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Effect of parental family history of Alzheimer's disease on serial position profiles

Asenath La Rue[a,*], **Bruce Hermann**[a,b], **Jana E. Jones**[a,b], **Sterling Johnson**[a,c,d], **Sanjay Asthana**[a,c,d], and **Mark A. Sager**[a,c]

[a]Wisconsin Alzheimer's Institute, Department of Medicine, University of Wisconsin School of Medicine and Public Health

[b]Department of Neurology, University of Wisconsin School of Medicine and Public Health

[c]Section of Geriatrics and Gerontology, Department of Medicine, University of Wisconsin School of Medicine and Public Health

[d]William S. Middleton Memorial Veterans Hospital, Madison, WI

Abstract

Background—An exaggerated recency effect (i.e., disproportionate recall of last-presented items) has been consistently observed in the word list learning of patients with Alzheimer's disease (AD). Our study sought to determine if there were similar alterations in serial position learning among asymptomatic persons at risk for AD due to parental family history.

Methods—Subjects included 623 asymptomatic middle-aged children of patients with AD (median = 53 years) and 157 control participants whose parents survived to at least age 70 without AD or other memory disorders. All participants were administered the Rey Auditory Verbal Learning Test which requires learning and recall of 15 unrelated nouns.

Results—There was no significant difference in total words recalled between the AD children and control groups. However, compared to controls, AD children showed a significantly greater tendency to recall words from the end (recency) versus beginning (primacy) of the list. Serial position effects were unrelated to apolipoprotein allele epsilon 4 (APOE ε4) or depressive symptoms.

Conclusions—Asymptomatic persons at risk for AD by virtue of family history do not show a difference in total words recalled compared to controls, but exhibit a distinctly different serial position curve suggesting greater reliance on immediate as opposed to episodic memory. This is the same serial position pattern observed in mild AD, seen here in reduced severity. Longitudinal follow-up is planned to determine whether changes in serial position patterns are a meaningful marker for preclinical detection of AD.

Keywords

Alzheimer's disease; memory; serial position effect; prospective study; family history of dementia

*Address correspondence to: Asenath La Rue, Ph.D., Wisconsin Alzheimer's Institute, 7818 Big Sky Drive, Ste. 215, Madison, WI 53719. Phone: 608-829-3308; Fax: 608-829-3315; e-mail: E-mail: larue@wisc.edu.

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1. Introduction

There is increasing evidence that Alzheimer's disease (AD) is a life-course illness with neurobiological substrates detectable by mid-life or earlier [1–4]. It has also been shown that the risk of developing AD is influenced by potentially modifiable health and lifestyle factors, raising the possibility of preventive strategies to delay the onset of clinically significant dementia symptoms. An important factor for a preventive approach is knowing which individuals are at greatest risk and most likely to benefit from prevention efforts.

Identification of early cognitive changes in at-risk populations is important because neuropsychological studies suggest that mild cognitive deficits in asymptomatic persons may presage the development of AD. This has been most clearly established in adults 65 years or older for predictive intervals of approximately two to ten years before dementia diagnosis. Mild preclinical impairments in episodic learning and memory, global cognitive ability, executive functioning, and perceptual speed show the strongest relationships with subsequent dementia in older populations [5].

A smaller number of prospective longitudinal studies suggest that cognitive performance in *middle age* may aid in identifying persons at increased risk for developing AD many years later. Participants in the Framingham Study who remained free of dementia for at least 10 years after baseline testing, but subsequently developed AD after age 65, scored lower on verbal memory and abstract reasoning at baseline than those who did not develop dementia [6]. Similarly, within the Baltimore Longitudinal Study of Aging, participants with an increased rate of errors at baseline on a visual memory task had twice the risk of developing AD than those with better visual memory performance across predictive intervals of up to 15 years [7]. Added to these findings are the results of the Nun Study, which documented increased rates of AD in older women who demonstrated paucity of ideas in verbal narratives written in their late teens or early 20s [8].

An aspect of learning and memory that may prove useful in preclinical AD research is the serial position effect. When asked to learn and recall a list of items that exceeds their working memory span, cognitively normal individuals recall more items from the beginning (primacy effect) and end (recency effect) of the list than those positioned in the middle [9]. Different memory systems are thought to underlie distinct portions of the serial position curve, with episodic memory playing a crucial role in the learning and recall of primacy and middle position items, whereas recall of recency items is believed to reflect the operation of immediate or working memory systems [10]. Left hippocampal lesions preferentially reduce the primacy effect and simultaneously increase the recency effect on word list learning tasks [11], presumably by adversely affecting episodic memory and increasing reliance on working memory. Normal aging does not affect the basic shape of the serial position curve, even though the total amount recalled is typically lower for older persons [10,12]. By contrast, patients with AD, even in very mild stages, show an exaggerated recency effect compared to primacy [13–15], likely reflecting a decline in hippocampal function early in the illness [16,17]. Elderly depressed patients may have selective difficulty with recall of middle position items [18,19], perhaps as a result of compromised function in other brain regions (e.g., frontal areas) known to affect serial position curves.

To the degree that subtle pathology in the hippocampus or its afferents (entorhinal cortex) may antedate clinical AD, it may be possible to identify subtle but distinct differences in features of the serial position curve among persons with increased risk of AD well before diagnosable disease becomes apparent. To that end, we compared serial position effects for middle-aged children of AD parents and control participants without a family history of AD. Although several studies have documented an increased risk of AD among siblings of AD patients or

combined samples of first-degree relatives [20,21], our investigation is the largest prospective study of AD offspring as a separate group. To the extent that serial position effects might be a marker of cognitive vulnerability and/or a preclinical sign of AD, we hypothesized that AD children would exhibit significant differences in their serial position curves compared to controls with either decreased primacy and/or increased recency effects. We also examined serial position effects in relation to apolipoprotein epsilon 4 (APOE ε4) genotype, because subtle deficits in memory and attention have been reported among middle-aged clinically asymptomatic APOE ε4 carriers [22–24].

2. Methods

2.1. Participants

A description of the development of the Wisconsin Registry for Alzheimer's Prevention (WRAP) and study methods can be found in Sager et al [25]. Briefly, participation in WRAP requires that a person be between the ages of 40 and 65 years, English speaking, and have a parent with either autopsy-confirmed or probable AD as defined by NINCDS-ADRDA research criteria [26]. Adult children of persons with AD were volunteers whose parent had been evaluated in a memory assessment clinic at the University of Wisconsin-Madison or one of the satellite memory assessment clinics affiliated with the UW Wisconsin Alzheimer's Institute, and others who learned about the study from educational presentations or word of mouth. To verify the diagnosis of AD in parents not directly assessed, autopsy reports or parental medical records were reviewed. Sixty-five (10%) had parents with autopsy-confirmed AD. For an additional 181 (29%), diagnosis of AD in the parent was made at a UW memory assessment clinic, and for the remaining 377 cases (61%), diagnosis of AD in the parent was based on evaluations performed at affiliated memory diagnostic clinics and/or review of medical records, applying NINCDS-ADRDA criteria to identify probable AD. Control participants had mothers who survived to at least age 75, and fathers to at least age 70, without Alzheimer's disease, other dementia, or significant memory deficits. Controls were recruited through community presentations and word of mouth. Enrollment into WRAP began in 2001 and is ongoing. The sample for present analyses (N = 780) included all WRAP participants with complete baseline data on a verbal list learning task.

2.2. Procedures

WRAP participants were seen for a baseline assessment which included APOE genotyping (Athena Diagnostics, MA and the Laboratory for Endocrinology, Aging, and Disease, William S. Middleton Memorial Veterans Hospital, Madison, WI), selected laboratory tests and clinical measurements, completion of a health history form, and a battery of neuropsychological tests (see Sager et al. [25], for a description of the complete cognitive battery). Previous analyses of cognitive test outcomes indicated no baseline differences in neuropsychological performance among AD children as a function of APOE allele status [25], and additional analyses (unpublished) have shown no significant performance differences between AD children and controls on standard outcome measures from the cognitive tests. Present analyses were designed to take a closer look at qualitative features of verbal list learning, specifically, serial position effects.

2.2.1. Word list learning and measures of serial position—The Rey Auditory Verbal Learning Test (AVLT), which entails learning and recall of a list of 15 unrelated nouns, was administered according to standard procedures [27]. Percentages of items recalled from primacy, recency, and middle regions of the word list were computed by dividing the number of items recalled from each region by the total number of items presented in that region over the five learning trials. The primacy region was defined as serial position items number 1 through 4, the middle region as items 5 through 11, and recency region as items 12 through

15. These *regional* scores adjust for the differing numbers of items in different sections of the list [11,18,19]. Standard clinical outcomes from the AVLT (total correct responses across the five learning trials and delayed recall score) were also examined.

2.2.2. Additional measures—The 20-item Center for Epidemiologic Studies-Depression scale (CES-D) [28] was completed by each participant as part of the health history form. Intellectual performance was estimated by the Wechsler Abbreviated Scale of Intelligence (WASI) [29].

2.3. Data analysis

Demographic variables, APOE allele status, and health and lifestyle variables were compared for AD children and controls by χ^2 or univariate *F* tests, using the Bonferroni correction to control for multiple comparisons. Serial position findings for AD children and controls were examined by analyses of covariance, with age, education, and gender covaried. The principal dependent measures were regional serial position scores and difference scores comparing percentages of items recalled from the recency region versus primacy and middle regions. Secondary measures were sum correct on learning trials and delayed recall scores from the AVLT.

3. Results

Table 1 shows characteristics of AD children and controls. On average, AD children were slightly younger than controls, more likely to be APOE e4 carriers, reported more depressive symptoms, and had higher values on some indicators of cardiovascular health (systolic and diastolic blood pressure and non-fasting cholesterol). There were no significant differences in health history as measured by self-reported medical diagnoses, lifestyle characteristics such as exercise or use of alcohol or tobacco, or estimated IQ.

Table 2 summarizes serial position scores for AD children and Controls as well as standard AVLT scores. On average, AD children recalled a significantly smaller percentage of items from the primacy region than control participants, $F(1, 775) = 5.51$, $p = .019$. There was a trend for AD children to recall a smaller percentage of middle region items than controls, $F(1, 775) = 3.53$, $p = .061$, but there was no difference in recall of recency items for the two groups, $F(1, 775) = 0.85$, $p = .356$. When differences in percentages recalled from different regions were compared, the relative dominance of recency effects for AD children as opposed to controls was confirmed for both the recency-primacy comparison, $F(1, 775) = 5.54$, $p = .019$, and the recency-middle region comparison, $F(1, 775) = 4.99$, $p = .026$. There were no significant differences between AD children and controls on standard AVLT summary scores (total words recalled during learning and delayed recall).

Preliminary analyses indicated that there were no significant associations between serial position scores and APOE allele status, depression ratings, blood pressure, or cholesterol levels. However, ANCOVAs were repeated, including these factors as predictors, because each has been associated with memory performance in prior studies. There were no significant differences on serial position measures or AVLT summary scores between APOE ε4 carriers and non-carriers (all p's $\geq .20$) and no significant interactions between APOE ε4 status and family history group (all p's $\geq .30$). When systolic and diastolic blood pressure and cholesterol level were included as covariates in the ANCOVAs, the pattern of outcomes as shown in Table 2 was essentially unchanged. For example, compared to controls, AD children recalled a smaller percentage of items from the primacy region ($p = .03$), and the percent difference scores for recency-primacy and recency-middle region also remained significant ($p \leq .03$). The same pattern of results was obtained when CES-D score was included as a covariate; i.e., AD children recalled significantly less from the primacy region ($p = .03$) and had larger recency-primacy

and recency-middle region percent difference scores than controls ($p \leq .04$). There were no significant family history effects on standard AVLT summary scores when cardiovascular risk factors and CES-D scores were included as covariates.

Additional ANCOVAs were performed to determine whether AD children whose parents were diagnosed with AD in different ways (autopsy, UW memory clinic assessment, or medical record review) also differed in AVLT performance. There were no significant effects of qualifying method on serial position measures or AVLT summary scores (all p's >.57). We also repeated ANCOVAs, limiting the sample of AD children to those whose parents had onset of AD symptoms ≤ 70 years for affected fathers or ≤ 75 years for affected mothers (the ages to which controls' parents had to have survived without dementia symptoms). There were 325 AD children whose parents developed AD at these relatively young ages. When this subgroup was compared to controls, the main effect for family history group remained significant for the recency-primacy percent difference ($p = .03$) and the recency-middle region percent difference ($p = .01$), although results for percentages retrieved from individual regions were no longer statistically significant. There were no significant differences between AD children and controls on the standard AVLT summary scores.

4. Discussion

The primary finding of this investigation is the identification of subtle but significant differences in serial position recall among asymptomatic persons at risk for AD compared to healthy controls, despite comparable overall memory performance (total words recalled). The nature and pattern of the differences indicate greater reliance on immediate memory at the expense of episodic memory in the at-risk subjects, a pattern that has been shown to be associated with hippocampal dysfunction and repeatedly observed among patients in early stages of AD, but exhibited here in a milder form.

It is possible that the findings of this study represent the first cognitive changes of preclinical AD, and that differences in serial position profiles for AD children and controls will increase as the population ages. The relative prominence of recency in memory among AD children is consistent with the hypothesis that early declines in function in the hippocampus and entorhinal cortex in preclinical AD [16,17] may be masked for a time by reliance on compensatory strategies or recruitment of other brain regions to maintain memory performance [30,31]. If this is the case, we would expect to see progression of the serial position effects in subsequent waves of testing, without changes in total words recalled; as underlying disease progresses, however, overall recall performance would eventually be expected to decline. At present, as might be expected in a middle-aged asymptomatic cohort, the effect sizes of the serial position findings are small and not clinically meaningful. Follow-up is planned to determine what significance, if any, serial position patterns may have for preclinical detection of AD.

A strength of this investigation is that it utilized a rarely studied cohort of middle-aged persons who have one or both parents diagnosed with AD. This study was undertaken because little is known about how and when first symptoms of dementia are expressed in this important at-risk group, or about the genetic or environmental factors that underlie the presumed increased risk. The few prospective studies that have been conducted on AD relatives have involved mixed samples of siblings and children and small sample sizes [32,33] or lack comparison groups of individuals without a family history of AD [22–24]. Also, the focus of the most recent of these studies [22–24] has been on documenting associations between cognitive performance and APOE, rather than examining family history as a potential predictor of preclinical cognitive patterns.

Our results suggest a specific effect of family history on preclinical memory performance which is independent of APOE. Two recent functional neuroimaging studies, one based on data from a subsample of WRAP participants [4] and the other on an independent family history cohort [34], have reported hippocampal activation patterns that are unique for family history, and like our cognitive findings, are independent of APOE genotype. These neuroimaging results provide a possible neurobiological basis for the subtle differences we observed in serial position patterns for AD children, since the hippocampus is crucial for the episodic memory processes necessary for normal primacy effects. Taken together, these findings suggest that an unknown family history factor may be an important confounder in most studies of preclinical AD.

The absence of APOE effects on memory performance was somewhat surprising, since several previous studies of cognitively intact samples [35] have found small, statistically significant, APOE effects. However, other recent investigations, including the largest prospective study of young and middle-aged adults reported to date [36] have found no effect of APOE on cognition.

We noted the possibility that mild memory deficits observed at midlife could be a prodrome of AD, that is, a pattern of cognitive performance reflecting very early symptoms of underlying AD pathology. An alternative possibility is that mild memory problems at midlife reflect a distinctive cognitive phenotype, that is, a set of neurocognitive characteristics that may or may not be progressive and may not necessarily be predictive of AD. Greenwood and colleagues [23] have suggested that the attentional deficits that they have observed in middle-aged persons in relation to APOE genotype may be more consistent with a cognitive phenotype than an AD prodrome. Unlike the findings of Greenwood and colleagues, the serial position changes reported in this study are characteristic of AD and are less likely to represent a non-AD phenotype. Clearly, however, longitudinal data will be needed to establish a static or progressive pattern for the serial position findings and the relationship of this pattern to AD risk.

Whether alterations in serial position recall, a known correlate of AD, have promise as a marker of preclinical AD remains to be determined. The WRAP project and other studies of AD children which are now underway (e.g., the Washington University Adult Children Study [37] and as yet unpublished findings from the Framingham Offspring Study) will provide the data to address this question. It is unlikely that any single cognitive predictor will prove sufficiently discriminating at preclinical stages to identify individuals at risk of developing AD; however, combining early cognitive indicators with neuroimaging results or other biological markers such as the amyloid-binding ligand, Pittsburgh Compound-B [38] may allow for the identification of groups of individuals who are at risk for the disease. This risk profiling would allow for prevention trials directed at slowing change in cognitive or biological markers of AD in asymptomatic persons.

This study has several limitations. Because autopsy confirmation of AD in a parent was available for only 10% of participants in the AD children group, there is a possibility of error in parental diagnoses of AD. We attempted to minimize any diagnostic misclassification by reviewing parental medical records to confirm the diagnosis of AD using NINCDS-ADRDA criteria. Another limitation concerns the relatively young ages of dementia-free survival that we required of control subjects' parents. We were concerned that requiring both parents to survive without signs of dementia to age 85, for example, would severely limit the number of eligible controls. As additional autopsy information is obtained on AD children's parents, and as control subjects' parents continue to age, the accuracy of group membership can be clarified to some extent. As is the case with any prospective study of preclinical AD, we cannot be

certain which children of AD parents will one day develop this condition and which will remain free of AD as they age. Longitudinal follow-up is planned.

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Table 1

Characteristics of AD children and controls.

Characteristic	AD children (n = 623)	Controls (n = 157)
Demographics		
Age - years	52.37 (6.51)	55.70 (5.86)*
Education - years	16.00 (2.68)	16.57 (2.89)
Female gender - % (n)	72 (450)	63 (99)
White/Caucasian - % (n)	98 (612)	99 (155)
APOE ε4 allele - % (n)	44 (274)	15 (23)*
Health History		
Heart disease - % (n)	10 (62)	10 (16)
Hypertension - % (n)	16 (99)	20 (31)
High cholesterol - % (n)	32 (197)	31 (48)
Diabetes - % (n)	2 (14)	1 (2)
Stroke - % (n)	1 (7)	1 (1)
Head injury - % (n)	13 (79)	10 (15)
Neurological disorder - % (n)	6 (36)	1 (2)
Laboratory values/vitals		
Homocysteine	7.95 (2.30)	7.71 (2.40)
Creatinine	0.94 (0.17)	0.98 (0.17)
Folic acid ≤20 - % (n)	47 (290)	51 (80)
Cholesterol (nonfasting)	209.68 (34.93)	199.55 (34.79)*
Body Mass Index	28.46 (6.00)	28.01 (5.55)
Systolic blood pressure	132.13 (16.81)	126.46 (17.02)*
Diastolic blood pressure	76.44 (9.76)	73.53 (10.28)*
Life style variables		
Exercise frequency per month†	3.63 (0.71)	3.80 (0.53)
Alcohol use per week‡	1.21 (0.41)	1.21 (0.41)
Smoked tobacco in past month - % (n)	8 (51)	10 (6)
Depression rating (CESD)	6.51 (6.61)	4.49 (4.55)*
IQ estimate (WASI)	112.80 (9.26)	114.75 (8.69)

Note: Values are means (SDs) unless otherwise indicated.

WRAP = participants with one or both parents diagnosed with Alzheimer's disease; controls = participants with parents free of dementia to age 75

CESD = Centers for Disease Control Depression scale; WASI = Wechsler Abbreviated Scale of Intelligence

*$p < .0004$ (Bonferroni correction for multiple comparisons with α at .01).

†1 = never, 2 = once per month, 3 = 1 to 4 times per month, 4 = > once per week

‡0 = never, 1 = < once per week, 2 = 1 to 2 days, 3 = 3 to 4 days, 4 = 5 to 6 days, 5 = daily

Table 2

Word list learning of AD children and controls.

Measure	AD children (n = 623)	Controls (n = 157)
AVLT serial position scores		
Primacy (% recalled)	72.96 (14.63)	74.55 (14.16)*
Middle region (% recalled)	60.19 (15.24)	61.24 (15.59)
Recency (% recalled)	77.69 (13.01)	76.43 (13.28)
Recency – Primacy (difference in % recalled)	4.73 (19.18)	1.88 (19.31)*
Recency – Middle region (difference in % recalled)	17.50 (17.65)	15.20 (17.96)*
Standard AVLT scores		
AVLT learning total (sum of 5 trials)	51.41 (8.08)	51.89 (8.08)
AVLT delayed recall	10.65 (2.93)	10.47 (2.75)

Note: Values are means (SD). Age, education, and gender were covaried in statistical comparisons.

AVLT = Rey Auditory Verbal Learning Test

* $p < .05$