Remote memory for public figures in Alzheimer's disease: Relationships to regional cortical and limbic brain volumes

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Abstract

This study examined the relationships between regional cortical and hippocampal brain volumes and components of remote memory (recall, recognition, sequencing, and photo naming of presidential candidates) in 13 individuals with Alzheimer's disease (AD). Recognition and sequencing of remote memory for public figures were associated with regional *cortical* volumes. Specifically, lower recognition and sequencing scores were associated with smaller parietal–occipital cortical volumes; poorer sequencing was also associated with smaller prefrontal cortical volumes. By contrast, poorer anterograde but not remote memory scores were correlated with smaller *hippocampal* volumes. Within the constraints of the brain regions measured, these findings highlight the importance of the posterior cortical areas for selective remote memory processes and provide support for the dissociation between cortically mediated remote memory and hippocampally mediated anterograde memory. (*JINS*, 2001, 7, 384–390.)

Keywords: Remote memory, Alzheimer's disease, MRI, Cortex, Hippocampus

INTRODUCTION

Alzheimer's disease (AD) results in compromised remote memory (e.g., Beatty et al., 1988; Fama et al., 2000; Kopelman, 1989; Sagar et al., 1988). Dissociations have been reported between component processes of remote memory, for example, between people and events (McCarthy & Warrington, 1992), public figures/events and personal (autobiographical) events (Greene & Hodges, 1996), and content and contextual information (Sagar et al., 1988). These reports offer insight into brain systems mediating component processes of remote memory.

Remote memory impairment is thought to result from cortical abnormalities (Damasio & Damasio, 1993; Kapur et al., 1994; Squire et al., 1993; Ungerleider, 1995). A number of

individual cases have been cited (e.g., Hodges, 1995; Kapur et al., 1992, 1994) where focal neocortical lesions, exclusive of medial temporal lobe damage, have been associated with inability to retrieve previously learned information. Thus, although the structures of the medial temporal lobes are critical for the initial encoding and storage of information, long-term memories are not permanently stored in this area, but rather are distributed throughout the cortex (Squire et al., 1993).

Precisely where in the cortex particular memories are stored is thought to be determined by which cortical areas were initially involved in the processing of this information (Ungerleider, 1995). Based on lesion and PET imaging studies in humans and nonhuman primates, the cortical association areas in particular have been hypothesized to be storage sites for remote memories (Ungerleider, 1995). It has been postulated that a hierarchical processing system operates, in which the more basic visual processing (e.g., perception of features of a face) occurs more posteriorly (e.g., occipi-

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tal and parietal areas) and the integration of this information (e.g., association of a face with a name) occurs more anteriorly (e.g., temporal areas).

Frontal lesions may compromise organizational and strategic search capabilities, resulting in retrieval deficits for previously learned information (Kopelman, 1999; Mangels et al., 1996) as well as contextual processing of temporal and spatial aspects of memoranda, such as dates of public events (Sagar et al., 1988). Temporal cortical regions have been associated with retrieval of semantic memories, factual knowledge and other information, which is not necessarily bound by temporal or contextual cues (Hodges, 1995; Kapur et al., 1992, 1994; Markowitsch et al., 1993), and with recognition and naming of famous or familiar faces (Eslinger et al., 1996; Evans et al., 1995; Gorno Tempini et al., 1998; Kopelman, 1999). Posterior lesions involving the parietal or occipital cortex can result in focal retrograde amnesia (Hunkin et al., 1995; Parkin, 1996; Rubin & Greenberg, 1998).

In this study, we examined the relationships between content and contextual components of remote memory and MRI-derived measures of regional cortical and hippocampal brain integrity. In a previous study of AD patients, some of whom are in the present study, we observed a selective association between anterograde memory and hippocampal volume (Fama et al., 1997). Based on the literature and our previous results, we expected that remote memory performance would be associated with cortical but not hippocampal volumes and that anterograde memory performance would be associated with hippocampal but not cortical volumes. Secondly, we hypothesized that, given the semantic nature of

the measure used in this study (i.e., recall and recognition of presidential candidates), we would observe a relationship between content memory and volume of the temporal neocortex (Kapur et al., 1992, 1994). Thirdly, we hypothesized an association between contextual memory (i.e., dating of election and sequencing of candidates) and prefrontal volumes (Sagar et al., 1988). Finally, we expected that photo naming would correlate with posterior cortical and temporal neocortical volumes (cf. Eslinger et al., 1996; Hodges et al., 1993; Ungerleider, 1995).

METHODS

Research Participants

Participants included 13 AD patients (see Table 1) recruited from the Geriatric Psychiatry Rehabilitation Unit and the Aging Clinical Research Center. All patients met the National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association criteria for probable Alzheimer's disease (Khachaturian, 1985; McKhann et al., 1984).

The normal control (NC) group for remote memory measures comprised 29 participants, spanning the age range of the AD patients (AD: 60–83 years of age; NC: 61–77 years of age) and represented a subset of the group reported in a previous study on remote memory in AD (Fama et al., 2000). Potential control participants who scored below 25 on the Mini-Mental State Examination (Folstein et al., 1975) were excluded from the study as were those with significant history of psychiatric or neurological disorder, past or present

Table 1. Demographics and test scores for AD and NC participants

Variable	AD M	AD (SD)	NC M	NC (SD)
Age (years)	70.0	(5.6)	68.3	(4.8)
Age of symptom onset	65.6	(8.3)	—	—
Years since diagnosis	4.9	(5.9)	—	—
Education (years)	14.8	(3.1)	16.1	(2.4)
NART IQ	105.5	(8.3)	115.1	(6.0)
WAIS–R Vocabulary age scaled score	9.8	(2.0)	13.2	(2.5)
MMSE	20.4	(3.1)	28.9	(1.2)
DRS Total Score	120.0	(9.7)	—	—
Memory Subscale	13.9	(3.2)	—	—
WAIS–R Information age scaled score	7.3	(2.4)	—	—
Boston Naming Test (max. = 42)	28.7	(9.3)	—	—
Presidents Test				
Candidate Recall (max. = 28)	2.9	(2.2)	11.0	(4.4)
Candidate Pair Recognition (max. = 18)	9.7	(3.1)	14.7	(2.6)
Election Date Recognition (max. = 18)	3.5	(1.9)	10.7	(3.8)
Candidate Sequencing (max. = 36)	15.6	(5.1)	26.6	(6.8)
Photo Naming (max. = 22)	6.6	(4.1)	15.2	(3.2)

Note. NART = National Adult Reading Test (Nelson, 1982); maximum IQ = 128 points. WAIS–R = Wechsler Adult Intelligence Scale–Revised (Wechsler, 1981). MMSE = Mini-Mental State Exam (Folstein et al., 1975); maximum = 30 points. DRS = Dementia Rating Scale (Mattis, 1988); maximum = 144 points.

alcohol or drug abuse, or other serious medical condition. Written informed consent was obtained from all participants.

Neuropsychological Measures

Participants received tests of overall cognitive functioning (Mini-Mental State Exam, MMSE; Folstein et al., 1975), premorbid intellectual level (National Adult Reading Test, NART; Nelson, 1982), remote memory (Presidents Test; Fama et al., 2000; Hamsher & Roberts, 1985), anterograde memory (Dementia Rating Scale, DRS, Memory subtest; Mattis, 1988), semantic knowledge (Information and Vocabulary subtests of the Wechsler Adult Intelligence Scale–Revised; Wechsler, 1981), and confrontation naming (Modified Boston Naming Test; Huff et al., 1986). Not all participants had all tests.

Presidential Candidates Test

The principal memoranda for this test were the Democratic and Republican presidential candidates (elected and defeated) from 1920 to 1988 (see Fama et al., 2000; Hamsher & Roberts, 1985). The test comprised four parts, administered as follows:

1. *Candidate Recall*: Participants wrote the names of all the Democratic and Republican presidential candidates since 1920, the political party with which they were affiliated, and the year(s) candidates ran for office. Last names of the candidates were deemed sufficient for credit.

2. *Candidate and Date Recognition*: Each recognition item comprised six names and three dates: two candidates who ran against each other in a particular election and four high profile individuals politically or socially active in the same era as the candidates. The dates were the correct election year and two foils.

3. *Candidate Sequencing*: Participants sequenced the names of candidates within a single political party. Three sets of index cards, each card containing the name of a candidate, were presented in a random order (fixed across participants) for each political party (Set 1 = 1920–1940; Set 2 = 1944–1964; Set 3 = 1968–1988) and participants placed the candidates in chronological order (maximum score for each trial = 6).

4. *Photo Naming*: Participants were shown 22 black-and-white photographs of all presidential candidates from the elections of 1920 to 1980 and asked to name each of them.

MRI Scanning and Quantification

MRI was conducted with 1.5 T General Electric Signa scanners. Image acquisition and quantification procedures for the series used herein have been previously described (axial: Pfefferbaum et al., 1994; coronal: Sullivan et al., 1995). For the axial series, the cortical rim was segmented into gray matter, white matter, and CSF compartments and was also

divided into six regions: prefrontal, frontal, anterior superior temporal, posterior superior temporal, anterior parietal, and posterior parietal–occipital (see Figure 1a). Ten of the 13 AD participants completed a coronal acquisition protocol, from which volumes of the hippocampus and temporal cortex were derived (see Figure 1b).

Statistical Analysis

The volumes of each brain region of interest in the AD patients were corrected for variation attributable to intracranial volume and age using regression analyses (Pfefferbaum et al., 1992, 1994) based on control data from 95 men and 41 women for axial MRIs and 84 men and 28 women for coronal MRIs (Fama et al., 1997). Each regional brain measure was expressed as a z score, where the expected mean of the control participants at any age was 0 ± 1 standard deviation. For the AD participants, z scores provide volume estimates relative to that which would be expected for control participants of a particular head size and age. Lower z scores for tissue measures reflect greater abnormality.

Relationships between remote memory measures and bilateral regional brain volumes were examined with Spearman correlations. To limit the number of comparisons, only bilateral volume measures were used to test the study hypotheses.

RESULTS

MRI Volume Abnormalities and Memory Test Deficits

Based on head-size and age-corrected z scores, this sample of AD patients showed regional cortical and hippocampal volume deficits of 0.7 to 2 standard deviations from volumes measured in the normal control group. Relative to age-matched controls, the AD patients were impaired on all measures of the Presidents Test (Fama et al., 2000) and scored in the impaired range on the memory subscale of the DRS according to the published norms (Mattis, 1988; see Table 1). There was a floor effect on the free recall portion of the Presidents Test, with 9 of the 13 AD participants recalling 3 or fewer presidential candidates. In addition, the AD group did not perform better than chance level on the date recognition subtest. Recognition, sequencing, and photo naming of presidential candidates displayed good score variability within the AD group. All AD participants scored at or below the 19-point cut-off score used to indicate impairment on the DRS memory subtest. Summary scores for the control group (within the age range of the AD group) are presented in Table 1.

MRI Correlates of the Presidents Test and the DRS Memory Subscale in AD

Spearman correlations for the recognition, sequencing, and photo naming subtests of the Presidents Test and the DRS
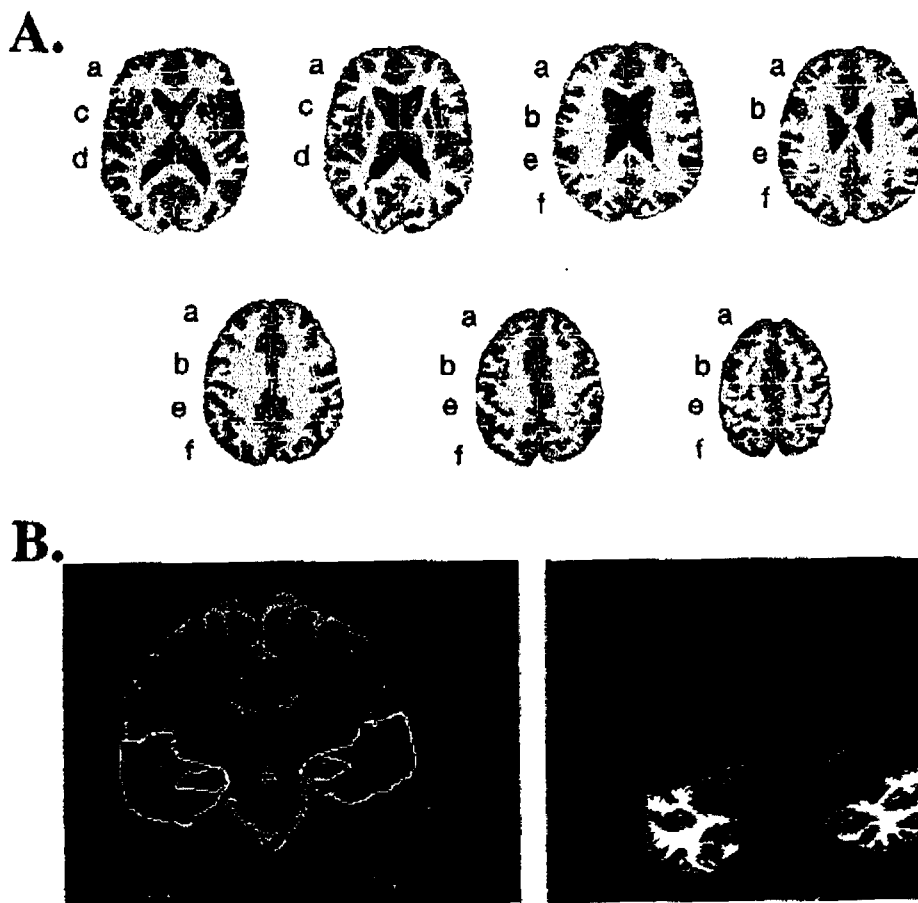
A.

B.

Fig. 1. A: Axial MR images were 5 mm thick (2.5 mm skip) and acquired in an oblique plane using a dual-echo spin-echo sequence (TE = 20, 80 ms) with a 24-cm field of view and a 256 × 256 matrix. Acquisition was gated to every other cardiac cycle for an effective TR of >2400 ms with one excitation for each of 256 phase encodes. Seven consecutive slices, beginning with the anterior horns of the lateral ventricles, were segmented into gray matter (shown in dark gray), white matter (light gray), and cerebrospinal fluid (black). Each measured MRI slice was divided into an outer 45%, which represented cortical regions, and an inner 55%, which included ventricular regions. The cortical area was then divided into regions that roughly correspond to lobar anatomy: 'a' indicates prefrontal, Slices 1 to 7; 'b,' frontal, Slices 3 to 7; 'c,' anterior superior temporal, Slices 1 to 2; 'd,' posterior superior temporal, Slices 1 to 2; 'e,' anterior parietal, Slices 3 to 7; 'f,' posterior parietal–occipital, Slices 3 to 7. **B:** Early echo coronal MRI with hippocampi and temporal lobes outlined. With this protocol 22 contiguous 3-mm thick coronal images were acquired with a dual-echo, flow compensated, cardiac gated pulse sequence [TE = 40, 80 ms; effective TR ≈ 2800 ms; field of view = 24 cm, NEX = 1, 256 × 256 matrix; image acquisition oriented perpendicular to the anterior commissure–posterior commissure (AC–PC) line]. The hippocampus and temporal lobes were outlined on consecutive slices in each hemisphere and volumes were derived by adding the areas of each measured slice.

memory subtest and bilateral regional brain volumes are presented in Table 2. Because the AD group performed at floor level on the free recall subtest and at chance level on the date recognition subtest, correlations between these remote memory measures and regional brain volumes were not tested. *Post-hoc* analyses examining laterality effects in each brain region measured, regardless of whether the bilateral regional cortical volume was significantly correlated with a memory measure, did not yield significant findings in the predicted direction.

Recognition scores on the Presidents Test were significantly correlated with posterior parietal–occipital volumes (r_s = .61, p < .04; see Figure 2) but were not related to hippocampal volumes. Follow-up analyses indicated that the correlation between recognition score and posterior parietal–occipital volume and the correlation between recognition score and hippocampal volume were significantly different from one another (Fisher z transformation, t = 2.93, p < .02). Lower *sequencing* scores were significantly correlated with smaller prefrontal (r_s = .80, p < .03), anterior

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Table 2. Spearman correlations between MRI volumes and President Test subtests

Volume	Recognition	Sequencing	Photo Naming	DRS–Memory
Axial MRI Cortical Gray Matter Regions				
Prefrontal	.48	.80*	−.36	.21
Frontal	.28	.53	−.28	.19
Anterior superior temporal	.01	.56	−.62	.31
Posterior superior temporal	−.28	.02	−.59	.59
Anterior parietal	.32	.73*	−.18	.26
Posterior parietal–occipital	.61*	.73*	−.04	.47
Overall cortical	.54	.76*	−.32	.47
Coronal MRI				
Temporal lobe	.00	.71	−.41	−.32
Hippocampus	−.18	.46	−.32	.82*

*$p < .05$.

parietal ($r_s = .73, p < .04$), posterior parietal–occipital ($r_s = .73, p = .04$), and overall cortical ($r_s = .76, p < .04$) volumes (see Figure 2) but not with hippocampal volumes. *Photo naming* scores did not correlate significantly with any cortical or limbic volumes.

The *DRS memory* score correlated significantly with total hippocampal volume ($r_s = .82, p < .05$; see Figure 2) but not with any regional cortical volume measured.

Post-hoc analyses reexamining the relationships between memory measures and regional brain volumes for only
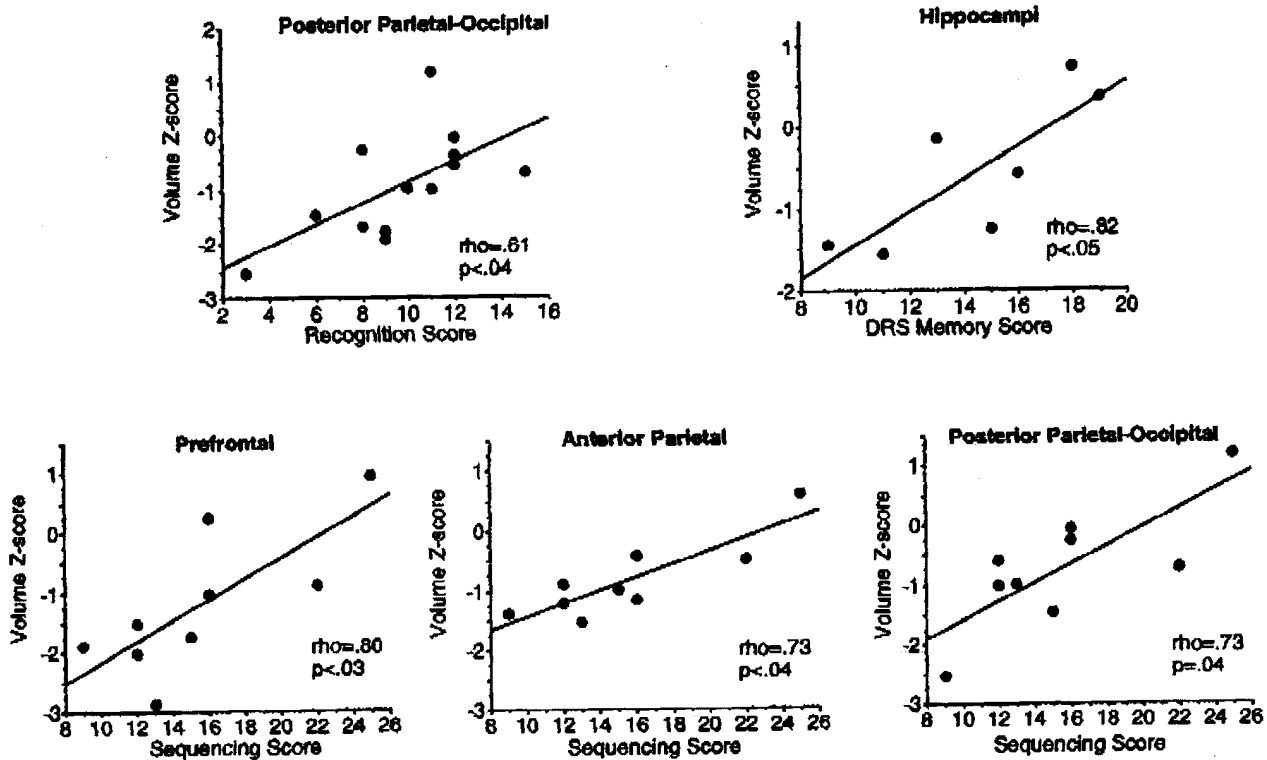

Fig. 2. Scatterplots depicting brain–behavior relationships reported. Lower recognition scores were significantly correlated with smaller posterior parietal–occipital gray matter volumes, lower memory scores from the Dementia Rating Scale were significantly correlated with smaller bilateral hippocampal volumes, and lower sequencing scores were significantly correlated with smaller prefrontal, anterior parietal, and posterior parietal–occipital gray matter volumes.

those participants who received all test measures ($n = 7$) confirmed the pattern of results reported above.

DISCUSSION

These results provide evidence that selective component processes of remote memory were associated with regional cortical but not hippocampal volumes in patients with Alzheimer's disease, despite the presence of severe volume deficits in both cortical and hippocampal regions. Specifically, recognition of public figures was associated with posterior parietal–occipital cortical volume, and sequencing of remote public figures was associated with prefrontal as well as posterior cortical volumes. In contrast to remote memory processing substrates and as previously observed in a larger AD sample (Fama et al., 1997), anterograde memory was associated with hippocampal but not cortical volumes. These results are consistent with previous reports that, although the hippocampus is important for the encoding and consolidation of new memories, retrieval of remote memories is primarily mediated by the cortex (Squire et al., 1993; Ungerleider, 1995). The present findings based on structural imaging highlight the importance of parietal–occipital cortical areas in the storage and retrieval of specific component processes of remote memories and are consistent with previously reported functional imaging studies that cite the importance of posterior cortical areas in the retrieval of declarative memories (Hunkin et al., 1995; Ungerleider, 1995).

Sequencing of remote memories was significantly related to the prefrontal regions. As others have shown using various populations and imaging techniques (Buckner & Tulving, 1995; Perani et al., 1993), integrity of prefrontal regions and their connections are associated with the ability to sequence and order information. Consistent with recognition of presidential candidates, temporal sequencing of these candidates was associated with posterior cortical regions. Both the recognition and the sequencing subtests used visually presented text of candidates' names. The sequencing task required an additional manipulation or abstraction of the information for successful performance compared to the recognition subtest, and this may be reflected in the relationship of sequencing with the prefrontal as well as posterior cortical regions.

Even though all remote memory tasks involved the same basic stimuli, that is, past presidential candidates, each involved different task demands. The dissociability of the component processes tapped by these demands was further evidenced by the different brain–behavior relationship observed among these tasks. Similarly, McCarthy and Warrington (1992) reported differences in the ability to retrieve remote memories depending upon the nature of the question asked (e.g., asking "who was" vs. "what happened" questions, even in instances when the person in question was known primarily through a single event).

We did not observe the associations between remote memory and temporal cortical regions that others have reported (Kapur et al., 1992, 1994). Our free recall measure did not allow an adequate test of this hypothesis, however, in that the AD group performed at floor level on this measure. In light of our modest sample size we would stress caution in the interpretation of this absence of association between recall and recognition of the names of public figures and the temporal neocortex. These results do, however, highlight the importance of extratemporal cortex in the mediation of certain component processes of remote memory.

Although we observed several brain–behavior associations between components of remote memory and selective cortical regions, we do not claim that remote memories are localizable to a specific brain region. Instead, we have identified certain cortical regions that contribute significantly to the mediation of component processes of remote memory. This depiction follows from the hypothesis that remote memories are likely distributed throughout the cortex (see Squire et al., 1993; Ungerleider, 1995). Nonetheless, this study provides evidence for a double dissociation between cortically mediated remote memory processes of recognition and sequencing and hippocampally mediated anterograde memory. Further, these results suggest a role for parietal–occipital cortical regions in the storage and/or retrieval of remote memories for public events and a role for prefrontal regions in the sequential ordering of these events.

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