Table 1 for results of all moderation analyses). Results of the sensitivity analyses largely remained unchanged from the main analyses. In a subsample of 80 participants who were considered free from cognitive impairment across the first three visits, primacy scores declined ($\beta = -.046$, $SE = .012$, $p = .001$) and recency scores increased over time ($\beta = .026$, $SE = .009$, $p = .010$). No other significant changes in total or composite memory scores were observed. In the final moderation model, only atherosclerosis ($\beta = -.064$, $SE = .028$, $p = .027$) but not tangle density ($p = .271$) moderated the primacy score trajectories.

Discussion

In a sample of older adults who were free of dementia at study enrollment and who later showed evidence of limited, early-stage entorhinal and hippocampal Alzheimer's pathologies at death, we observed alterations in serial position scores over a period of up to 22 years. To the best of our knowledge, this is the first study to examine longitudinal change in serial position scores. As hypothesized, the primacy score showed significant decline over time, whereas total recall and composite memory scores did not show any substantial change. An unexpected increase in recency scores was noted and may reflect compensatory mechanisms or practice effects. Consistent with our prediction, greater neurofibrillary tangle density was associated with faster primacy score decline. The presence of atherosclerosis was also independently associated with faster primacy score decline, indicating potential additive effects of vascular disease on subtle cognitive decline.

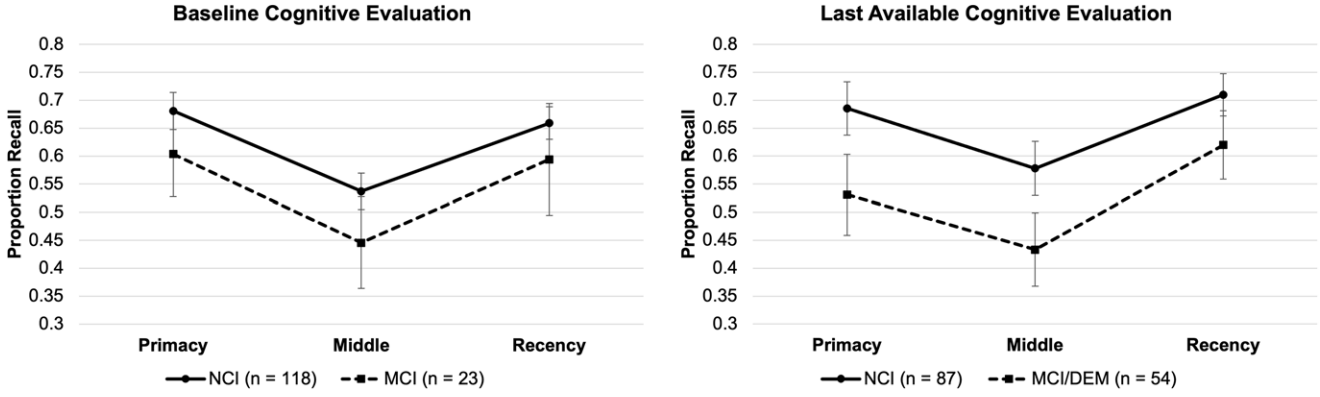

Figure 2. Serial position profiles for the baseline cognitive evaluation (left panel) and last available cognitive evaluation (right panel) stratified by cognitive status (NCI = not cognitive impaired; MCI = cognitively impaired; DEM = dementia). Scores represent the proportion of words recalled in each of the primacy, middle, and recency regions. Error bars represent 95% confidence intervals.

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Table 2. Mixed effects models for trajectories of change in cognitive outcome

	Model 1. Primacy		Model 2. Recency		Model 3. Immediate recall		Model 4. Delayed recall		Model 5. Episodic memory	
Variable	β (SE)	p-value	β (SE)	p-value	β (SE)	p-value	β (SE)	p-value	β (SE)	p-value
Time	−.032 (.009)	<.001	.021 (.008)	.012	−.001 (.009)	.884	−.012 (.009)	.177	−.013 (.007)	.084
Age at study entry	−.015 (.008)	.070	−.004 (.009)	.696	−.021 (.010)	.028	−.018 (.008)	.034	−.008 (.006)	.152
Education	.045 (.016)	.005	.069 (.027)	.014	.050 (.019)	.010	.033 (.016)	.045	.034 (.011)	.003
Sex (male)	−.352 (.107)	.001	1.127 (.603)	.064	−.384 (.130)	.004	−.403 (.113)	.045	−.157 (.077)	.045
APOE ϵ4 (positive)	.092 (.157)	.557	.209 (.175)	.236	.125 (.191)	.513	.014 (.165)	.935	.034 (.114)	.762
Sex*Education	–	–	−.077 (.035)	.029	–	–	–	–	–	–
Observations	1094		1095		1092		1095		1100	

Note. $n = 140$ for all models. APOE = apolipoprotein E.
The Sex*Education interaction term was only significant for Model 2, and therefore it was not included in the other models.

Table 3. Final mixed effects moderation model for primacy score trajectories

	Primacy score		
Variable	β	SE	p-value
Time	.031	.023	.179
Age at study entry	-.014	.008	.077
Education	.044	.157	.005
Sex (male)	-.342	.110	.002
APOE ϵ4 (positive)	.082	.158	.604
Tangle density	.100	.120	.407
Atherosclerosis	-.004	.131	.975
Time*Tangle density	-.038	.019	.046
Time*Atherosclerosis	-.445	.192	.024

Note. $n = 140$. Number of observations = 1094; APOE = apolipoprotein E.

The finding of selective primacy score decline complements existing literature that indicates alterations in serial position effects, mostly primacy performance, can predict future decline in global cognitive functioning among older adults who are considered cognitively normal (Bruno et al., 2013, 2016), those with MCI (Egli et al., 2015), and those with probable AD (Marra et al., 2000). Reduced primacy performance has also been linked with subsequent decline in subjective and performance-based functional measures of daily living in older adults without dementia (Weitzner et al., 2021), providing convergent evidence for the utility of primacy performance in predicting clinically relevant functional changes. Importantly, the primacy score appears to be uniquely suited to differentiating early stage (i.e., MCI (Cunha et al., 2012) or at-risk for AD (La Rue et al., 2008)) groups compared to healthy controls. By contrast, the effect sizes from meta-analytic work suggest that immediate recall ($g = -2.29$) and delayed recall ($g = -2.79$) scores better differentiate Alzheimer's dementia from healthy persons compared to the primacy score ($g = -1.61$; (Weitzner & Calamia, 2020)). Our current findings support the notion that in the earliest stages of AD, it is likely that primacy performance is especially vulnerable to an accumulating burden of neurofibrillary tangles in the entorhinal and hippocampal region that is critical for the encoding of primacy list words in long-term memory stores; however, the overall level of memory performance may be otherwise maintained for a period of time through compensation that involves recruitment of alternate networks (Colangeli et al., 2016; Scheller et al., 2014; see further discussion below). This so-called maintenance period may in fact reflect a very protracted phase of relatively "silent" pathophysiological changes, which is supported by evidence for significant time gaps between detection of cerebrospinal fluid total tau level and routine memory score changepoints (~19–23 years) prior to dementia onset (Younes et al., 2019).

The unexpected increase of the recency score is notable, and if this finding is replicated in the context of primacy score decline, it may explain the absence of early change in total recall and composite memory scores as being masked by opposing process score effects. While most studies report a general preservation of the recency in the context of MCI and Alzheimer's dementia (Weitzner & Calamia, 2020), an increased recency effect seems somewhat counterintuitive. One possibility is this reflects a practice effect that may be apparent given participants did not meet criteria for dementia at study enrolment. An alternative explanation is that this increase may reflect a compensatory mechanism by which individuals who are facing progressively greater memory encoding difficulties due to hippocampal dysfunction may engage a learning strategy that relies on short-term memory to maintain performance (Greene et al., 1996). This idea is best captured by Bruno et al. (2016, 2018) who developed the recency ratio to demonstrate that individuals with Alzheimer's dementia show an over-reliance on recency recall during immediate recall trials, but this effect is lost upon delayed recall because recency items were previously accessed solely from working memory stores. Only two other aging studies have reported findings that support this interpretation whereby there was better recency recall in persons with MCI and dementia (Jones et al., 2011) compared to persons without dementia. While there is ample neuroimaging evidence to support functional compensation in older adults (Colangeli et al., 2016; Scheller et al., 2014), more work is needed comparing the functional dynamics of primacy and recency performance *in vivo* between healthy and clinical groups.

The moderating role of pathologies on primacy decline helps elucidate the differential contributions that AD and vascular disease have to cognitive impairment. We found an increasing density of neurofibrillary tangles in the brain was associated with a steeper rate of primacy decline, but no such association was observed for neuritic plaques or global amyloid burden. Our findings complement PET and autopsy studies that show tau pathology is more strongly associated with cognitive functioning than amyloid pathology (Buckley et al., 2017; Chen et al., 2021; Nelson et al., 2012), and that tau pathology may be more sensitive to cognitive changes in preclinical AD (Ossenkoppele et al., 2019).

It is unclear why the presence of atherosclerosis, but not other vascular pathologies, was related to primacy decline. Previous work in ROS/MAP found that the effects of AD pathology and atherosclerosis on cognition may emerge earlier compared to other age-related neuropathologies (Boyle et al., 2017). Cerebrovascular disease, however, is remarkably heterogeneous in terms of its

https://doi.org/10.1017/S1355617722000595 Published online by Cambridge University Press

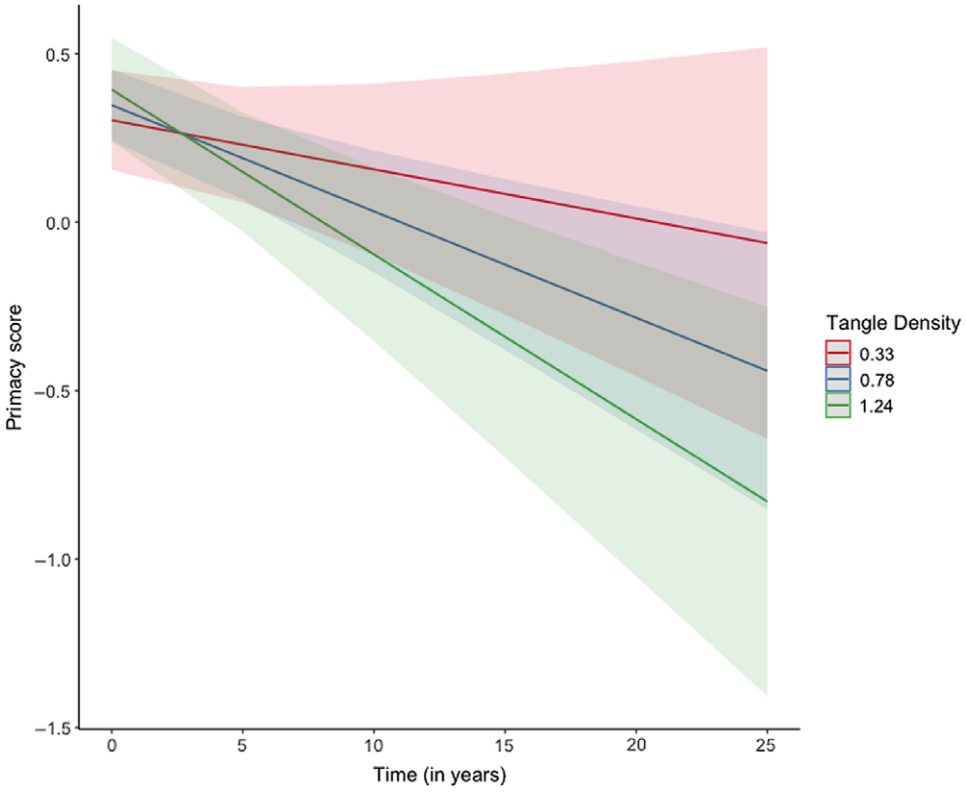

Figure 3. Change in primacy scores over time as a function of neurofibrillary tangle density (mean +/- 1SD).

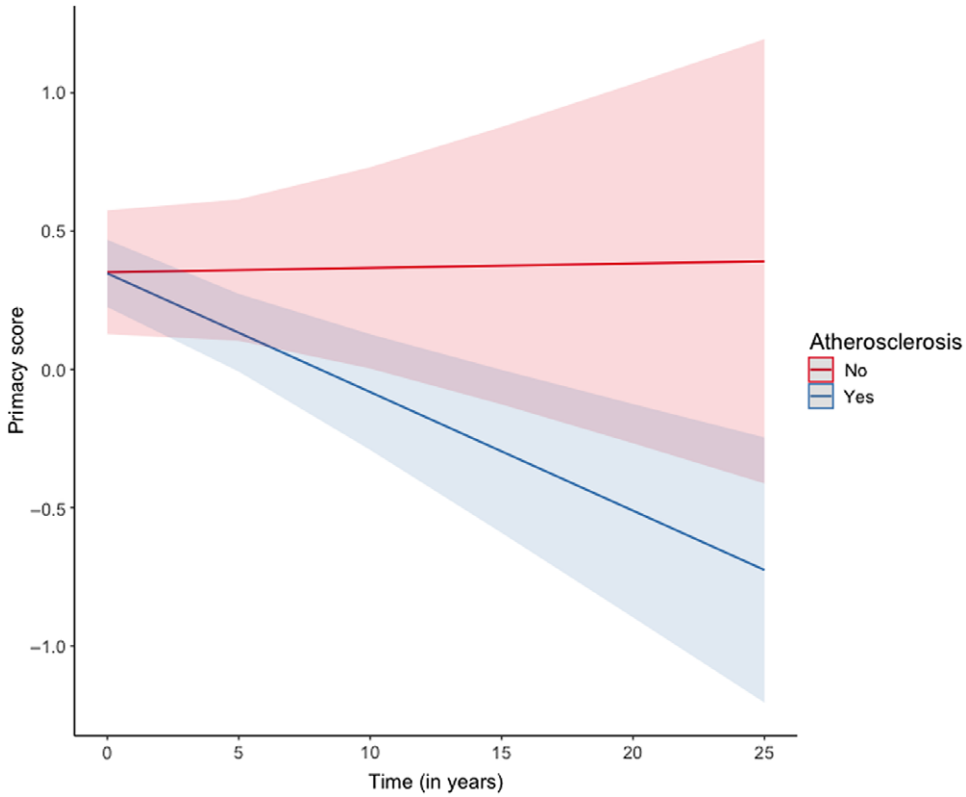

Figure 4. Change in primacy scores over time as a function of atherosclerosis (present or absent).

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pathological distribution and therefore its relationship with clinical outcomes is likely dependent upon on the unique ways in which focal lesions perturb structural and functional networks (ter Telgte et al., 2018). Our findings showed that AD and vascular pathologies have independent effects on primacy decline, which remains consistent with more comprehensive neuropathological analyses carried out in the overall ROS/MAP cohorts (Boyle et al., 2018, 2021). The broader literature is somewhat mixed with respect to whether comorbid neuropathologies exert additive or synergistic effects on cognition (Kapasi et al., 2017). While we did not observe an interaction effect of neurofibrillary tangles and atherosclerosis on primacy decline, identification of such effects may require a larger sample size. Nonetheless, there remains a continued need to examine pathological interactions in preclinical and at-risk groups because converging evidence from large-scale clinical-pathologic cohort studies indicate that dementia predominantly arises as a function of mixed pathologies in the brain (Au et al., 2012; Rahimi & Kovacs, 2014; White et al., 2016).

Limitations to the current study must be noted. The subsample of cases selected for this study were individuals who died in old age and met criteria for being in Braak stage I or II upon autopsy. We labeled this group as being in the putative preclinical stage of AD. However, we cannot determine whether these individuals would have progressed to a more advanced Braak stage and eventually met criteria for pathologic AD had they not died, or if their pathological profile might be better characterized as a primary age-related tauopathy (Crary et al., 2014; Dubois et al., 2016). Second, we only examined the presence or absence of co-morbid pathologies. Follow-up investigations should localize and quantify the severity of vascular pathologies to obtain a more nuanced understanding of the impacts on cognition. We also excluded cases with advanced TDP-43 but it is commonly comorbid with AD pathology and thus future investigations should take this into consideration when examining preclinical and at-risk for AD groups (Huang et al., 2020). Finally, our sample was small and consisted predominantly of highly educated White persons who were in the late stages of life and therefore our findings may not generalize well to the broader aging population. The main strengths of this study are the high rates of participation in annual follow-up and autopsy, yielding rich longitudinal clinical data linked to gold-standard assessments of brain disease, thereby increasing internal validity.

This work highlights the unique sensitivity of serial position scores in detecting subtle cognitive changes that otherwise evade detection on standard neuropsychological assessments in the preclinical or at-risk state of AD. In conjunction with routine neuropsychological scores, a process score approach that integrates primacy performance with existing approaches for defining subtle cognitive decline (Thomas et al., 2018) could help identify individuals at risk of progressing to Alzheimer's dementia much earlier and thereby widen the window of opportunity for pharmacologic and lifestyle intervention. Future studies should consider examining primacy effects in the context of the AT(N) biomarker framework, as recent work has proposed adding a measure of cognitive status could help improve prediction of cognitive decline in adults without dementia (O'Shea et al., 2021). More broadly, an exciting direction for this work will be to harness digital process scores from technologically advanced assessment tools that enable us to uncover novel cognitive parameters with enhanced sensitivity to preclinical AD (Au et al., 2017).

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S1355617722000595

Acknowledgements. We thank the faculty and staff of the Rush Alzheimer's Disease Center, and the participants in ROSMAP.

Author contributions. KMG: study conceptualization and design, data analysis and interpretation, writing original draft; WGH: study design, review, editing; SEL: study design, data interpretation, review, editing; RSW: data acquisition, study design, review, editing; PAB: data acquisition, study design, review, editing, funding acquisition; JAS: data acquisition, review, editing; DAB: data acquisition, review, editing, funding acquisition.

Funding statement. ROSMAP was supported by the following NIH grants: P30AG10161, P30AG72975, R01AG15819, R01AG17917, R01AG034374. ROSMAP data can be requested at https://www.radc.rush.edu.

Conflicts of interest. None.

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