

Differential Associations Between Entorhinal and Hippocampal Volumes and Memory Performance in Older Adults

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Magnetic resonance imaging-derived entorhinal and hippocampal volumes were measured in 14 nondemented, community-dwelling older adults. Participants were selected so that memory scores from 2 years prior to scanning varied widely but were not deficient relative to age-appropriate norms. A median split of these memory scores defined high-memory and low-memory groups. Verbal memory scores at the time of imaging were lower, and entorhinal and hippocampal volumes were smaller, in the low-memory group than in the high-memory group. Left entorhinal cortex volume showed the strongest correlation ($r = .79$) with immediate recall of word lists. Left hippocampal volume showed the strongest correlation ($r = .57$) with delayed paragraph recall. These results suggest that entorhinal and hippocampal volumes are related to individual differences in dissociable kinds of memory performance among healthy older adults.

Declarative (Cohen & Squire, 1981), or consciously recollected, memory for episodes (Tulving, 2002) declines in many otherwise

healthy older adults (Craik, 1994; Koivisto et al., 1995; Petersen, Smith, Kokmen, Ivnik, & Tangalos, 1992; Small, Stern, Tang, & Mayeux, 1999). The exact neural structures involved in this mild age-related decline are under investigation (Cabeza, 2001; Prull, Gabrieli, & Bunge, 2000; Raz, 2000). Multiple brain regions participate in declarative memory (e.g. Eichenbaum, 2000), but pathology in the medial temporal lobe (MTL) is associated with particularly severe memory failure (Rempel-Clower, Zola, Squire, & Amaral, 1996; Scoville & Milner, 1957). The MTL has multiple pathways and structures, the disruption of which results in memory impairments (Hampson, Hedberg, & Deadwyler, 2000; Leonard, Amaral, Squire, & Zola-Morgan, 1995; Squire & Zola-Morgan, 1991).

Several structures within the MTL region have been implicated in age-related declines in declarative memory (e.g., Geinisman, deToledo-Morrell, Morrell, & Heller, 1995; Small, Nava, Perera, Delapez, & Stern, 2000), with the most evidence pointing toward the hippocampal formation and the entorhinal cortex. Entorhinal cortex and hippocampal formation are adjacent MTL structures that are strongly connected and essential for declarative memory (Squire & Zola-Morgan, 1991). Entorhinal cortex, located in the anterior parahippocampal gyrus, receives projections from many neocortical association and limbic areas and in turn gives rise to the perforant path, the major cortical excitatory input to the hippocampal formation. The goal of this study was to examine

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whether there is a relation, in healthy older people, between memory performance and volumes of the hippocampal formation and entorhinal cortex.

Several studies have examined the association between hippocampal volume and memory performance in older adults, but few have examined the relation between entorhinal volume and memory performance. In fact, only one study has reported a correlation between entorhinal volume and memory performance in nondemented older adults (deToledo-Morrell, Goncharova, Dickerson, Wilson, & Bennett, 2000). This likely reflects the fact that reliable quantitative protocols for the entorhinal cortex were developed more recently (Bobinski et al., 1999; Goncharova, Dickerson, Stoub, & deToledo-Morrell, 2001; Honeycutt et al., 1998; Insausti et al., 1998) than such protocols for hippocampal volumes. Magnetic resonance imaging (MRI)-derived hippocampal volumes have correlated with declarative memory scores in demented people with Alzheimer's disease (AD; Convit et al., 1997; deToledo-Morrell, Dickerson, et al., 2000; Heun et al., 1997; Kohler et al., 1998; Petersen et al., 2000; Wilson et al., 1996), nondemented individuals with focal cognitive impairments, and individuals with intact overall cognition (deToledo-Morrell, Goncharova, et al., 2000; Golomb et al., 1994; Hackert et al., 2002). Left hippocampal volume was the best predictor of verbal recall in patients with mild AD (deToledo-Morrell, Dickerson, et al., 2000). This finding suggests that right and left medial temporal lobes process different kinds of material, with the left hippocampus more selective for verbal information.

Because the entorhinal cortex and hippocampus are so interconnected, it is unlikely that there would be a complete dissociation between their relations to various aspects of declarative memory. There are, however, suggestions in the literature that the two MTL structures may subservise memory processes that are disproportionately important for different aspects of declarative memory. Two candidate aspects are the duration of the study-test interval and the nature of the to-be-remembered material. Entorhinal cortex has been associated more closely with memory after shorter retention intervals than after longer retention intervals, by virtue of correlations with volume in humans (deToledo-Morrell, Goncharova, et al., 2000) and by virtue of lesions in rats (Hampson, Jarrard, & Deadwyler, 1999). Specifically, on nonmatching-to-sample tasks in rats, entorhinal cortex lesions lead to increased proactive interference with delays of less than 10 s, whereas hippocampal lesions lead to errors with longer delays (Hampson et al., 1999; Squire & Zola-Morgan, 1991). Further, in humans, hippocampal volume is correlated more with delayed recall than with immediate recall in patients with AD (deToledo-Morrell, Dickerson, et al., 2000; Kohler et al., 1998; Petersen et al., 2000; Wilson et al., 1996), people with mild cognitive impairment (MCI; Convit et al., 1997), and healthy older adults (Golomb et al., 1994). Differential contribution of the hippocampus to different kinds of verbal material is demonstrated by evidence that hippocampal volume in AD is correlated more with memory for a meaningful paragraph than memory for a list of unrelated words (Wilson et al., 1996). Therefore, the present study tested memory for both kinds of verbal materials at both shorter and longer study-test intervals.

The goal of the present study was to examine whether hippocampal or entorhinal volumes are more strongly related to individual differences in various verbal declarative memory tasks among healthy older adults. We selected a group of 14 community-

dwelling older adults from a sample of 120 older adults who participated in a memory training study 10 years prior to the current study (1991-1993). In order to have sufficient variability in performance to detect a relationship between brain structures and performance, we selected participants across a wide range of memory abilities, on the basis of an aggregate score from memory screening tests administered 2 years prior to the current study. Participants were divided into two groups (low-memory and high-memory) based on a median split of the aggregate memory screening scores. The two measures of declarative memory, taken at the time of scanning, were the Verbal List Learning Test from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) and the East Boston Memory Test (EBMT; Albert et al., 1991). The CERAD has demonstrated reliability, validity, and normative standardization with regard to pathological memory decline (Morris et al., 1989, 1993; Welsh et al., 1994). The EBMT was also administered because scores on this test were correlated with hippocampal volume in patients with AD (Wilson et al., 1996).

As in the study by deToledo-Morrell, Goncharova, et al. (2000), the protocol for volumetric measurement of the entorhinal cortex developed by Goncharova et al. (2001) was applied. This protocol optimizes the independent measurement of adjacent hippocampal and entorhinal regions by delineating hippocampal and entorhinal volumes from the same set of coronal sections, taken perpendicular to the long axis of the hippocampus. Although it is likely that both MTL structures are affected by aging and disease and thus correlate with declarative memory tasks to some degree, guarding against overlapping regions of interest is crucial for examining differential relationships.

Method

Participants

Fourteen healthy older adults provided informed consent and were paid for participation in imaging and cognitive testing. Participants were recruited from a group of 120 individuals who had undergone memory training and cognitive screening at the Palo Alto Veterans Administration Health Care System 8 years prior to the current study (McKittrick et al., 1999). Upon entry to the memory training program, participants were given cognitive and psychiatric testing (Time 1). In addition, participants completed the Memory Functioning Questionnaire, a standardized self-report measure of memory ability (Gilewski, Zelinski, & Schaie, 1990; Zelinski, Gilewski, & Anthony-Bergstone, 1990). These people were brought back 5 years later, and memory measures were repeated (Time 2; O'Hara et al., 1998). The current study was conducted 2 years after Time 2 memory testing. After health screening and matching for demographic variables, 14 participants were selected so that their aggregate memory scores covered a range of memory abilities. The group of participants was divided, on the basis of a median split of memory scores from Time 2, into high- and low-memory groups (see Table 1; scores from Time 1 are also presented to provide information on relative memory status across time for the two groups). All 14 participants were Caucasian, and Table 2 reports demographic variables and scores on neuropsychological tests.

Memory performance selection criteria. Memory tests administered at both Time 1 (1991-1993) and Time 2 (1995-1997, approximately 5 years later) included the Wechsler Memory Scale subtests Logical Memory (WMS-LMI) and Paired Associates (WMS-PAI) immediate recall (Wechsler, 1956), the Benton Visual Retention Test-Revised (Benton, 1974), and a locally developed memory recall task. In this memory recall task, participants studied a list of 16 words for 4 min. After a 5-min

Table 1
Mean (\pm SD) Raw Scores Used for Participant Selection

Measure	Time 1		Time 2		<i>p</i>	
	Low memory	High memory	Low memory	High memory	Time 1	Time 2
Benton Visual Retention Test—Revised	6.29 \pm 0.75	7.00 \pm 1.63	6.14 \pm 0.90	6.71 \pm 1.25	.31	.34
WMS Verbal Paired Associates, Immediate	23.14 \pm 2.12	26.71 \pm 3.15	22.71 \pm 2.50	27.57 \pm 1.99	.02*	.01*
WMS Logical Memory, Immediate	13.36 \pm 3.29	15.43 \pm 4.51	14.71 \pm 4.42	22.21 \pm 4.72	.25	.01*
Memory recall	6.86 \pm 2.80	10.00 \pm 4.55	6.86 \pm 2.27	11.00 \pm 2.45	.14	.01*

Note. WMS = Wechsler Memory Scale.

* $p < .05$, *t* tests comparing high- and low-memory participants at the two time points.

distractor task during which participants completed word puzzles, they were asked to recall the words in the order originally presented (Brooks, Friedman, Pearman, Gray, & Yesavage, 1999). An average proportion correct on these four measures at Time 2 was used to rank participants in terms of memory functioning. This aggregate memory score, along with health screening and demographic matching, served as a basis for selection of the participants in the current study. The reason for choosing Time 2 was that it was the most recent measure available for selection and would thus most likely reflect current individual differences in memory ability. Imaging occurred approximately 2 years after these memory tests. Participants were initially selected from the top and bottom thirds of the distribution of the aggregate memory scores at Time 2. They were also selected so that they could participate in a functional MRI study. Selection stopped when 8 high- and 8 low-functioning older adults were chosen (these were all the participants who met all criteria for structural and functional imaging, were in good health, were willing to participate, and were not near the mean of the overall group on memory test scores). For technical reasons, structural MRIs of sufficient quality were not available from 2 of these participants in the low-memory group. Rather than having unequal sample sizes, the high- and low-memory groups were divided into two groups of 7 on the basis of a median split of the aggregate memory score (high-memory, low-memory). Thus, the final high- and low-memory groups had nonoverlapping aggregate memory scores but did not represent the extremes of the entire sample. Raw scores and standard deviations of the scores that served as the basis for selection are presented in Table 1. Participant selection was based only on Time 2 scores, but the low-memory group scored significantly lower on the WMS-PAI at Time 1 as well, $t(12) = 2.49$, $p < .05$. Analyses of variance of each measure (Group \times Time) revealed an interaction for logical memory, $F(1, 12) = 4.77$, $p < .05$, such that the difference between high- and low-memory groups increased from Time 1 to Time 2. The scores of the high-memory group actually improved on some measures from Time 1 to Time 2, a practice effect that is commonly observed in longitudinal studies (e.g., Wilson et al., 2002) and that reflects

declarative memory savings from the initial testing. Main effects of group (low-memory performed worse than high-memory) were observed for the WMS-PAI, $F(1, 12) = 21.58$, $p < .001$, and memory recall, $F(1, 12) = 9.23$, $p < .05$, at Time 2.

Other selection criteria. Participants were selected so that they were community dwelling and denied any history of neurological or psychiatric illness, or significant health problems that involved vascular risk factors. Because the participants also underwent a functional MRI study (Rosen et al., 2002), potential participants were excluded if an MRI could not be safely performed (e.g., ferromagnetic implants), if they were unwilling to participate in brain imaging, or if they were taking any medication that had the potential for altering the vasculature of the brain (and, potentially, the hemodynamic response function) or cognitive-emotional functioning (e.g., antihypertensive medication or antidepressants). This additional constraint excluded many potential participants. Participants were also matched for age and education. All participants selected for the current study were right-handed (Oldfield, 1971) and scored above 26 on the Mini-Mental Status Examination (MMSE; Folstein, Folstein, & McHugh, 1975) during the current study.

Follow-up contacts. Two years after MRI scanning, 12 of the 14 participants (6 from each group) were reached by telephone interview. All 12 were still living independently, and none reported any formal diagnosis of AD or other dementia, or any memory complaint or significant disability beyond that expected during normal aging.

Procedure

Acquisition and quantification of MRI data. MRI imaging was performed at the Lucas Center at Stanford University on a 1.5-Tesla GE Signa scanner (Rev. 5.8; GE Medical Systems, Milwaukee, WI) equipped with the GE custom receive-only whole-head coil. Head movement was minimized by using a "bite-bar" formed from each participant's dental impression. Axial spoiled GRASS (gradient-recalled acquisition at steady state)

Table 2
Demographic and Cognitive Functioning Measures for High- and Low-Memory Performers

Measure	Low memory	High memory	<i>p</i>
Demographic			
<i>n</i>	7	7	<i>ns</i>
Age	71.3 (5.1)	68.7 (7.3)	<i>ns</i>
Health rating (10 = excellent)	8.00 (2.0)	7.93 (2.2)	<i>ns</i>
Years of education	16.57 (1.8)	15.71 (1.5)	<i>ns</i>
Gender	5 F, 2 M	7 F, 0 M	
General cognitive function/ability			
MMSE	29 (1.2)	29 (0.6)	<i>ns</i>

Note. Standard deviations are listed in parentheses where appropriate. F = female; M = male; MMSE = Mini-Mental Status Examination.

images were acquired with the following parameters: 124 slices, 1.5 mm thick, in-plane resolution = .9375, 24-cm FOV, TE = 2 s, TR = 11.1 s, 1 NEX, flip angle = 15.

Volumetric measurements were performed at Rush-Presbyterian-St. Luke's Medical Center by the fourth author, Travis Stoub (TRS), and a collaborator, Leyla deToledo-Morrell (LdeT-M), both of whom were blind to psychometric and demographic information. Regions of interest were manually segmented with the Analyze program (Version 3; Mayo Clinic Foundation, Rochester, MN) running on a Silicon Graphics computer. To correct for individual differences in brain size, entorhinal and hippocampal volumes were normalized by dividing each measure by the total intracranial volume derived from sagittally cut slices. To compute intracranial volume, the inner table of the cranium was traced in consecutive sagittal sections spanning the entire brain. At the level of the foramen magnum, a straight line was drawn from the inner surface of the clivus to the most anterior extension of the occipital bone.

Both entorhinal and hippocampal volumes were computed separately for the right and left hemispheres from coronal slices taken perpendicular to the long axis of the hippocampal formation, by means of protocols developed in our laboratory (Goncharova et al., 2001; see Figure 1). For this purpose, axially acquired scans were resliced as 1.6-mm coronal images. For the entorhinal cortex, tracing began with the first section in which the gyrus ambiens, amygdala, and the white matter of the parahippocampal gyrus appeared visible. The superomedial border in rostral sections was the sulcus semiannularis; and in caudal sections, the subiculum. The shoulder of the collateral (or rhinal) sulcus was used as the lateral border (see Figure 1). This border was constructed by drawing a straight line from the most inferior point of the white matter to the most inferior tip of the gray matter. The latter is somewhat of a conservative criterion that allowed consistency in tracings and avoided the use of different lateral borders, depending on individual differences in the depth of the collateral sulcus (e.g., Insausti et al., 1998). The last section traced was three 1.6-mm slices rostral to the image in which the lateral geniculate nucleus first appeared visible. Validation procedures, as well as intra- and interrater reliability scores for entorhinal cortex measurements, are described in Goncharova et al. (2001).

The protocol and validation procedures used for quantifying hippocampal volume were published previously (deToledo-Morrell et al., 1997; Wilson et al., 1996). Tracings of the hippocampal formation started with the first section where the hippocampal formation could be clearly differentiated from the amygdala, and included the fimbria, dentate gyrus, the hippocampus proper, and the subiculum. All sections in which the hippocampus could be clearly seen without partial volume averaging were included. The last section traced was the one immediately prior to the full appearance of the fornix. All tracings were performed by TRS (who was trained to be within 95% of LdeT-M) and were checked, slice by slice, by LdeT-M. Inter- and intrarater correlation coefficients for TRS, based on a sample of 10, were .97 and .97, respectively, for the hippocampal formation and .99 and .99, respectively, for the entorhinal cortex.

Neuropsychological screening. Participants underwent cognitive testing within 2 weeks of the imaging studies. These tests included measures of general cognitive status (MMSE; Folstein et al., 1975), single word reading (the American modification of the National Adult Reading Test [AMNART]; Grober & Sliwinski, 1991; Nelson & O'Connell, 1978; G. E. Smith, Bohac, Ivnik, & Malec, 1997; Spreen & Strauss, 1998), working memory (Listening Span; Salthouse & Babcock, 1991), perceptual-motor speed (Symbol Digit Modalities Test; A. Smith, 1973), short term memory (Wechsler Adult Intelligence Scale—Revised Digit Span subtest, Wechsler, 1981), and the Category Fluency and Constructional Praxis measures from the CERAD (Morris et al., 1989).

Memory measures. Two types of verbal memory tests were administered: paragraph recall (EBMT) and word list learning (CERAD). Immediate and delayed recall scores were obtained for both measures, but the interval for delayed recall was brief (approximately 5 min). During the EBMT paragraph recall test, participants listened to and recalled short stories (Albert et al., 1991). The CERAD word list learning task has several components (Morris et al., 1993; Welsh et al., 1994), including the Word List Memory (WLM) score, a measure of immediate free recall. Participants completed three trials in which they read a list of 10 words in different orders. After each reading, participants recalled as many words as possible. The WLM score was the sum of the number of words recalled across all three trials (maximum score of 30). There was approximately a 5-min delay, during which the Symbol Digit Modalities Test was administered. After the delay, measures of free recall (Word List Delayed Recall), and yes-no forced choice recognition (Word List Recognition) were obtained. The Savings score was a measure of the amount of information retained over a delay ($[\text{Delay} \div \text{Trial } 3] \times 100$).

Results

Neuropsychological Screening and Memory Performance

The high- and low-memory groups did not differ significantly on any measures except those of declarative memory (see Table 3). The AMNART was used as an estimate of verbal intellectual abilities. The high- and low-memory groups did not differ with regard to estimated high average Verbal IQ (high-memory and low-memory estimated Verbal IQ = 115) and number of years of education (all college graduates). Standard scores are also presented for measures in order to convey where the groups scored relative to the normative population of older adults. Standard CERAD measures are corrected for age, education, and gender.

The only cognitive measures on which the two groups differed were declarative memory measures (Table 3). High-memory participants scored significantly higher than low-memory participants

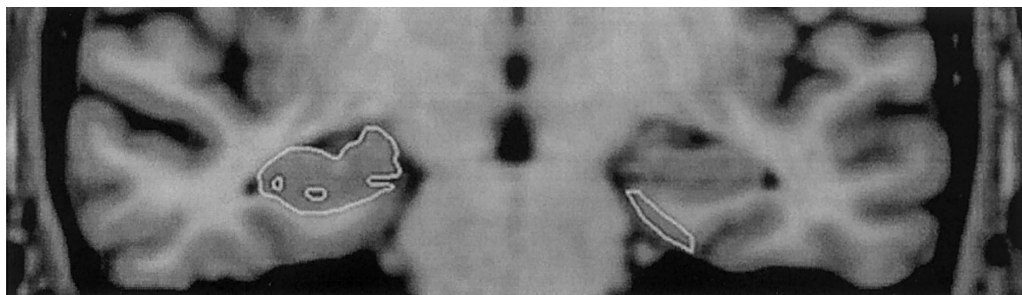


Figure 1. Regions of interest. The hippocampal formation is outlined on the left, and the entorhinal cortex is outlined on the right.

Table 3
Neuropsychological Results Comparing High- and Low-Memory Performers

Measures	Low memory			High memory			<i>p</i>	Effect size
	<i>M</i>	<i>SD</i>	<i>SS</i>	<i>M</i>	<i>SD</i>	<i>SS</i>		
Estimated IQ								
AMNART correct/est. VIQ (max = 45) ^a	38.4	2.8	115	39.1	3.9	115	<i>ns</i>	0.20
Attention/executive/speed								
Symbol Digit Modalities Test ^a	47.0	5.4	93	52.1	5.5	99	<i>ns</i>	0.20
WAIS-R Digit Span (ACS) sum raw ^b	14.6	2.4	12	14.9	2.1	11	<i>ns</i>	0.12
Listening Span	2.1	0.4		2.3	0.8		<i>ns</i>	0.23
CERAD Category Fluency ^c	18.1	0.8	104	18.0	1.0	103	<i>ns</i>	0.09
Memory								
CERAD 10-word list ^c								
WLM Immediate (3 trials, max = 30)	18.1	3.9		22.3	1.6		.031	1.39
Trial 1	4.0	1.0	86	5.3	0.8	96		
Trial 2	6.6	1.7	90	8.3	0.9	107		
Trial 3	7.6	2.1	92	8.7	0.8	102		
Delayed recall (1 trial, max = 10; <i>SS</i>)	6.1	2.5	91	8.6	1.0	110	.047	1.26
% savings (max = 100)	79.5	13.5	94	98.6	10.4	110		
Recognition (hits/false alarms, max = 10)	9.3	1.1		9.9	0.4	115	<i>ns</i>	0.68
East Boston Memory Test								
Immediate (proportion correct)	0.73	0.08		0.85	0.10		.032	1.30
Delayed (proportion correct)	0.71	0.13		0.86	0.10		.048	1.18
Construction (max = 4/4)	4			4			<i>ns</i>	

Note. Results of cognitive testing. Standardized scores (*SS*) are shown where appropriate to indicate how these participants perform relative to the population of controls. WAIS-R digit span age corrected score (ACS) has a mean of 10 and a standard deviation of 3. AMNART Verbal IQ estimates (est. VIQ) were generated by using the regression equation of Smith et al. (1997). All other standard scores listed here have a mean of 100 and a standard deviation of 15. The *p* values at the right reflect uncorrected *t* test comparisons. AMNART = National Adult Reading Test, American version; WAIS-R = Wechsler Adult Intelligence Scale—Revised; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; WLM = Word List Memory; max = maximum.

^a Normative data are with reference to age- and education-matched reference groups. ^b Normative data are with reference to age-matched reference group. ^c Normative data are with reference to age-, education-, and gender-matched reference groups.

on all measures of immediate and delayed recall. The groups did not differ reliably in recognition, on which scores may have been limited by ceiling performance. Relative to normative CERAD scores, the high-memory group performed in the average to high average range, whereas the low-memory group generally performed in the low average to the low end of the average range. The difference between estimated IQ and memory performance appears to reach the 1.5 *SD* discrepancy proposed by Petersen et al. as a psychometric criterion for amnesic MCI (Petersen et al., 1999, 2001; G. E. Smith et al., 1996).

Self-Perception of Memory Ability

Overall self reported memory complaints did not differ between the groups. There was a trend toward significantly more memory complaints for the low-memory group on Factor 1 of the Memory Functioning Questionnaire, $t(11) = 1.49, p < .08$ (one tailed). Two subtests within that factor were significantly greater in the low-memory group than in the high-memory group: Frequency of Forgetting During Reading Newspapers and Magazines, $t(11) = 2.82, p < .05$, and Remembering Past Events, $t(11) = 2.91, p < .05$. In addition to being administered the Memory Functioning Questionnaire, participants were asked directly for self-assessments of their memory abilities. Twelve participants said "yes" to the question "Do you have a problem with your memory?" The only exceptions were 2 people in the low-memory group. Few participants said "yes" to "Do you feel you have more

problems with memory than most?" (3/7 high-memory, 0/7 low-memory).

Entorhinal and Hippocampal Volumes

Separate analyses of variance were conducted for entorhinal and for hippocampal volumes. Each analysis included a between-subjects factor of group (high-memory vs. low-memory) and a within-subject factor of hemisphere (right vs. left). Volumes of the hippocampus, $F(1, 12) = 12.29, p < .01$, and entorhinal cortex, $F(1, 12) = 12.66, p < .01$, were larger in the high-memory participants than in the low-memory participants (see Table 4). There were no other significant main effects or interactions. *t* tests confirmed that there was a significant difference between high- and low-memory groups in both left, $t(12) = 3.93, p < .01$, and right, $t(12) = 2.37, p < .05$, entorhinal cortex volume. The two groups also differed in left, $t(12) = 3.05, p < .01$, and right, $t(12) = 2.88, p < .05$, hippocampal volumes.

Relationship of MTL Volumes to Memory Measures

The relation between MTL volumes and memory performances was examined with four separate stepwise forward regression analyses with normalized volumes. In each of the analyses, one of the four different memory measures (WLM and EBMT, immediate and delayed recall) served as a dependent variable, and the four regions (right and left, hippocampal and entorhinal cortex) served

Table 4
Normalized Volumetric Comparisons of High- and Low-Memory Performers

Region	High memory		Low memory	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Entorhinal cortex				
Left	691	56.9	585	42.8
Right	701	62.4	600	93.1
Hippocampus				
Left	2,198	191.0	1,871	210.0
Right	2,261	170.0	2,028	131.0

Note. Volumetric measurements were divided by the intracranial volumes (ICVs) to provide normalized scores ([absolute volume of structure in mm³ ÷ ICV in mm³] × 1000). All values are greater in the high-memory groups than in the low-memory groups. Analyses of variance and confirmatory *t* tests are discussed in the Results section.

as independent variables (predictors). Left entorhinal cortex volume was the best predictor of performance on the WLM (CERAD immediate word list recall; $R = .79, p < .001$). Left entorhinal cortex volume was also the best predictor of performance on the WLR (CERAD delayed word list recall; $R = .66, p = .01$). In contrast, left hippocampal volume was the best predictor of EBMT delayed paragraph recall ($R = .57, p = .032$). Although left hippocampal volume also seemed to be the best predictor of EBMT immediate paragraph recall ($R = .52, p = .058$), this was only a trend. Failure to reach significance was likely due to inadequate power (with $\alpha = .05$, power = 0.476); however, the effect was clearly weaker than the other results. MTL volumes were correlated with each other and with multiple memory scores (see Table 5). Scatter plots of the correlation between WLM and entorhinal cortex volume and the correlation between delayed EBMT and hippocampal volume are displayed in Figure 2.

Discussion

Entorhinal and hippocampal volumes were related to individual differences in memory performance among healthy older adults. Individuals who scored better on memory measures (high-memory group) had significantly larger entorhinal and hippocampal volumes than those who scored worse on memory measures (low-memory group). These verbal declarative memory and MTL volume differences occurred despite the lack of significant differences between the groups in age, education, and non-mnemonic cognitive measures. In addition, there was no evidence of gross functional impairment in either group in everyday living over the approximately 10 years they were followed. In this sense, all the older adults appear to be nondemented. Further, there was some specificity in the relations between MTL structures and test performance within the domain of verbal declarative memory. Left entorhinal volume correlated most strongly with immediate verbal recall on the CERAD WLM task, and, in general, more strongly with list recall than with paragraph recall. Left hippocampal volume correlated most strongly with EBMT delayed paragraph recall and, in general, more strongly with paragraph recall than with list recall. The correlational results are strikingly similar to prior findings (deToledo-Morrell, Goncharova, et al., 2000; Wilson et al., 1996). In the study by Wilson et al., EBMT paragraph recall, but not list learning, correlated with hippocampal volume, suggesting that the hippocampus plays a greater role in paragraph memory than in list memory. In the study by deToledo-Morrell et al. (deToledo-Morrell, Goncharova, et al., 2000), which assessed verbal memory recall by using the “controlled learning” task (Buschke & Grober, 1986; Grober & Buschke, 1987), entorhinal volume correlated most strongly with immediate recall, whereas hippocampal volume correlated with delayed recall. This suggests that the absence or presence of a delay alters the relative importance of the entorhinal cortex and hippocampus for recall. The current study extends both of those results in an important way by

Table 5
Correlations Between Hippocampal and Entorhinal Cortex Volumes and CERAD Memory Recall (WLM and EBMT) Scores

Measure	Hippocampus		Entorhinal cortex		Word list	
	Right	Left	Right	Left	Immediate	Delay
Hippocampus						
Right	—	.67*	.56*	.49	.37	.33
Left	.67*	—	.33	.40	.26	.06
Entorhinal cortex						
Right	.56*	.33	—	.62*	.52	.65*
Left	.49	.40	.62*	—	.79*	.66*
Word list						
Immediate	.37	.26	.52	.79*	—	.76*
Delay	.33	.06	.65*	.66*	.76*	—
Paragraph recall						
Immediate	.51	.52	.27	.24	.11	.13
Delay	.40	.57*	.38	.39	.37	.31

Note. CERAD = Consortium to Establish a Registry for Alzheimer’s Disease; WLM = Word List Memory; EBMT = East Boston Memory Test.
* $p < .05$.

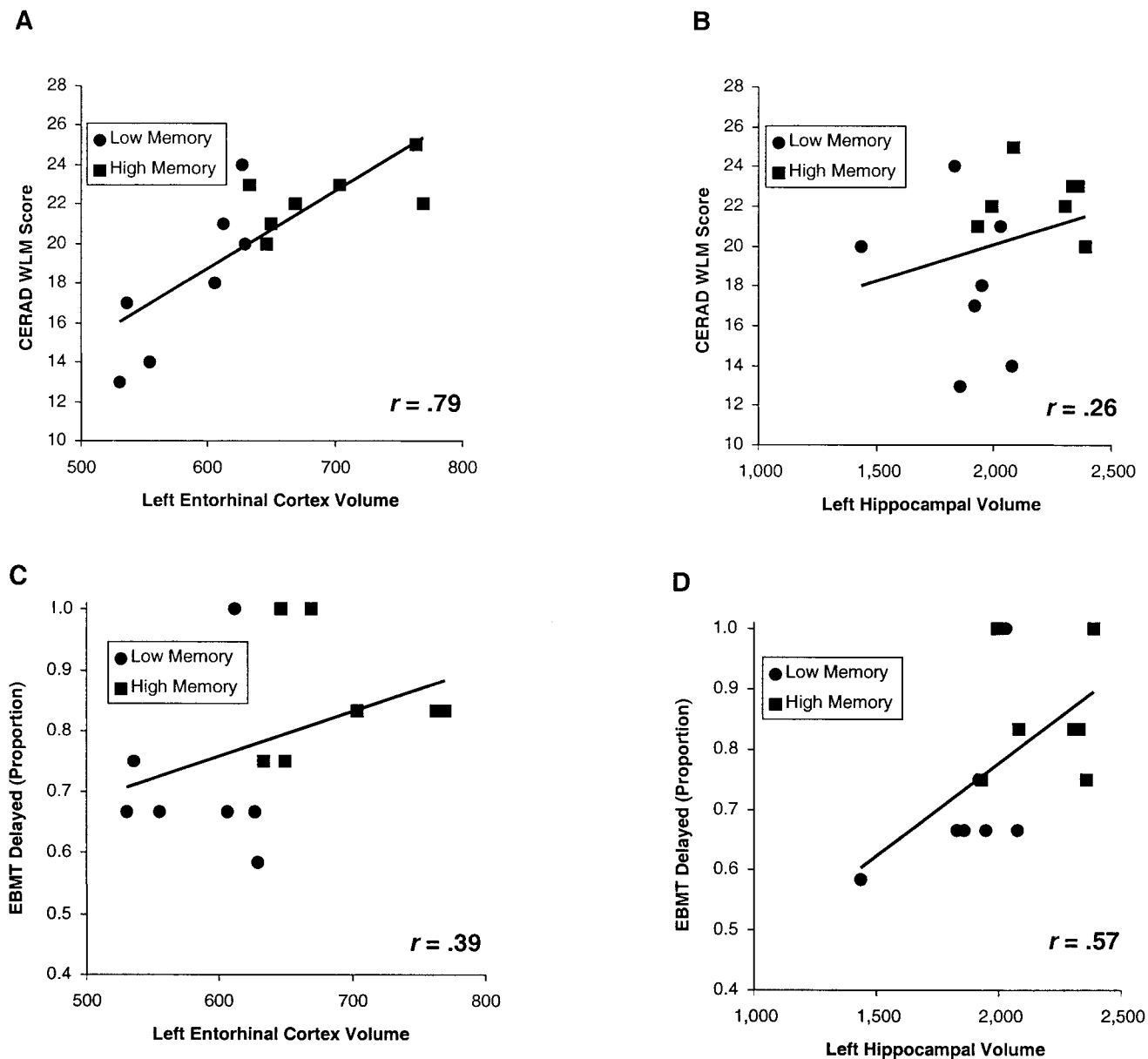


Figure 2. Correlations between (A) Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word List Memory (WLM) scores and left entorhinal cortex volume ($p < .001$), (B) WLM and left hippocampal volume (ns), (C) paragraph (East Boston Memory Test [EBMT]) delayed recall and left entorhinal cortex volume (ns), and (D) paragraph (EBMT) delayed recall and left hippocampal volume ($p < .05$).

demonstrating structure–function dissociations between these tasks in a single sample of participants.

The two independent dimensions of verbal recall considered were study–test intervals (immediate vs. delayed recall) and materials (lists of unrelated words vs. a meaningful paragraph). The present findings suggest that declarative memory processes supported by the entorhinal cortex are more salient for unrelated lists of materials and for shorter study–test intervals, whereas processes supported by the hippocampus are more salient for meaningful paragraphs and for longer study–test intervals. The stronger association between entorhinal volume and immediate recall and be-

tween hippocampal volume and delayed recall is consistent with animal lesion findings (Hampson et al., 1999). This dissociation was observed despite the fact that the delays in the current study were relatively brief and similar to those used by Wilson et al. (1996), on the order of 3–5 min. The materials difference may relate to the role of memory integration across time for unrelated words in a list versus related words in a meaningful paragraph. For unrelated words in a list, there is little integration over time as each word is presented for study. For words in a meaningful paragraph, in which words form sentences and sentences form a narrative, there is considerable integration of words and sentences as the

passage meaning or story is comprehended. Integration of words in a story context may involve binding or linking of memories across time, a process that may particularly involve the hippocampus (Eichenbaum, Dudchenko, Wood, Shapiro, & Tanila, 1999). Thus, both temporal and material dimensions of long-term memory may be differentially related to entorhinal and hippocampal regions.

The cross-sectional anatomic comparison between high- and low-memory groups cannot determine with certainty whether the low-memory group is declining disproportionately in memory performance rather than simply having lower memory scores across the lifespan. Analyses of the memory test scores, however, show that the difference in memory performance between low- and high-memory groups increased over time before the groups were scanned (Table 2). There was a significant interaction between time and group on the WMS-LMI test, and the two groups, which had not differed reliably at Time 1, differed reliably at Time 2 on both the WMS-PAI and Memory Recall tests. Therefore, these longitudinal behavioral data suggest that the low-memory group had a disproportionate and specific decline in memory ability relative to the high-memory group between the initial assessment in 1991–1993 and the reassessment in 1995–1997. Thus, not only was the low-memory group inferior in memory performance, but also that inferiority was increasing over time.

Older adults with disproportionate memory impairment, such as those classified as having age-associated memory impairment (Crook et al., 1986) or amnesic MCI (Petersen et al., 2001), may represent a prodromal or preclinical stage of AD, because individuals with MCI convert to AD at an increased rate relative to age-matched controls (Petersen et al., 1999). Some studies have found smaller hippocampal volumes in individuals with MCI relative to age-matched controls (Convit et al., 1997; de Leon et al., 1996; Dickerson et al., 2001; Jack et al., 1999; Xu et al., 2000), whereas others have not found this for age-associated memory impairment (Laakso et al., 1998; Soininen et al., 1994). Smaller hippocampal volume in individuals with MCI is associated with greater risk of converting to AD (Jack et al., 1999, 2000; Jack, Xu, & Petersen, 2001). Other studies have found reduced entorhinal volume in persons with MCI and incipient AD relative to age-matched controls (deToledo-Morrell, Goncharova, et al., 2000; Dickerson et al., 2001; Du et al., 2001; Killiany et al., 2000, 2002; Xu et al., 2000). Indeed, longitudinal studies indicate that entorhinal volume is even more strongly predictive than hippocampal volume of development of AD (deToledo-Morrell, Goncharova, et al., 2000; Dickerson et al., 2001; Killiany et al., 2002; but see Xu et al., 2000). In fact over the course of 12–77 months, a 10-unit decrease in entorhinal volume ($[\text{absolute volume in mm}^3 \div \text{intracranial volume in mm}^3] \times 1,000$) was associated with a 7% increased chance of converting to AD (deToledo-Morrell, Goncharova, et al., 2000). In our study, the correlations were stronger between entorhinal cortex and memory performance than between hippocampus and memory performance, even considering the material specificity. All these data are consistent with histopathological studies of MCI demonstrating involvement of entorhinal cortex (Kordower et al., 2001). The entorhinal cortex is a site of early involvement in AD (Braak & Braak, 1996), but it remains to be studied whether differences in the integrity of entorhinal cortex underlie memory differences in people who are not imminently converting to AD.

Given this focal difference in memory performance in the present study, and reduced hippocampal and entorhinal volumes in the low-memory group, it may be asked whether the low-memory group is in some early stage of AD pathological decline. The individual differences in memory abilities in the current group of nondemented older adults were so subtle that if any of these participants had incipient AD, they were quite early in the course of such a cognitive decline and only longitudinal follow-up can determine this. We were unable to reassess or perform full clinical evaluations to examine this question.

There are a number of limitations of our findings. Because the sample was small and demographically homogeneous, additional studies are necessary to verify the generalizability of the results. For example, most participants were highly educated, Caucasian, and not in the “old-old” age range over 80. The present study attempted to exclude participants with vascular risk factors. Whether this relationship between memory performance and entorhinal cortex volume holds in the presence of small vascular insults is a topic for further study. In addition, only MTL volumes were measured, and it is possible that memory performance could also relate to the volume of other brain regions. Finally, this study focused on verbal memory performance, and future work needs to be done to determine the relationship between nonverbal memory and entorhinal cortex volume.

There are other brain regions that are important for memory and undergo age-related declines in volumes. Among these, the frontal lobes are often found to have disproportionately large volume reductions in aging, and many age-related changes in cognition are associated with frontal-lobe functions (for a review, see West, 1996). In our study, however, neuropsychological measures that are sensitive to frontal-lobe dysfunction, including demanding tests of psychomotor speed, working memory capacity, and verbal fluency, were equivalent in the high- and low-memory groups. This suggests that frontal-lobe functional integrity was similar between the two groups.

The present findings may be consonant with a two-factor model of age-related decline in memory processes, with one factor related to the frontal lobes and another to MTL structures. Many studies have found disproportionate age-related declines on tests of memory known to be particularly affected by frontal-lobe injuries, such as memory for source and temporal order or recency (for a review, see Prull et al., 2000). This may reflect a life-long linear decline in frontostriatal neural systems that is characteristic of normal aging and is exacerbated by diseases that target this system, such as Parkinson's disease (Gabrieli, 1996). The present study and other studies suggest that a second factor may involve changes in MTL structures. Not only does atrophy of the entorhinal cortex predict the development of AD (deToledo-Morrell, Goncharova, et al., 2000; Dickerson et al., 2001; Killiany et al., 2002; but see Xu et al., 2000), but entorhinal cortex hypometabolism also predicts the development of MCI in apparently healthy aging (de Leon et al., 2001). Thus, entorhinal dysfunction may impair memory in many older people many years prior to any clinical problems.

In the present study, approximately 10 years prior to the volumetric measurement, the high- and low-memory individuals did not report any memory difficulty beyond what they expected for their age. The low-memory group, however, had lower memory scores and more reports of memory difficulty in specific aspects of daily life. This raises the possibility that subtle memory difficul-

ties, perhaps related to entorhinal pathology, occur a decade or more prior to the potential onset of AD. Given the high incidence and prevalence of AD in older adults (Evans et al., 1989; Hebert, Beckett, Scherr, & Evans, 2001), and what appears to be a long prodromal decline in MTL volume and memory ability prior to AD onset, it may be that many such individuals are present in populations studied as examples of normal, non-pathological aging. If so, this subpopulation would lead to an overestimate of declarative memory decline in normal aging. It is unknown, however, whether the low-memory individuals in this study will convert to AD, or whether other factors account for their low and relatively declining memory performance. Only longitudinal and postmortem data can further specify the etiology of individual differences in memory ability among the elderly. In turn, many normative studies of age-related changes in memory performance must include many such individuals if AD develops very slowly over many years. Alternatively, there may be individual differences in the vulnerability of MTL structures to age. Only longitudinal research and postmortem data can differentiate these etiologies of individual differences in memory ability.

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Call for Nominations: *JPSP:Attitudes*

The Publications and Communications (P&C) Board has opened nominations for the editorship of the *Journal of Personality and Social Psychology: Attitudes and Social Cognition* section for the years 2006–2011. Patricia G. Devine, PhD, is the incumbent editor.

Candidates should be members of APA and should be available to start receiving manuscripts in early 2005 to prepare for issues published in 2006. Please note that the P&C Board encourages participation by members of underrepresented groups in the publication process and would particularly welcome such nominees. Self-nominations also are encouraged.

David C. Funder, PhD, has been appointed to chair the search.

Candidates should be nominated by accessing APA's EditorQuest site on the Web. Using your Web browser, go to <http://editorquest.apa.org>. On the Home menu on the left, find Guests. Next, click on the link "Submit a Nomination," enter your nominee's information, and click "Submit."

Prepared statements of one page or less in support of a nominee can also be submitted by e-mail to Karen Sellman, P&C Board Search Liaison, at ksellman@apa.org.

The first review of nominations will begin December 8, 2003. The deadline for accepting nominations is **December 15, 2003**.